AstraZeneca

DRUG PRODUCT DRUG SUBSTANCE(S) Formoterol DOCUMENT NO. SD-037-CR-0718 VERSION NO. 01 STUDY CODE SD-037-0718 DATE 15 March, 2002		**Synopsis** REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)

FINAL

A comparison of efficacy between formoterol Turbuhaler and salbutamol pressurized metered dose inhaler and spacer, in subjects with acute severe bronchial obstruction

STUDY CENTRE(S)

This study was performed in Thailand in five centres.

STUDY PERIOD		**PHASE OF DEVELOPMENT**
- **DATE OF FIRST subject ENROLLED**	15 January, 2001	Therapeutic use
- **DATE OF LAST subject COMPLETED**	28 September, 2001	

PUBLICATION (REFERENCE)

To be decided.

OBJECTIVES

The primary objective of the study was to compare the efficacy of formoterol Turbuhaler and salbutamol pMDI and spacer in the treatment of subjects with acute severe bronchoconstriction.

The secondary objective was to study the safety of formoterol Turbuhaler compared with salbutamol pMDI with spacer during four hours when administered in the treatment of acute severe bronchoconstriction.

STUDY DESIGN

The design of the study was double-blind, double-dummy, randomized, reference-controlled with parallel groups.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Subjects presenting to the Emergency Department with acute bronchoconstriction were eligible for the study after consenting if their age was ≥ 18 and ≤ 70, if they had an FEV_1 of ≥ 30 and ≤ 60% of predicted normal values, and if their pulse rate was ≥ 100 beats per minute (only if ≥ 50 years of age).

Subjects were excluded if the acute bronchoconstriction required treatment with nebulized or IV β_2-agonists and if transfer to the intensive care unit was required at initial assessment. Other exclusion criteria were oxygen saturation (SaO_2) < 91% in room air as well as any known severe cardiovascular disorder such as ischemic heart disease, tachyarrhythmias or severe heart failure.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Formoterol fumarate dihydrate (Oxis®), inhalation powder, via Turbuhaler®, 4.5 μg/ inhalation, cumulative doses (batch Nos: BA 19, AI 23). Total dose was 54 μg administered as four inhalations on three occasions (18 μg per occasion at time 0 and 30 and 60 minutes after first dose).

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Salbutamol sulphate, via pressurized metered dose inhaler and spacer, 100 μg/inhalation, cumulative doses (batch Nos: AAR99A, AAQ90A). Total dose was 2 400 μg administered as 4x2 puffs in a spacer on three occasions (800 μg per occasion at time 0 and 30 and 60 minutes after first dose).

DURATION OF TREATMENT

The study treatment was administered as cumulative doses at time 0 and 30 and 60 minutes after first dose. Efficacy and safety variables were assessed up to four hours after administration of first dose of study drug.

MAIN VARIABLE(S):

The primary variable was the relative increase, compared with baseline, in FEV_1 (forced expiratory volume during one second) after 75 minutes after first dose of study drug when compared with baseline.

- **EFFICACY**

The secondary efficacy variables were:
- change in FEV_1 (at other time-points than 75 minutes)
- proportion of subjects who require no additional intervention within four hours after first drug administration and/or require hospitalization
- subject evaluation of asthma symptom severity (Visual Analogue Scale, VAS)

- **SAFETY**

The variables to assess safety were:
- adverse events
- electrocardiogram; heart rate, sinus rhythm, QTc and overall evaluation
- blood pressure
- serum potassium

- **HEALTH-RELATED QUALITY OF LIFE**

To evaluate the subjects' level of well-being during treatment of an acute severe bronchoconstriction, the following forms were completed:
- acute Asthma Quality of Life Questionnaire (acute AQLQ)
- Overall Treatment Evaluation question (OTE)

STATISTICAL METHODS

Treatment was compared using a multiplicative analysis of variance (ANOVA) model with fixed factor treatment and baseline FEV_1 as a covariate. As secondary variables, the increases in FEV_1 from baseline to 15 and 45 minutes after first drug administration were used as well as the average FEV_1 from 75 to 240 minutes and the VAS score at 240 minutes. Similar ANOVA models were used to compare these parameters. The number of subjects with treatment failure (subjects who required additional treatment within 240 minutes of first study drug administration and/or hospitalization) was compared between treatments using the $\chi 2$-test.

As safety parameters, the minimum and average post study drug values for serum potassium and diastolic blood pressure were compared between treatments as well as the maximum and average post study drug values for systolic blood pressure, heart rate and QTc. Additive ANOVA models were used to assess differences between treatments regarding safety. The assessments of ECG, i.e. sinus rhythm and overall evaluation, are presented as descriptive statistics.

SUBJECTS

Eighty subjects were to be randomly allocated to either of the two treatment groups at three clinics (approximately 25 to 30 subjects per centre). Five centres participated in the study.

	Formoterol Turbuhaler	**Salbutamol pMDI**	**Total**
No. of planned subjects	40	40	80
No. randomized subjects	44	44	88
Males/Females	14/30	10/34	24/64
Mean age, years	45 (18-67)	43 (18-61)	44 (18-67)
IGCS treatment, N	17	16	33
IGCS at study entry, μg	853 (400-1600)	881 (300-1200)	868 (300-1600)
FEV_1 , L	1.06 (0.38-1.74)	1.08 (0.47-2.0	1.07 (0.38-2.0)
FEV_1 % predicted normal	44 (17-60)	44 (21-59)	44 (17-60)
SaO_2 , %	96 (91-100)	97 (91-100)	96 (91-100)
Pulse, beats/min.	104 (73-137)	101 (60-129)	102 (60-137)
Acute AQLQ, overall score	2.7 (1.5-6.1)	2.5 (1.0-6.4)	2.6 (1.0-6.4)

Figures within brackets = range

SUMMARY

- EFFICACY RESULTS

The analysis of the primary variable, the relative increase, compared with baseline, in FEV_1 at 75 minutes (E_{75}) after the first dose of study drug, did not show a statistically significant difference between the treatments (see Table 1). The average percentage increase in FEV_1 at 75 minutes after first dose of study drug was 37.0 in the formoterol group and 27.8 in the salbutamol group.

Table 1. Treatment comparison of FEV_1 at 75 minutes, FEV_1 average and FEV_1 maximum.

	mean ratio		
Variable	form/salb	95% Conf.Limits	p-value
FEV_1 (L) E_{75}	107.2	(96.8, 118.7)	0.18
FEV_1 (L) E_{av}	111.7	(100.9, 123.6)	0.033
FEV_1 (L) E_{max}	111.1	(100.6, 122.8)	0.039
E = Effect			

The statistical analysis of maximum and average FEV_1 over four hours (E_{max} and E_{av}) displayed a statistically significantly greater increase in the formoterol group as compared to the salbutamol group. The average percentage maximum increase in FEV_1 was 51.2 in the formoterol group and 36.1 in the salbutamol group.

There was a change in the VAS score from 63.7 to 9.4 in the formoterol group and from 64.4 to 12.7 in the salbutamol group. No statistically significant difference between the treatment groups was detected.

- **SAFETY RESULTS**

Ten AEs were reported in the formoterol group and 3 in the salbutamol group, all classified as mild. The most commonly reported AE was palpitation (5 subjects in the formoterol group and 3 in the salbutamol group) which is a well known β_2-agonist class effect. The other AEs reported in the formoterol group were single events comprising different symptoms.

No SAEs were reported nor were there any discontinuations due to AEs.

There was no statistically significant differencein mean heart rate between the treatment groups. Initially the heart rate decreased in both groups and thereafter it increased again and reached a maximum after 75 minutes (average maximum was 99.6 beats per minute in the formoterol group and 99.4 beats per minute in the salbutamol group).

There was no statistically significant difference in mean QTc between the treatment groups. The highest measured QTc in a single subject was 568 ms (formoterol group at 180 minutes after first dose of study drug). The average maximum value was 449.6 ms in the formoterol group and 443.3 ms in the salbutamol group.

There was no statistically significant difference between the groups for the variables systolic and diastolic blood pressure.

The statistical analysis displayed a significantly larger decrease in serum potassium in the formoterol group on both average potassium value and average minimum value compared with the salbutamol group. The serum potassium decreased up to 180 minutes in the formoterol group after the first dose of study drug and up to 120 minutes in the salbutamol group. The mean minimum potassium value was 3.2 mmol/L in the formoterol group and 3.5 mmol/L in the salbutamol group. The lowest measured concentration in a single subject was 2.3 mmol/L (salbutamol group).

- **HEALTH-RELATED QUALITY OF LIFE**

The acute AQLQ scores increased after treatment from 2.67 to 5.88 in the formoterol group and 2.49 to 5.69 in the salbutamol group. The subject's perceived efficacy of the treatment as measured by the OTE question supported the change of the scores on the acute AQLQ. There were no statistically significant differences between the treatments neither for the acute AQLQ nor for the OTE scores.

The highest correlation coefficient (r=0.58) was between the change in acute AQLQ overall score and the OTE at 240 minutes.