AstraZeneca

Clinical Study Report Synopsis	
Drug Substance	Budesonide/Formoterol
Study Code	D5897C00005
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An Open-label, Randomised, No-treatment-controlled, Single-centre, Phase I, Crossover Study Evaluating the Suppression of Plasma Cortisol from Symbicort® (budesonide/formoterol) pMDI 80/2.25 µg, 8 Actuations bid, versus Symbicort® Turbuhaler® 160/4.5 µg, 4 Inhalations bid, in Healthy Subjects

Study dates: First subject enrolled: 19 December 2007
Last subject completed: 11 March 2008

Phase of development: Clinical pharmacology (I)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Study centre

The study was conducted at 1 centre in Sweden: AstraZeneca Clinical Pharmacology Unit (CPU) Lund. The principal investigator was Gabriella Samuelsson Palmgren, MD. The first subject entered the study on 19 December 2007 and the last subject finished the study on 11 March 2008.

Publications

None at the time of finalising this report.

Objectives

The primary objective of the study was to demonstrate that the systemic effects of 8 actuations of Symbicort pMDI 80/2.25 µg bid are not greater than those of 4 inhalations of Symbicort Turbuhaler 160/4.5 µg bid by assessment of the average plasma cortisol (P-cortisol) concentration during 24 hours in healthy subjects on Day 7 of each treatment period.

The secondary objective of the study was to evaluate the safety and tolerability of Symbicort pMDI 80/2.25 µg by assessment of adverse events (AEs).

Study design

This was a randomised, open-label, three-period, no-treatment-controlled, crossover, single-centre study including 30 subjects.

Target subject population and sample size

Healthy subjects of either sex, aged 18 to 45 years (inclusive), who were not smokers, were included in the study. The included subjects had to have a body mass index (BMI) between ≥18 and ≤30 kg/m^2 and a body weight between ≥50 and ≤100 kg.

Based on study SD-039-0675 a residual standard deviation of 0.13 (logarithmic scale) for the P-cortisol concentrations could be expected. With 25 subjects (completed), the probability would be 90% to show equivalence between Symbicort pMDI and Symbicort Turbuhaler. This was based on a true difference of at most 10.5%. In order to achieve approximately 25 randomised subjects with complete data, a total of 30 were to be randomised.

Investigational products: dosage, mode of administration and batch numbers

Investigational products:
Symbicort pMDI (budesonide/formoterol). Batch number 07-011938AZ of Symbicort pMDI was used in the study.
Dosage: 80/2.25 µg (delivered dose), 8 actuations twice daily by inhalation

Symbicort Turbuhaler (budesonide/formoterol) (**Comparator)**. Batch number 07-012109AZ of Symbicort Turbuhaler was used in the study.
Dosage: 160/4.5 µg (delivered dose), 4 inhalations twice daily

The total daily budesonide/formoterol dose was 1280/36 µg in both treatments.

Duration of treatment

Following 2 enrolment visits, the subjects participated in 3 randomised treatment periods in a crossover fashion. All 3 treatment periods consisted of 7.5 days. The treatment periods were separated by wash-out periods of 6.5 to 22 days.

Criteria for evaluation - pharmacodynamics (main variables)

Primary variable: P-cortisol concentration during 24 hours
Secondary variable: P-cortisol concentration at 30 and 60 minutes after adrenocorticotropic hormone (ACTH) stimulation

Criteria for evaluation - safety (main variables)

AEs (nature, incidence, severity)

Statistical methods

The average P-cortisol concentration over 24 hours ($AUC_{0-24h}/24$) was compared between the treatments and analysed in a multiplicative analysis of variance (ANOVA) model with treatment, visit, and subject as fixed factors, and the baseline measurement as a covariate (log-transformed). All hypothesis testing was done using two-sided alternative hypotheses. P-values less than 5% were considered statistically significant (95% confidence interval) according to the statistical analysis plan (SAP). The equivalence limits were 0.8 to 1.25. AEs were evaluated by descriptive statistics and qualitative analysis.

Subject population

The study was planned to include 30 subjects. Thirty subjects were randomised and all of them received treatment and were analysed for both safety and pharmacodynamics. Twenty-nine subjects completed the study.

Summary of pharmacodynamic results

The results of the statistical analysis of the average 24-hour P-cortisol is given in Table S1 and Table S2. The estimated suppression after treatment was 38.9% for Symbicort pMDI, 59.7% for Symbicort Turbuhaler and 3.2% for the no-treatment period.

The ratio after/before treatment for Symbicort pMDI was larger than that for Symbicort Turbuhaler by a factor of 1.516 (95% confidence interval: 1.294 to 1.775). The factor differed significantly from 1 ($p<0.001$). Since the confidence interval did not fall within the pre-specified equivalence limits of 0.8 to 1.25, equivalence had not been established. Both active treatments depressed the average P-cortisol level more than no-treatment did (in both cases $p<0.001$).

Table S1 **Geometric mean values and ranges for the average 24-hour P-cortisol concentration (nmol/L)**

		Before treatment		Ratio after/before		Adjusted[a]	
Treatment	**n**	**Gmean**	**Range**	**Gmean**	**Range**	**ratio**	**Suppression**
Symbicort pMDI	30	207.7	145-370	0.604	0.25-1.31	0.611	38.9%
Symbicort TBH	30	204.1	144-299	0.407	0.15-0.87	0.403	59.7%
No treatment	28	205.2	122-273	0.976	0.65-1.68	0.968	3.2%

Gmean geometric mean; pMDI pressurized metered dose inhaler; TBH Turbuhaler.
[a] Adjusted for baseline and period by ANCOVA.

Table S2 **Treatment comparisons of the change from baseline in average 24-hour P-cortisol concentration (nmol/L)**

Contrast	**Estimated ratio**	**95% confidence interval**	**p-value**
pMDI vs. TBH	1.516	(1.294, 1.775)	<0.001
pMDI vs. No treatment	0.631	(0.537, 0.742)	<0.001
TBH vs. No treatment	0.417	(0.354, 0.490)	<0.001

pMDI pressurized metered dose inhaler; TBH Turbuhaler.

The statistical analysis of P-cortisol concentration after ACTH stimulation gave a mean value that was 12.5% higher after treatment with Symbicort pMDI than after treatment with Symbicort Turbuhaler (p=0.0013). Compared to no-treatment, there was a suppression by 12.6% after treatment with Symbicort pMDI and by 22.3% after treatment with Symbicort Turbuhaler.

Summary of safety results

No deaths, other SAEs, DAEs or other significant AEs occurred in the study. All AEs reported more than twice after the first intake of investigational product are presented by preferred term in decreasing order of frequency as summarized over all treatments in Table S3. The results from the safety evaluation showed that there was no apparent difference in the pattern of reported AEs between the treatment with Symbicort pMDI and the treatment with Symbicort Turbuhaler. The majority of the reported AEs after both active treatment periods were considered mild in intensity. The most commonly reported AE during the Symbicort pMDI and Symbicort Turbuhaler treatments was the typical β_2-agonist class effect tremor. There was no obvious difference between the Symbicort pMDI and Symbicort Turbuhaler treatments regarding the frequency of this AE. No class effects of inhaled GCSs were reported.

Table S3 Number (%) of subjects with AEs reported more than twice by preferred term, sorted by frequency as summarized over all treatments

Preferred term	Symbicort pMDI n=30	Symbicort TBH n=30	No treatment n=29
Tremor	7 (23%)	6 (20%)	0
Nasopharyngitis	4 (13%)	2 (7%)	4 (14%)
Headache	3 (10%)	5 (17%)	1 (3%)
Pharyngolaryngeal pain	2 (7%)	3 (10%)	1 (3%)
Dysmenorrhoea	2 (7%)	2 (7%)	1 (3%)
Pyrexia	2 (7%)	1 (3%)	1 (3%)

AE adverse event; pMDI pressurized metered dose inhaler; TBH Turbuhaler.
Reported more than twice over all 3 study periods.