AstraZeneca

**Clinical Study Report**

Drug substance: Budesonide

Document No.:

Edition No.:

Study code: SD-004-0620

Date: 7 July 2005

# A Placebo-Controlled Comparison of the Efficacy and Safety of the Current US Version of PULMICORT (Budesonide) TURBUHALER® and the New Version of PULMICORT TURBUHALER® in Asthmatic Adults Currently Treated with Inhaled Steroids

**Study dates:** First subject enrolled: 16 July 2002
Last subject completed: 28 October 2004

**Phase of development:** Phase III

**International Coordinating Investigator:** Not applicable

This study was performed in compliance with Good Clinical Practice.

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|---|---|---|---|
| Drug product: | PULMICORT TURBUHALER | **SYNOPSIS** | |
| Drug substance(s): | Budesonide | | |
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# A Placebo-Controlled Comparison of the Efficacy and Safety of the Current US Version of PULMICORT (Budesonide) TURBUHALER® and the New Version of PULMICORT TURBUHALER® in Asthmatic Adults Currently Treated with Inhaled Steroids

**International coordinating investigator**

Not applicable

**Study center**

A total of 127 centers (110 US, 17 Asian [10 Philippine and 7 Indonesian]) enrolled subjects to the point of consent. Of those centers, 74 US centers and 16 Asian centers had at least 1 subject each who returned for assignment to randomized treatment.

**Publications**

None at report time.

| **Study dates** | | **Phase of development** |
|---|---|---|
| **First subject enrolled** | 16 July 2002 | Phase III |
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## Objectives

**Primary:** To compare the efficacy of budesonide delivered by the current PULMICORT TURBUHALER M0-ESP[1] to that of budesonide delivered by the new PULMICORT TURBUHALER M3) in asthmatic adults currently treated with inhaled steroids.

**Secondary:** (1) To compare the safety of budesonide delivered by TURBUHALER M0-ESP to that of budesonide delivered by TURBUHALER M3 in asthmatic adults currently treated with inhaled steroids and (2) to compare the pharmacokinetics of budesonide delivered by TURBUHALER M0-ESP to that of budesonide delivered by TURBUHALER M3. A subset of subjects selected from each treatment group was targeted for inclusion in the pharmacokinetics analyses.

**Tertiary:** To assess the functionality of 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 adults with asthma. The study consisted of a 5- to 40-day single-blind, placebo run-in period, a 12-week randomized treatment period, and a follow-up safety visit 2 weeks after the last visit.

Subjects who met entry criteria at Visit 1 entered the run-in period and began treatment with placebo TURBUHALER twice daily. Ongoing treatment with orally inhaled corticosteroids was discontinued; rescue medication was used as needed. Once in the run-in period, subjects had up to 40 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 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 daily; 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.[2]

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

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

[2] Spirometry data from Visit 5.1 were used to ensure that subjects had not met any discontinuation criteria in the interval between Visit 4 and Visit 5.1. However, these data were not collected.

and night asthma symptom scores; nighttime awakenings due to asthma (yes/no); daytime and nighttime use of rescue medication; and study drug use. Data were stored in a centralized database that was accessed by study personnel on an ongoing basis.

A subset of subjects (24 from each active treatment group) was targeted for inclusion in the pharmacokinetics (PK) analyses. Blood sampling for this purpose occurred for up to 12 hours after drug administration either at Visit 5.1 (the PK visit) 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 perceived as 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 at least 18 years old with a diagnosis of asthma (as defined by the American Thoracic Society) for at least 6 months. To enter the run-in period, subjects were also required to have the following: a forced expiratory volume in 1 second ($FEV_1$) of ≥60% and ≤90% of predicted normal values, airway reversibility (after a standard dose of albuterol or salbutamol) of ≥12% and ≥0.20 L (compared with prebronchodilator values), and a recent medication history that included the use of orally inhaled corticosteroids (ICS) for at least 3 months prior to Visit 1. At Visit 2, subjects who met additional entry criteria related to rescue medication use and asthma symptom scores during the run-in period plus visit-specific $FEV_1$ requirements were assigned to randomized treatments (as previously described).

The sample size calculation was made with respect to the primary efficacy variable, namely, the change in $FEV_1$ 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.

To detect a true difference of 0.23 L (standard deviation of 0.50 L) between the PULMICORT TURBUHALER M3 and placebo treatment groups with 90% power for a 2-sided test at a 5% level of significance, 101 evaluable subjects per treatment group (4 active treatment groups, 1 combined placebo group) were required (for a total of 505 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): 180 μg x 2 inhalations (360 μg of budesonide) bid (total daily dose of 720 μg)
- PULMICORT TURBUHALER M3 (60-dose device): 180 μg x 1 inhalation (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 180 μg metered dose (60-dose unit): Batch nos. CL16, EE19, EB18.
- PULMICORT TURBUHALER M3 180 μg metered dose (120-dose unit): Batch nos. CL20, EE24, EB25, FA26.
- Placebo PULMICORT TURBUHALER M0-ESP (excipients only): Batch nos. CF11, DK12, EE13, EI14.
- Placebo PULMICORT TURBUHALER M3 (lactose only, 60-dose unit): Batch nos. CL14, EB15.
- Placebo PULMICORT TURBUHALER M3 (lactose only, 120-dose unit): Batch nos. CL14, CL13, EE14.
- 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 5- to 40-day run-in period between Visits 1 and 2, subjects were treated with single-blind, twice-daily placebo. Once assigned to a randomized treatment, subjects received treatment for up to 12 weeks.

**Criteria for evaluation (main variables)**

**Efficacy and pharmacokinetics**

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

- Secondary variables: Change in forced vital capacity (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, daytime and nighttime $\beta_2$-agonist use (puffs used and number of days used), and subjects who met predefined asthma-related discontinuation criteria

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

**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); and change in mouth and throat findings from Visit 2 to Visit 6 (or end of treatment).

**Statistical methods**

The efficacy 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 $FEV_1$ from baseline to average over the treatment period (ie, the primary efficacy variable). The $FEV_1$ mean changes from baseline for each of the placebo groups are as follows: 0.19 L and -0.02 L for the placebo PULMICORT TURBUHALER M0-ESP 200 ug qd group and placebo PULMICORT TURBUHALER M3 180 ug qd group, respectively; 0.11 L and 0.18 L for the placebo PULMICORT TURBUHALER M0-ESP 400 ug bid group and placebo PULMICORT TURBUHALER M3 360 ug bid group, respectively.

The statistical model used to assess change in $FEV_1$ from baseline to treatment period was an analysis of covariance (ANCOVA), adjusted for the study factors of treatment and region (US or Asia) and the covariate of baseline (Visit 2) $FEV_1$. 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 qd and PULMICORT TURBUHALER M0-ESP 200 μg qd.

Secondary variables were analyzed as described for the primary efficacy variable.

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 data set included 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 adverse events 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 significant findings for both laboratory variables and vital signs were summarized.

**Subject population**

A total of 621 randomized subjects with asthma were assigned to 1 of 5 treatment groups. Demographic and baseline characteristics were generally similar across treatment groups. Most subjects were Caucasian (64.4%), with black subjects comprising 6.1% of the population and Oriental subjects comprising 29.0% of the population. Across the geographic regions, 450 (72.5%) randomized subjects were from US sites and 171 (27.5%) subjects were from Asian sites. The distribution of male and female subjects (approximately 35% male and 65%

female overall) was similar across the treatment groups. Mean age was 40 years (range 18 to 80 years).

On average, subjects had a 20-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 asthma.

The safety analysis set is comprised of all randomized subjects. Approximately 24% 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 a predefined asthma-related discontinuation criterion (86 subjects [13.8%]): 19 subjects (14.6%) in the PULMICORT TURBUHALER M3 360 µg bid group, 20 subjects (15.5%) in the PULMICORT TURBUHALER M0-ESP 400 µg bid group, 30 subjects (24.8%) in the PULMICORT TURBUHALER M3 180 µg qd group, 33 subjects (29.2%)in the PULMICORT TURBUHALER M0-ESP 200 µg qd group, and 57 subjects (47.9%) in the placebo group. The percentage of subjects withdrawn in the placebo group (48.4%) was higher than the other active treatment groups (ranging from 31.7% to 19.2%).

**Efficacy and pharmacokinetic results**

The primary analysis of $FEV_1$ (L) was an analysis of covariance of the change The primary analysis of $FEV_1$ (L) was the change from baseline to the subject's average $FEV_1$ (L) during the 12-week treatment period. Table S1 and Table S2 summarize treatment means and treatment comparisons, respectively, for change in $FEV_1$ (L) from baseline to the average during randomized treatment for the primary variable, $FEV_1$ (L).

**Table S1 Treatment means for treatment-period change in $FEV_1$ (LOCF), ITT population**

| Treatment | N | $FEV_1$, mean (SE) | | | (From ANCOVA) | | |
|---|---|---|---|---|---|---|---|
| | | Baseline | Treatment period | Change | LSmean change | SE | 95% CI |
| PULMICORT TBH M3 360 μg bid | 128 | 2.14 (0.05) | 2.44 (0.06) | 0.30 (0.02) | 0.28 | 0.029 | 0.22 to 0.34 |
| PULMICORT TBH M0-ESP 400 μg bid | 128 | 2.15 (0.05) | 2.52 (0.06) | 0.36 (0.03) | 0.34 | 0.029 | 0.29 to 0.40 |
| PULMICORT TBH M3 180 μg qd | 119 | 2.09 (0.05) | 2.29 (0.06) | 0.19 (0.02) | 0.18 | 0.030 | 0.12 to 0.24 |
| PULMICORT TBH M0-ESP 200 μg qd | 110 | 2.19 (0.06) | 2.46 (0.07) | 0.27 (0.03) | 0.25 | 0.031 | 0.19 to 0.31 |
| Placebo[a] | 114 | 2.14 (0.05) | 2.26 (0.06) | 0.12 (0.03) | 0.10 | 0.031 | 0.04 to 0.16 |

[a] All placebo groups combined.
ANCOVA Analysis of covariance; CI Confidence interval; $FEV_1$ Forced expiratory volume in 1 second; ITT Intention-to-treat; LOCF Last observation carried forward; LSmean Least squares mean; SE Standard error of the mean; TBH TURBUHALER.
PULMICORT TURBUHALER M3, new device. PULMICORT TURBUHALER M0-ESP, current device.
Data derived from Table 11.2.1.2.1, Section 11.2.

**Table S2 Treatment comparisons of treatment-period change in $FEV_1$: ANCOVA results (LOCF), ITT population**

| Comparison | LSmean difference | SE | 95% CI | p-value |
|---|---|---|---|---|
| PULMICORT TBH M3 360 µg bid – PULMICORT TBH M0-ESP 400 µg bid | -0.06 | 0.04 | -0.14 to 0.02 | 0.117 |
| PULMICORT TBH M3 180 µg qd – PULMICORT TBH M0-ESP 200 µg qd | -0.07 | 0.042 | -0.16 to 0.01 | 0.089 |
| PULMICORT TBH M3 360 µg bid – placebo[a] | 0.18 | 0.041 | 0.1 to 0.26 | <0.001 |
| PULMICORT TBH M3 180 µg qd – placebo[a] | 0.07 | 0.042 | -0.01 to 0.16 | 0.078 |
| PULMICORT TBH M0-ESP 400 µg bid – placebo[a] | 0.24 | 0.041 | 0.16 to 0.32 | <0.001 |
| PULMICORT TBH M0-ESP 200 µg qd – placebo[a] | 0.15 | 0.043 | 0.06 to 0.23 | <0.001 |

[a] All placebo groups combined.
ANCOVA Analysis of covariance; CI Confidence interval; $FEV_1$ Forced expiratory volume in 1 second; ITT Intention-to-treat; LOCF Last observation carried forward; LSmean Least squares mean; SE Standard error of the mean; TBH TURBUHALER.
PULMICORT TURBUHALER M3, new device. PULMICORT TURBUHALER M0-ESP, current device.
Data derived from Table 11.2.1.2.1, Section 11.2.

Compared to the mean increase of 0.1 L in the placebo group, the increases from baseline were statistically significantly higher for the PULMICORT TURBUHALER M3 360 µg bid group (mean increase of 0.28 L, p<0.001), PULMICORT TURBUHALER M0-ESP 400 µg bid group (mean increase of 0.34 L, p<0.001), and the PULMICORT TURBUHALER M0-ESP 200 µg qd group (mean increase of 0.25 L, p<0.001). The difference from placebo approached significance for the PULMICORT TURBUHALER M3 180 µg qd group (mean increase of 0.18 L, p=0.078).

Comparability between the high-dose groups of PULMICORT TURBUHALER M3 and PULMICORT TURBUHALER M0-ESP was established with a difference between groups of -0.06 L and an associated 95% confidence interval of -0.14 L to 0.02 L 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 -0.07 L and an associated 95% confidence interval of -0.16 L to 0.01 L for the PULMICORT TURBUHALER M3 minus PULMICORT TURBUHALER M0-ESP.

Results of the analysis of secondary efficacy variables indicated statistically significant differences between the active treatment groups and placebo for: $FEF_{25\%-75\%}$ (except for the PULMICORT TURBUHALER M3 180 µg qd group), morning PEF, evening PEF, daytime asthma symptoms, nighttime asthma symptoms, and daily rescue medication use.

Predefined asthma-related discontinuation criteria were based on data recorded in the daily diary and the results of pulmonary function tests. For this variable, the earliest date at which a subject met any criterion for a predefined asthma-related discontinuation event was used to determine the time from randomization to the first predefined asthma-related discontinuation event. The percentage of subjects who met criteria for predefined asthma-related discontinuation during the study ranged from 14.6% to 29.2% of subjects in the active treatment groups compared to 47.9% of the subjects in the placebo group. There were statistically significant differences (log rank test) in favor of each active treatment group when compared to the placebo group.

Mean baseline $FEV_1$ values were lower in the subgroup of patients from sites in Asia compared to the sites in the US whether expressed as the measured value or as a percent of the predicted value. Pulmonary function (mean $FEV_1$) improved in all groups compared to placebo in both geographic subgroups (US and Asia), although the profile across doses was different. In the US sites PULMICORT TURBUHALER M0-ESP 200 μg qd improved $FEV_1$ by 0.30 L and PULMICORT TURBUHALER M0-ESP 400 μg bid improved $FEV_1$ by 0.41 L. The corresponding improvements for PULMICORT TURBUHALER M3 180 μg qd and PULMICORT TURBUHALER M3 360 μg bid were 0.20 L and 0.34 L, respectively. The corresponding change in the US placebo group was 0.14 L. Sample sizes per treatment group were approximately twice as large in the US than in Asia. All treatment groups from Asian sites improved $FEV_1$, without evidence of a substantial difference between doses. The $FEV_1$ changes for PULMICORT TURBUHALER M0-ESP 200 μg qd and PULMICORT TURBUHALER M0-ESP 400 μg bid from the Asian subgroups were 0.19 L and 0.23 L, respectively, whereas the corresponding changes for the PULMICORT TURBUHALER M3 180 μg qd and PULMICORT TURBUHALER M3 360 μg bid groups were 0.19 L and 0.21 L, respectively. The mean $FEV_1$ change in the placebo group from Asian sites was 0.07 L. When a treatment by region interaction term was included in an analysis model, the p-value for the interaction term was 0.40. The results were generally consistent between the ITT population and the per-protocol (PP) population, regardless of whether analysis was conducted on data with LOCF used or if only observed data were used. There was statistically significant improvement in all treatment groups compared to placebo, based on the PP population.

A total of 77 subjects participated in the PK analyses. Due to the high degree of variability in budesonide plasma concentrations, it is difficult to make any definitive conclusions about the comparability of systemic exposure for PULMICORT TURBUHALER M3 versus PULMICORT TURBUHALER M0-ESP. The primary analysis of all treated subjects indicated that systemic exposure to budesonide was generally similar between PULMICORT TURBUHALER M3 and 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 307 subjects reported AEs during the study: 55 subjects (42.3%) in the PULMICORT TURBUHALER M3 360 µg bid group; 71 subjects (54.6%) in the PULMICORT TURBUHALER M0-ESP 400 µg bid group; 58 subjects (47.2%) in the PULMICORT TURBUHALER M3 180 µg qd group; 60 subjects (52.6%) in the PULMICORT TURBUHALER M0-ESP 200 µg qd group; and 63 subjects (50.8%) in the placebo group.

There were no reported deaths or OAEs in this study. The most frequently occurring AEs in subjects in the safety analysis set during the randomized treatment period were headache, nasopharyngitis, asthma, upper respiratory tract infection, and pharyngolaryngeal pain. 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. Twenty-two subjects (3.5%) 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 the majority were of mild or moderate intensity.

Two 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 drug-related. Twenty-six subjects had a total of 29 DAEs, 6 of which were considered by the investigator to be 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 the placebo. For hematology parameters there were no clinically concerning changes from baseline or differences across treatment groups. There were no meaningful treatment group differences in shifts in individual subject data (using standard and extended reference ranges) at any visit. For systolic or diastolic blood

pressure, pulse rate and weight, results of the ANCOVA analysis of mean change from baseline showed no clinically concerning changes or treatment group differences. There were no physical exam or vital sign findings of concern across treatment groups.

Overall, PULMICORT TURBUHALER M3 was well tolerated when used in the treatment of asthma in adult subjects. No new safety concerns were identified. No difference in the safety profile of PULMICORT TURBUHALER M3 and PULMICORT TURBUHALER M0-ESP was observed.