AstraZeneca

**STUDY REPORT SUMMARY**

**ASTRAZENECA PHARMACEUTICALS**

**FINISHED PRODUCT:** Symbicort Turbuhaler®

**ACTIVE INGREDIENT:** Budenosid

| **Study No: D5890L00016** |
|---|
| A comparison of Symbicort Single inhaler Therapy (Symbicort Turbuhaler 160/4.5 µg, 1 inhalation b.i.d. plus as needed) and conventional best practice for the treatment of persistent asthma in adults - a 26-week, randomised, open-label, parallel-group, multicentre study – **PASSION Study** |

**Developmental phase:** Therapeutic confirmatory (IIIb)

**Study Completion Date:** 18 September 2008

**Date of Report:** 02 September, 2009

**OBJECTIVES:**

Primary objective

The primary objective was to compare the efficacy of Symbicort Turbuhaler 160/4.5 µg, 1 inhalation b.i.d. plus as needed (SMART) with treatment according to conventional best practice (CBP) in adult patients with persistent asthma.

Secondary objective

A secondary objective was to collect safety data for treatment in the two treatment groups in adult patients with persistent asthma.

**METHODS:**

The study was a randomized, open, parallel-group, multicentre study

**Diagnosis and patient selection criteria**

The study was carried out in patients diagnosed with diagnosis of persistent asthma.

Inclusion criteria: The following criteria were to have been fulfilled:

1. Signed informed consent form.
2. Ability to read and write in Turkish.
3. Female or male outpatients aged ≥18 years.
4. Minimum of 3 months history of asthma, diagnosed according to the American Thoracic Society (ATS) definition (9).

5. Prescribed inhaled GCS at a dose of ≥320 µg/day and within the approved label for the relevant drug during the last 3 months prior to Visit 1.
6. Daily maintenance treatment with both inhaled GCS and long-acting $\beta_2$-agonist (LABA) ***or*** daily treatment with inhaled GCS alone (i.e. without LABA) **and** a history of suboptimal asthma control the month prior to enrolment as judged by the investigator **and** use of ≥3 inhalations of as needed medication for symptom relief during the last 7 days before enrolment.

Exclusion criteria: None of the following criteria were to have been fulfilled:

1. Previous treatment with Symbicort Single inhaler Therapy (use of Symbicort Turbuhaler for both maintenance treatment and as needed in response to symptoms as described in Section 3.4.2 of the protocol).
2. Use of any β-blocking agent, including eye-drops.
3. Use of oral GCS as maintenance treatment.
4. Known or suspected hypersensitivity to study therapy or excipients.
5. A history of smoking ≥ 10 pack years (1 pack year = 1 pack (20 cigarettes) per day for one year or equivalent).
6. Pregnancy, breast-feeding or planned pregnancy during the study. Fertile women not using acceptable contraceptive measures, as judged by the investigator.
7. Any significant disease or disorder, which, in the opinion of the investigator, may put the patient at risk because of participating in the study.
8. Any non-asthma related, clinically significant abnormal finding in physical examination and/or vital signs at Visit 1, which in the opinion of the investigator, may put the patient at risk because of his/her participation in the study.
9. Asthma exacerbation requiring change in asthma treatment during the last 14 days prior to or at Visit 1.
10. Planned in-patient hospitalisation during the course of the study.
11. Suspected poor capability to follow instructions of the study, e.g. because of a history of drug abuse, difficulty in reading and/or understand instructions or any other reason, as judged by the investigator.
12. Previous allocation of randomisation code in this study.
13. Participating in another clinical trial during the course of this study or within 30 days prior to Visit 1.
14. Involvement in the planning or conduct of this study.

**Duration of treatment**

26 weeks

**Study design**

This is a 26-week, randomised, open-label, parallel group study. Patients were randomised to one of the following two treatment groups in a balanced (1:1) way:

- Symbicort 160/4.5µg, 1 inhalation b.i.d. + as needed (in response to symptoms). Titration of the maintenance dose to 2 inhalations b.i.d and back to 1 inhalation b.i.d, and/or addition of one other class of asthma controller medication (as specified) is allowed after study visit one according to the investigators judgment.
- Conventional best practice, active stepwise individualized treatment according to asthma treatment guidelines.

There were additional unscheduled visits at the initiative of physician and/or subject were allowed.

| | | | | |
|---|---|---|---|---|
| | Symbicort Turbuhaler 160/4.5µg b.i.d. + as needed (change in treatment allowed after visit1, as described in 3.3.3. of the protocol) | | | |
| | Conventional best practice, active stepwise treatment according to asthma treatment guidelines. | | | |
| | **?** | **?** | **?** | **?** |
| **Week** | **0** | **4** | **13** | **26** |
| **Visit** | **1** | **2** | **3** | **4** |

**Main variables**

Efficacy: Time to first severe asthma exacerbation was the primary outcome variable while number of severe asthma exacerbations, mean use of as-needed medication and prescribed asthma medication were the secondary outcome variables for the efficacy.

Safety: Safety was assessed from SAEs and discontinuations due to AEs recordings performed at each visit.

Patient-reported outcome (PRO): Asthma Quality of Life Questionnaire, Standardized Version [AQLQ(S)], developed to evaluate the impact of asthma on patients' everyday functioning and well-being was performed in each visit. The (AQLQ) (S) was self-administered at the clinic visits, before any other study related procedures take place, except at visit 1. At visit 1 the AQLQ(S) assessment was performed after signing of the informed consent.

**Statistical methods**

All efficacy analyses were based on the full analysis set, as defined in ICH E9 guidelines. Time to first severe asthma exacerbation was compared between treatments using a Cox proportional hazards model with treatment as factor. The mean number of severe asthma exacerbations per patient was compared between treatments using a Poisson regression model. Safety data were analysed by means of descriptive statistics.

**Patients**

According to patient flow data shown in Table 1, from 432 subjects initially enrolled inthe study, two (0.5%) were not included in analysis population since they did not fulfill

all subject selection criteria (one of them did not sign informed consent and the other was younger than 18 years of age) (Ttable 1). Therefore study population was composed of 430 patients with persistent asthma including 94 males (21.9%) and 336 females (78.1%) with mean age of 44.7±12.4 years.

**Table 1.** Patient flow

| | **SMART** | **CBP** | **Total** |
|---|---|---|---|
| **Enrolled patients** | | | **432** |
| **Randomized** | 209 | 221 | 430 |
| Discontinued | 44 | 42 | **86** |
| - Incorrect inclusion | 0 | 0 | **0** |
| - Severe protocol violation | 5 | 1 | 6 |
| - Adverse event | 3* | 3 | 6 |
| - Patient's voluntary withdrawal | 6 | 3 | **9** |
| - Lost to follow-up | 25 | 31 | **56** |
| - Patient's incorrect randomization | 0 | 0 | 0 |
| - Other reason | 4** | 3*** | 7 |
| - Unknown / Unreported | 1 | 1 | 2 |
| **Completers** | 165 | 179 | **344** |

* one death
** one pregnancy, three "investigator moved away"
*** one pregnancy, two treatment failure

## RESULTS

## EFFICACY RESULTS

The results indicate that the treatment groups were well matched at entry with respect to disease history and patient characteristics. The primary efficacy variable was the time to first severe asthma exacerbation

### Primary efficacy variable

- **Time to first severe asthma exacerbation**:

  Time to severe exacerbation among patients were 104 and 120 days in CBP group and SMART group, respectively (the difference was not significant**).**

### Secondary efficacy variables

- **Number of severe asthma exacerbations**

Severe exacerbation (defined as either hospitalization for at least one day or treated with oral steroid for at least 3 days) happened in 10 patients in each study groups (10 of 221: 4.5% in CBP group and 10 of 209: 4.8% in SMART groups). Average number of severe astma exacerbations experienced during the course of study were similar in CBP and SMART groups (1.09±0.3 vs 1.18±0.4; among 4.8 vs 4.5% of subjects, respectively; $p>0.05$). Proportions of patients treated with oral steroid for at least 3 days (among

criteria of severe exacerbation) were similar also (5 of 221: 2.3% in CBP group and 7 of 209: 3.3% in SMART groups). Time to steroid treatment in these patients were 86 and 90 days in CBP group and SMART group, respectively (the difference was not significant). Proportions of patients hospitalized for at least one day (among criteria of severe exacerbation) were similar also (7 of 221: 3.2% in CBP group and 6 of 209: 2.9% in SMART groups). Time to hospitalization in these patients were 125 and 142 days in CBP group and SMART group, respectively (the difference was not significant).

**Table 2.** Efficacy parameters

| **Number and incidence of severe asthma exacerbations** [a] | | **n** | **% AEs** |
|---|---|---|---|
| **CBP** | **No** | 211 | 95.5% |
| | **Yes** | 10 | 4.5% |
| | **Mean number** [e] | 1.09±0.3 | |
| **SMART** | **No** | 199 | 95.2% |
| | **Yes** | 10 | 4.8% |
| | **Mean number**[e] | 1.18±0.4 | |
| **Time to first severe asthma exacerbation** | | | |
| **CBP** | Mean±SD | 103.7± 71.0 days | |
| **SMART** | Mean±SD | 120.3± 73.3 days | |
| **Oral steroid treatment for at least 3 days**[b] | | | |
| **CBP** | **No** | 216 | 97.7% |
| | **Yes** | 5 | 2.3% |
| | **Time to treatment** | 85.6±56.4 days | |
| **SMART** | **No** | 202 | 96.7% |
| | **Yes** | 7 | 3.3% |
| | **Time to treatment** | 90.4±67.0 days | |
| **Hospitalization for at least one day**[d] | | | |
| **CBP** | **No** | 214 | 96.8% |
| | **Yes** | 7 | 3.2% |
| | **Time to hospitalization** | 125 days | |
| **SMART** | **No** | 203 | 97.1% |
| | **Yes** | 6 | 2.9% |
| | **Time to hospitalization** | 142 days | |

*[a-d]Chi-square ($?^2$) test; [e]Mann-Whitney U test; p>0.05*

**SAFETY RESULTS**

There was not any significant difference with regards to frequencies of adverse events (AE) in study groups. Totally 76 AEs occurred in 50 patients (22.6%) and 73 AEs occurred in 46 patients (22.0%) in CBP group and SMART group. Most of the patients in the CBP (16.3% among all patients and 72.0% among patients with AEs) and SMART (13.4% among all patients and 60.9% among patients with AEs) groups experienced an adverse event only for once during the course of the study.

Serious adverse event incidence was similar between CBP and SMART groups (1% among all patients and 4.0-4.3% among patients with AEs). Reason for seriousness was requiring or prolongation of hospitalization (n=2) in the CBP and death (n=1) and requiring or prolongation of hospitalization (n=1) in SMART group.

**Table 3.** Safety parameters

| | | | n | % all pts | % pts with AEs |
|---|---|---|---|---|---|
| **Adverse event occurred** | | | | | |
| **Conventional Best Treatment (CBP)** | | | 76 AEs/50 pts | 22.6% | |
| **SMART** | | | 73 AEs/46 pts | 22.0% | |
| **Serious AEs** | | | | | |
| **CBP** | Total number | | 2 | 1.0% | 4.0% |
| | Reason | Requiring or prolongation of hospitalization | 2 | | |
| **SMART** | Total number | | 2 | 1.0% | 4.3% |
| | Reason | Death | 1 | 0.5% | 2.1% |
| | | Requiring or prolongation of hospitalization | 1 | | |

*p>0.05; Chi-square test($?^2$)*

**Note:** The data from PASSION Study will be pooled with SPAIN* Study which is similar in design and primary objective and statistical analysis will be performed in Spain*.

** A comparison of Symbicort Single inhaler Therapy (Symbicort Turbuhaler 160/4.5 mg, 1 inhalation b.i.d. plus as needed, SMART) and conventional best practice for the treatment of persistent asthma in adults: A 26 week, randomised, open-label, parallel group, multicentre study- SPAIN Study.*