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A Placebo-Controlled Comparison of the Efficacy, Safety, and Pharmacokinetics of the Current US Version of PULMICORT (Budesonide) TURBUHALER® and the New Version of PULMICORT TURBUHALER® in Asthmatic Children and Adolescents

TITLE PAGE

Study dates: First subject enrolled: 14 November 2002
Last subject completed: 21 September 2004

Phase of development: Phase III

International Coordinating Investigator: Not applicable

This study was performed in compliance with Good Clinical Practice.

Drug product:	PULMICORT TURBUHALER	**SYNOPSIS**	
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A Placebo-Controlled Comparison of the Efficacy, Safety, and Pharmacokinetics of the Current US Version of PULMICORT (Budesonide) TURBUHALER® and the New Version of PULMICORT TURBUHALER® in Asthmatic Children and Adolescents

International coordinating investigator

Not applicable

Study center

A total of 84 centers (69 US, 15 Asian [5 Philippines, 5 Indonesia, 3 Thailand, and 2 Singapore]) enrolled subjects to the point of consent. Of those centers, 54 US centers and 14 Asian centers [4 Philippines, 5 Indonesia, 3 Thailand, and 2 Singapore] each had at least 1 subject who returned for assignment to randomized treatment.

Publications

None at report time.

Study dates		**Phase of development**
First subject enrolled	14 November 2002	Phase III
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Objectives

Primary: The primary objective was to compare the efficacy of budesonide delivered by PULMICORT TURBUHALER M0-ESP[1] to that delivered by PULMICORT TURBUHALER M3 in asthmatic children and adolescents, aged 6 to 17 years.

Secondary: (1) to compare the safety of budesonide delivered by PULMICORT TURBUHALER M0-ESP to that of budesonide delivered by PULMICORT TURBUHALER M3 in asthmatic children and adolescents, and (2) to compare the pharmacokinetics of budesonide delivered by PULMICORT TURBUHALER M0-ESP to that of budesonide delivered by PULMICORT TURBUHALER M3. A subset of randomized subjects selected from each treatment group was targeted for inclusion in the pharmacokinetics (PK) and pharmacodynamic (PD) analyses.

Tertiary: To assess the functionality of the PULMICORT TURBUHALER M3 device at the end of its intended life.

Study design

The study was a double-blind, placebo-controlled, randomized, parallel-group, multicenter study in asthmatic children and adolescents aged 6 to 17 years. The study consisted of a 14-day run-in period, a 12-week randomized treatment period, and a follow-up (via telephone call or visit) 2 weeks after the last visit.

Subjects who met entry criteria at Visit 1 entered the run-in period, during which all subjects could have continued to take their regular inhaled corticosteriod (ICS) treatment (if applicable), and began treatment with placebo once daily. Once in the run-in period, subjects had up to 14 days to qualify for continued study participation and assignment to one of the following randomized treatments (at Visit 2): budesonide from PULMICORT TURBUHALER M3 at a dosage of 180 μg once daily (qd) or 360 μg twice daily (bid); budesonide from PULMICORT TURBUHALER M0-ESP at a dosage of 400 μg bid or 200 μg qd; or placebo. The placebo group was split so that subjects received placebo matched to 1 of the 4 active treatments. Subjects continuing in the study were expected to return for 4 more visits during the 12-week treatment period. Subjects performed spirometry maneuvers at each visit, with testing conducted before the morning dose of study treatment.

At study entry (Visit 1), subjects received electronic diaries, which were used to record and transmit the following information on a daily basis: morning and evening peak flow rates; day and night asthma symptom scores; night awakenings due to asthma (yes/no); day and night

[1] ESP refers to enhanced spheronization process. PULMICORT TURBUHALER is a trademark of the AstraZeneca group of companies.

use of rescue medication; and study treatment use. Data were stored in a centralized database that was accessed by study personnel on an ongoing basis.

A subset of 15 subjects from each treatment group was targeted for inclusion in the PK analyses. An additional 9 subjects per treatment participated in just the PD evaluation. Blood sampling for this purpose occurred for up to 12 hours after drug administration either at Visit 5.1 or Visit 6.

At US centers, study personnel collected used PULMICORT TURBUHALER M3 inhalers returned at Visits 5 and 6 for overnight shipment back to the supplier, who then forwarded the devices to AstraZeneca (Lund, Sweden) for functionality and performance assessments. Any PULMICORT TURBUHALER M3 device that was perceived to be defective at any time during the study (at any center) was forwarded from the study center to AstraZeneca (Lund, Sweden) for examination of the perceived defect.

Target subject population and sample size

Subjects sought for enrollment were males and females aged 6 to 17 years who had a diagnosis of asthma (as defined by the American Thoracic Society) for at least 3 months. To enter the run-in period, subjects were also required to have the following: for subjects aged 6 to 11 years, an FEV_1 of ≥75% and ≤90% of Polgar predicted normal values and for subjects aged 12 to 17 years, an FEV_1 of ≥60% and ≤90% of Polgar predicted normal values; airway reversibility (after a standard dose of albuterol or salbutamol) of ≥12% (compared with prebronchodilator values); and a recent medication history that included the use of ICS for no more than 30 days prior to Visit 1, or be ICS naive. Subjects who had an FEV_1 of >90% and ≤95% predicted value may have also been included if they had an absolute FEV_1/FVC ratio measured on screening spirometry of <80%.

The sample size calculation was made with respect to the primary efficacy variable, namely, the change in % predicted FEV_1 from baseline to the average value over the treatment period. Because the study was not designed as a clinical equivalence study, the sample size estimate was based on the comparison between active treatments and placebo.

Assuming a standard deviation of 16%, 90% power and a two-sided test at a 5% level of significance, 86 evaluable subjects per treatment group will be required in order to detect a true difference of 8% between the PULMICORT TURBUHALER and placebo treatment groups. In order to allow for the possibility that data from approximately 5% of the randomized subjects could not be used in the analysis, at least 92 subjects per treatment group were targeted to be randomized into the study to achieve this goal (for a total of 430 evaluable subjects).

Investigational product, active control agent, and rescue medication: dosage, mode of administration, and batch numbers

Once randomized, subjects began treatment with 1 of the following dosages (while the metered dose for these products may differ, the delivered doses are comparable, ie 200 μg

metered from PULMICORT TURBUHALER M0-ESP delivers 160 μg, and 180 μg metered from PULMICORT TURBUHALER M3 delivers 160 μg):

- PULMICORT TURBUHALER M3 (60-dose device): 90 μg x 4 inhalations (360 μg of budesonide) bid (total daily dose of 720 μg)
- PULMICORT TURBUHALER M3 (60-dose device): 90 μg x 2 inhalations (180 μg of budesonide) every morning
- PULMICORT TURBUHALER M0-ESP (200-dose device): 200 μg x 2 inhalations (400 μg of budesonide) bid (total daily dose of 800 μg)
- PULMICORT TURBUHALER M0-ESP (200-dose device): 200 μg x 1 inhalation (200 μg of budesonide) every morning
- placebo PULMICORT TURBUHALER M3 (60-dose device): 2 inhalations every morning or 4 inhalations bid to match active treatment
- placebo PULMICORT TURBUHALER M0-ESP (200-dose device): 1 inhalation every morning or 2 inhalations bid to match active treatment

Batch numbers –

- PULMICORT TURBUHALER M0-ESP 200 μg metered dose: Batch nos. CH1497, DA1629, DK1762, ED1904, and EM1959.
- PULMICORT TURBUHALER M3 90 μg metered dose: Batch nos. CL13, EB18, EF21, EK22, EF20.
- Placebo TURBUHALER: Batch nos. CL14, EB15.
- Albuterol delivered by pMDI (90 μg/actuation): Batch nos. AM-656, BN2000044978, and BN2000052100); salbutamol delivered by pMDI (100 μg/actuation): Batch nos. JV5568, JV5564, JV5556, KW0004, KW0080, KW0009, KW0010, and D0367760.

Duration of treatment

During the 14-day run-in period between Visits 1 and 2, subjects were treated with single-blind placebo TURBUHALER once daily. Once assigned to a randomized treatment, subjects received treatment for up to 12 weeks.

Criteria for evaluation (main variables)

Efficacy, pharmacokinetics, and other assessments

- Primary variable: Change in % predicted FEV_1 (L) from baseline to average over the treatment period, with baseline value defined as the Visit 2 % predicted FEV_1 and treatment-period value defined as the average % predicted FEV_1 from Visits 3, 4, 5, and 6 (ie, the average 4-visit % predicted FEV_1)

- Secondary variables: Change in FVC and $FEF_{25\%-75\%}$ from baseline to average over the treatment period, change in FEV_1 (L), FVC, and $FEF_{25\%-75\%}$ from baseline to each visit, change from baseline to average over the treatment period in morning and evening PEF, day and night asthma symptom scores, day and night β_2-agonist use (puffs used and number of days used), and asthma-related discontinuations.

- Secondary PK variables: AUC_{0-t}, maximum concentration (C_{max}), and time to C_{max} (T_{max})

- Other assessments: Peak inspiratory flow (PIF) and device functionality

Safety

Safety was measured relative to the incidence of adverse events (AEs), with AEs categorized by system-organ class (SOC) and preferred term (Medical Dictionary for Regulatory Activities [MedDRA], version 7.1); the incidences of serious adverse events (SAEs), AEs leading to study discontinuation (DAEs), and other significant AEs (OAEs); the incidence of AEs by causality; changes in vital signs, physical examination findings, and clinical laboratory test results from baseline to Visit 6 (or end of treatment); urinary cortisol; and change in mouth and throat findings from Visit 2 to Visit 6 (or end of treatment).

Statistical methods

The ITT analysis set included data from all randomized subjects who took at least 1 dose of study treatment and contributed sufficient data from the treatment period to enable the calculation of at least 1 efficacy endpoint. For all analyses, data from the 4 placebo treatment groups were combined and analyzed if they came from a single treatment group. To assess treatment response among the subjects who took placebo, the 4 placebo treatment groups were compared for change in % predicted FEV_1 from baseline to average over the treatment period (ie, the primary efficacy variable).

The statistical model used to assess change in % predicted FEV_1 from baseline to average over the treatment period was an analysis of covariance (ANCOVA), adjusted for the study factors of treatment and region (USA or Asia) and the covariate of baseline (Visit 2) % predicted FEV_1. To assess absolute efficacy, subject responses to PULMICORT TURBUHALER M3 were compared with responses to placebo. To address multiplicity, comparisons between the PULMICORT TURBUHALER M3 and placebo treatment groups were made in a step-down fashion. Specifically, the high-dose PULMICORT TURBUHALER M3 group was first compared with the pooled placebo group. If the difference was statistically significant at the

5% level, then the low-dose PULMICORT TURBUHALER M3 group was compared with the pooled placebo group at the 5% level.

Comparability between PULMICORT TURBUHALER M3 and PULMICORT TURBUHALER M0-ESP was assessed via 95% confidence intervals (95% CIs) on the differences between treatments derived from the same ANCOVA model. Confidence intervals were constructed for comparisons between the 2 high-dose groups—PULMICORT TURBUHALER M3 360 μg bid and PULMICORT TURBUHALER M0-ESP 400 μg bid—and between the 2 low-dose groups—PULMICORT TURBUHALER M3 180 μg daily and PULMICORT TURBUHALER M0-ESP 200 μg daily.

FEV_1, FVC, and $FEF_{25\%-75\%}$ were assessed using spirometric methods, as described for the primary efficacy variable. Individual morning and evening PEF values (L/min), day and night asthma symptom scores, β_2-agonist use, and asthma-related discontinuation criteria were taken directly from the subject's electronic diary; therefore, no derivations were required.

Data for PIF was summarized using descriptive statistics by visit and the average across visits including the change from baseline (Visit 2).

Subjects who participated in the PK portion of the study were included in PK analysis if they provided blood samples viable for analysis. Budesonide PK parameters were summarized using descriptive statistics for each treatment and compared between treatment groups (low dose to low dose, high dose to high dose) primarily through the use of confidence intervals, using analysis of variance techniques.

The safety analysis set is comprised of all randomized subjects who took at least 1 dose of study treatment. All safety data were summarized using descriptive statistics. For AEs that occurred in ≥3% of subjects in any treatment group, pairwise p-values (among all treatment pairs) were calculated using a Fisher's exact test for purposes of flagging AEs that might require further investigation. Changes from baseline to end-of-treatment for continuous laboratory variables were analyzed using an ANCOVA model, with treatment and region (US or Asia) as study factors and baseline value (per variable) as the covariate. Changes from baseline to last visit for vital signs were analyzed using the same ANCOVA model. In these analyses, pairwise nominal p-values were reported for flagging purposes only, as was done for AEs. Clinically important findings for both laboratory variables and vital signs were summarized. Twenty-four hour urinary cortisol, urine cortisol concentration, 24-hour urinary creatinine, urine creatinine concentration, total volume, and the cortisol:creatinine ratio were summarized using descriptive statistics. In addition 24-hour urinary cortisol and cortisol:creatinine ratio values at 12 weeks of treatment and the end of treatment were analyzed with both an additive ANOVA and a multiplicative ANOVA. The results of the multiplicative ANOVA were considered primary.

Results

Subject population

A total of 516 randomized subjects with mild asthma were assigned to 1 of 5 treatment groups, with the number of subjects well balanced across treatment groups. Demographic and baseline characteristics were generally similar across treatment groups. Most subjects were Caucasian (52.1%), with Black subjects comprising 12.4% of the population and Oriental subjects comprising 33.3% of the population. Across the geographic regions, 347 (67.2%) randomized subjects were from US sites and 169 (32.8%) subjects were from Asian sites. The distribution of male and female subjects (approximately 65% male and 35% female overall) was similar across the treatment groups. Mean age was 11.6 years (range 6 to 17 years), with 45% (n=232) of subjects between the ages of 6 and 11 years and 55% (n=284) subjects between the ages of 12 and 17 years. Age distribution was similar across treatment groups.

On average, subjects had a 7-year history of asthma, with baseline disease characteristics highly reflective of study entry criteria. Treatment groups were comparable at screening with respect to disease severity characteristics indicative of mild asthma, including mean predose FEV_1. A total of 18 (3.5%) randomized subjects had asthma treated by a regimen of ICS during the single-blind placebo run-in period.

The ITT analysis set is comprised of all randomized subjects. Approximately 12% of subjects in the ITT analysis set were excluded from the PP analysis set, with exclusions similarly distributed across treatment groups.

The most common reason for discontinuation among randomized subjects including the placebo group was development of study-specific asthma discontinuation criteria (37 subjects [7.2%]). The percentage of subjects withdrawn in the PULMICORT TURBUHALER M0-ESP 400 µg group was somewhat lower (16.7%) than the other active treatment groups (ranging from 20.2% to 21.3%).

Efficacy and pharmacokinetic results

The primary analysis of % predicted FEV_1 was the change from baseline to the subject's average % predicted FEV_1 during the 12-week treatment period. Table S1 and Table S2 summarize treatment means and treatment comparisons, respectively, for change from baseline to the average during randomized treatment for the primary variable, % predicted FEV_1.

Table S1 Treatment means for treatment-period % predicted FEV_1 (LOCF), ITT population

Treatment	N	% predicted FEV_1, mean (SE)			(From ANCOVA)		
		Baseline	Treatment period	Change	LSmean change	SE	95%CI
PULMICORT TURBUHALER M3 360 µg bid	90	84.16 (0.95)	89.98 (1.10)	5.82 (0.98)	5.57	0.83	3.94 to 7.20
PULMICORT TURBUHALER M0-ESP 400 µg bid	98	86.60 (0.76)	90.69 (0.84)	4.09 (0.74)	4.44	0.80	2.88 to 6.01
PULMICORT TURBUHALER M3 180 µg qd	103	84.65 (1.02)	87.34 (1.20)	2.68 (0.81)	2.55	0.78	1.03 to 4.08
PULMICORT TURBUHALER M0-ESP 200 µg qd	101	84.43 (0.91)	87.31 (1.03)	2.89 (0.79)	2.69	0.79	1.1 to 4.24
Placebo[a]	101	84.45 (0.93)	84.82 (0.99)	0.37 (0.75)	0.19	0.79	-1.36 to 1.73

[a] All placebo groups combined.
LSmean Least squares mean. SE Standard error of the mean.
PULMICORT TURBUHALER M3, new device. PULMICORT TURBUHALER M0-ESP, current device.

Table S2 Treatment comparisons of treatment-period % predicted FEV_1: ANCOVA results (LOCF), ITT population

Comparison	LSmean difference	SE	95% CI	p-value
PULMICORT TURBUHALER M3 360 µg bid – PULMICORT TURBUHALER M0-ESP 400 µg bid	1.13	1.14	-1.11 to 3.36	0.323
PULMICORT TURBUHALER M3 180 µg qd – PULMICORT TURBUHALER M0-ESP 200 µg qd	-0.14	1.09	-2.28 to 2.00	0.897
PULMICORT TURBUHALER M3 360 µg bid – placebo[a]	5.38	1.13	3.17 to 7.60	<0.001
PULMICORT TURBUHALER M3 180 µg qd – placebo[a]	2.37	1.09	0.23 to 4.50	0.030
PULMICORT TURBUHALER M0-ESP 400 µg bid – placeboa	4.26	1.10	2.09 to 6.43	<0.001
PULMICORT TURBUHALER M0-ESP 200 µg qd – placebo[a]	2.51	1.09	0.36 to 4.66	0.022

[a] All placebo groups combined.
LSmean Least squares mean. SE Standard error of the mean.
PULMICORT TURBUHALER M3, new device. PULMICORT TURBUHALER M0-ESP, current device.

Compared to the mean increase of 0.19% in the placebo group, the increases from baseline were statistically significantly higher for the PULMICORT TURBUHALER M3 360 μg group (mean increase of 5.57%, p<0.001), PULMICORT TURBUHALER M0-ESP 400 μg group (mean increase of 4.44%, p<0.001), PULMICORT TURBUHALER M3 180 μg group (mean increase of 2.55%, p=0.030), and PULMICORT TURBUHALER M0-ESP 200 μg group (mean increase of 2.69%, p=0.022).

Comparability between the high-dose groups of PULMICORT TURBUHALER M3 and PULMICORT TURBUHALER M0-ESP was established with a difference between groups of 1.13% and an associated 95% confidence interval of -1.11% to 3.36% for the PULMICORT TURBUHALER M3 minus PULMICORT TURBUHALER M0-ESP difference. Similarly, the low-dose groups of PULMICORT TURBUHALER M3 and PULMICORT TURBUHALER M0-ESP were comparable with a mean difference of -0.14% and an associated 95% confidence interval of –2.28% to 2.00% for the PULMICORT TURBUHALER M3 minus TPH M0-ESP difference.

Treatment means and treatment group differences were consistent between regions (US and Asia).

For the analyses of secondary efficacy variables in this mild asthma population, PULMICORT TURBUHALER M3 360 μg bid and PULMICORT TURBUHALER M0-ESP 400 μg bid resulted in a significant improvement in FEF_{25-75} and both AM and PM PEF, but did not result in statistically significant improvement for the other secondary efficacy measures. PULMICORT TURBUHALER M3 180 μg qd and PULMICORT TURBUHALER M0-ESP 200 μg qd did not result in statistically significant improvement in any secondary efficacy measure.

In this population of mild asthmatics, the distribution of subjects who met predefined asthma-related discontinuation criteria during the study was similar among the active treatment groups (range of 11.1% to 13.8% of subjects) and was slightly higher for the placebo group (17.3%). There were no clinically relevant or statistically significant differences between any of the treatment groups as determined from the survival analysis.

PIF values were generally comparable across the treatment groups. There was a general monotonic increase in mean PIF across the age categories within each treatment group. This trend was also seen when the data were combined across treatments. There was no indication of a relationship between baseline PIF and response to treatment, and there was no indication of an increased risk of meeting asthma discontinuation criteria associated with PIF values <60 L/min.

A total of 32 subjects participated in the PK analyses. Geometric means for AUC_{0-12h} were similar between the PULMICORT TURBUHALER M3 360 μg bid and PULMICORT TURBUHALER M0-ESP 400 μg bid groups (mean ratio 101.1, CI 59.1 to 172.9), and between the PULMICORT TURBUHALER M3 180 μg qd and PULMICORT

TURBUHALER M0-ESP 200 µg qd groups (mean ratio 100.2, CI 61.6 to 162.9). The PK data suggest that systemic exposure to budesonide is generally similar for PULMICORT TURBUHALER M3 compared with PULMICORT TURBUHALER M0-ESP.

Results of the functionality testing showed that the PULMICORT TURBUHALER M3 device worked as intended after being used in the clinical study. All parts of the examined inhalers were intact. The average delivered dose level was slightly lower, and the average relative standard deviation was higher, for the clinical returns compared to the release data. The batch average-delivered dose ranged from 88% to 103% for the returned inhalers. The corresponding range at release was 93% to 104%. These differences, given the nature of the test and that some inhalers were beyond the normal dosing interval, were considered to be negligible. The batch average of the fine-particle dose for the used inhalers ranged from 96% to 111%, with an average of 107% when compared to the values obtained at release testing. The difference was considered to be negligible. The amounts of moisture in the spheronized powder were generally slightly higher compared to the release data. This was to be expected since the inhalers had been subjected to moisture during use. The amount of water in the inhaler desiccant ranged from 3% to 25%. The amount of water found after 30 months storage at 25°C/60% RH was approximately 6%. The large variability indicated both that the subjects had been adhering to the instructions very differently and that the climatic conditions (ambient humidity) had been variable in the different regions. The results indicated no or very limited growth and the microbial status of the inhalers tested was judged to be acceptable. Complaint inhalers were studied separately. All inhalers tested were shown to operate as intended and none of the complaints could be confirmed.

Safety results

A total of 261 subjects reported AEs during the study: 44 (45.8%) subjects in the PULMICORT TURBUHALER M3 360 µg bid group; 49 (48.0%) subjects in the PULMICORT TURBUHALER M0-ESP 400 µg bid group; 57 (52.8%) subjects in the PULMICORT TURBUHALER M3 180 µg qd group; 53 (51.0%) subjects in the PULMICORT TURBUHALER M0-ESP 200 µg qd group; and 58 (54.7%) of subjects in the placebo group.

There were no reported deaths or OAEs in this study. The overall incidence of AEs was higher in the placebo group compared to the active treatment groups. The incidences of AEs between the PULMICORT TURBUHALER M3 360 µg bid group and the PULMICORT TURBUHALER M0-ESP 400 µg bid group were generally similar, as were the incidences of AEs between the PULMICORT TURBUHALER M3 180 µg qd group and the PULMICORT TURBUHALER M0-ESP 200 µg qd group. The most frequently occurring AEs during the randomized treatment period were headache, nasopharyngitis, pharyngolaryngeal pain, pyrexia, upper respiratory tract infection, and cough. The incidence of each of these events was generally similar across the treatment groups. The majority of the AEs were of mild to moderate intensity. AEs generally appeared to be evenly distributed across the treatment groups for each demographic subgroup that was assessed, with the exception of region where a higher percentage of subjects in US sites reported AEs compared with Asian sites. Six (1.2%) subjects had AEs that were considered by the investigator to be causally related to

study drug. The overall incidence of drug-related AEs was low and similar between treatment groups, and all were of mild or moderate intensity.

Three subjects had SAEs during the randomized treatment period. None of the SAEs that occurred during the randomized treatment period were determined by the investigators to be study-drug related.

Ten subjects had a total of 10 DAEs, 2 of which were considered by the investigator to be study-drug related. The overall percentage of subjects who had drug-related DAEs was low for all treatment groups.

For the majority of laboratory variables assessed, the PULMICORT TURBUHALER M3 and PULMICORT TURBUHALER M0-ESP groups did not demonstrate any clinically significant changes in laboratory values compared with placebo. There were no clinically meaningful changes from baseline or differences across treatment groups for most hematology and clinical chemistry parameters. There were no meaningful treatment group differences in shifts in individual subject data (using standard and AstraZeneca extended reference ranges) at any visit. There were no substantial mean differences between either of the PULMICORT TURBUHALER M3 groups and the placebo group, or between either of the PULMICORT TURBUHALER M0-ESP groups and the placebo group for 24-hour urine cortisol assessments or for the assessment of the cortisol/creatinine ratio. No clinically meaningful changes or treatment group differences were observed in vital signs (heart rate, diastolic and systolic blood pressure) and physical exam findings.

Overall, PULMICORT TURBUHALER M3 was well tolerated when used in the treatment of asthma in subjects aged 6 to17 years. No new safety concerns were identified. No difference in the safety profile was observed between PULMICORT TURBUHALER M3 360 µg bid group and the PULMICORT TURBUHALER M0-ESP 400 µg bid group, or between the PULMICORT TURBUHALER M3 180 µg qd group and the PULMICORT TURBUHALER M0-ESP 200 µg qd group.