AstraZeneca

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| DRUG PRODUCT<br>DRUG SUBSTANCE(S) Budesonide<br>DOCUMENT NO. SD-004-CR-0210<br>VERSION NO. 01<br>STUDY CODE SD-004-0210<br>DATE 15 December, 2000 | | **Synopsis**<br>REFERRING TO PART OF THE DOSSIER | (FOR NATIONAL AUTHORITY USE ONLY) |

FINAL

# Efficacy and safety of Pulmicort® (budesonide) via Turbuhaler®, new version, in corticosteroid-using adult asthmatic patients

## INVESTIGATOR

## STUDY CENTRE(S)

| **Country**: | **Center numbers:** |
|---|---|
| Czech Republic | 101-107 |
| France | 201-213 |
| Israel | 301-305 |
| Poland | 401-434 |
| Hungary | 501-504 |
| South-Africa | 601-610 |

## PUBLICATION (REFERENCE)

N/A

| **STUDY PERIOD** | | **PHASE OF DEVELOPMENT** |
|---|---|---|
| - **DATE OF FIRST PATIENT ENROLLED** | November 1, 1999 | Phase IIIA |
| - **DATE OF LAST PATIENT COMPLETED** | June 21, 2000 | |

## OBJECTIVES

The primary objective of the study was to compare the efficacy of 80 $\mu$g and 480 $\mu$g delivered dose b.i.d. budesonide (BUD) via Turbuhaler® new version (NV) with 100 $\mu$g and 600 $\mu$g metered dose b.i.d. BUD Turbuhaler current version (CV) in inhaled corticosteroid-using, adult asthmatic patients.

The secondary objective was to determine the safety of the doses of budesonide used in this study.

**STUDY DESIGN**

The study was designed as a double-dummy, double-blind, randomised, parallel group, multicentre study in inhaled corticosteroid-treated adult patients with moderate to severe asthma. After a two week run-in period all patients that fulfilled all the inclusion criteria and none of the exclusion criteria were randomised into a 12-week treatment period where they received either 80 or 480 $\mu$g of budesonide b.i.d via Turbuhaler new version or 100 or 600 $\mu$g budesonide b.i.d. via Turbuhaler current version.

**DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION**

Major inclusion criteria:

- An initial diagnosis of asthma
- A history of being prescribed inhaled steroids at least 6 months before visit 1. The daily inhaled dose had to be within the range of 500 - 1200 $\mu$g (BUD Turbuhaler or fluticasone propionate any inhalation device) or 750 - 1600 $\mu$g of other inhaled steroids. The dose had to be fixed for at least the last 30 days prior to visit 1
- $FEV_1$ (L) before inhalation of $\beta_2$-agonist at visit 1 had to be 50-80% of predicted normal value

Randomisation criteria:

- Morning PEF data recorded on at least 7 of the last 10 days of the run-in period
- $FEV_1$ (L) before inhalation of $\beta_2$-agonist had to be 50-80% of predicted normal value or within 10% of the absolute $FEV_1$-value (L) at visit 1
- A reversible airway obstruction of 200 mL and ≥ 12% of basal $FEV_1$-value

Major exclusion criteria:

- Patients with unstable asthma as defined by:

  a. hospitalization or emergency room treatment for uncontrolled asthma during the last 6 months prior to visit 1, or
  b. use of oral or parenteral GCS during the last 60 days prior to visit 1

- Current or previous tobacco smokers with a history of ≥ 10 pack-years

## TEST AND COMPARATOR PRODUCTS, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

| Treatment (daily doses) | Turbuhaler No. 1 | Turbuhaler No. 2 | Turbuhaler No. 3 | Turbuhaler No. 4 | Batch No. |
|---|---|---|---|---|---|
| 160 $\mu$g BUD NV | 1 x 80 $\mu$g NV | 1 x placebo NV | 1 x placebo CV | 1 x placebo CV | BUD NV 80: ZI 13/1<br>Placebo NV: AH 11/1<br>Placebo CV: AD 32 |
| 960 $\mu$g BUD NV | 1 x 320 $\mu$g NV | 1 x 160 $\mu$g NV | 1 x placebo CV | 1 x placebo CV | BUD NV 160: ZI 21/1<br>BUD NV 320: ZI 33/I<br>Placebo CV: AD 32 |
| 200 $\mu$g BUD CV | 1 x placebo NV | 1 x placebo NV | 1 x 100 $\mu$g CV | 1 x placebo CV | BUD 100 CV: AB 364<br>Placebo NV: AH 11/1<br>Placebo CV: AD 32 |
| 1200 $\mu$g BUD CV | 1 x placebo NV | 1 x placebo NV | 1 x 400 $\mu$g CV | 1 x 200 $\mu$g CV | BUD CV 200: AD 1102<br>BUD CV 400: AA 640<br>Placebo NV: AH 11/1 |

## DURATION OF TREATMENT

The run-in period between visits 1 and 2 was two weeks long. The treatment period between visits 2 and 5 was 12 weeks long with approximately four weeks between visits. The total number of treatment days during the randomised period was not allowed to exceed 90 days.

## MAIN VARIABLE(S):

- **EFFICACY**

- Primary: morning PEF (peak expiratory flow) registered daily in diary cards
- Secondary: $FEV_1$ (forced expiratory volume in one second), FVC (forced vital capacity), evening PEF, asthma symptoms and $\beta_2$-agonist usage

- **SYSTEMIC ACTIVITY**

- Plasma-cortisol measurements

- **SAFETY**

AE (Adverse Event) assessment

## STATISTICAL METHODS

An Intention-To-Treat type of analysis was used with all available data. The primary endpoint, change from baseline to end of treatment, was analysed by an analysis of variance model with fixed factors treatment and country. For diary variables, baseline was the mean during the last 14 days of run-in and end of treatment was the mean during the last 60 days of treatment period. For spirometric variables, baseline was the value measured at visit 2 and end of treatment was the mean value from visits 3-5.

## PATIENTS

| | New version b.i.d. | | Current version b.i.d. | | |
|---|---|---|---|---|---|
| | 80 μg | 480 μg | 100 μg | 600 μg | Total |
| **No. of planned evaluable pts** | 125 | 125 | 125 | 125 | 500 |
| **No randomized and treated** | 148 | 145 | 147 | 149 | 589 |
| Females/Males | 93/55 | 88/57 | 73/74 | 84/65 | 338/251 |
| Mean age (range) | 42.8 (19-68) | 43.9 (18-74) | 43.7 (18-73) | 43.8 (19-70) | 43.6 (18-74) |
| **Baseline values:**<br>Inhaled GCS dose (μg/day) | 885 | 888 | 889 | 904 | 892 |
| $FEV_1$ (% of predicted) | 69.2 | 69.7 | 70.1 | 69.0 | 69.5 |
| Reversibility (%) | 25.5 | 23.8 | 24.2 | 231 | 24.2 |
| **No. analysed for efficacy** | 148 | 145 | 147 | 149 | 589 |
| **No. analysed for safety** | | | | | |
| **No. completed** | 135 | 132 | 134 | 137 | 538 |

## SUMMARY - CONCLUSION(S)

### - EFFICACY RESULTS

The primary objective of the study was to compare the efficacy of budesonide delivered via Turbuhaler® CV and NV by means of their Relative Dose Potency, RDP. With morning PEF the estimated relative dose potency did not differ statistically significantly from 1. The RDP was estimated to 2, with 95% confidence intervall (0.7, 11.08). As the confidence intervall covers 1, there is no evidence of a difference in dose potency between the Turbuhaler devices. A difference in RDP could not be detected for any of the secondary variables.The dose response slope was statistically significantly different from 0 for all variables, i.e. a dose response was established. In the Table below the estimated contrasts from ANOVA for change in morning PEF are shown.

| Parameter | Contrast | Mean | 95% CL | P-value |
|---|---|---|---|---|
| Morning PEF (L/min) | NV 80 μg bid | -5.09 | -12.49 - 2.31 | |
| | NV 480 μg bid | 8.73 | 1.21 - 16.26 | |
| | CV 100 μg bid | 1.21 | -6.21 - 8.63 | |
| | CV 600 μg bid | 11.70 | 4.32 - 19.08 | |
| | NV 80 μg bid vs CV 100 μg bid | -6.30 | -16.12 - 3.52 | 0.2083 |
| | NV 480 μg bid vs CV 600 μg bid | -2.97 | -12.79 - 6.86 | 0.5531 |
| | NV 480 μg bid vs NV 80 μg bid | 13.82 | 3.96 - 23.69 | 0.0061 |
| | CV 600 μg bid vs CV 100 μg bid | 10.49 | 0.70 - 20.28 | 0.0358 |

- **SYSTEMIC ACTIVITY RESULTS**

The RDP for the plasma cortisol measurements was estimated in the same manner as for the efficacy variables. Again, the RDP did not differ statistically significantly from 1. In the Table below the estimated contrasts from ANOVA for P-cortisol (%of baseline) are shown.

| Parameter | Contrast | Mean | 95% CL | P-value |
|---|---|---|---|---|
| | NV 80 μg bid | 102.31 | 92.92 - 112.65 | |
| P-Cortisol | NV 480 μg bid | 91.25 | 82.60 - 100.81 | |
| (% of baseline) | CV 100 μg bid | 95.88 | 87.13 - 105.51 | |
| | CV 600 μg bid | 88.23 | 80.32 - 96.93 | |
| | NV 80 μg bid vs CV 100 μg bid | 106.71 | 94.11 - 120.99 | 0.3106 |
| | NV 480 μg bid vs CV 600 μg bid | 103.42 | 91.29 - 117.16 | 0.5963 |
| | NV 480 μg bid vs NV 80 μg bid | 89.19 | 78.59 - 101.23 | 0.0766 |
| | CV 600 μg bid vs CV 100 μg bid | 92.03 | 81.31 - 104.16 | 0.1879 |

- **SAFETY RESULTS**

- The nature and frequency of AEs were similar between the different treatment groups.
- No deaths were reported during the study.
- All of the 12 SAEs reported during randomised treatment were considered unrelated to the investigational product. The SAEs were evenly distributed in the different treatment groups.
- Twenty-two patients discontinued treatment due to AE DUS deteriorated, and eight due to other AEs. The DAEs were similarly distributed between the treatment groups.

**DATE OF THE REPORT**

15 December, 2000