CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-441/S002

MEDICAL REVIEW(S)

OCT 8 1998

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:	NDA 20-441 SE2-002	APPLICATION TYPE:	Efficacy Supplement
SPONSOR:	Astra USA	PRODUCT/PROPRIETARY NAME:	Pulmicort Turbuhaler
	Westborough, MA	USAN / Established Name:	Budesonide
CATEGORY OF DRUG:	Corticosteroid	ROUTE OF ADMINISTRATION:	Inhaled
MEDICAL REVIEWER:	Mary E. Purucker, M.D., Ph.D.	REVIEW DATE:	8 October 1998

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
6 October 1997	8 October 1997	Efficacy supplement for once daily dosing	Received in 47 volumes; also electronic submission
13 March 1998 (FAX)		Information request	Stratified analysis of secondary endpoints for pivotal study 004-0009 (by baseline inhaled corticosteroid usage)

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
22 February 1994	NDA 20-441	Original submission of Pulmicort Turbuhaler, approved 24 June 1997.
	IND [redacted]	Original IND for Pulmicort Turbuhaler

Overview of Application/Review: This is an efficacy supplement providing for once daily dosing of budesonide via Pulmicort Turbuhaler for adults and children age six years and older with mild to moderate chronic asthma. The sponsor proposes to dose this product starting at 200 or 400 mcg once daily and thereafter at a maintenance dose of 200 or 400 mcg once daily. The submission is comprised of one pivotal U.S. study and 13 supportive non-U.S. studies, six of which were included in the original application and were deemed inadequate to support once daily dosing at that time. The controlled clinical trials contained in this application, in particular pivotal clinical trial 004-0009, support once daily Pulmicort Turbuhaler 200 mcg/day or 400 mcg/day as an alternative dosing strategy for patients with mild to moderate chronic asthma previously stabilized on inhaled corticosteroids. Data is inadequate to support once daily Pulmicort as initial therapy for patients with mild to moderate asthma who require inhaled corticosteroids, but who are inhaled corticosteroid-naïve.

Recommended Regulatory Action:	N drive location:
Efficacy / Label Supp.: ___X___ Approvable	_____ Not Approvable
Signed: Medical Reviewer: /S/	Date: 8 October 1998
Medical Team Leader /S/	Date: 8th/Oct 1998

SYNOPSIS OF REVIEW AND RECOMMENDATIONS

The submission is an efficacy supplement to provide for once daily dosing of Pulmicort Turbuhaler 200 or 400 µg/day for children and adults age 6 and older with mild to moderate asthma. Data submitted in support of this indication include one pivotal, placebo-controlled US trial with 309 patients and 13 supportive non-US trials. Six of these trials were previously reviewed in this division and found to be inadequate to support once daily dosing. Of the remaining seven, two are placebo-controlled. The efficacy review is based upon the pivotal trial and the two placebo-controlled supportive trials. All trials submitted in this supplement were utilized in the safety review.

The results of pivotal trial #004-0009 support labeling of Pulmicort Turbuhaler for once daily dosing as an option for adult patients with mild to moderate asthma stabilized on inhaled corticosteroids, but do not support once daily dosing as initial therapy for patients who are inhaled corticosteroid-naïve. The suggested dose is 200 or 400 mcg/day. Supportive study #04-3083 also demonstrated that once daily Pulmicort at 200 mcg/day was statistically superior to placebo for clinically stable adult patients with mild to moderate disease already receiving inhaled corticosteroids. No corticosteroid-naïve patients were studied. The once daily dosing arm in this study used a different device from the twice daily dosing arm; and because their dose proportionality has not been demonstrated, no definitive conclusions concerning the relative efficacy of these two dosing options can be made. Clinical trial #04-3084 studied once daily dosing compared to twice daily dosing in corticosteroid-naïve children age 6-17 years with mild asthma. This trial failed to demonstrate statistical superiority of either once or twice daily Pulmicort compared to placebo and cannot be used to support once daily labeling.

Once daily dosing did not appear to change the frequency, severity, or nature of the adverse events in patients receiving Pulmicort. Early dropouts in trials where stable patients were switched from twice daily to once daily dosing indicates that not all mild to moderate asthmatics will tolerate this dosing change. However, the once daily dosing regimen does not appear to constitute a significant safety problem.

In conclusion, a labeling change for Pulmicort Turbuhaler 200 mcg/actuation is recommended to permit once daily dosing at 200 or 400 mcg/day as an option for some patients with mild to moderate asthma who are clinically stabilized on inhaled corticosteroids.

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1.0 INTRODUCTION AND BACKGROUND

Pulmicort is a dry powder inhalation formulation of budesonide dispensed from an inspiratory flow-driven device called a "Turbuhaler." The dry powder is comprised exclusively of budesonide, without any propellants or other excipients. The NDA for Pulmicort Turbuhaler (NDA 20-441) was approved by this division on 24 June 1997, becoming the first powder formulation of an inhaled corticosteroid available in the US. The sponsor sought and received approval for two strengths of Pulmicort at that time, 200 mcg/actuation and 400 mcg/actuation. Presently, only the 200 mcg/actuation product is marketed in this country.

The original submission of this NDA for Pulmicort Turbuhaler was made in February 1994, but the division refused to file the NDA at that time because the to-be-marked device (M0) was different from the device used in the NDA studies (M2). The revised NDA was resubmitted on 15 June 1995 and later given an "approvable" rating. Among the 42 controlled clinical trials included in this revised

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document, three placebo-controlled trials and one dose comparison study were proposed by the sponsor as supportive of once daily dosing. These studies were reviewed and declared inadequate for this indication by the division, although twice daily dosing was approved.

Included in this efficacy supplement is one new placebo controlled clinical trial (004-0009) utilizing the M0 device which has been designated as pivotal by the sponsor. The document also includes eight new supportive studies using the M2 device, two of which, 04-3083 and 04-3084, are placebo controlled. Finally, the sponsor has also included the four previously submitted controlled clinical trials (above) as supportive of once daily dosing of Pulmicort Turbuhaler.

1.1 Indications, Current Labeling, And Proposed Changes

Pulmicort Turbuhaler is presently labeled for 200 mcg twice daily to 800 mcg twice daily, the lower dose being indicated for milder asthmatics and for children. The sponsor proposes to add 200 mcg or 400 mcg once daily to these recommendations. This information is summarized below, which is taken from the sponsor's proposed package insert.

	Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Adults:	Bronchodilators alone	[redacted] 200 mcg to 400 mcg twice daily	400 mcg twice daily
	Inhaled Corticosteroids	[redacted] 200 mcg to 400 mcg twice daily	800 mcg twice daily
	Oral Corticosteroids	400 to 800 mcg twice daily	800 mcg twice daily
Children:	Bronchodilators alone	[redacted] 200 mcg twice daily	400 mcg twice daily
	Inhaled Corticosteroids	[redacted] 200 mcg twice daily	400 mcg twice daily
	Oral Corticosteroids	The highest recommended dose in children is 400 mcg twice daily	

1.2 Ingredients

Pulmicort Turbuhaler is approved in two strengths in the US, 200 mcg/actuation and 400 mcg/actuation, which deliver approximately 160 mcg and 320 mcg, respectively, of pure budesonide, without excipients. Only the 200 mcg/actuation strength is presently being marketed in the US, and at this strength, only as the 200 dose unit. The placebo Turbuhaler used in the clinical studies contained [redacted]

1.3 Relevant Marketing History

A total of 35 countries have approved Pulmicort for treatment of asthma. All 35 have approved the twice daily dosing schedule, and seven have also approved the once daily schedule. Five countries have approved pediatric use. The sponsor manufactures three dosage strengths of

the Pulmicort Turbuhaler, 100 mcg/actuation, 200 mcg/actuation, and 400 mcg/actuation, but as is the case in the US, not all of these strengths are available in each country.

In addition to the [ ] are also available in a few other countries.

1.4 Approach To Review And Materials Reviewed

The submission is comprised of 36 volumes, the first 22 of which contain the relevant controlled clinical trials which have been reviewed in this document. The placebo-controlled clinical trial 004-0009 was submitted as the pivotal study for safety and efficacy, hence the bulk of this review deals solely with this trial (Section 2.0). As stated earlier, six of the thirteen supportive studies included in the submission were previously reviewed in this division and were found to be inadequate to support once daily dosing for Pulmicort Turbuhaler. Detailed review of these trials has not been repeated in this document. Of the remaining eight studies, two were placebo controlled. These two trials, 04-3083 and 04-3084, are comprised of one adult study comparing once daily to twice daily Pulmicort and a pediatric study comparing twice daily therapy to two doses of once daily Pulmicort. (Sections 3.0 and 4.0, respectively). Of the remaining six studies, four were active control, double blinded (04-3073, 04-3068, 04-3085, 04-9267). These four trials include one clinical pharmacology study of HPA axis effects and one pediatric and two adult studies of twice daily compared to once daily Pulmicort (Section 5.0). The final two studies, 04-9290 and 04-9253, were open label and not placebo controlled. These were reviewed for safety only.

The Integrated Summary of Efficacy (ISE, Section 6.0) made use of data primarily from pivotal trial 004-0009. Supportive data was taken from the two placebo controlled trials, 04-3083 and 04-3084, and two active control, double blind trials, 04-3085 and 04-9267. These latter four were chosen because they provided information relevant to pediatric patients, the inhaled corticosteroid-naïve subset of patients, and comparative data between once and twice daily therapy.

The Integrated Summary of Safety (ISS) is contained in Section 7.0. The discussion of patient demographics and extent of exposure made use of data from all 14 of the clinical trials submitted for consideration with this supplement. Data concerning the occurrence of adverse events in once daily patients relative to twice daily patients utilized all double blind studies which included both of these arms. Quantitative data comparing adverse events in once daily patients compared to placebo utilized the placebo controlled trials only. Safety issues such as HPA axis effects made use of data from the specific trials which studied it.

1.5 Abbreviations And Nomenclature:

In the pivotal trial 004-0009, the sponsor uses the convention "GCS-free" to refer to patients not managed on inhaled corticosteroids and "GCS-dependent" for patients receiving inhaled corticosteroids at the time of recruitment. "Steroid dependent" has other clinical connotations, therefore this reviewer has attempted to substitute "inhaled GCS (+)" and "inhaled GCS (-)" for "inhaled GCS-dependent" and "inhaled GCS -free," respectively, in the text of the review of that study wherever possible (figures, tables, and other graphics copied from the electronic version of this submission could not be adjusted).

GCS	Glucocorticosteroid
BDP	Beclomethasone dipropionate

MDI	Metered dose inhaler
DPI	Dry Powder Inhaler
LVCF	Last value carried forward
AE	Adverse Event (also called "ADR")
200/200	Refers to the patient group who received 200 mcg of Pulmicort as a single daily dose in both the Treatment as well as the Maintenance Phases of Pivotal Clinical Trial DS 004-0009.
400/200	Refers to the patient group who received 400 mcg of Pulmicort as a single daily dose during the Treatment Phase and 200 mcg of Pulmicort as a single daily dose during the Maintenance Phase of Pivotal Clinical Trial DS 004-0009.
GCS (+)	Patient receiving inhaled GCS at baseline
GCS (-)	Patient not managed on inhaled GCS at baseline.

2.0 PIVOTAL STUDY DS-004-0009 (Vol. 1, p.35)

Summary:

The sponsor has submitted this clinical trial as pivotal to support the safety and efficacy of once daily dosing of Pulmicort Turbuhaler, 200 or 400 mcg/day, for initial treatment or for maintenance treatment of mild to moderate asthma. Randomization of 309 eligible patients was stratified for prior inhaled GCS usage. Patients previously managed on inhaled GCS (57% of enrollment) were switched to equivalent doses of inhaled BDP during the two week run-in phase. The run-in phase was followed by a 6 week treatment phase with three arms, budesonide 200 mcg/day, budesonide 400 mcg/day, or placebo. The treatment phase was followed by a 12 week maintenance phase in which all patients who had received budesonide during treatment either had it maintained at, or reduced to, 200 mcg/day, while the placebo patients continued to receive placebo. The primary endpoints, AM PEFR and FEV1, were reported separately for the two study phases. The difference from baseline in FEV1 compared to placebo achieved statistical significance for both single daily doses of budesonide for both the treatment and the maintenance phases of the study. The difference from baseline in PEFR compared to placebo achieved statistical significance for both single daily doses of budesonide for the maintenance phase, but was significant only for the 400 mcg/day dose for the treatment phase, although the 200 mcg/day dose was very close (p=0.056). Close examination of the data, however, including separate analyses based upon prior GCS usage at the time of randomization, showed that significance was driven by spirometric deterioration of the GCS-(+) placebo patients, rather than by improvement in the budesonide-treated patients, whether or not they had previously received inhaled GCS. The GCS-(-) subgroup failed to show statistical significance on either primary endpoint for the treatment phase, although significance was demonstrated for both doses during the maintenance phase on FEV1. These data support labeling of once daily dosing of Pulmicort for maintenance treatment of asthma in mild to moderate asthmatics already stabilized on an inhaled Pulmicort. They also support the initial treatment of mild to moderate asthmatics who are presently stabilized on an inhaled GCS other than Pulmicort. They do not support labeling of this product for initial treatment of asthma in patients who require, but who are not presently managed on, an inhaled GCS.

2.1 Study Description

2.1.1 Design:

This was a randomized, double-blind, placebo-controlled, parallel group multicenter

study. Eligible patients underwent a 2 week baseline period at which time inhaled GCS (+) patients were switched to an "equivalent" dose of inhaled BDP. Patients were then randomized (stratified for inhaled GCS use at baseline) to receive placebo or Pulmicort Turbuhaler 200 mcg/day or Pulmicort Turbuhaler 400 mcg/day dosed in the morning for the initial 6-week treatment phase of the study. Double-blind treatment was continued for an additional 12-week maintenance phase. Patients assigned to the 400 mcg/day arm had their dose reduced to 200 mcg/day at that time (the "400/200" group), while patients assigned to the 200 mcg/day arm(the "200/200" group) or to the placebo group received the same dose as during the treatment phase.

2.1.2 Population:

A total of 309 patients of either sex between the ages of 18 and 70 years with mild-to-moderate asthma were randomized: 104, 103, and 102 patients assigned to the placebo, Pulmicort Turbuhaler 200/200 mcg qd and Pulmicort Turbuhaler 400/200 mcg qd, respectively.

2.1.3 Materials:

Pulmicort Turbuhaler 200 and Pulmicort Turbuhaler 400 mcg/inhalation were used. Placebo was a Turbuhaler containing ( ) Each Turbuhaler contains 200 doses. A new Turbuhaler was distributed at the start of the treatment phase and at the start of the maintenance phase. Each dose was given as one inhalation daily in the morning, hence, the Turbuhaler was always at least half full throughout this study. The breakthrough drug was albuterol 90 mcg/actuation administered by pressurized MDI.

2.1.4 Objective:

The primary objective of the treatment phase of this trial was to determine the efficacy of once daily dosing of two dosages (200 or 400 mcg/day) of Pulmicort Turbuhaler versus placebo in patients with mild-to-moderate chronic asthma. The primary objective of the maintenance phase of this trial was to compare the maintenance of efficacy for 12 weeks of a single dose level (200 mcg) of Pulmicort Turbuhaler versus placebo in this same patient population. A further objective was to evaluate the safety of Pulmicort Turbuhaler in this patient population.

2.1.5 Inclusion/Exclusion Criteria:

Male or female patients aged 18-70 years with a history of chronic asthma for at least the previous 6 months were eligible for study enrollment. Both patients who had not received inhaled GCS for the previous 6 months ["GCS-free" or "GCS (-) patients] and patients who had taken inhaled GCS for at least the previous 8 weeks ["GCS-dependent" or "GCS (+) patients] were eligible for the study. Inhaled GCS-(+) patients were required to have an FEV1 of ≥75% of predicted, while inhaled GCS-(-) patients were required to have an FEV1 of ≥ 60% and ≤90% of predicted. All patients were required to have documented airways reversibility, as evidenced by an increase in FEV1 of ≥15% following administration of two puffs of an albuterol MDI. The following medications were not permitted during the study: cromolyn or nedocromil (at least 4 weeks washout prior to the start of the baseline period), beta-blockers, oral or parenteral GCS (at least 4 weeks washout), ipratropium bromide (at least 2 weeks washout), salmeterol (24 hour

washout), and OTC asthma medications.

2.1.6 Conduct:

During a 2 week baseline period, patients' eligibility was checked and routine screening tests were carried out (medical history and physical exam, vital signs, clinical laboratory, serum pregnancy testing, PFTs with reversibility, PEFR, quality of life assessment). If the patient was inhaled GCS (+), they were switched to a comparable dose of inhaled BDP at that time. Eligible patients next entered the 6 week treatment phase, at which time they were stratified for inhaled GCS usage and randomized to treatment groups of equal size in balanced blocks of three patients by center. Treatment arms were placebo or Pulmicort Turbuhaler 200 mcg/day or 400 mcg/day. Patients received instructions in how to use the device and were told to dose themselves once daily in the morning. Daily PEFR readings were to be performed and recorded immediately upon arising and before any breakthrough or study medications were taken, as well as in the evening upon retiring. Diary assessments of daytime and nighttime asthma symptom scores were to be recorded on a 4-point scale at the same time as PEFR assessments were made. Patients were to be seen in clinic at week 0, 3, and 6 (Visits 2, 3, and 4), where PFTs were recorded, before 10:00 AM and prior to dosing of study medication. PFT maneuvers were conducted in triplicate, and the highest FEV1 was recorded, along with the corresponding FEF25-75 and FVC. At the conclusion of the 6 week treatment phase, patients entered the 12 week maintenance phase. Patients who received either 200 or 400 mcg of budesonide daily were maintained at 200 mcg daily, or reduced to 200 mcg daily, without unblinding. Clinic visits occurred at weeks 10, 14, and 18 (Visits 5, 6, and 7). Daily patient self-assessment continued as previously described, as did clinic assessments.

2.1.7 Data Analysis:

The protocol-specified primary efficacy variables were mean change from baseline for AM PEFR and mean change from baseline for FEV1. The baseline for AM PEFR was computed as the mean of the values recorded (in the patients' diary) during the 2-week baseline period. The AM PEFR for the treatment and maintenance phases was expressed as the mean of the daily values for Weeks 0-6 and for Weeks 6-18, respectively. The baseline FEV1 was calculated as the mean of the values from Visit 1 and Visit 2. The FEV1 for treatment and maintenance phases was the average of values obtained in clinic for Weeks 3-6 and Weeks 10-18, respectively. Patients who prematurely discontinued treatment had their last available value for spirometry or last available visit-to-visit mean value of AM PEFR carried forward for the remaining visits. The primary analysis was based on the intent-to-treat population using the last value carried forward through phases described above. ANOVA analysis with factors for center and treatment was carried out. An additional analysis was carried out in which the dichotomous stratification variable [inhaled GCS-(+) or (-)] was included in the ANOVA model for the two primary efficacy parameters only. Two additional analyses were performed. One was based upon the intent-to-treat population using the last value carried forward within phases, and the other was a "per-protocol" analysis.

This protocol specifies multiple endpoints. There were two primary efficacy variables, FEV1 and PEFR, two different phases of this trial, treatment and maintenance,

and two different doses of budesonide, 400 mcg/day reduced to 200 mcg/day and 200 mcg/day continued at 200 mcg/day. Accepted statistical practice would dictate that the p-values be adjusted using a Bonferroni correction or its equivalent for the multiple comparisons. The sponsor has not included an explanation as to how this would be handled in the analysis.

In the originally submitted protocol, the sponsor specified seven secondary efficacy variables: daytime and nighttime asthma symptom severity scores, concomitant bronchodilator use, evening PEFR, spirometry variables other than FEV1, quality of life assessments (Juniper EF et al, Am Rev Respir Dis 1993; 147:832-8), the rate at which patients dropped out of the study, and time to treatment response. Evening PEFR, spirometry variables, concomitant bronchodilator use, and QOL parameters were analyzed using ANOVA. For QOL, a difference in score of ≥ 0.5 units was considered clinically significant. Time to response was determined using 5-day running averages of AM PEFR measurements. Response was defined as a 10% or more increase from baseline in AM PEFR. The time at which response occurred was considered to be the last day of the 5-day interval in which response was achieved. Dropouts who did not meet the definition of response were censored at the time of discontinuation. Treatment groups were compared using the log-rank test. The numbers of patients who discontinued were compared between the Pulmicort Turbuhaler group and placebo using a Chi-square test. A formal survival analysis was not performed.

With regard to sample size, it was estimated that approximately 85 evaluable patients per group would provide a 90% power (alpha=0.05) to detect a difference of 30 L/min and 0.25 L in AM PEFR and FEV1, respectively. Assuming a 20% dropout rate, 300 patients were planned to be randomized in this study.

2.2 Patient Disposition

Three hundred and nine patients were randomized: 104 to placebo, 103 to Pulmicort Turbuhaler 200/200 mcg/day and 102 to Pulmicort Turbuhaler 400/200 mcg/day. These data can be found in the sponsor's Table B, volume 1, page 77.

2.2.1 Patient Demographics:

The three treatment groups were similar in terms of demographics and other baseline characteristics. Overall, approximately two thirds of the patients were male, their mean age was 36 years, their duration of asthma was approximately 18 years, and their ethnicity primarily Caucasian (86%).

With regard to efficacy variables, compared to placebo and the 400/200 group, mean PEFR was slightly lower for the 200/200 group (348 L/min for 200/200 compared to 381 for placebo and 369 for 400/200). The minimum value of the PEFR range was also slightly lower (PEFR 119—564 L/min for 200/200 compared to 188-746 L/min for placebo and 198-663 L/min for 400/200). However, the percent predicted FEV1 was comparable across the three groups (81-83%).

With regard to pre-study asthma medication (Appendix Table 9; Vol 1, p.159), the 3 groups were also similar. The baseline characteristics of the inhaled GCS-free compared to GCS-dependent patients were reported by the sponsor in Appendix Tables 3.1 and 4.1 (Vol.1 p.136-8, 140). As might be expected, the GCS-free patients had somewhat worse baseline lung function, but overall the two groups were similar in terms of demographics and other characteristics.

2.2.2 Treatment Discontinuations:

Of the 309 patients who were randomized, 258 completed the study. There were 35 dropouts during the 6 week treatment phase and 16 dropouts during the 12 week maintenance phase. Most of the dropouts during the treatment phase occurred in the placebo group (22 patients, compared to 9 in the 200/200 and 4 in the 400/200). Comparable numbers of patients in each group dropped out during the maintenance phase (placebo: 4; 200/200: 6; 200/400: 6). The number of patients discontinued from the study can be found in Table C, volume 1, p. 78.

Reasons patients were discontinued included adverse events (mostly asthma exacerbation; 17 patients), disease deteriorated or not improved (16 patients), and other reasons (lost to follow up, pregnancy, etc.; 18 patients). Of the 16 patients who discontinued the study due to deterioration of their disease, 11 were in the placebo group, four were in the 200/200 group, and one was in the 400/200 group (compared to placebo, p=0.074 vs. 200/200; p=0.019 vs. 400/200). It does not appear that adverse events described as "asthma exacerbation" were included in these calculations, however. From Table 7.2 (Vol. 1, p. 149), there were five such patients in the placebo group (16 total), two in the 200/200 group (six total), and four in the 400/200 group (five total). If these patients are included in the analysis, then the difference between the treated and placebo groups becomes smaller and it is unclear whether the p-values would have achieved statistical significance. (However, dropout rate due to worsening of asthma was not a prospectively identified endpoint).

With regard to when these patients dropped out of the study, four of the six in the 200/200 group discontinued during the 6 week treatment phase rather than the longer duration 12 week maintenance phase. Similarly, three of the five dropouts due to worsening asthma in the 400/200 group also occurred during the 6 week treatment phase, suggesting that some patients may not tolerate a switch to, or initiation of, once daily therapy..

2.3 Efficacy Results

The sponsor carried out 3 types of analyses: the intent-to-treat LVCF across phases analysis (i.e. last value carried forward across phases), the intent-to-treat LVCF within phases analysis (i.e. last value carried forward within phases), and the per-protocol analysis (i.e. evaluable). A subgroup analysis based on patient use of inhaled corticosteroids at baseline was performed for the two primary efficacy parameters only.

Of the 309 patients who were randomized, four patients who received study medication were not included in the intent-to-treat efficacy analysis: two were in the placebo group and two were in the 200/200 group. Three of these patients were lost to follow up while one was discontinued after a confirmed positive pregnancy test. For the per-protocol analysis, an additional 16 patients were excluded, 8 in the placebo group, 5 in the 200/200 group, and 3 in the 400/200 group. Reasons for exclusion included taking non-permitted medications (7 patients), receiving study medication for under 14 days (8 patients) and inclusion criterion not being met (one patient).

This review will focus on the analyses for the intent-to-treat LVCF across phases, since it is the most comprehensive of the three analyses, including data from each primary efficacy parameter and all secondary efficacy endpoints. It will also serve as the basis for a "survival analysis." The per-protocol analysis will not be completely presented, since it tends to reflect

the bias inherent in post-study exclusions. At times it may help to refine inconclusive data from the intent-to-treat analysis, and at these points it will be included.

Finally, this review must examine closely the "subgroup" analysis of the GCS-(+) compared to GCS-(-) patients with regard to the primary efficacy endpoints. Although the study was not adequately powered to detect a significant difference in the primary endpoints within these subgroups, the labeling submitted specifically refers to dosing for the GCS-(-) subgroup (i.e. "...adults or children managed on bronchodilators alone can be safely and effectively started on Pulmicort Turbuhaler at 200 or 400 mcg/day using the once daily dosing regimen..."). It is therefore imperative that evidence be provided to support the safety and efficacy of the proposed labeling for this subgroup.

2.3.1 Primary Endpoint: AM PEFR

2.3.1.1 Intent-to-Treat:

As shown in Table 15.1 (Vol.1, p. 176), using the intent-to-treat LVCF across phases data set, patients who received either dose of Pulmicort had numerically greater improvement in AM PEFR compared to placebo during either the treatment or the maintenance phase of the trial. At the end of the treatment phase, the absolute change from baseline was 0.6 L/min for placebo, 10.4 L/min for 200/200, and 14.4 L/min for 400/200. Only the 400/200 arm had achieved statistical significance relative to placebo (13.8 L/min, p=0.007), although the 200/200 group was close (9.8 L/min, p=0.056).

The absolute change during the maintenance phase was 0.7 L/min for placebo, 21.8 L/min for 200/200, and 22.8 L/min for 400/200. This change was statistically significant for both the 200/200 and 400/200 Pulmicort groups for the maintenance phase (20.3 L/min, p=0.004 and 21.3 L/min, p=0.002 vs. placebo, respectively).

It is noteworthy that the absolute change from baseline was small for both Pulmicort groups for both treatment phases, less than the pre-specified clinically significant 30 L/min given in the power analysis, although these numbers achieved statistical significance.

2.3.1.2 Analysis of Inhaled GCS-(-) and GCS-(+) Patients: Mean AM PEFR was reported separately for patients who were GCS-(+) and who were GCS-(-) prior to randomization. Data are displayed in Table 17.1 and Figures 1 and 3 for the GCS-(-) population (Vol. 1, pp.192, 257, 259) and Table 17.2 and Figures 2 and 4 for the GCS-(+) population (Vol .1, pp. 193, 258, 259). Please see Figure B (all patients treated), Figure 1 (GCS-(-)), and Figure 2 (GCS-(+)) at the end of this review for the graphical representation of treatment response vs. time.

2.3.1.2.1 Inhaled GCS-(-) Patients

Treatment Phase: The GCS-naïve patients had an adjusted mean change from baseline for AM PEFR during the treatment phase of 12.2 L/min for placebo, 18.2 L/min for the 200/200 group, and 20.1 L/min for the 400/200 group (Table 17.1). Compared to placebo, this change was not significant (6.0 L/min, p=0.369 for 200/200 and 7.9 L/min, p=0.230 for 400/200).

Maintenance Phase: The GCS-(-) patients had an adjusted mean change from baseline for AM PEFR for the maintenance phase of 15.8 L/min for placebo, 33.7 L/min for the 200/200 group, and 27.5 L/min for the 400/200 group. Compared

to placebo, this change was significant for the 200/200 group (17.9 L/min, p=0.050) but not the 400/200 group (11.7 L/min, p=0.191; see Figure 3, vol.1, p.259). The ΔPEFR vs. time curve (Figure 1, vol.1, p.257) shows that the two budesonide-treated groups appeared to reach their maximum level of improvement at about Week 10, then to remain at that apparently stable plateau until the end of the study at Week 18.

2.3.1.2.2 Inhaled GCS-(+) Patients

Treatment Phase: The GCS-dependent patients had an adjusted mean change from baseline for AM PEFR during the treatment phase of -13.6 L/min for placebo, -0.4 L/min for the 200/200 group, and 5.9 L/min for the 400/200 group. The change from baseline compared to placebo was significant for the 400/200 group (19.5 L/min, p=0.010), but not for the 200/200 group (13.2 L/min, p=0.077). It should be recognized that the absolute change from baseline was small for both treatment groups, and significance was driven primarily by the deterioration in the measured lung function of the placebo group. This is consistent with the expected "washout" of inhaled corticosteroids.

Maintenance Phase: The GCS-(+) patients had an adjusted mean change from baseline for AM PEFR during the maintenance phase of -17.7 L/min for placebo, 3.6 L/min for the 200/200 group, and 13.8 L/min for the 400/200 group. This time, the change from baseline compared to placebo was significant for both the 400/200 group (21.3 L/min, p=0.002) and for the 200/200 group (31.5 L/min, p=0.038). As before, significance was driven primarily the deterioration of the placebo group. The GCS-(+) patients in the 400/200 group achieved and maintained a level of improvement in lung function relative to placebo which was consistently numerically superior to the 200/200 group throughout the study, in spite of receiving the same dosage of budesonide during the final 12-week maintenance phase of the study (shown graphically in figure 2, vol. 1, p. 258).

Reviewer's Comment:. This observation, if consistent, has possible clinical implications. That is, it may be advisable to start at a higher dose when switching to once daily dosing, then titrate down after the first 6 weeks of therapy.

2.3.2 Primary Endpoint: FEV1

2.3.2.1 Intent-to-Treat:

Using the all-patients-treated, last value carried forward analysis, it could be shown that patients who received either dose of Pulmicort had numerically greater improvement in FEV1 compared to placebo during either the treatment or the maintenance phase of the trial. The absolute change from baseline during the treatment phase was -0.03 L for placebo, 0.12 L for 200/200, and 0.13 L for 400/200. This change was statistically significant compared to placebo for both the 200/200 and 400/200 Pulmicort groups for the treatment phase (0.15 L, p=0.002 and 0.17 L, p=0.001 vs. placebo, respectively). For the maintenance phase, the absolute change from baseline was -0.09 L for placebo, 0.10 L for 200/200, and 0.11 L for 400/200. Compared to placebo, the change was statistically significant for both treatment arms (0.19 L for the 200/200 arm, p<0.001; 0.21 L for the 200/200 arm, p<0.001). Again,

it is noteworthy that the absolute change from baseline for both treatment groups was small (the pre-specified clinically significant change in FEV1 was 0.25 L), and significance depended upon decline in FEV1 in the placebo group.

2.3.2.2 Analysis of Inhaled GCS-(-) and GCS-(+) Patients:

Mean FEV1 was reported separately for patients who were GCS-(+) and who were GCS-(-) prior to randomization. Data can be found in Table 17.3 and Figures 5 and 7 for the GCS-free population (Vol. 1, pp.194, 260, 262) and Table 17.4 and Figures 6 and 8 for the GCS-dependent population (Vol. 1, pp. 195, 261, 262).

2.3.2.2.1 Inhaled GCS-(-) Patients

Treatment Phase: The GCS-naïve patients had an adjusted mean change from baseline for FEV1 during the treatment phase of 0.08 L for placebo, 0.20 L for the 200/200 group, and 0.19 L for the 400/200 group. Compared to placebo, this change approached but did not achieve statistical significance for either Pulmicort group (0.12 L, p=0.054 for 200/200 and 0.11 L, p=0.072 for 400/200).

Maintenance Phase: The GCS-(-) patients had an adjusted mean change from baseline for FEV1 for the maintenance phase of 0.02 L for placebo, 0.19 L for the 200/200 group, and 0.17 L for the 400/200 group. Compared to placebo, this change was significant for both the 200/200 group (0.17 L, p=0.015) and for the 400/200 group (0.15 L, p=0.026).

2.3.2.2.2 Inhaled GCS-(+) Patients

Treatment Phase: The GCS-(+) patients had an adjusted mean change from baseline for FEV1 during the treatment phase of -0.18 L for placebo, 0.01 L for the 200/200 group, and 0.05 L for the 400/200 group. The change from baseline compared to placebo was significant for both the 200/200 group (0.19 L, p=0.007) and the 400/200 group (0.22 L, p=0.002). As noted in the analysis of GCS-(+) patients for the other primary efficacy variable PEFR, the numerical difference from placebo and the statistical significance were driven primarily by the deterioration in the measured lung function of the placebo group, consistent with "washout" of inhaled corticosteroids.

Maintenance Phase: During the maintenance phase, the GCS-(+) patients had an adjusted mean change from baseline for FEV1 of -0.24 L for placebo, -0.03 L for the 200/200 group, and 0.02 L/min for the 400/200 group. Again, the change from baseline in FEV1 compared to placebo was significant for both the 200/200 group (0.21 L, p=0.007) and for the 400/200 group (0.27 L, p=0.001) The maximum treatment effect of 0.27 L at the end of the study in the 400/200 group exceeded the pre-specified 0.25 L, but was almost entirely accounted for by lung function deterioration in the placebo group.

2.3.3 Secondary Efficacy Endpoints: All Patients Treated

Seven secondary efficacy variables were specified in the original protocol: daytime and nighttime asthma symptom severity scores, concomitant bronchodilator use,

evening PEFR, spirometry variables other than FEV1, quality of life assessments (QOL), time to treatment response, and the rate at which patients dropped out of the study. Evening PEFR, spirometry variables, concomitant bronchodilator use, and QOL parameters were analyzed using ANOVA. For QOL, a difference in score of ≥0.5 units was considered clinically significant. Time to response was determined using 5-day running averages of AM PEFR measurements. Response was defined as a 10% or more increase from baseline in AM PEFR. The time at which response occurred was considered to be the last day of the 5-day interval in which response was achieved. Treatment groups were compared using the log-rank test. The numbers of patients who discontinued were compared between the Pulmicort Turbuhaler group and placebo using a Chi-square test. A formal survival analysis was not performed.

2.3.3.1 Asthma Symptom and Diary Score Results:

Asthma symptom scores were assessed by the patients twice daily on a 4-point scale (0=none to 3=severe) and recorded in their diaries. Patients were also expected to record their evening PEFR and the total number of times they required rescue bronchodilators during that day. The results of these four parameters measured at baseline compared to the end of the treatment and maintenance phases have been summarized in Table 20 , shown below (Vol. 1, p. 201).

Daytime symptom scores, which ranged from [redacted] at baseline, were essentially unchanged in the placebo group throughout both phases of the study, but had significantly decreased in both Pulmicort arms during both the treatment and maintenance phases of the study. The same was true of nighttime symptom scores, although p-values for the 400/200 arm during the treatment phase (p=0.064) and the 200/200 arm during the maintenance phase (p=0.060) approached but did not achieve statistical significance.

Evening PEFR was significantly improved from baseline compared to placebo for both Pulmicort arms for the maintenance phase (p=0.009 200/200; p<0.001 400/200). For the treatment phase, the change from baseline in PEFR compared to placebo was significant for the 400/200 arm (p=0.015), and approached significance for the 200/200 arm (p=0.065).

Rescue bronchodilator use decreased on average by slightly under one puff/day for both Pulmicort doses for the treatment phase, and by slightly over one puff/day for both Pulmicort doses for the maintenance phase. Each of these changes were statistically significant compared to placebo (p=0.002 to 0.009).

2.3.3.2 Secondary Efficacy Spirometry Values:

Spirometry values other than FEV1 were also measured (Table 22.1, vol. 1, p.206). Both the forced vital capacity (FVC) and the mid-flow (FEF25-75) showed a statistically significant improvement compared to placebo for both doses of Pulmicort, during both the treatment and the maintenance phases of this study, corroborating the findings of the primary efficacy endpoint FEV1.

2.3.3.3 Secondary Efficacy Variables: "Quality of Life (QOL)" Data

Quality of life, as assessed by the [redacted] was calculated as the

mean score for a patient's responses to all items on the QOL questionnaire, which included activity limitations due to asthma, asthma symptoms, emotional function, and level of tolerance to noxious environmental stimuli. The summary statistic, Overall Quality of Life (Table 22.2, vol.1, p. 208), showed statistically significant improvement in each one of the QOL scores which made up the composite. This was true for both doses of Pulmicort and both phases of the study. However, the planning or incortporation of these assessments into the trial was not adequate to support a claim.

2.3.3.4 Study Discontinuation

The sponsor did not specify in the original protocol how study discontinuations would be analyzed. As stated above, a formal survival analysis was not carried out. The numerical difference in total number of dropouts between the two treatment groups and placebo was assessed by using a chi-square test. More patients were discontinued from the placebo group (26 patients, 25%) than from the 200/200 group (15 patients, 15%) or the 400/200 group (10 patients, 10%). Compared to the placebo group, differences in discontinuations from the study were statistically significant for the 400/200 group (p=0.005) and approached significance for the 200/200 group (p=0.064).

2.3.3.5 Time to Treatment 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 AM PEFR for Pulmicort Turbuhaler 200/200 mcg/day or 400/200 mcg/day to exceed the baseline value by ≥10%. The median time to response was 28 days for the 200/200 group and 42 days for the 400/200 group (p=0.016 and p=0.368, respectively, versus placebo).

Reviewer's Comment: It is difficult to know what to make of this endpoint, since the sponsor specified that "Time to Response" could be taken as either an increase in AM PEFR of 15% from baseline, or as an increase of only 10% of baseline (if not enough patients achieved a 15% response!). Nevertheless, this analysis appears at odds with other data, which suggest that the onset of 400 mcg is faster than 200 mcg.

2.3.4 Secondary Efficacy Variables: Subgroup Analysis

Reviewer's Comment: Plans for a stratified analysis by inhaled GCS use at baseline was not included in the original submission. If a determination of the efficacy of once daily Pulmicort in GCS-(-) patients is based solely upon an analysis of the two primary endpoints in this trial, then it must be concluded that these data are inadequate. For this reason, a subgroup analysis of the GCS-(-) compared to the GCS-(+) patients for selected secondary endpoints was requested.

The results of the stratified analyses of the selected secondary efficacy endpoints, daytime asthma symptom scores, nighttime asthma symptom scores, evening PEFR, and rescue bronchodilator usage, were generally consistent with the result of the stratified analyses of the two primary endpoints. Significant differences from placebo were achieved in secondary endpoints for the GCS-dependent subgroup, while differences between treatment groups generally were not statistically significant in the GCS-free

subgroup (see table at end of review).

2.3.4.1 GCS-(-) Subgroup

On daytime symptoms, the GCS-(-) patients had baseline symptoms scores of 1.22, 1.28, and 1.15 for the placebo group, the 200/200 Pulmicort arm, and the 400/200 Pulmicort arm, respectively, using the 4-point scoring system discussed above. At the end of the 6-week Treatment Phase, these scores had decreased by the following amount in each of the three groups: -0.13 for placebo, -0.40 for 200/200, and -0.26 for 400/200. The change for the 200/200 group was statistically significant compared to placebo (p=0.002; see summary table, below) while the change for the 400/200 group was not, although it trended in that direction (p=0.111). At the end of the subsequent 12-week Maintenance Phase, changes in symptom scores were -0.20 for placebo, -0.37 for the 200/200 Pulmicort arm, and -0.43 for the 400/200 Pulmicort arm. In the 200/200 arm, the change approached significance while in the 400/200 arm it achieved statistical significance compared to placebo (p=0.085 and p=0.016, respectively). It is paradoxical that the lower dose group, 200/200, achieved significance on this endpoint during the treatment phase but not during the subsequent 12 week maintenance phase, although the p-value was close. The pattern for the higher dose group, 400/200, resembled the pattern noted overall for this GCS-free subgroup, that is, it trended in the right direction for treatment but did not achieve significance until the end of the maintenance phase.

The nighttime asthma symptom scores were not as favorable for this subgroup. Baseline values were lower overall for this endpoint, especially for the 400/200 group, which may have made it more difficult to demonstrate a difference, 0.98, 0.89, and 0.76, respectively, for the placebo, 200/200, and 200/400 groups. The change in score during the Treatment Phase was -0.13 for placebo, -0.28 for the 200/200 group, and -0.21 for the 400/200 group. Neither of the two Pulmicort arms were significant compared to placebo (see table below). During the subsequent Maintenance Phase, the change in score was -0.18 for placebo, -0.27 for the 200/200 group, and -0.28 for the 200/400 group. Again, the change in score for the two Pulmicort arms was significant for neither compared to placebo.

With regard to the evening PEFR, baseline values were similar across treatment groups, 394, 348, and 382 L/min for the placebo, 200/200, and 400/200 groups, respectively. The change in PEFR across treatment arms over the first 6 weeks of the trial (Treatment Phase) did not even show a trend toward significance, with an improvement of 11.2 L/min for placebo, 10.3 L/min for the 200/200 group (p=0.955) and 15.5 L/min for the 400/200 group (p=0.501). During the Maintenance Phase, these values had improved to 21.5 L/min for the 200/200 group and 26.3 L/min for the 400/200 group, which compares to 9.6 L/min for placebo. The change during this phase was significant for the 400/200 group (p=0.050) but not for the 200/200 group (p=0.130).

Finally, use of rescue bronchodilators was assessed for this subgroup. During both the Treatment and Maintenance Phases of this study, bronchodilator use decreased from baseline for both Pulmicort treatment arms. However, this change

was not statistically significant compared to placebo for either phase (see table below). Bronchodilator use at baseline was 3.92 puffs for placebo, 3.99 puffs for the 200/200 group, and 3.59 puffs for the 400/200 group. During the Treatment Phase of the study, this value decreased by -0.96 puffs for placebo, -1.15 puffs for the 200/200 group, and -1.32 puffs for the 400/200 group (p=0.288 and p=0.126, respectively, compared to placebo). During the 12 week Maintenance Phase which followed, there was no further change for placebo, which stayed at -0.96 puffs, while the 200/200 and 400/200 Pulmicort arms did decrease slightly, -1.33 puffs and -1.49 puffs, respectively (p=0.388 and p=0.220, respectively, compared to placebo).

2.3.4.2 GCS-(+) Subgroup

As might be expected, the pattern of significance for most of the secondary endpoints for the GCS-dependent subgroup paralleled the pattern observed for the all patients treated group, as was the case with the primary endpoints. P-values for the comparison between each Pulmicort dose group and placebo for each treatment phase is given in the table below. Absolute numerical changes for each of these secondary endpoints add little to the discussion and will not be presented.

2.4 Safety Review

2.4.1 Adverse Events

The most common adverse events reported by patients during this study were respiratory infection, headache, pharyngitis, and sinusitis (Table 1, vol.1, p. 103). This profile is consistent with the current package labeling, the four most frequent adverse events being identical between the two. The next three most common adverse events, rhinitis, bronchitis, and accident/injury, also appear in the current product label, although at a slightly higher frequency than reported in the current study. Possible explanations for this discrepancy include the smaller number of patients, the briefer duration of the trial, the lesser severity of disease, the presence or absence of coexisiting conditions among the patients studied during this trial, or the once daily dosing schedule itself. There did not appear to be any new or unexpected adverse events with this dosing schedule, however.

2.4.2 Dropouts, Serious AEs, and Deaths

No deaths occurred during this study. There were four adverse events which met the regulatory criteria for serious. These included one allergic reaction (400/200 group, during the baseline period), one symptomatic ovarian cyst (400/200 group), and two episodes of severe bronchospasms (placebo group and 400/200 group). None appeared to have a causal relationship with active study drug.

There were 17 discontinuations from the study due to an adverse event. These included 8 in the placebo group, 4 in the 200/200 group, and 5 in the 400/200 group. Eleven of the 17 events were classified as bronchospasm, and curiously, the relative proportion of events due to bronchospasm was relatively constant across the three treatment groups: five of eight events in the placebo group, two of four in the 200/200

group, and four of five in the 400/200 group. The other events included emotional lability, abnormal vision, and respiratory infection (all three in the placebo group), bronchitis and fracture (200/200 group), and back pain (400/200 group). Attribution to active study medication was unlikely in most of these cases.

2.4.3 Clinical Laboratory

Routine clinical laboratory studies were performed for each patient at the start of the study and at its conclusion. Included in the panel were serum electrolytes, blood sugar, renal function tests, urinalysis, liver function tests, and complete blood count with differential. No laboratory assessment of HPA axis function, either basal or stimulated, was made.

There were no mean changes in any laboratory parameter from the beginning compared to the end of the study for any of the three patient groups. There were a few laboratory abnormalities recorded for individual patients which were considered to be clinically relevant by the investigators. These abnormalities appeared to be evenly distributed across the three study groups. With the exception of changes in eosinophil counts, there did not appear to be any causal relationship to the study drug.

2.4.4 Other Safety Endpoints

Other safety endpoints included changes in physical examination and vital signs (VS) at the completion compared to the start of the study. ECG's were not performed. There were no significant mean changes in VS from beginning to end of study. Likewise, there did not appear to be any individual changes in physical examinations or VS at the beginning compared to the end of the study which could be attributed to study medication. Although oral candidiasis was mentioned in the adverse event database, it was not recorded as a finding for any patient at the conclusion of the study. Systolic or diastolic hypertension did not emerge as a significant treatment related problem, either.

2.5 Conclusion and Recommendation:

This pivotal trial DS-004-0009 supports once daily administration of Pulmicort, 200 or 400 mcg, for the treatment of patients with mild to moderate asthma who are already stabilized on inhaled corticosteroids. Data are inadequate to support once daily Pulmicort for the initial treatment of asthma in patients who require inhaled corticosteroids, but who are inhaled corticosteroid-naïve. No outstanding safety issues attributable to the once daily schedule emerged during this study.

3.0 NON-PIVOTAL STUDY 04-3083

Reviewer's Comment: Of the eight new supportive trials submitted to this NDA supplement by the sponsor, this study was selected for closer scrutiny because it included both a placebo arm and an informative active control arm. The active control was Pulmicort at the same total daily dose as the investigational arm, but administered according to a BID regimen.

3.1 Title

Once daily versus twice daily treatment of mild asthma using low dose Pulmicort Turbuhaler.

3.2 Study Center

This study was conducted at 24 sites in Canada between 28 August, 1995 and 18 November, 1996.

3.3 Study Objective

The primary objective of the study was to compare the efficacy of once daily administration of Pulmicort 200 mcg dosed in the evening with twice daily administration of Pulmicort 100 mcg dosed in the morning and in the evening and with placebo in adults with mild asthma in a stable and well-controlled state. The primary variable was morning PEFR.

Reviewer's Comment: Essentially, this means that all of the patients were receiving orally inhaled corticosteroids at baseline. This clinical trial was not designed to answer the question of whether once daily Pulmicort is efficacious in corticosteroid-naïve asthmatics.

3.4 Protocol

3.4.1 Design and Methods

The study was described as a dose-regimen comparison, double-blind, randomized, placebo-controlled, parallel group, multi-center trial. A two-week run-in period, during which the patients continued on their pre-study dose of BDP 200-250 mcg BID, was followed by a 12-week double-blind treatment period. To be included, patients had to have had the diagnosis of asthma for at least 3 months and be presently well-controlled on orally inhaled beclomethasone dipropionate (BDP), also for at least three months. Well-controlled was defined as the absence of any acute asthma exacerbation for the 3 months prior to the study, and FEV1 which was at least 80% of predicted. Patients of either sex between the ages of 18 and 70 years were eligible. Exclusion criteria included any use of systemic corticosteroids, cromolyn sodium, or nedocromil products in the prior 3 months.

Reviewer's Comment: It is odd that the sponsor did not exclude smokers from this trial or stratify enrollment by current smoking status. A patient's reactive airway disease could be explained by COPD or chronic bronchitis rather than asthma alone if there is a current or prior history of cigarette use, and such patients would not be expected to benefit from inhaled corticosteroid therapy to the same degree as pure asthmatics. As it turned out, the mean and median ages of patients in this study was approximately 35 years, and Atrovent was very rarely listed as a concomitant or baseline medication, favoring asthma as the true diagnosis. Finally, sponsor assessment of baseline demographics showed smokers to be evenly distributed between the three study arms.

The primary efficacy endpoint was AM PEFR. Secondary endpoints included FEV1, FVC, asthma symptoms, bronchodilator use, and evening PEFR. Patients were enrolled at Visit 1, at which time they entered a two-week run-in period. During the run-in, patients received BDP via pressurized MDI, either as Beclovent® 200 mcg BID or Becloforte® 250 mcg BID (both products manufactured by [redacted]). They were also issued a [redacted] a diary to record AM/PM PEFR and symptoms, and rescue bronchodilator (Bricanyl®Turbuhaler: terbutaline DPI 0.5 mg per dose). At the end of the run-in, patients were seen in clinic for a second time, their diaries were reviewed and, if appropriate, they were randomized to one of three arms in a 2:2:1 ratio, respectively:

- Pulmicort once daily in the evening (via Pulmicort Turbuhaler 200 mcg/actuation) and Placebo Turbuhaler in the morning.
- Pulmicort twice daily in the morning and evening (via Pulmicort Turbuhaler 100 mcg/actuation).

- Placebo Turbuhaler twice daily in the morning and evening.

Reviewer's Comment: The comparator device is the Pulmicort Turbuhaler 100 mcg/actuation, which is not approved in this country. Strict dose proportionality between the 100 mcg and the 200 mcg/actuation Pulmicort products cannot be assumed. Therefore, no firm conclusions should be drawn regarding the relative efficacy of once daily compared to twice daily Pulmicort dosing. In addition, unlike the pivotal study #004-0009 which used the (U.S. approved) M0 device, this study used the M2 device.

There is another problem with the design of this study. The patient is dosed once daily in the evening, but the primary endpoint, AM PEFR, is not measured at the end of the dosing interval; that measurement, PM PEFR, is included among the secondary endpoints.

At the second (randomization) visit, study medication was dispensed. Each patient received two Turbuhaler devices, one designated for use in the morning, the other for evening dosing. Each device was expected to last for the 12-week duration of the trial, although the rescue bronchodilator, Bricanyl, was dispensed as needed. Patients were instructed to take the study medication(s) at 8:00 AM and 8:00 PM each day, and to record this dose in their diaries. Patients were also instructed on the form and content of the additional information which they were to record each day in their diaries (see "Assessments," below). There were a total of four clinic visits during the 12-week treatment period, after weeks 1, 4, 8, and 12 of therapy (see figure below; Volume 19, p. 13).

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Investigational schedule:

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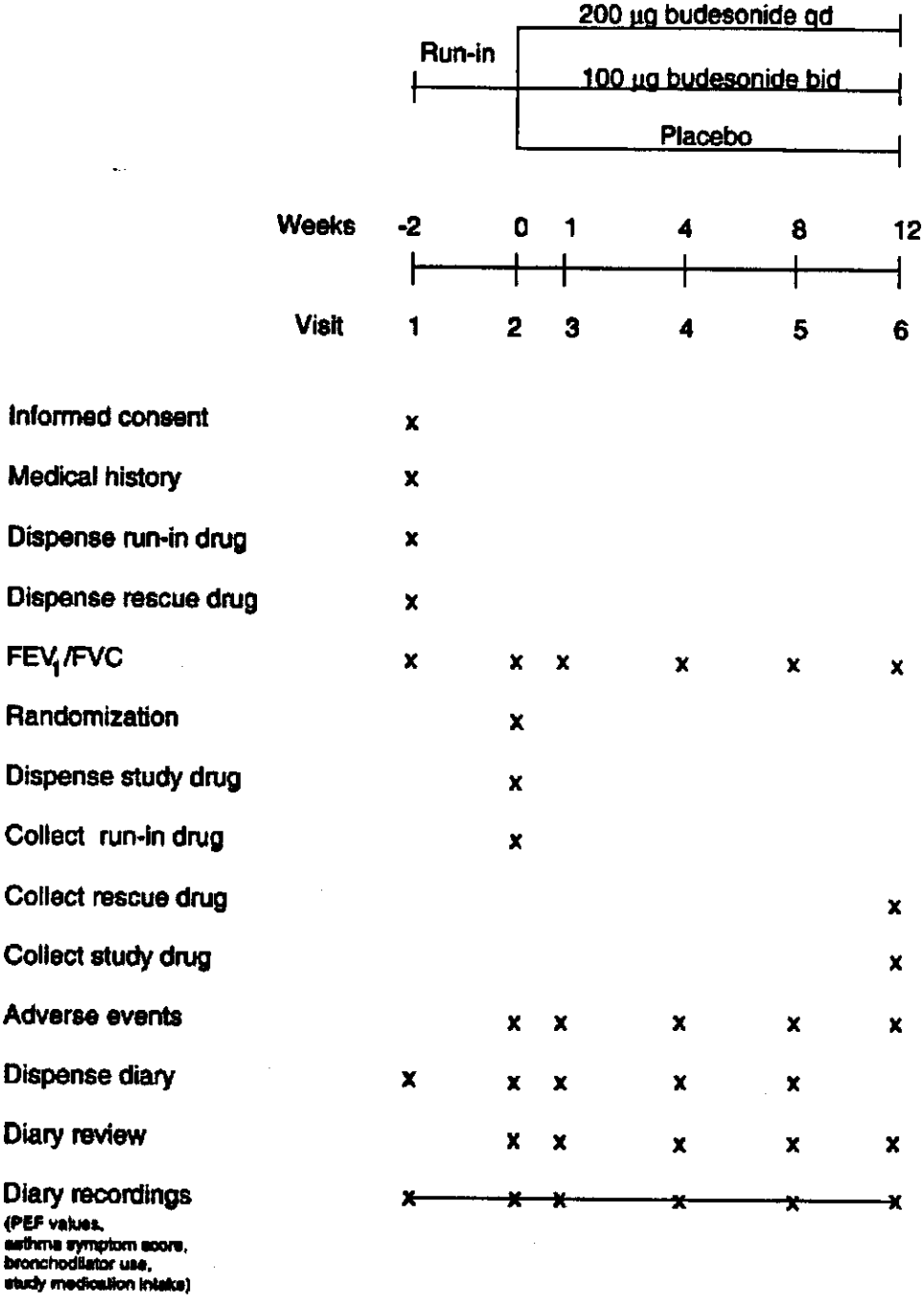

Figure 1. Investigational schedule

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3.4.2 Assessments

Clinic visits were scheduled at the same time of day throughout the trial, and patients were instructed to withhold their inhaled bronchodilators for at least 6 hours before hand, if possible. Starting after the first clinic visit, patients were instructed to record asthma symptoms scores, number of nocturnal awakenings due to asthma, bronchodilator use, AM and PM PEFR, and study medication usage. This information was reviewed at each subsequent clinic visit, along with Turbuhaler technique and PEFR technique.

Spirometry was performed at each clinic visit, including FEV1 and FVC. Measurements were conducted in triplicate, and the highest value for each reading was recorded in the case file. Predicted normals were calculated using the

PEFR was performed by the patients each morning upon arising and each evening before bedtime, both measured prior to dosing with study medication. Other than instruction in correct technique, PEFR was not performed during clinic visits. Patients used the for this purpose.

Asthma symptom scores were calculated on a four-point scale, with the value of zero assigned to no symptoms and the value of three taken as severe symptoms. Scores were recorded by patients twice each day, to reflect daytime and nighttime asthma symptoms.

The number of puffs of rescue bronchodilator, if any, were recorded in the diary on a daily basis. Asthma exacerbation during the treatment period was defined as an AM PEFR which was more than 30% below the baseline on two consecutive days, the baseline mean value being calculated from the means of the last 10 days of the run-in period. It was also defined by the investigator-determined need for oral corticosteroid treatment, or other asthma treatment disallowed by the study.

Adverse events were reported for the baseline and treatment periods of the study, but none were reported in the run-out unless deemed possibly related to the study drug. Signs and/or symptoms of asthma were not considered to be adverse events unless they met the regulatory definition of serious, were inconsistent with a patient's prior pattern of asthma, or there was a reasonable probability they were caused by the study drug. This same reasoning was followed in classifying the reason for a patient's discontinuation from the study, that is, asthma exacerbation was reported as lack of efficacy unless it was serious, uncharacteristic of the patient, or possibly caused by the study drug. The occurrence of adverse events was elicited from patients at each clinic visit using a standard question: "Have you had any health problems or symptoms not usually associated with your asthma since your last visit?"

3.4.3 Statistical Plan

The sponsor assumed that the measured change from baseline in morning peak flow, "Δ AM PEFR", had a standard deviation in of 50 L/min. Allowing a two-sided α-error of 0.05 and a β-error of 0.80, the sponsor calculated that 100 patients in each active treatment arm and 50 patients in the placebo arm would be required to detect a 20 L/min. difference between the two active treatment arms and a 24 L/min. difference between placebo and an active treatment arm.
The sponsor defined the mean value for each of the six diary variables, AM/PM PEFR, AM/PM bronchodilator use, and AM/PM asthma symptom scores, as follows:

- Baseline: The mean of the last 10 days of the run-in period.
- Treatment Period Interval: The mean of the last 14 days of each of the following

three intervals:

* 1st Interval: Weeks 0 - 4
* 2nd Interval: Weeks 4 - 8
* 3rd Interval: Weeks 8 - 12

The sponsor considered the mean value calculated for the 3rd interval to be the endpoint from which the change from baseline was calculated, and for which the statistical analysis which follows was used. Analysis of change from baseline to any other interval was by descriptive statistics only.

An ANOVA model with the factor *treatment* and with *baseline* as a covariate was used for all variables to compare the treatment groups. The factor *center* was included for the primary variable only. An investigation of a *treatment-by-center* interaction was also carried out for the primary variable. No significant effect was found whether 10 small centers were excluded, or whether they were included but combined into three new larger "centers." (Both of these analyses had been specified in the original protocol as submitted). The comparison between treatments was performed using a two-tailed t-test with an α=0.05. The primary statistical analysis was based on an intent-to-treat model, and all patients who had received study medication were included. Two other analyses were performed, one including only those patients closely adherent to the protocol, the other excluding all data from study center 13 (where baseline data from the primary variable were missing). Missing values were handled by applying the "Last Value Extended" principle.

3.5 Results

3.5.1 Patient Disposition

A total of 341 patients were enrolled into the study, of whom 288 were randomized and received study medication: 115 to once daily dosing, 112 to twice daily, and 61 to the placebo group. Of this total, 50 patients dropped out prior to completion of the study, 19 in the once daily group, 14 in the twice daily group and 17 in placebo. This information is summarized in the figure below (Vol. 19; p. 33) and will be discussed further in the "efficacy" and "safety" sections below.

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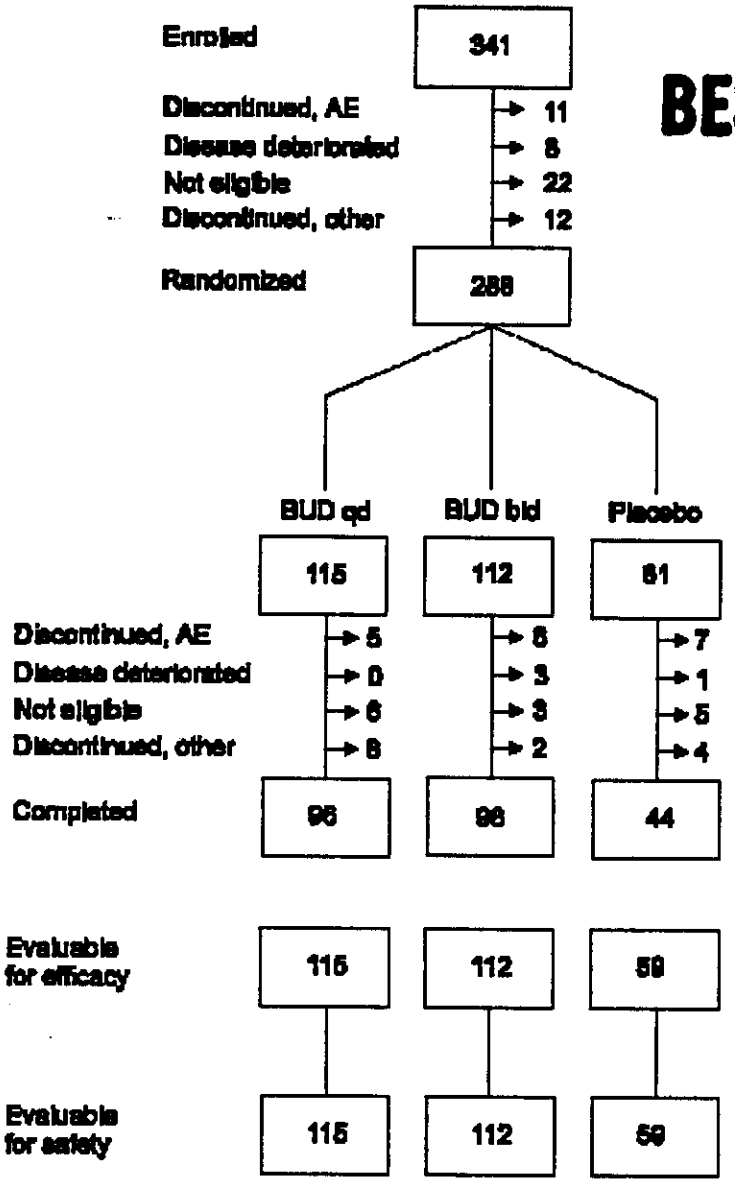

Figure 2. Disposition of patients in the study

A total of 18 centers were participating at the start of the study. By the completion of the study, two centers had been dropped for poor enrollment and seven new centers had been added. The enrollment period needed to be extended by six months in order to recruit the required number of patients. Each of these changes was documented in a protocol amendment.

Reviewer's Comment: A total of five new centers contributing a total of 49 patients (17% of the total) were added by a protocol amendment dated 15 September 1996, yet the last date of subject evaluation for the entire study was given as 19 November 1996 (8 ½ weeks later). Because it has been reported that no Treatment-by-Center effect was found using ANCOVA, the patients at these centers (#21-25) probably started the protocol prior to the amendment being submitted to the Agency and completed it on schedule.

Baseline demographics not related to asthma were comparable across the three treatment groups (vol 19, p. 36, data not reproduced here). The mean age of the participants was 36.2 years, two-thirds were female, and ethnically the group was overwhelmingly Caucasian. Approximately one fifth were active smokers, and about one fourth were former smokers. Again, this was very similar across treatment groups, in spite of no stratification by this variable being performed at randomization. Average mean and median height and weight were also not strikingly different between groups.

There was some imbalance with regard to indices of asthma severity, however. The placebo group had a shorter mean time since last asthma exacerbation, 18.1 months compared to 29.6 months in the twice daily Pulmicort group and 30.0 months in the once daily group. The median times since exacerbation corroborated this, being 8.8 months for placebo, 13.1 months for the twice daily group, and 12.4 months for once daily group. The placebo group also had lower baseline AM and PM PEFR values, higher baseline asthma symptom severity scores, and higher baseline bronchodilator use compared to either Pulmicort arm (see Table 5, vol. 19, p. 34). However, FEV_1 as percentage of predicted was comparable across the three groups (approximately 100% for each) as was the average (mean) duration of asthma (placebo: 11.0 years; twice daily Pulmicort: 11.4 years; once daily Pulmicort: 10.3 years).

3.5.2 Efficacy Results

The average duration of run-in was 15 days (range [redacted] days). Some patients were required to repeat the run-in because of inadequate data recording. The average duration of treatment was 76 days (range [redacted]) Compliance with study medical was assessed by diary entry, and was reported to be nearly 100% for all three study groups.

Each patient had been issued two different study inhalers, one for use in the morning and the other for evening use, although for the once daily group, only the device used in the evening contained the active drug.

Reviewer's Comment: *This dosing regimen poses a problem, since the primary efficacy endpoint was not measured at the end-of-dosing interval. It will be important to look at data from the secondary endpoint PM PEFR. Also, the placebo device contained [redacted] which would taste different than the active drug budesonide. This could have lead to some un-blinding during the trial.*

3.5.2.1 Primary Endpoint: AM PEFR

The primary efficacy variable was change from baseline in AM PEFR. The primary analysis was based on an all-patients-treated, last value extended (LVE) principle and included all patients except two in the placebo group with missing data. A per protocol analysis was also performed for which the sponsor excluded patients with major protocol violations, a total of 63. The most common reasons for exclusion included FEV_1<80% predicted, dose or duration of BDP not as specified, or an exacerbation occurring during the last 10 days of run-in. Relative to the total number of patients in each arm, there were slightly more patients in the once daily dosing group who were excluded compared to the placebo or twice daily dosing. In spite of these exclusions, this analysis yielded conclusions which were not appreciably different from the all-patients-treated analysis, and will therefore not be discussed in depth in this review.

A graph of the mean AM PEFR values during run-in and during treatment period for each of the three groups are shown in figure 5 below (Volume 19, p. 46). Notice that the AM PEFR was lower in the placebo group at baseline (397 L/min) compared to the baseline of the once daily group (408 L/min) or the BID group (406 L/min), giving the illusion of a very marked difference in PEFR between the placebo and the Pulmicort arms at end of the study. When adjusted for this unequal baseline value, the difference between the groups persists, but is more modest in magnitude (figure 14, below; Vol. 19, p. 132). The average change from baseline to end of treatment was 10 L/min in the Pulmicort 200 μg once daily group, 1 L/min in the Pulmicort 100 μg BID group, and -23 L/min in the placebo group. The difference between placebo and the once daily Pulmicort arm was statistically significant ($p<0.0001$; 95% CI 18, 46 L/min), as was the difference between placebo and the Pulmicort twice daily arm ($p=0.0014$; 95% CI 9, 39 L/min). However, there was no significant difference between the two Pulmicort arms ($p=0.14$; 95% CI -3, 21 L/min). As in the pivotal study #004-0009, it is the deterioration of AM PEFR in the placebo group associated with the "washout" of inhaled corticosteroid which drives the statistical significance of this endpoint.

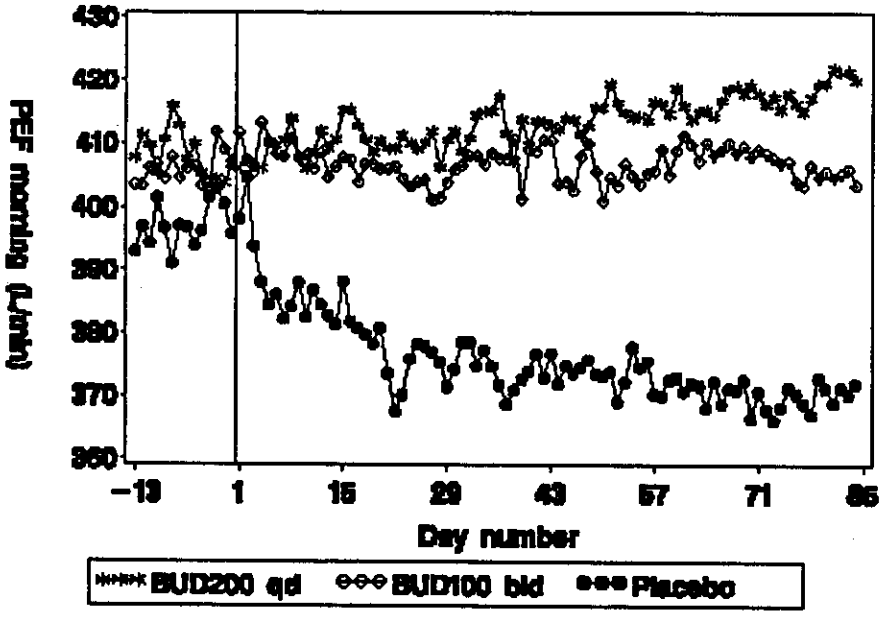

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Figure 5. PEF morning (L/min). Daily mean values during run-in and during treatment period by treatment group. LVE.

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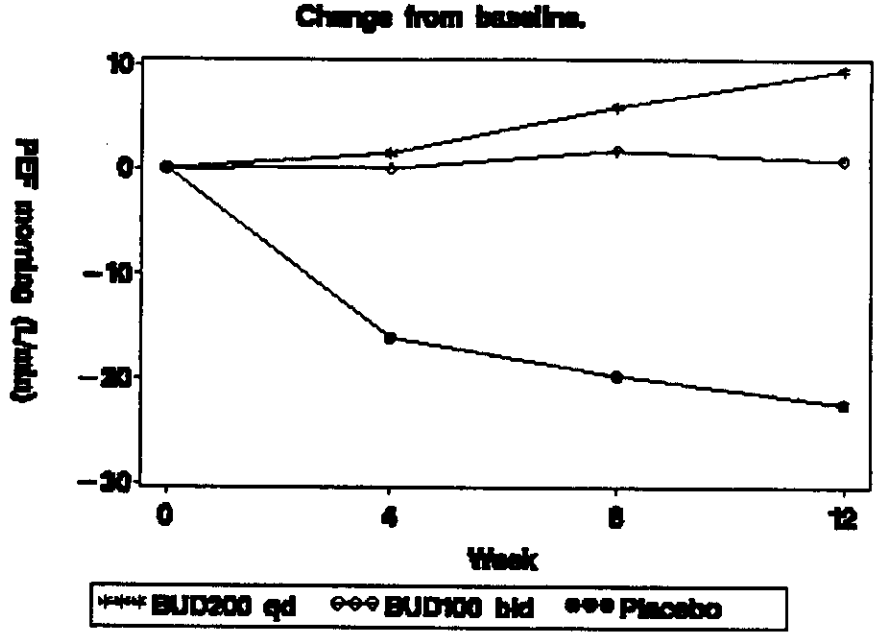

Figure 14. PEF morning (L/min). Change from baseline (mean during the last 10 days of run-in) by visit (mean during the last 14 days before visit) and treatment group.

When calculated as percent of predicted, an analysis of the primary endpoint gave results similar to those described above. Statistically significant differences were found between the once daily group and placebo and between the twice daily group and placebo. No statistically significant difference was found between the once daily and the twice daily groups (Tables 13, 14 in Vol. 19, p.46; not reproduced here).

3.5.2.2 Secondary Variables

The sponsor reported the following secondary efficacy endpoints: the diary variables PM PEFR, AM/PM symptom scores, and AM/PM rescue β-agonist use, and the spirometry variables FEV_1 and FVC. The sponsor did not include a written discussion or analysis of any of these endpoints in the text of this trial description, but did provide a summary table of pair-wise comparisons of each variable at study endpoint (see Table 15 at end of text; volume 19, p. 50), and tables of values of these variables at each study visit. With the exception of the spirometry variables FEV_1 and FVC, five of the seven secondary endpoints achieved statistical significance for once daily Pulmicort relative to placebo.

Reviewer's Comment: *In general, details of this trial as provided by the sponsor are rather sparse, most of the data being presented in a single volume. There was no original protocol including protocol amendments submitted, nor was there any explanation as to why the spirometry results were unfavorable, except that the spirometry was not rigorously standarized. Given the design and other regulatory limitations of this study, there did not seem to be merit in asking the sponsor to supply these details.*

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The secondary endpoint PM PEFR represents end-of-dosing interval for Pulmicort once daily, since patients were instructed to perform this measurement prior to dosing themselves (see section 3.4.2 above). The pair wise comparison between change from baseline in PM PEFR for once daily Pulmicort was statistically significant compared to placebo, whether the parameter was expressed as L/min or percent of predicted (p=0.0015, 0.0011 respectively). When expressed graphically as the adjusted change from baseline (see below; Vol. 19, p. 134), both of the Pulmicort arms again were superior to placebo, but were not statistically significant from each other (p=0.274 once vs. twice daily). These data suggest there is no decline in efficacy near the end-of-dosing-interval for Pulmicort once daily, as measured by the PEFR.

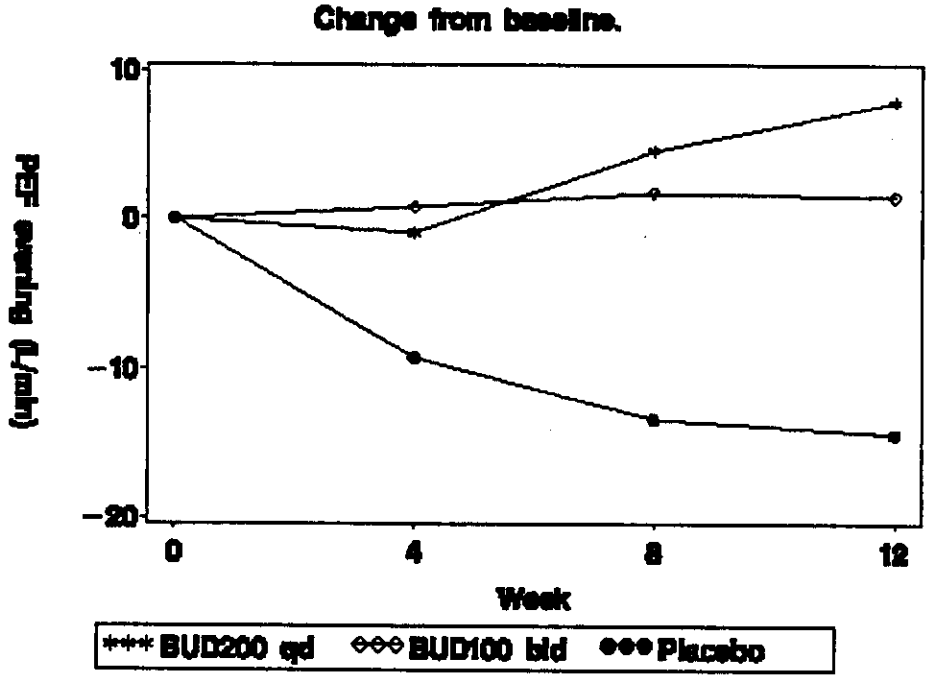


Figure 16. PEF evening (L/min). Change from baseline (mean during the last 10 days of run-in) by visit (mean during the last 14 days before visit) and treatment group.

Change in the secondary endpoints FEV_1 and FVC (clinic-measured spirometry) did not corroborate the the PEFR data. Not only were Pulmicort arms not statistically signficicantly different, but there did not appear to be even a numerical trend in favor of either Pulmicort arm. There is no obvious explanation for this, and the sponsor does not discuss it. This is somewhat disconcerting, since FEV_1 is usually considered a better index of asthma control and the preferred primary endpoint. It is possible that the patient population studied in this clinical trial had such mild disease that it was difficult to demonstrate a consistent, statistically significant difference between the treated groups compared to placebo (i.e. baseline FEV_1 was approximately 100% for all three treatment groups).

3.5.2.3 Efficacy Endpoints: Study Dropouts

As stated previously, a total of 288 patients were randomized into the study, 2:2:1 Pulmicort once daily: Pulmicort twice daily: Placebo, for a total 115 to once daily dosing, 112 to twice daily, and 61 to the placebo group. Of this total, 50 patients dropped out prior to completion of the study, 19 in the once daily group (17%), 14 in the twice daily group (13%), and 17 in placebo (28%), consistent with there being an advantage to treatment with Pulmicort. The main reason for study discontinuation among the three groups was "ineligibility" or "adverse event." These study dropouts will be discussed further under safety issues, below.

3.5.3 Results: Safety Evaluation

3.5.3.1 Adverse Events

Study medication was dispensed to 288 randomized patients, all but two of whom could be evaluated for safety (records were apparently lost for two). Of this total, 96 were men and 190 were women and had a mean age of 36 years (18-70 years). Reports of adverse events were distributed uniformly among the three arms, with 54% of the once daily group, 52% of the twice daily group, and 53% of the placebo group reporting at least one adverse event.

The most commonly affected system was pulmonary, with 38% of once daily and 31% of both placebo and twice daily reporting adverse events referable to this system. Two of the three most common adverse events were also pulmonary in nature and included respiratory infection, headache, and pharyngitis. The distribution of these events was not significantly different between the three groups.

3.5.3.2 Dropouts, Serious Adverse Events, and Deaths

There were nine serious adverse events, five in the once daily group, one in the twice daily group, two in the placebo group and one during the run-in period. Among the five AE's in the once daily group, there were two cases of acute bronchospasm requiring hospitalization. Both of the affected patients were women and each had been receiving once daily Pulmicort for several weeks (23 days for one patient and 75 days for the other). These two serious AE's were believed to be "unrelated to study medication" by the sponsor and investigators. Only one of these two patients was immediately terminated from the study because of this serious adverse event, the other one was terminated one week later because of "ineligibility."

Reviewer's Comment: While it may be true that Pulmicort did not directly "cause" each case of bronchospasm, it is possible that asthma control deteriorated on once daily therapy for these patients.

Also of possible importance is the coding of dropouts here. In section 3.5.2.3 above, the sponsor reported that most patients who were dropped during the trial were "ineligible." In this case, it appears that the patient was not eligible because she received a proscribed medication, systemic corticosteroids, to treat her acute bronchospasm. In this reviewer's view, this patient should have been

counted in the "deterioration of disease" category.

There were no such episodes of "serious" acute bronchospasm among the placebo or among the twice daily dosing patients. The other seven AE's were unlikely to be related to study medication.

There was one death reported for this study, a 22 year old man receiving twice daily Pulmicort who committed suicide.

There were 18 patients who dropped out of the study because of adverse events, 5 in the once daily group, 6 in the twice daily group, and 7 in the placebo group. All five of the once daily patients discontinued because of worsening asthma symptoms (see below). This was true for six out of seven placebo dropouts but only three out of six patients in the twice daily group.

Reviewer's Comment: Although superior to placebo, these and earlier data in this section suggest that once daily dosing of Pulmicort may lead to deterioration of asthma control in certain patients.

3.5.3.3 Other Safety Endpoints

The sponsor did not report results for safety parameters such as clinical laboratory results, physical examination, vital signs, or ECG.

3.6 Summary and Conclusions

In conclusion, based upon the primary endpoint AM PEFR, clinical trial #04-CR-3083 is supportive of once daily Pulmicort at 200 μg as an alternative dosing schedule for patients with mild to moderate asthma who are already stabilized on inhaled corticosteroids. The primary endpoint which is considered the "gold standard" by the Division, FEV_1, failed to demonstrate significance between Pulmicort at either dose and placebo, although spirometry was only a secondary endpoint for this trial. The relative efficacy of twice daily compared to once daily dosing cannot be clearly determined because of the lack of a statistical separation between these two treatment arms and because of the unknown dose proportionality between the two devices used to deliver budesonide.

With regard to safety, there does not appear to be any difference in the overall rate of AE's between the two Pulmicort dosing groups, nor is there any indication of new or unexpected adverse events with once daily dosing. Dropouts due to asthma exacerbation were more common with once daily compared to twice daily dosing, suggesting that some patients may not tolerate this lower frequency of dosing. This was not a primary endpoint, however, so no firm conclusions should be drawn, although this issue deserves further study.

4.0 NON-PIVOTAL STUDY 04-3084

Reviewer's Comment: Among the clinical trials in this submission, study #04-3084 was selected for closer scrutiny because it included children age 6 years and older, and as written, the labeling for once daily Pulmicort Turbuhaler would apply to this pediatric age group.

One additional design feature which makes this trial interesting was its exclusion of patients receiving inhaled corticosteroids at baseline. At this point in the review, there is inadequate evidence to support the sponsor's claim that corticosteroid-naïve asthmatics can be safely and effectively started on inhaled corticosteroids using Pulmicort Turbuhaler on a once daily schedule.

4.1 Title

Once daily versus twice daily initiation of Pulmicort Turbuhaler in asthmatic children not on steroid treatment.

4.2 Study Center

Pediatric Section for Allergy and Pulmonology N-0407 Oslo, Norway.

4.3 Study Objective

The primary objective of this study was to compare the clinical efficacy of 200 mcg of Pulmicort given once daily to the same total dose administered twice daily (100 mcg BID) and to placebo. A secondary objective was to compare the clinical efficacy of once daily Pulmicort at 100 mcg/day to once daily at 200 mcg/day and with placebo. Both of these objectives were to be measured in children with mild to moderate asthma not on any steroid treatment. The primary efficacy variable for both objectives was AM PEFR.

Reviewer's Comment: As in the prior study, dose proportionality between the 100 and 200 mcg/actuation devices has not been unequivocally demonstrated; therefore, the pair-wise comparison between Pulmicort 200 mcg/day and Pulmicort 100 mcg BID should not be used to support the superiority of one dosing strategy over another. In addition, the Pulmicort 200 mcg/actuation unit is the M2 device, which is not approved in this country.

This is a study with four arms, three active treatment one placebo, for which multiple pair-wise comparisons have been proposed. It may be important to ascertain that appropriate adjustments have been made in p-values and in the overall statistical plan.

4.4 Protocol

4.4.1 Study Design and Methods

This was a randomized, double-blind, placebo-controlled, parallel group clinical trial conducted at a single pediatric center in Oslo, Norway between 7 February 1995 and 12 June 1996. The study was comprised of a 2 week baseline period followed by a 12 week treatment period. Eligible children with mild to moderate asthma not concomitantly managed on inhaled corticosteroids were randomized to receive placebo or to receive inhaled budesonide in one of three active treatment groups, Pulmicort 100 mcg/day, Pulmicort 100 mcg BID, or Pulmicort 200 mcg/day. Children were assessed during the five scheduled clinic visits: two during the run-in period (at the beginning and end, Visits 1 and 2, respectively), and three during the active treatment period (at four week intervals, Visits 3, 4, 5). In reality, clinic visit 5 occurred on two separate days, because two of the final assessments (methacholine challenge and treadmill exercise test) could not be given on the same day.

All children were issued three inhalers, one containing terbutaline, to be used as rescue therapy, and two color coded study inhalers containing budesonide or placebo. The yellow device was to be used for morning dosing and the white one for evening. Children randomized to the 100 mcg BID arm had active drug contained in both inhalers while children enrolled in the 100 mcg or 200 mcg once daily had active drug only in the yellow inhaler (i.e. morning dosing). All four groups were

instructed to measure AM PEFR using a [redacted] prior to dosing, carrying out three peak flow maneuvers and recording the highest value of the three into their study diaries. Study participants were also expected to document in their diaries any use of rescue medication, their evening PEFR (also recorded prior to dosing) , and asthma symptom scores for daytime and night. Symptoms were scored on a four point scale, where "zero" indicated no asthma symptoms and "three" represented severe, incapacitating symptoms.

Reviewer's Comment: Once daily dosing of active medication occurred in the morning, therefore the primary endpoint AM PEFR will be measured at the end of a dosing interval.

4.4.1.1 Inclusion/Exclusion Criteria

- Age between 7 and 16 years, inclusive
- Diagnosis of mild to moderate asthma with FEV1 > 70% more than 8 hours after last β-agonist use (International Consensus Report; Scheffer AL, Bousquet J, Busse W et al, Eur. Respir J 1992;5:601-641)
- Corticosteroid restrictions: > 2 months for inhaled; > 4 weeks for enteral or parenteral
- Cromoglycate or nedocromil restrictions: > 4 weeks
- No asthma exacerbation or respiratory infection within prior 4 weeks
- No significant co-morbid condition
- Medications specifically excluded during the study included enteral, parenteral, or other inhaled corticosteroids; theophyllines; β-agonists other than the terbutaline issued during the study, orally inhaled cromolyn or nedocromil (intranasal or ocular OK); or anticholinergic medications. Other medications, including those purchased OTC, were to be considered on a case-by-case basis.

4.4.2 Assessments, Endpoints, and Compliance

As stated above, there was a single primary efficacy endpoint, AM PEFR. Secondary endpoints included other home assessments such as PEFR measured in the evening, daytime and night-time symptom scores, and rescue beta-agonist use. Assessments performed in clinic included spirometry (FEV_1, FVC, $FEF_{25\%}$, $FEF_{50\%}$, $FEF_{75\%}$; performed at all clinic visits), lung volumes (RV, TLC, and VC; performed in a [redacted] at all clinic visits, except Visit 1), methacholine challenge (Visits 2 and 5 only), treadmill exercise test (Visits 1 and 5), and reversibility of bronchoconstriction (Visit 1, only). Blood samples for the measurement of "inflammatory activity" were also taken (Visits 2 and 5; the nature of what was being assayed was not further described).

Mean values were calculated for all diary variables for the baseline period and for each four week interval during the treatment phase. Baseline mean was defined by the last 10 days of diary entries during the 14 day run-in period. The three treatment means were calculated using the last 14 days of each 28 day treatment period. For diary variables, endpoints were the change from baseline to each of the three periods during the treatment period. The change from baseline to the period preceding visit 5 was subjected to statistical analysis (see below).

For variables recorded at the clinic, endpoints were the change from visit 2 to each of the visits during the treatment period. The change from visit 2 to visit 5 was subjected to statistical analysis (see below).

Safety assessments were made by recording ongoing adverse events, graded as serious or non-serious by the usual regulatory criteria, whether or not the event contributed to study discontinuation, and the principle investigator's assessment of its possible relationship to study drug.

Compliance was determined by examining each patient's diary recordings.

4.4.3 Statistical Plan

Sample size was based on the assumption that the standard deviation of a change in AM PEFR was 30 L/min. Assuming a two-sided alpha level of 0.05, the sponsor calculated that 40 patients per treatment arm would be required for an 80% chance of detecting a 20 L/min difference between treatment groups.

All patients who received at least one dose of medication were to be included in the statistical analysis (the "All Patients Treated" approach). Missing values were handled by applying the "Last Value Extended" principle. For diary variables including the primary endpoint, this meant that the mean from the preceding period was extended to the end of study.

For the primary endpoint, the change from baseline to end of treatment was subjected to analysis of variance with the factor treatment. The ANOVA was only used to obtain estimates of the pair-wise differences between treatment effects and the standard deviation of each pair-wise difference between treatment effects. The estimates obtained through the ANOVA were compared using a two-sided t-test at a significance level of 0.05, as follows:

- Pulmicort 200 mcg once daily vs. Pulmicort 100 mcg BID ("primary objective")
- Pulmicort 200 mcg once daily vs. Placebo ("secondary objective")
- Pulmicort 100 mcg once daily vs. Placebo ("secondary objective" to be calculated only if the prior comparison was significant)

Reviewer's Comment: The sponsor has specified multiple comparisons in the protocol, yet does not appear to make appropriate adjustments in the statistical plan. Also, the protocol as originally presented specified the comparison of Pulmicort 200 mcg once daily to placebo as the primary objective.

Descriptive statistics was used to assess comparability of treatment groups at baseline, discontinuation rates between treatment groups, and adverse event rates.

4.5 Results

4.5.1 Patient Disposition

A total of 166 patients entered the run-in period and 163 completed it and were randomized, 40 to Pulmicort 100 mcg BID (BUD100bid), 42 to Pulmicort 200 mcg once daily (BUD200qd), 41 to Pulmicort 100 mcg once daily (BUD100qd), and 40 to placebo. Three patients were discontinued prior to randomization, two with asthma exacerbations and one for noncompliance. The 163 randomized patients had a mean age of 9.9 years, a mean height of 143.4 cm (range: 112.3 to 202.0), and mean weight of 37.7 kg (range: 19-81). The gender distribution was typical of childhood asthma, 34.4% girls and 65.6% boys. Other baseline demographic factors included history of atopy, duration of asthma, and reversibility in FEV_1, which was measured at visit 1 and was calculated as the increase in FEV_1 after bronchodilator over pre-bronchodilator FEV_1.

Reviewer's Comment: The group as a whole had very little reversibility, the mean being 3.0% (range: -28.2 to 20.0). Fewer than 10 patients had a reversibility of 12% or greater and 35 actually showed a decrease in FEV_1 with bronchodilator. The mild nature of the disease in general in this group could make it difficult to detect a difference between treatment and placebo, and especially difficult to detect a dose response or a significant difference between once and twice daily dosing regimens.

The distribution of baseline demographic factors was similar between the four groups, except that there were slightly more girls in BUD200qd (45%) and fewer in BUD100qd (24%) and the

placebo group tended to have had asthma for a slightly longer duration than the group as a whole. Baseline reversibility was comparable, and very low in all groups studied.

The distribution of baseline efficacy variables between groups is shown in the table below (Volume 20, page 41). In general, patients randomized to BUD200qd arm appeared to have slightly milder disease compared to patients in the placebo arm, whose disease was somewhat worse than the average for the group. The mean of the entire group for the primary endpoint, AM PEFR, was 253.5 L/min (87.1% predicted), and for FEV_1 was 2.20 L (102.7% predicted). The mean number of puffs of rescue β-agonists taken per patient during the run-in was 0.49 during the day and 0.11 at night.

Reviewer's Comment: *Again, these data point to very mild disease in the study population. Assuming the average dose of a β-agonist is two puffs, these children were dosing themselves only twice per week during the baseline period, even though they were receiving no regular asthma medication.*

Table 7. Baseline values for efficacy variables by treatment group (APT)

Variables	BUD 100 bid (N=40)			BUD 200 qd (N=42)			BUD 100 qd (N=41)			PLACEBO (N=40)		
	MEAN	MIN	MAX	MEAN	MIN	MAX	MEAN	MIN	MAX	MEAN	MIN	MAX
PEF morning (L/min)	260.0			272.1			244.7			236.5		
PEF morning (% of predicted)	86.0			91.0			86.3			84.0		
FEV_1 (L)	2.34			2.21			2.15			2.08		
FEV_1 (% of predicted)	105.0			101.2			102.7			101.8		
Max fall in FEV_1 (%) after treadmill exercise test	8.4			11.0			12.3			9.6		
Asthma symptoms during day (0-3)	0.56			0.21			0.45			0.37		
Asthma symptoms during night (0-3)	0.23			0.08			0.15			0.17		
Number of inhalations of β_2-agonist during day	0.78			0.18			0.59			0.41		
Number of inhalations of β_2-agonist during night	0.26			0.05			0.08			0.08		

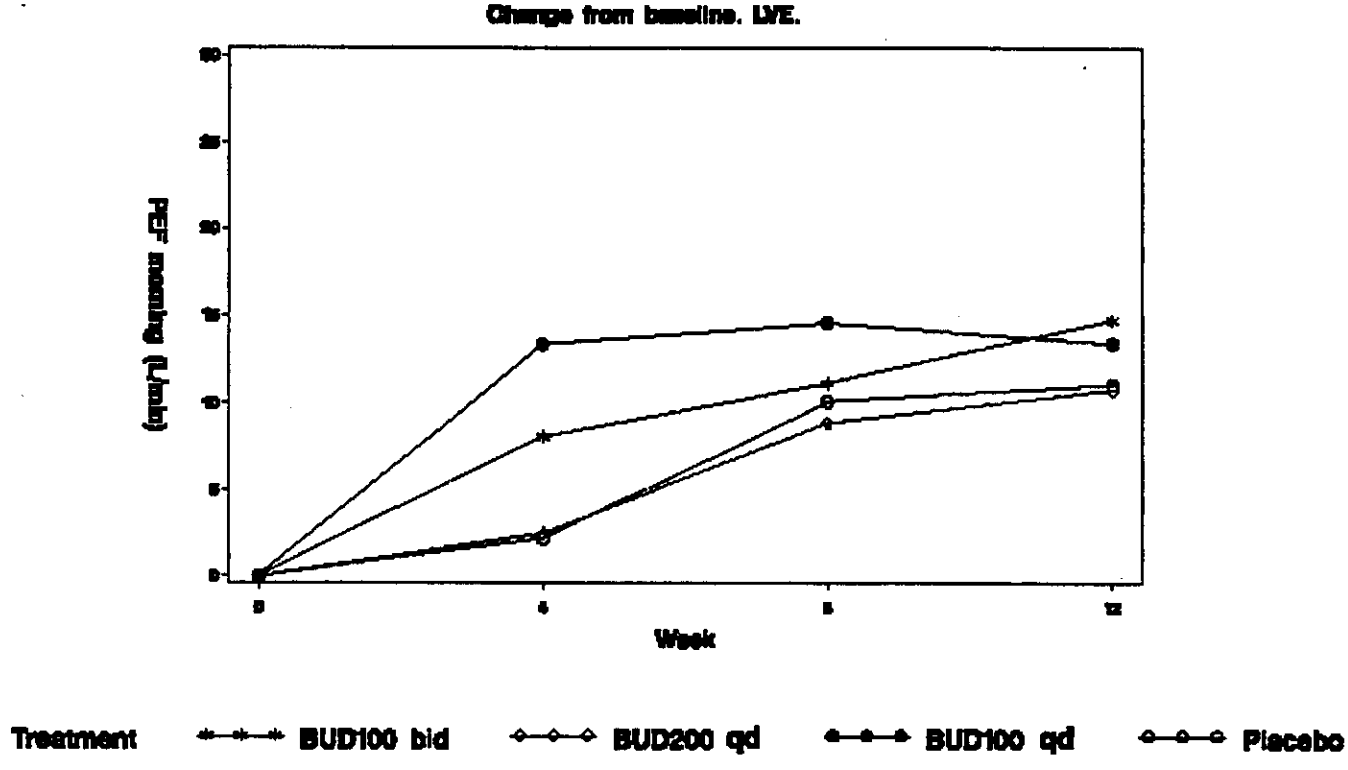
4.5.2 Efficacy Results

There were only three dropouts during the treatment phase of this study, all in the BUD100qd group. Two patients dropped out for disease deterioration and one for noncompliance. Given such a low dropout rate, it is not surprising that the mean duration of treatment was 84 days (range). Compliance was assessed by diary entries, and was found to range from 93 to 95%, with no significant difference between groups, or between the AM compared to PM scheduled doses.

4.5.2.1 Primary Endpoint: AM PEFR

Patients recorded their AM PEFR daily in diaries, and these data were used to calculate mean daily values and mean period values. For the 14 day run-in, the

final 10 days were used to calculate mean baseline PEFR. Three treatment means were calculated using the last 14 days of each 28 day treatment period in the 12 week phase of the study. Endpoints were the change from baseline to each of the three periods during the treatment period. The change from baseline to the period preceding visit 5 was subjected to statistical analysis (see below). Missing data were replaced by LVE and linear interpolation.



Baseline AM PEFR in the placebo group was lower than each of the three treatment groups (Table 7, prior section). This is somewhat misleading when the data are directly plotted as absolute PEFR (L/min) vs. time (Vol.20, p. 42; not shown) because it gives the impression of treatment superiority over placebo. When period means are used and data are expressed as change from baseline to end-of-period (Figure 17 shown above; Vol. 20, p. 117), the study results are clearer, but do not favor active treatment. The estimated difference in AM PEFR between placebo and BUD200qd was 2.9 L/min (95% CI : -11.0, 16.7; p=0.68). Although it is possible that failure to detect a difference between placebo and BUD200qd was due to height discrepancies between the groups, when AM PEFR is expressed as percent predicted (Zapletal et al; *Bull Physiopathol Respir* 1972; 8:535-44) and the differences recalculated, the results remain unfavorable (in fact, they are even worse; Figure 18, Vol. 20, p. 118, not shown).

Returning to Figure 17, above, the difference in AM PEFR between placebo and BUD100 bid was also not significant (5.8 L/min; 95% CI: -8.1, 19.7; p=0.41).

The BUD100qd arm had numerical superiority over placebo by AM PEFR, but this difference vanishes when expressed as percent predicted. The sponsor did not supply a p-value or 95% confidence intervals for this comparison because the statistical plan did not allow it unless the prior two comparisons were significant.

This study failed to detect a significant difference in the primary endpoint between placebo and any of the treatment groups. Assuming a Type II error, one reason for a false negative study may include the mild nature of the disease in the patient population as a whole (not much room for improvement) in combination with a placebo group which by chance was "sicker" than any of the treatment groups. Another possibility is that PEFR is inferior as a primary endpoint compared to FEV_1. It does not appear that the study was underpowered. On the other hand, it is also possible that none of these treatments are effective in children. The Pulmicort Turbuhaler 100 mcg/actuation device is not an approved product in this country, and once daily dosing using the approved Pulmicort Turbuhaler 200 mcg/actuation was not effective in inhaled corticosteroid-naïve patients in a prior study (study #004-0009).

4.5.2.2 Secondary Efficacy Endpoints

The sponsor specified multiple secondary endpoints, including PM PEFR, rescue bronchodilator use, symptom scores, lung volumes, spirometry variables, sensitivity to methacholine challenge, and an exercise test (see section 4.4.2 above). The secondary variables were analyzed using ANOVA with treatment as a factor and baseline as a covariate. Estimated change from baseline and 95% confidence intervals were determined for each variable (Vol. 20, Appendix 5). Pairwise comparisons were made between placebo and each one of the active treatment groups, including estimated difference, 95% confidence intervals, and p-values (Vol. 20, Appendix 6).

Reviewer's Comment: Unfortunately, the sponsor does not discuss in the methods section whether a correction for multiple endpoints was used (Bonferroni, etc.). Although these variables are secondary endpoints, and the Division does not usually demand this type of adjustment, the interpretation and value of these findings would have been easier to assess.

In general, the secondary endpoints were not significant compared to placebo for either the 100 mcg once daily or 200 mcg once daily treatment arms. The Pulmicort 100 mcg BID group did show significant improvement compared to placebo, however, with many of these secondary endpoints. In particular, the following endpoints were "statistically significant" compared to placebo for the BID dosing arm:

Endpoint	p-value (BID)	p-value (200qd)
FEV_1	0.0153	0.5679
FEV_1 % predicted	0.0084	0.5725
$FEF_{50\%}$	0.0014	0.8687
$FEF_{75\%}$	0.0280	0.8555
RV/TLC	0.0161	0.7393
(specific airway resistance) sRaw	0.0292	0.6317
(specific airway conductance) sGaw	0.0063	0.1257

PD_{20}	0.0426	0.7525

Not impacted by either once or twice daily Pulmicort were PM PEFR, day-time asthma symptom scores, and day/night bronchodilator use. Although there was a slight decrease in night-time symptoms scores with Pulmicort 200 mcg once daily, there was an increase in night-time rescue bronchodilator use in this group.

4.5.2.3 Results: Efficacy Conclusions

In conclusion, Pulmicort Turbuhaler 200 mcg/actuation dosed once daily in the morning was not effective in children with mild asthma who were not already receiving inhaled corticosteroids, as measured by the primary endpoint, AM PEFR. Based on this primary endpoint, none of the three active treatments, 100 mcg BID, 100 mcg qd, and 200 mcg qd, were superior to placebo in this study. Although these results may call the entire study into question, it may also mean that none of these treatments is effective in this patient population. On the other hand, a substantial number of secondary endpoints were significant compared to placebo for Pulmicort 100 mcg BID, including FEV_1 and Mid-flows. None of the same endpoints were favorable for either of the once daily treatments. Although not definitive, this study does offer some support to the notion that twice daily Pulmicort is superior over the same dose given once daily in corticosteroid-naïve patients with mild asthma.

4.5.3 Results: Safety

There were no deaths and no dropouts due to adverse events. There was one serious adverse event, an episode of acute pharyngitis requiring hospitalization and parenteral antibiotics, which occurred in the placebo group.

During the randomized treatment phase, 86% of patients in the 200 mcg once daily group experienced at least one adverse event compared to 93% of patients in the other three groups. As might be expected, the most frequently reported AE's were respiratory complaints, including two of the three most frequently reported events overall: respiratory infection, coughing, and headache. Because cough could indicate poorly controlled asthma, it is not surprising that the placebo group experienced the highest reported rate (placebo-38%, 200qd-29%, 100bid-28%, 100qd-30%). There were a few other differences in reported adverse events between groups, primarily between active treatment groups and placebo, but the number of patients per arm was small and relatively few patients could make a large difference in percentile. For example, two (5%) of placebo patients reported conjunctivitis compared to six (14%) of the 200qd group, 6 (15%) of the 100bid group, and eight (20%) of the 100qd group.

Only four patients reported adverse events classified as "severe" during the entire study, one during the run-in, and one each in the placebo, 100qd group, and 100bid group.

Qualitatively, the adverse event profile described in this trial is very similar to the prior two studies as well as the current package insert, including respiratory infection and headache among the three most common events. "Cough" was apparently considered to be a symptom of asthma rather than a separate adverse event in most other studies.

5.0 OTHER NON-PIVOTAL STUDIES

As stated earlier in this document, eight of the thirteen supportive studies submitted as part of this application had not previously been reviewed within this Division. Of these eight, only two (04-3083, 04-3084) included placebo arms for comparison, and these two have already been reviewed in detail for safety and efficacy (see Sections 3.0 and 4.0, above). Of the remaining six active control trials, two (04-9290, 04-9253) were open label and four (04-3073, 04-3068, 04-3085, 04-9267) were double-blind by design. The four double-blind studies are reviewed briefly in this section, and the adverse event data from each is included in the Integrated Summary of Safety (ISS, section 7.0). Because the efficacy data from the two open label studies are subjective and uncontrolled, it is not scientifically valid to merge them into the ISE (Integrated Summary of Efficacy, section 6.0). These trials will be reviewed qualitatively for safety, primarily for serious, severe, or unexpected adverse events.

5.1 Clinical Pharmacology Study #04-3073

5.1.1 Title "Effects on the HPA-Axis of Budesonide Inhaled Once Daily from Turbuhaler"

5.1.2 Study Center Clinical Research Laboratory, Astra Draco AB, Lund, Sweden.

5.1.3 Study Objective To investigate the effects on plasma cortisol of one week of daily budesonide 800 mcg given as a single dose in the morning, a single dose in the evening, or as 400 mcg twice daily compared to placebo.

5.1.4 Protocol

This was a randomized, double-blind, double-dummy, placebo controlled, crossover study conducted using normal volunteers. Twenty-four healthy adult male volunteers age 21-38 years (inclusion: 18-40 yrs.) were randomized to one of four treatment arms:

- Placebo Turbuhaler 2 puffs qAM + Placebo Turbuhaler 2 puffs qPM
- Pulmicort 400 mcg/actuation 2 puffs qAM + Placebo Turbuhaler 2 puffs qPM
- Placebo Turbuhaler 2 puffs qAM + Pulmicort 400 mcg/actuation 2 puffs qPM
- Pulmicort 200 mcg/actuation 2 puffs qAM + Pulmicort 200 mcg/actuation 2 puffs qPM

Volunteers received study medication according to one of these schedules for one week, followed by a wash-out period of at least 2 weeks. Each patient was studied while receiving placebo or Pulmicort according to each of the three dosing schedules. Doses were given at 08:00 and 22:00. Plasma cortisol AUC was determined by [redacted] starting one hour before the evening dose on the sixth day, then after the dose at one, two, four six, eight, and ten hours (just before the morning dose on the seventh day). Sampling continued after the morning dose beginning at one hour, then again at two hours, then every two hours for five more samples.

5.1.5 Results

Compared to placebo, all three of the budesonide dosing schedules suppressed cortisol secretion to a significant degree. Expressed as percent placebo, the plasma cortisol AUC for the entire 22 hour sampling period was 80.85% for budesonide 800 mcg qAM, 83.63% for budesonide 800 mcg qPM, and 80.66% for budesonide 400mcg BID.

Although there were no statistical differences between budesonide arms in plasma cortisol AUC integrated over the entire 22 hour sampling period, there was "blunting" of the normal early morning plasma cortisol surge compared to placebo. Not unexpectedly, this blunted response was most prominent in the group dosed in the evening and least prominent in the morning group, with the BID group somewhere in between. This relationship is true for both the plasma cortisol peak and the cortisol AUC summed over the interval from midnight to 10:00am on day seven. These data are shown below, with "Peak" indicating the mean of the maximum plasma cortisol concentration for each group (8:00am value for all four study groups):

Treatment Group	Peak(nmol/L)	$AUC_{0\text{-}10:00}$(nmol*hr/L)
Budesonide 800 mcg qAM	536.1	1632.6
Budesonide 800 mcg qPM	465.3	1110.3
Budesonide 400 mcg BID	506.5	1262.2
Placebo BID	538.1	1645.8

There were no reports of Cushing's syndrome or other clinical indication of hypercorticism in any of the volunteers. There were no other safety findings of significance in this study.

5.1.6 Summary and Discussion

A total daily dose of budesonide of 800 mcg gives statistically significant adrenal suppression compared to placebo whether it is administered as a single dose in the morning or in the evening or as 400 mcg dosed twice daily. There is a greater impact on the normal morning cortisol surge in the patients dosed in the evening compared to those dosed in the morning, with the twice daily group in between.

It is not surprising that budesonide at a total daily dose of 800 mcg can make a statistically significant impact the HPA axis, as measured by plasma cortisol AUC. It is somewhat surprising that all three dosing regimens cause the same degree of adrenal suppression when cortisol levels are assayed over an entire day, compared to their impact on peak cortisol (the AM cortisol surge). Whether it is clinically important to preserve this diurnal variation when selecting a dosing regimen for budesonide, assuming comparable efficacy with all three regimens, has not been determined.

5.2 Clinical Trial #04-3068

Reviewer's Comment: In addition to its double-blind phase, this study had a 16-week open-label step-down phase, during which once daily Pulmicort was first reduced to 200 mcg/day then 100 mcg/day. The open-label phase is not covered in this review.

5.2.1 Title "Once Daily Versus Twice Daily Initiation (And Minimal Once Daily Maintenance Dose) Of Pulmicort Turbuhaler In Non-Steroid-Using Asthmatics"

5.2.2 Study Center Multi-Center Study in Hungary and Spain

5.2.3 Study Objective To investigate whether to initiate inhaled steroid on a once or twice daily dosing regimen in a non-steroid-using patient population judged as needing steroid therapy (mild to moderate asthma). The primary variable was morning PEFR..

5.2.4 Protocol

This was a randomized, double-blind, double dummy, parallel group, multi-center trial with two treatment arms and no placebo group. (The sponsor considered it unethical to include a placebo arm). Approximately 200 mild to moderate adult asthmatics not on oral or inhaled corticosteroids were to be recruited in order to ensure at least 85 per treatment arm. Based on a standard deviation in the change for PEFR of 50 L/min, the study was powered to have an 80% chance of detecting a true mean difference of the change in PEFR of about 22 L/min between the two treatment groups, at a two-sided 5% significance level.

There was a two week run-in period during which patients' baseline data were recorded. Patients were then randomized to received Pulmicort 200 mcg/actuation, one puff twice daily or Pulmicort 400 mcg/actuation, one puff once daily in the evening (placebo in the morning), for a total of 8 weeks. Patients recorded the primary efficacy variable, their AM PEFR, in a diary. They also recorded PM PEFR, use of rescue bronchodilators, and asthma symptom scores. Spirometry was measured during scheduled clinic visits. Adverse events were recorded throughout the study period.

Reviewer's Comment: The primary endpoint was not measured at the end of the dosing interval. No data has been provided in this submission which demonstrates dose proportionality between the 200 mcg/actuation and 400 mcg/actuation devices.

5.2.5 Results

A total of 183 patients were randomized, 90 into once daily budesonide and 91 into twice daily. Baseline characteristics including smoking status and efficacy variables were comparable between the two groups. There were 17 dropouts in the once daily arm compared to 11 in the twice daily. It was reported that only one patient per arm discontinued due to disease deterioration, one per arm due to adverse events, and 14 in once daily and 9 in twice daily due to "other." Details of "other" have not been provided in this submission.

The mean change from baseline to the end of treatment for AM PEFR was 16.9 L/min in the once daily group and 17.2 L/min in the twice daily group. The difference between these two treatments 0.3 L/min, not statistically significant, indicating there was no difference between the two treatment effects (p=0.97). A similar analysis was performed with the secondary endpoints, which found that change from baseline in FEV_1, was 0.03 L for both once and twice daily and the PM PEFR was 12.9 L/min for the once daily group and 2.9 L/min for the twice daily. Other secondary endpoints tended to show numerical superiority of the twice daily over the once daily dosing, but the difference was small and did not achieve statistical significance. The sponsor concluded that the study demonstrated statistically significant improvements in AM PEFR with no difference between a once daily AM, once daily PM, or a twice daily dosing regimen.

Reviewer's Comment: No firm conclusions regarding the efficacy of either once or twice daily dosing regimens can be made without a placebo arm. Even if the baseline period prior to study medication is used as a "placebo period," and the change from baseline to end-of-study the primary endpoint, neither treatment arm achieved the pre-specified difference of 22 L/min. In addition, it is

unlikely that 16.9 or 17.2 L/min is an accurate reflection of the size of the treatment effect, since placebo patients typically improve during trials such as this one (as long as they are not being withdrawn from corticosteroids!). This was the case for pivotal trial 004-0009, for example, in which the "GCS-free" placebo patients increased their PEFR by 12.2 L/min during the initial 6-week treatment phase. Recall from that study that the AM PEFR for the two treatment arms, 200 and 400 mcg once daily, were 18.2 and 20.1 L/min, respectively. Neither one was statistically significant.

The safety findings reported from the double blind portion of this trial were unremarkable. There were 32 patients in the once daily group and 45 in the twice daily group who reported adverse events. There seemed to be a slightly higher incidence of respiratory infection in the twice daily group accounting for part of this difference. The three most frequently reported events were rhinitis, respiratory infection, and pharyngitis. One patient in the once daily group experienced a serious adverse event, an exacerbation with concurrent respiratory infection, and was withdrawn. One other patient, in the twice daily group, withdrew due to pain in the antecubital fossa.

5.2.6 Summary and Conclusions

Few firm conclusions may be drawn from this trial. On the surface, both once daily and twice daily budesonide therapy at the same nominal dose appear to be comparably safe in this population of corticosteroid naïve mild to moderate asthmatics. The improvement in PEFR was modest in both treatment groups and probably not statistically significant for either, although there was no placebo group to confirm this impression. Although there was "no difference" between the two treatment arms, this study was not designed as an equivalency trial and therefore the two treatments cannot be said to be equivalent in efficacy in this population.

5.3 Clinical Trial #04-3085

5.3.1 Title:

"A comparison of efficacy of Pulmicort Turbuhaler, 200 and 400 mcg/day, administered either once or twice daily in children with well controlled asthma (already receiving inhaled corticosteroids)"

5.3.2 Location: Multiple centers in Sweden.

5.3.3 Study Objective:

To compare once daily to twice daily administration of budesonide in children with well-controlled asthma in a stable phase. The efficacy variables included AM and PM PEFR, spirometry, and diary data. The primary efficacy variable was AM PEFR (end-of-dosing interval for once daily).

5.3.4 Design:

This was a randomized, active control (no placebo), double-blind, double-dummy, parallel-group, multi-center study of approximately 200 children age 5-13 years with asthma already managed on Pulmicort Turbuhaler 100 mcg BID or 200 mcg BID. There was a two week run-in during which children were maintained on their current dose of budesonide, and baseline data were obtained. Children were stratified by total daily dose (200 or 400 mcg/day), then randomized to receive this dose either once or twice daily in a blinded fashion during the

12-week treatment phase. The once daily arm received the active drug only in the morning. Efficacy variables including AM and PM PEFR were recorded daily in the patient diary. Spirometry was assessed at 4 wks and 12-weeks (end-of-study). Use of rescue β-agonist, terbutaline, was also recorded in the diary. Adverse events were recorded and reported throughout the study. Statistical Considerations: Based on a standard deviation of 25 L/min. for AM PEFR, the sponsor defined a mean difference between treatment groups of ≤ 10 L/min. at study endpoint as demonstrating "equivalence" between the two groups. In order to have an 80% power to declare true equivalence, assuming a two-sided α-error of 5%, the sponsor calculated 100 patients per treatment group would be required.

Reviewer's Comment: To accept this power analysis, it is necessary to agree that a between-group difference in treatment effect of under 10 L/min is small enough to conclude the groups are equivalent. While a change in PEFR of 10 L/min is clinically very small, even for children, Pediatric Study 04-3084 used a value of 2/3rds of the standard deviation of PEFR to conclude that there was a clinically significant difference in PEFR. In the case of this trial, the value would have been 16.7 L/min., and the difference between it and the equivalence boundary of 10 L/min is only 6.7 L, one fourth of the standard deviation or <4% of the mean PEFR of the group as a whole. This places the boundaries for "significant" and "equivalent" so close together as to seem implausible. Perhaps a parameter unrelated to the usual primary response variable should be selected in a trial such as this one, in order to define equivalence.

5.3.5 Results:

There were 206 patients randomized, 107 to once daily and 99 to twice daily therapy. Of this total, 100 patients in the once daily and 91 in the twice daily completed the trial. Five patients in the once daily and six in the twice daily discontinued for either adverse events or disease deterioration. Baseline demographic characteristics were comparable between the two groups. Efficacy variables showed a slightly higher AM PEFR at baseline in the once daily compared to the twice daily groups, 271.4 L/min vs. 264.2 L/min, respectively.

The change from baseline to endpoint for the primary variable AM PEFR was -0.3 L/min for the once daily group and 2.5 L/min. for the twice daily. The adjusted mean difference between the two arms was -2.8 L/min. (95% CI [-10.4, 4.5]), which is just outside the boundaries declared for equivalence [-10, 10].

The estimated difference between treatment arms for all secondary variables was small and numerically in favor of the twice daily dose for seven out of ten variables. The equivalence boundaries for these endpoints were not specified, nor were adjustments for multiple endpoints, if needed in an equivalency trial.

The adverse event profile for both dosage groups was comparable. Approximately 78% of patients in the once daily group reported adverse events compared to 76% in the twice daily group. There were three discontinuations because of adverse events, two in the twice daily and one in the once daily. None appeared to be causally related to study medication. Similarly, there were three serious adverse events, one in the twice daily and two in the once daily. Again, the causal relationship to study medication appears unlikely.

5.3.6 Summary and Conclusions

In summary, this active control clinical trial was designed as an equivalence study to compare the same total daily dose of budesonide administered once daily vs. divided twice daily in patients with mild to moderate asthma already stabilized on an inhaled corticosteroids. In the

opinion of this reviewer, the sponsor has not adequately justified the selection of the primary endpoint for assessment of equivalence, or how the boundaries were determined. The primary variable, difference in AM PEFR between the two arms in treatment effects, fell immediately outside the pre-specified equivalency boundaries. The difference in treatment effects as measured by most secondary variables was small but tended to favor the twice daily regimen. Because equivalency boundaries were not pre-specified for these endpoints, it is difficult to interpret their meaning. The safety profile of the two dosing regimens, as measured qualitatively and quantitatively by adverse events, was very similar. Once daily dosing was not associated with a significantly increased incidence of dropouts or exacerbation.

In conclusion, the results of this trial are supportive of once daily dosing of Pulmicort Turbuhaler as being comparable to the same dose divided and administered twice daily, although a small but consistent difference in primary over secondary endpoints tend to favor twice daily as probably more effective than once daily in patients already stabilized on inhaled corticosteroids. There was no appreciable difference in safety between the two.

5.4 Clinical Trial #04-9267

5.4.1 Title

"The relative efficacy and safety of Pulmicort Turbuhaler (budesonide) 400 mcg/day once daily compared to Pulmicort Turbuhaler 200 mcg BID in children with stable mild asthma."

5.4.2 Location

Multiple centers in the Netherlands from November 1993 to February 1995.

5.4.3 Objective

To compare the efficacy of once daily dosing of 400 mcg of Pulmicort in the morning with 200 mcg twice daily in the morning and evening, in children with mild to moderate asthma already managed on inhaled corticosteroids. The primary efficacy variable was FEV_1. A secondary endpoint was to assess safety by comparing urinary cortisol excretion between the two groups.

5.4.4 Design

This was a randomized, double blind, double dummy, active control (no placebo) parallel trial. Fifty-one children age 6-12 years with mild asthma controlled on 300-500 mcg inhaled corticosteroid daily were randomized to receive budesonide 400 mcg once daily in the morning (27 children) or budesonide 200 mcg twice daily in the morning and evening (24 children). The two treatment arms used different devices, Pulmicort Turbuhaler 400 mcg/actuation in the morning and placebo at night for the once daily group and Pulmicort Turbuhaler 200 mcg/actuation for the twice daily group. There was a 2-week run-in period in which children were assessed on prior therapy followed by a 12-week treatment period. Children were seen in clinic at 4 week intervals at which time lung function was assessed, including the primary endpoint, FEV1. Urine was collected for cortisol excretion at the start of therapy (visit 2) and at the end of 12 weeks of therapy (visit 5).

Based on a standard deviation of 5%, the sponsor assumed that a clinically significant change in FEV1 was 5%, and that 50 patients or 25 per arm would be needed to have an 80% chance of detecting this difference with an alpha level of 10%.

Reviewer's Comment: The sponsor did not design this study as an equivalency trial. The reasons for selecting a less stringent α-level than is usual for a study of this type were not given.

5.4.5 Results

Fifty-two patients were randomized and received study medication after the run-in period, 27 in the once daily and 25 in the twice daily groups. Baseline demographics were comparable between the two groups. Mean age was approximately 9 years. Unlike previous studies, nearly equal numbers of boys and girls were enrolled. Efficacy variables were also comparable, except the once daily group had a slightly lower percent predicted FEV_1 (77.6% vs. 81.3%). All but two patients completed the trial. Both dropouts were in the once daily group, and the reason for discontinuation was asthma exacerbation for both.

The primary efficacy variable FEV_1 increased during the 12-weeks of treatment for the twice daily group, but did not change for the once daily group. The magnitude of the difference between the two treatments was calculated as 6.95%, which exceeded the pre-specified 5% increase needed to call the change in FEV_1 clinically significant. Hence the treatments could not be declared equivalent.* With regard to secondary variables, the treatment effects of twice daily compared to once daily budesonide generally favored the twice daily arm. Although numerically superior, however, the difference in favor of twice daily treatment did not always reach significance. For example, $FEF_{25-75\%}$ increased from 1.78 L/s to 2.01 L/s in the twice daily group while it decreased from 1.76 L/s to 1.67 L/s in the once daily group. The difference, -0.32 L/s in favor of twice daily, was not statistically significant (p=0.15; 90% CI -0.04, -0.57), and therefore the treatments were declared not significantly different from each other. Change from baseline to endpoint for each treatment arm for other secondary endpoints are given below:

2° Variable	Twice Daily	Once Daily	p-value
AM PEFR	17 L/min	0	p=0.34
PM PEFR	16.5 L/min	13.1 L/min	p=0.69
Diurnal Variability (in PEFR)	-1.6%	0.6%	p=0.24
Night-time Symptoms (scale 0-3)	-0.35	0.13	**p=0.003**
Daytime Symptoms	-0.42	-0.02	**p=0.03**

With regard to safety, quantitatively and qualitatively, adverse events were comparable between the two groups. In total, 49 adverse events were recorded for 18 patients in the once daily group compared to 41 adverse events for 17 patients in the twice daily group. Urinary cortisol excretion after 12 weeks of therapy compared to baseline increased from 117.2 nmol/L to 138.4 nmol/L for the once daily group and from159.2 nmol/L to 169.9 nmol/L for the twice daily group. This difference was not statistically significant.

*The standard deviation observed during this clinical trial was somewhat higher than predicted, 10 % compared to 5 %, which decreased the power of this study.

5.4.6 Summary and Conclusions

In conclusion, this trial appears to support the superiority of Pulmicort Turbuhaler 400 mcg/day given as 200 mcg twice daily over Pulmicort Turbuhaler 400 mcg/day given once daily in the morning for the control of asthma in this population of children already receiving inhaled corticosteroids. No firm statement can be made regarding the overall efficacy of either treatment since the study did not include a placebo arm.

6.0 INTEGRATED SUMMARY OF EFFICACY

The sponsor has submitted one pivotal trial (#004-0009) and 13 supportive trials for consideration in this once daily supplement. As discussed earlier, eight of these 13 trials are new to this application, but only two included a placebo arm, crucial to providing a meaningful assessment of a drug product's efficacy (04-3083 and 04-3084). Finally, there are two active control trials which provide some useful information regarding the comparability of once daily to twice daily dosing (04-3085 and 04-9267). Results of the five trials will be discussed in this section.

The pivotal trial DS-004-0009, was a two part study comprised of a 6 week treatment phase followed by a 12 week maintenance phase. The two primary endpoints, change from baseline in AM PEFR and FEV1, were measured separately for each of the two phases. A total of 309 patients with mild to moderate chronic asthma, approximately half of whom were receiving inhaled corticosteroids, were randomized to receive placebo, budesonide 200 mcg once daily, or budesonide 400 mcg once daily during the treatment phase, followed by placebo (if in the placebo arm) or budesonide 200 mcg/day during the maintenance phase. The sponsor was able to demonstrate that patients previously stabilized on inhaled corticosteroids could be safely switched to budesonide dosed at 200 or 400 mcg once daily without deterioration in asthma control, and that they could be safely maintained on this dosing regimen for at least 12 weeks. However, patients with mild to moderate chronic asthma not previously maintained on inhaled corticosteroids did not achieve significant asthma improvement compared to placebo during the treatment phase of the study. This clinical trial therefore supports once daily dosing of Pulmicort Turbuhaler 200 mcg/day or 400 mcg/day for patients with mild to moderate chronic asthma presently stabilized on inhaled corticosteroids. It does not adequately support a recommendation for initial therapy for mild to moderate chronic asthmatics who are inhaled corticosteroid-naïve.

Clinical trial 04-3083 was a 12-week, double blind, placebo controlled trial with a 2-week run-in comparing once daily Pulmicort Turbuhaler 200 mcg with Pulmicort Turbuhaler 100 mcg dosed twice daily and with placebo. A total of 288 adult patients with mild to moderate asthma already receiving inhaled corticosteroids were studied. Based on the primary endpoint, AM PEFR, this trial was successful in demonstrating that both once and twice daily budesonide at the same nominal dose were more effective than placebo in the treatment of asthma in this patient population. However, the relative efficacy of twice daily compared to once daily dosing cannot be clearly determined because of the lack of a statistical separation between these two treatment arms and because of the unknown dose proportionality between the two devices used to deliver budesonide. In summary, this trial was also supportive of once daily Pulmicort at 200 μg as an alternative dosing schedule for patients with mild to moderate asthma who are already stabilized on inhaled corticosteroids.

Clinical trial 04-3084 was a 12-week, double-blind, placebo-controlled clinical trial which studied 163 inhaled corticosteroid-naïve children age 6 - 12 years with mild to moderate asthma. The study design allowed for the comparison of placebo to once daily dosing of Pulmicort Turbuhaler 200 mcg/day and to the same total daily dose divided and given as Pulmicort Turbuhaler 100 mcg BID. A statistically significant finding for both of these treatment arms compared to placebo would have allowed for additional comparisons to be made to a fourth treatment arm, Pulmicort Turbuhaler 100 mcg once daily. The primary endpoint, AM PEFR, which was not measured at the end of dosing interval, failed to show statistical superiority of any of the active treatment arms relative to placebo. However, the majority of the secondary endpoints including spirometry were numerically and statistically favorable for the Pulmicort 100 mcg BID. This was not true for either of the once daily arms. In summary, this trial was unsuccessful in demonstrating the efficacy of once daily Pulmicort given at a dose of 100 mcg or 200 mcg daily to inhaled corticosteroid-naïve children with mild asthma. There is also a suggestion that the twice daily dosing schedule may be superior and hence the preferable regimen

in this patient population.

Clinical trial 04-3085 was a 12-week, active control (no placebo), double-blind study which was designed as an equivalency trial. The goal was to compare Pulmicort Turbuhaler 200 mcg/day given once daily with Pulmicort Turbuhaler 100 mcg twice daily. The study population included 206 children age 5-13 years with mild to moderate asthma already managed on inhaled corticosteroids. The difference in treatment effects for the primary endpoint, AM PEFR, for the two treatment arms fell outside of the prespecified equivalency boundaries. Hence this trial failed to demonstrate that once and twice daily Pulmicort were equivalent therapies in this patient population. The difference in treatment effects for many of the secondary endpoints tended to favor twice daily therapy over once daily, however, this was numerically only and no statistical assessment was made.

Finally, clinical trial 04-9267 was a 12-week, double blind, active control (no placebo) study to compare once daily with twice daily Pulmicort at a total dose of 400 mcg/day among children age 6-12 years with mild asthma already controlled on inhaled corticosteroids. This was not a trial to prove or disprove equivalency, as was 04-3085 (above) but rather to determine "difference" or "no difference" in treatment effects, comparing one arm to the other. The primary endpoint FEV_1 showed a statistically significant treatment effect in favor of twice daily therapy. In addition, among secondary endpoints there was numerical superiority in favor of twice daily dosing over once daily dosing for five of seven of these variables, two of which also achieved statistical significance. In conclusion, this trial failed to demonstrate that there was "no difference" between Pulmicort 200 mcg BID and Pulmicort 400 mcg qd among this population of children with mild asthma already receiving inhaled corticosteroids. The data also suggest that twice daily Pulmicort is the more effective dosing regimen.

In summary, two placebo controlled trials which included a total of 597 patients, #004-0009 and #04-3083, demonstrated that once daily Pulmicort Turbuhaler 200 mcg or 400 mcg was more effective than placebo in controlling disease among adult patients with mild to moderate asthma. In the former study, #004-0009, 133 patients out of a total of 309 were receiving inhaled corticosteroids at baseline compared to 176 patients who were not. Only the subgroup of patients already managed on inhaled corticosteroids clearly benefited by switching to once daily dosing. In the second study, #04-3083, all 288 of the subjects were receiving inhaled corticosteroids at baseline. The only other trial to study inhaled corticosteroid-naïve patients was #04-3084, and it failed to demonstrate a statistically significant change in the primary endpoint in the Pulmicort 200 mcg once daily arm compared to placebo.

With regard to the relative efficacy of once daily compared to twice daily Pulmicort, two of the placebo-controlled trials, #04-3083 and #04-3084, included both a once daily and twice daily arm at the same total daily dose of budesonide. In the former study, there was no statistical separation between the once and twice daily time vs. efficacy (PEFR) curves, making such a determination impossible. However, the dose proportionality between the two different Pulmicort devices used in that trial is not entirely clear. The other placebo-controlled trial, #04-3084 failed to show statistical significance using the primary endpoint for either once daily or twice daily dosing, although most of the secondary endpoints favored twice daily over once daily. Of the two active control trials, the one designed to show equivalency between the two dosing strategies, #04-3085, failed to do so as measured by the primary efficacy variable PEFR. The magnitude and direction of change of the primary endpoint in this trial favored the twice daily arm, however, although not statistically. The other active control trial, #04-9267, failed to demonstrate that there was no difference between the once daily and twice daily Pulmicort 400 mcg/day. In this trial, the difference between once daily and twice daily Pulmicort in treatment effect numerically favored the twice daily dosing by the primary and most secondary endpoints.

With regard to efficacy in the pediatric population, none of the trials submitted has demonstrated

that once daily Pulmicort is superior to placebo among children with asthma. However, twice daily Pulmicort is indicated for children with asthma as young as 6 years. Given the evidence of efficacy in the adult population, and the similarity in disease between adult and pediatric patients, it is reasonable to assume that children with mild to moderate asthma stabilized on inhaled corticosteroids can be switched to once daily Pulmicort at the same total daily dose and still maintain effective control over their disease.

In conclusion, the data submitted with this application are supportive of once daily dosing of Pulmicort Turbuhaler at 200 or 400 mcg/day in adults or children with mild to moderate asthma controlled on an inhaled corticosteroid. There is insufficient evidence to recommend once daily therapy for inhaled corticosteroid-naïve patients. The evidence also suggests that twice daily dosing with Pulmicort Turbuhaler is superior to once daily dosing, implying that patients who do not maintain control on once daily therapy should be switched back to twice daily at an equal (or higher) dose, as appropriate

7.0 INTEGRATED SUMMARY OF SAFETY

As stated previously, the Pulmicort Turbuhaler once daily supplement is comprised of one pivotal and thirteen supportive trials, each of which contained at least one "once daily" arm. The studies were conducted at domestic sites as well as internationally, over a time span of approximately seven years. The duration of these trials ranged from one week for clinical pharmacology studies to 22 weeks for one dose titration study. If patients from all of these trials are included (i.e. including the seven trials from the original NDA submission), a total of 2514 patients were studied, 1379 of whom received once daily Pulmicort Turbuhaler. The once daily doses studied ranged from 100 mcg to 800 mcg per day, with the 200 mcg and 400 mcg per day doses studied most frequently during these trials.

The demographics of the patients exposed to once daily therapy resembled those of patients exposed to inhaled budesonide at the approved BID dosage, except that more patients with mild to moderate asthma were studied rather than patients with more severe disease. There were four pediatric trials, which included a total of 531 children with an age range of 4-17 years. The other ten trials were primarily adult studies, although several included adolescents age 12-17 years. The adults ranged in age from 18-80 years. The precise distribution of ages of these patients was not included with this application. With regard to gender, slightly under two thirds of the participants in the adult trials were women and approximately one-third to one-half were girls in the pediatric trials, reflecting the characteristics of the asthmatic population in general. The ethnicity of study participants was primarily Caucasian, >86% in all trials (>95% in most European studies).

With regard to adverse events, quantitatively and qualitatively once daily dosing with budesonide closely resembled twice daily dosing. As with twice daily dosing, the most common adverse events reported were usually respiratory and included respiratory infection, pharyngitis, and sometimes cough, depending on how it was coded, as well as headache. There did not appear to be an excess number of severe adverse events or adverse events leading to study discontinuation in the once daily dosing group compared to twice daily. Nor did once daily dosing appear to lead to large numbers of dropouts due to asthma exacerbation compared to twice daily. Compared to placebo, data from the pivotal trial #004-0009 and the two placebo controlled trials #04-3083 and #04-3084 are shown below; recall that trial #04-3084 was a pediatric trial:

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Dose Pulmicort (# pts.)	Adverse Events (#, %)	Serious AE (#, %)	Dropout AE (#, %)
SD-004-0009			
placebo (104)	67 (65%)	1 (1%)	8 (8%)
200/400 qd (103)	63 (61%)	0	4 (4%)
400/200 qd (102)	76 (75%)	3 (3%)	5 (5%)
# 04-3083			
placebo (81)	43 (53%)	2 (2.5%)	7 (8.6%)
200 qd (115)	62(54%)	5 (4.3%)	5 (4.3%)
100 BID (112)	58 (52%)	1 (<1%)	6 (5.4%)
#04-3084 (Pediatric)			
placebo (40)	37 (93%)	1 (2.5%)	0
100 BID (40)	37 (93%)	0	0
200 qd (40)	34 (86%)	0	0
100 qd (41)	37 (93%)	0	2 (4.9%)

These data show that once daily dosing with Pulmicort Turbuhaler was not associated with an excessive number of adverse events, serious adverse events, or study discontinuations relative to placebo. Once daily doses ranged from 100 mcg to 400 mcg in these three trials, and up to 800 mcg once daily was studied in other clinical trials. The relationship of total dose given once daily to the occurrence of adverse events remains unclear, however, because relatively few patients were studied at the extreme doses, and comparisons would need to be made across studies. An additional problem is study design, that is, patients in several trials were not maintained on a single once daily dose, but were titrated up or down for clinical reasons or because the protocol called for it.

The specific safety issue of HPA axis suppression was addressed in two clinical trials, the clinical pharmacology study #04-3073 conducted in adults and the active control, dosage comparison study #04-9267 conducted in children. The adult study compared 800 mcg of Pulmicort administered once daily in the morning and in the evening to the same dose administered as 400 mcg BID using plasma cortisol AUC (and to placebo). Although there were no statistical differences between the three treatment arms, numerically the once daily dose given in the morning was associated with less HPA axis suppression than either the once daily dose given in the evening or the same total daily dose divided BID (1632 nmol*hr/L compared to 1110 and 1262 nmol*hr/L, respectively). The reason for this appears to be less "blunting" of the early morning cortisol surge by the AM timing of the dose, as illustrated by the peak serum cortisol for each (800qAM: 536 nmol/L; 800qPM: 465 nmol/L; 400BID: 506 nmol/L). Although a once daily evening dose was not given, the results of pediatric study #04-9267 corroborated this result. This study compared Pulmicort 400 mcg given once daily in the morning to Pulmicort 200 mcg BID using urinary free cortisol excretion in children receiving inhaled corticosteroids at baseline. Compared to baseline, the children receiving the once daily AM dose increased urinary cortisol excretion by 18% compared to 7% for the children receiving twice daily Pulmicort. Although relatively few patients were studied overall (24 adults, 52 children), and the measured differences in HPA axis effect were small, these results may have important clinical implications. With regard to growth in children, for example, it has been demonstrated that systemic effects of inhaled and intranasal corticosteroids may occur even in the absence of measurable changes in tests of HPA axis function. It is therefore imperative that these studies be repeated, or similar studies designed, to find dosing strategies which minimize potential systemic effects while maintaining adequate control of disease.

Finally, one issue which was not specifically addressed by the sponsor in this submission, and

which was alluded to in the text above, is the relative impact on growth velocity in children of twice daily dosing of Pulmicort Turbuhaler compared with once daily dosing in the morning or evening. A controlled clinical trial could be designed and conducted by the sponsor to answer these growth questions. If it could be demonstrated that the impact of inhaled corticosteroids on growth velocity is minimized by once daily dosing in the morning as opposed to dosing on other schedules, this information would be clinically very valuable.

In conclusion, relative to twice daily dosing and to placebo, once daily dosing with Pulmicort Turbuhaler 200 mcg/day or 400 mcg/day is not associated with any unique or unexpected adverse events or other outstanding safety concerns.

8.0 LABELING REVIEW

Please see the revised document attached to this review for specific changes. The rationale behind these changes is summarized below:

1. Under **CLINICAL PHARMACOLOGY, Pharmacodynamics:** There was no adequate "onset-of-action" determination made in any of the studies submitted with this supplement.
2. Under **CLINICAL TRIALS, Patients Receiving PULMICORT Turbuhaler Once Daily:** There are several inaccuracies in the description of the pivotal controlled clinical trial 004-0009. First, the text specifically mentions inhaled corticosteroid naïve patients as deriving statistically significant benefit from once daily therapy. The data presented are inadequate to support such a claim. Second, patients in this trial are described as showing clinically and statistically significant improvement in lung function with once daily therapy. Although the difference between placebo and treatment was statistically significant for both primary endpoints, the absolute change from baseline was small for both treatment groups, less than the pre-specified clinically significant change (30 L/min for PEFR and 0.25 L for FEV1). The statistical significance was driven by deterioration in lung function in the placebo group, possibly associated with "wash-out" of inhaled corticosteroids. Third, favorable changes in multiple secondary endpoints were cited as evidence of efficacy and clinical benefit of once daily dosing. It is preferable, and more scientific, to limit the discussion of efficacy to the two primary endpoints, PEFR and FEV1. Not all of these secondary endpoints have been adequately validated, and no statistical adjustments were made for multiple endpoints.
3. Under **PRECAUTIONS, General** and **Pediatric Use:** More precise language describing the growth effects of inhaled corticosteroids in children is needed. Because "class labeling" specifically addressing this issue is pending for all approved inhaled and intranasal corticosteroids, changes in this section can be deferred until the class labeling request has been issued by the Agency.
4. Under **DOSAGE AND ADMINISTRATION**, it should be explicit that once daily dosing is an option for patients with mild or moderate asthma who are already controlled on inhaled corticosteroids. As stated earlier, data are inadequate to support labeling for once daily dosing for inhaled corticosteroid naïve patients.

9.0 CONCLUSIONS, APPROVABILITY, AND SIGN-OFF

In conclusion, this efficacy supplement SE2-002 for NDA #20-441 for Pulmicort Turbuhaler, which provides for once daily dosing, is recommended for approval, provided that the sponsor agrees to implement the changes suggested by the division to the proposed label (see 8.0 LABELING REVIEW). These labeling changes restrict the patients for whom once daily Pulmicort Turbuhaler is recommended to individuals with mild to moderate asthma which is controlled on inhaled corticosteroids. There is insufficient data to support once daily dosing for inhaled corticosteroid-naïve patients.

10.0 APPENDIX

PRIMARY AND SECONDARY ENDPOINTS FOR PIVOTAL TRIAL 004-0009

Patient Subgroup	Phase	Pulmicort Arm	AM PEFR	FEV1	daytime sx	evening sx	PM PEFR	rescue bronchodilators
All pts	Treatment	200/200	0.056	0.002	<0.001	0.011	0.065	0.002
		400/200	0.007	0.001	0.005	0.064	0.015	0.007
	Maintenance	200/200	0.004	<0.001	0.034	0.060	0.009	0.008
		400/200	0.002	<0.001	<0.001	<0.014	<0.001	0.009
GCS-free	Treatment	200/200	0.369	0.054	0.002	0.079	0.955	0.288
		400/200	0.230	0.072	0.111	0.323	0.501	0.126
	Maintenance	200/200	0.050	0.015	0.085	0.331	0.170	0.388
		400/200	0.191	0.026	0.016	0.279	0.050	0.220
GCS-use	Treatment	200/200	0.077	0.007	0.060	0.068	0.006	0.001
		400/200	0.010	0.002	0.020	0.132	0.005	0.029
	Maintenance	200/200	0.038	0.007	0.246	0.100	0.021	0.003
		400/200	0.002	0.001	0.001	0.019	0.001	0.016

CHANGE FROM BASELINE IN PEFR CLINICAL TRIAL 004-0009
ALL PATIENTS TREATED

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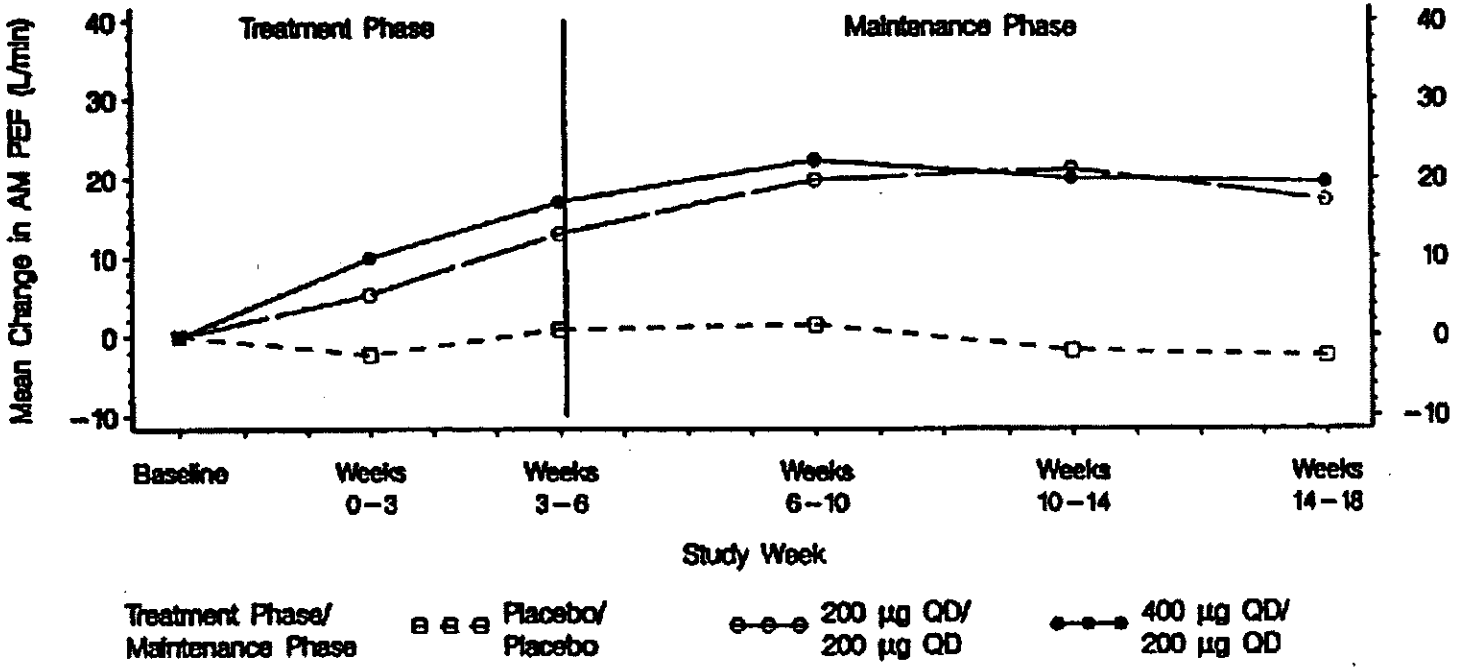
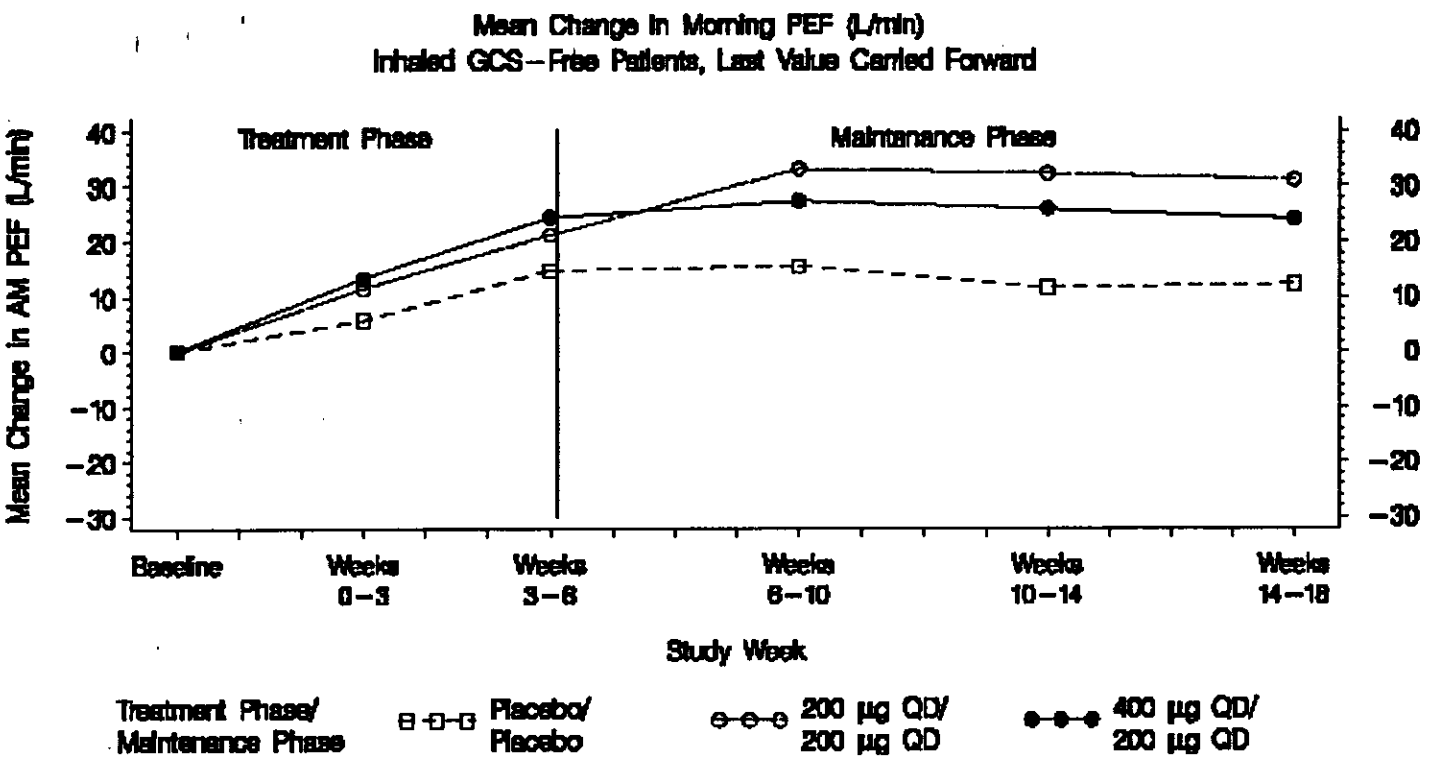
Figure B. Mean Change in Morning PEF (L/min) All Patients Treated, Last Value Carried Forward



CHANGE FROM BASELINE IN PEFR CLINICAL TRIAL 004-0009
GCS-NAÏVE SUBGROUP

Figure 1



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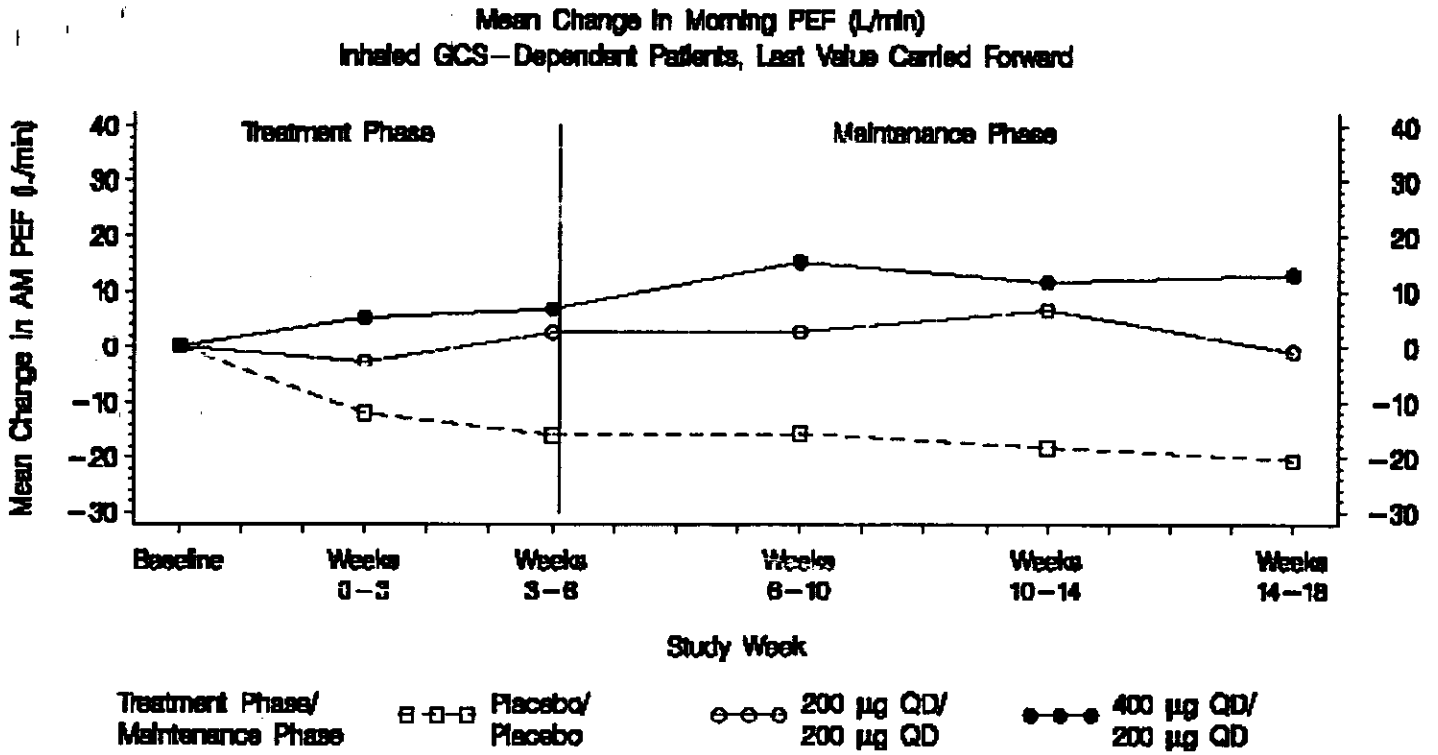
CHANGE FROM BASELINE IN PEFR CLINICAL TRIAL 004-0009

GCS-(+) SUBGROUP

Figure 2



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NON-PIVOTAL STUDY 04-3083
SECONDARY ENDPOINTS

Table 15. Pairwise comparisons of treatment groups. All variables.

	BUD200 qd - BUD100 bid				BUD200 qd - placebo				BUD100 bid - placebo			
	Est. diff.	lower limit CI	upper limit CI	p-value	Est. diff.	lower limit CI	upper limit CI	p-value	Est. diff.	lower limit CI	upper limit CI	p-value
PEF evening (L/min)	6.42	-5.11	17.94	0.2740	22.64	8.71	36.57	0.0015	16.22	2.24	30.20	0.0231
PEF evening (% of pred.)	1.24	-1.06	3.55	0.2893	4.67	1.89	7.46	0.0011	3.43	0.63	6.23	0.0164
Symptoms day (0-3)	-0.04	-0.16	0.08	0.5365	-0.16	-0.31	-0.01	0.0390	-0.12	-0.27	0.03	0.1190
Symptoms night (0-3)	-0.02	-0.11	0.07	0.6584	-0.19	-0.30	-0.08	0.0012	-0.17	-0.28	-0.05	0.0040
Inhal. beta2 day	-0.13	-0.33	0.08	0.2295	-0.42	-0.66	-0.17	0.0011	-0.29	-0.54	-0.04	0.0232
Inhal. beta2 night	-0.07	-0.21	0.08	0.3670	-0.36	-0.53	-0.18	0.0001	-0.29	-0.47	-0.11	0.0015
FEV_1 (L)	0.00	-0.15	0.16	0.9741	0.02	-0.16	0.21	0.8010	0.02	-0.17	0.21	0.8221
FEV_1 (% of pred.)	0.12	-4.08	4.31	0.9565	0.37	-4.76	5.50	0.8880	0.25	-4.90	5.40	0.9237
FVC (L)	-0.03	-0.24	0.18	0.7673	-0.05	-0.31	0.20	0.6764	-0.02	-0.28	0.23	0.8611
FVC (% of pred.)	-0.75	-5.46	3.96	0.7554	-1.42	-7.18	4.35	0.6291	-0.67	-6.46	5.12	0.8199