| | | | |
|---|---|---|---|
| Drug product: | Symbicort Forte | **SYNOPSIS** | |
| Drug substance(s): | Budesonide/formoterol | | |
| Edition No.: | 1.0 | | |
| Study code: | D5892L00002 | | |
| Date: | 16 April 2008 | | |

# A randomised, double blind, double dummy, multicentre phase III study comparing the efficacy of budesonide/formoterol (Symbicort® forte Turbuhaler®) and oral prednisolone + formoterol (Oxis® Turbuhaler) during two weeks, in COPD patients with an acute exacerbation, followed by twelve weeks open follow up period with budesonide/formoterol (Symbicort forte Turbuhaler) - SPACE

**Study centre(s)**

This was a multicentre study conducted in Sweden (14 centres), Denmark (6 centres), Germany (5 centres), Norway (2 centres) and Finland (2 centres). A total of 29 centres have participated.

**Publications**

None at the time of writing this report.

| **Study dates** | | **Phase of development** |
|---|---|---|
| **First patient enrolled** | *15 September 2005* | Therapeutic confirmatory (III) |
| **Last patient completed** | *11 July 2007* | |

**Objectives**

**Primary objective**

To assess if a double standard dose of Symbicort forte Turbuhaler was as effective as an oral course of prednisolone + Oxis Turbuhaler for the treatment, of an acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD) - during a two week period.

**Secondary objective**

To assess if disease control was equally well established during twelve weeks follow up treatment with Symbicort forte Turbuhaler following the two weeks acute treatment.

**Study design**

This was a randomised, double blind, double dummy, parallel-group, multicentre study comparing the efficacy and safety of Symbicort forte Turbuhaler (1280/36 µg/day) with oral prednisolone (30 mg/day) + Oxis Turbuhaler (18 µg/day) during two weeks when given to COPD patients with an acute COPD exacerbation followed by a twelve week open follow up period where all patients received Symbicort forte Turbuhaler (640/18 µg/day).

**Target patient population and sample size**

Male and female patients aged 40 years and older with moderate to severe COPD and with a history (within the last week) of progressing dyspnoea and/or increase in sputum production and/or volume, Forced Expiratory Volume in one second ($FEV_1$) of 30-60% of predicted normal value after initial standardised acute treatment at the primary care/hospital centres.

**Investigational product and comparator(s): dosage, mode of administration and batch numbers**

Treatment during the two week double blind treatment (DOB) period consisted of:

Budesonide/formoterol fumarate dehydrate (Symbicort forte Turbuhaler 320µg/9 µg per inhalation)(batch numbers: HD492, GI354, FM221, GE289) four times daily and placebo (batch numbers: HD13, FD12) for two weeks

or

Prednisolone (Prednisolon Recip, 30mg oral tablets)(batch numbers: RF418A, RF1310A) once daily (batch numbers:RF1310PA; RF1412PA) and formoterol fumarate dehydrate (Oxis Turbuhaler 9µg per inhalation) (batch numbers: FH30, HD33) and placebo (batch numbers: FH39, HD52) twice daily for two weeks

Doses were given in a double-dummy fashion owing the difference in route of administration.

Ipratropiumbromide 40 µg/inhalation (Atrovent® Boehringer Ingelheim )(batch numbers: 501921, 506126, 506916) was used as reliever medication for two weeks.

Treatment during the 12 week follow up treatment (follow up) period consisted of:

Budesonide/formoterol fumarate dehydrate (Symbicort forte Turbuhaler 320µg/9 µg per inhalation) twice daily for 12 weeks plus inhaled terbutalin/salbutamol or ipratropiumbromide as reliever medication.

**Duration of treatment**

A randomised double blind treatment period of 2 weeks was followed by a follow up period of 12 weeks.

**Criteria for evaluation (main variables)**

**Efficacy and pharmacokinetics**

- Primary variable: Forced Expiratory Volume during 1 second ($FEV_{1)}$ (mean of Visits 2 and 3 during the two weeks double blind treatment period)
- Secondary variables:
  - $FEV_1$ (at each visit)
  - daily morning and evening Peak Expiratory Flow (PEF) and $FEV_1$ (home measurements)
  - number of patients with treatment failures (defined as requirement for additional treatment on top of study treatment, except antibiotics and reliever medication) during the DOB period
  - time to first exacerbation (defined as worsening of COPD that required a course of oral steroids for treatment and/or hospitalisation) during the twelve week open follow up period
  - number of patients developing an exacerbation (defined as worsening of COPD that required a course of oral steroids for treatment and/or hospitalisation) during the twelve week open follow up period

**Patient reported outcomes (PROs):**

- Diary cards with COPD symptom scores and use of reliever medication
- Clinical COPD Questionnaire (CCQ) (at each visit)
- St. George´s Respiratory Questionnaire (SGRQ) at Visits 3 and 4

**Safety**

- Adverse Events (AEs) during the DOB period
- Serious Adverse Events (SAEs) and Discontinuation due to Adverse Events (DAEs) (at each visit)
- Vital signs (pulse and blood pressure, at each visit)
- Physical examination (at each visit)

## Statistical methods

The primary non-inferiority analysis was done on the full analysis set (FAS). In addition a Per-Protocol (PP) analysis of the primary efficacy variable was performed. In the PP analysis all patients included in the FAS with confirmed $FEV_1$ measurements (at Visits 1, 2 and 3) were included except those with major protocol violations.

The analysis was performed by log transforming $FEV_1$ as % predicted using a ANCOVA model with centre as factor and log-transformed baseline $FEV_1$ as % of predicted as a covariate. The Least-Squared Means resulting from this model was used to calculate the one-sided 97.5% confidence interval for the log-transformed difference between the treatments: log (Symbicort forte Turbuhaler) minus log (prednisolone+Oxis Turbuhaler). The lower limit given the equivalence limit was, in this calculation, selected to be 90% and this value was rather arbitrary selected without pinpointing this value as a general applicable difference.

## Patient population

In total 113 patients from 29 centres were randomised. Of the 113 patients 58 were randomized to treatment with budesonide/formoterol and 55 to treatment with prednisolone + formoterol. 109 were included in the FAS analysis and 84 in the Per Protocol(PP) analysis.

There were more female patients in the budesonide/formoterol group and consequently their FEV (L) and PEF were lower. In the same treatment group the s-CRP was higher at baseline. Otherwise no important differences were seen between the two groups.

The patients included were given an acute treatment at the clinic before being enrolled into the study. After the first two weeks with treatment in the double-blind period all patients continued with 12 weeks follow-up on Symbicort forte Turbuhaler.

There were no important differences between the study groups neither in previous maintenance medications nor in the acute treatment before study entry.

**Table S1 Patient disposition, safety analysis set**

| | **Budesonide/ formoterol** | **Prednisolone + formoterol** | **Total** |
| --- | --- | --- | --- |
| Number of patients enrolled | | | 113 |
| Number of patients randomised | 58 | 55 | 113 |
| Number of patients in full analysis set (FAS) | 55 | 54 | 109 |
| Number (%) of patients who discontinued during the study | 17 (29.3) | 10 (18.2) | 27 (23.9) |
| Reasons for discontinuation: n (%) | | | |
| Incorrect Randomization | 2 (3.4) | 3 (5.5) | 5 (4.4) |
| Severe Non-Compliance to protocol | 1 (1.7) | 0 (0.0) | 1 (0.9) |
| Safety reasons (Treatment failures) | 2 (3.4) | 0 (0.0) | 2 (1.8) |

## Table S1 Patient disposition, safety analysis set

| | Budesonide/ formoterol | Prednisolone + formoterol | Total |
|---|---|---|---|
| Development of Study-Specific Discontinuation Criteria | 5 (8.6) | 1 (1.8) | 6 (5.3) |
| Voluntary discontinuation by Patient | 3 (5.2) | 1 (1.8) | 4 (3.5) |
| Other | 4 (6.9) | 5 (9.1) | 9 (8.0) |
| Number (%) of patients who completed the study | 41 (70.7) | 45 (81.8) | 86 (76.1) |

Note: Percentages calculated for each reason are based on the number of patients randomised
SOURCE DOCUMENT: DISPOSITION.SAS GENERATED: 10:32:10 13SEP2007 DB version DEV: D5892L00002

## Table S2 Demographic details and baseline characteristics, Full Analysis Set

| | Budesonide/ formoterol (FAS=55) | Prednisolone + formoterol (FAS=54) | Total (FAS=109) |
|---|---|---|---|
| Sex , n (%) | | | |
| Male | 25 (45) | 31 (57) | 56 (51) |
| Female | 30 (55) | 23 (43) | 53 (49) |
| Age (years) | | | |
| n | 55 | 54 | 109 |
| Mean (SD) | 67.2 (9.7) | 66.7 (9.3) | 66.9 (9.5) |
| Median | 70.2 | 66.2 | 68.7 |
| Range | 40 , 85 | 45 , 84 | 40 , 85 |
| Smoking Status: n (%) | | | |
| Ex-Smoker | 35 (64) | 35 (65) | 70 (64) |
| Occasional Smoker | 2 (3.6) | 4 (7.4) | 6 (5.5) |
| Habitual Smoker | 18 (33) | 15 (28) | 33 (30) |
| Number of pack years: (y) | | | |
| Mean (SD) | 33.2 (18.4) | 33.4 (15.2) | 33.3 (16.8) |
| Time with diagnose: (y) | | | |
| Mean (SD) | 8.0 (5.7) | 5.9 (4.3) | 7.0 (5.1) |
| Body Mass Index ($kg/m^2$) | | | |
| Mean (SD) | 25.2 (4.8) | 26.0 (5.3) | 25.6 (5.1) |
| $FEV_1$ (L) | | | |
| Mean (SD) | 1.16 (0.34) | 1.23 (0.37) | 1.19 (0.36) |
| $FEV_1$ (% of predicted normal) | | | |
| Mean (SD) | 45.05 (8.91) | 45.00 (9.48) | 45.02 (9.15) |
| $FEV_1$/ FVC ration | | | |
| Mean (SD) | 0.49 (0.12) | 0.51 (0.11) | 0.50 (0.11) |
| CCQ overall, scores | | | |
| Mean (SD) | 3.27 (0.93) | 3.33 (1.00) | 3.30 (0.96) |

SOURCE DOCUMENT: KAP6_DEMO.SAS GENERATED: 11:13:11 13SEP2007 DB version DEV: D5892L00002

Data derived from Table 54, Table 62, Table 63, and Table 67 .

**Efficacy results**

The treatment with budesonide/formoterol was found to be non-inferior to treatment with prednisolone + formoterol, when measured as change in $FEV_1$ from Visit 1 to mean of Visits 2 and 3.

The treatment with budesonide/formoterol was also found to be non-inferior to treatment with prednisolone + formoterol when compared as change in $FEV_1$ from Visit 1 to Visits 2 and 3 respectively.

The mean $FEV_1$ values measured at home twice daily during the DOB period showed no statistically significant difference between the two treatment groups. Neither did the PEF values recorded at the same time.

There were two treatment failures during the DOB period. Both occurred in the budesonide/formoterol group.

During the follow period there were 11 patients with 14 exacerbations (1 hospitalisation) in the group previously treated with budesonide/formoterol and 10 patients with 14 exacerbations (3 hospitalisations) in the group previously treated with prednisolone + formoterol. The difference was not statistically significant.

There were no statistically significant differences in COPD symptom scores, use of reliever medication, CCQ and SGRQ scores between the two treatment groups.

**Table S3 Primary objective. Change in $FEV_1$ (% of predicted normal) from Visit 1 to mean of Visits 2 and 3 measured at clinic, FAS**

| | **Budesonide/ formoterol (FAS=55) Baseline** | **Change** | **Prednisolone + formoterol (FAS=54) Baseline** | **Change** |
|---|---|---|---|---|
| $FEV_1$ (% of predicated) | | | | |
| n | 55 | | 54 | |
| Geometric mean (CV) | 44.2 (5.3) | 2.46 | 44.0 (5.7) | 2.46 |
| Mean (SD) | 45.1 (8.9) | 3.0 (8.2) | 45.0 (9.5) | 2.9 (9.0) |
| Median | 44.9 | 1.6 | 43.7 | 1.5 |
| Range | 31 , 67 | -10 , 35 | 26 , 63 | -15 , 35 |
| Budesonide/formoterol vs. Prednisolone + formoterol: | Adjusted mean difference | 1-sided 97.5% CI lower limit | | |
| Value | 99.43 | 92.04 | | |

**Safety results**

AEs were only collected during the DOB period while SAEs and DAEs were collected the whole study.

15 patients in the budesonide/formoterol group had 18 AEs with different preferred terms and 14 patients in the prednisolon + formoterol group had 15 AEs with different preferred terms.

There was one death during the follow up period in a patient treated with prednisolone + formoterol during the DOB period. The death was assessed as non-related to the study treatment by the investigator..

There were 6 patients reporting SAEs not leading to death in the budesonide/formoterol group (2 of these were reported during the DOB period) and 8 in the prednisolone + formoterol group (1 of these were reported during the DOB period).

5 patients in the budesonide/formoterol group (3 during the DOB period) and 2 in the prednisolone + formoterol group (both during the follow up period) discontinued due to AE.

**Table S4 Number (%) of patients who had an adverse event in any category, safety analysis set**

| **Category of adverse event** | **Budesonide/ formoterol (N=58)** | **Prednisolone + formoterol (N=55)** | **Total (N=113)** |
| --- | --- | --- | --- |
| Number (%) | | | |
| Any Adverse events during DOB period | 15 (25.9) | 14 (25.5) | 29 (25.7) |
| Serious adverse events leading to death | | | |
| Follow up period | 0 | 1 (1.8) | 1 (0.9) |
| Serious adverse events not leading to death | | | |
| DOB Period | 2 (3.4) | 1 (1.8) | 3 (2.7) |
| Follow up period | 4 (6.9) | 7 (12.7) | 11 (9.7) |
| Discontinuation of study treatment due to adverse events | 5 (8.6) | 2 (3.6) | 7 (6.2) |
| DOB Period | 3 (5.2) | 0 | 3(2.7) |
| Follow up period | 2 (3.4) | 2 (3.6) | 4 (3.5) |
| Other significant adverse events | 0 | 0 | 0 |
| Total number of adverse events | | | |
| Any Adverse events | 18 (31.0) | 15 (27.3) | 33 (29.2) |
| Serious adverse events Total study period | 6 (10.3%) | 9 (16.4%) | 15 (13.3) |
| Other significant adverse events | 0 | 0 | 0 |

Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

**Table S5 Number (%) of patients with adverse events reported during DOB treatment, sorted by decreasing order of frequency and summarised over all treatment groups, safety analysis set**

| Preferred term | Budesonide/ formoterol (N=58) | Prednisolone + formoterol (N=55) | Total (N=113) |
| --- | --- | --- | --- |
| Preferred term | | | |
| Chronic obstructive pulmonary disease | 2 (3.4) | 0 (0) | 2 (1.8) |
| Dizziness | 0 (0) | 2 (3.6) | 2 (1.8) |
| Insomnia | 1 (1.7) | 1 (1.8) | 2 (1.8) |
| Muscle spasms | 2 (3.4) | 0 (0) | 2 (1.8) |
| Non-cardiac chest pain | 1 (1.7) | 1 (1.8) | 2 (1.8) |
| Oral candidacies | 2 (3.4) | 0 (0) | 2 (1.8) |
| Otitis media | 1 (1.7) | 1 (1.8) | 2 (1.8) |
| Palpitations | 0 (0) | 2 (3.6) | 2 (1.8) |

Events reported in more than one patient across all treatment groups are included in this table.
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