AstraZeneca

Drug product:	Oxis Turbuhaler	**SYNOPSIS**	
Drug substance(s):	Formoterol		
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A randomized single blind comparison between formoterol, inhaled via Turbuhaler and inhaled via a pressurized Metered Dose Inhaler, connected to a large volume spacer, used as bronchodilator in patients with acute and severe airway obstruction, visiting the emergency department.

Publications

An abstract has been accepted at ATS 2006, results were presented as a poster.

Study dates		**Phase of development**
First subject enrolled	04 July 2003	Therapeutic use (IV)
Last subject completed	18 May 2005	

Objectives

To investigate whether formoterol, inhaled via Turbuhaler (Oxis® Turbuhaler®), is equally effective as when inhaled via a pressurized Metered Dose Inhaler (Foradil® pMDI) in a setting of acute severe dyspnoea and bronchoconstriction. The study population consisted of adult patients with dyspnoea and airflow obstruction, either Asthma or Chronic Obstructive Pulmonary Disease (COPD), presenting at the emergency department. The cause of this dyspnoea and bronchoconstriction was in most cases an exacerbation of their disease.

Study design

A single blind, randomised study with double dummy technique on a single test day and with one hour follow-up. Upon presenting at the Emergency department ("Spoed Eisende Hulp) or with an unscheduled visit to the outpatients clinic of the Catharina Ziekenhuis with acute dyspnoea, obtaining informed consent and measuring of baseline lung function with a portable spirometer, patients received 24 μg formoterol (2 doses of 12 μg) via one of the two devices and a placebo via the other device (for Turbuhaler®, 12 μg "metered dose" is equivalent with 9 μg "delivered dose"). Lung function was assessed before and 5, 15 and 30 minutes after inhalation. At 30 minutes, again 24 μg formoterol was given and lung function was measured after an additional 15 and 30 minutes. Further treatment was given as considered appropriate by the investigational team.

Target subject population and sample size

Subjects (75) with moderate to severe reversible airway obstruction (asthma or COPD) of either sex were included, aged >18 years and having a FEV_1 <70% of predicted but >0.50 L upon presenting at the emergency department. After enrolment the diagnosis was made in more detail, a subgroup with "proven" COPD was defined as those age >45 yr, a smoking history of >15 packyears and a FEV_1/VC ratio <0.70, measured in a stable situation the previous 12 months.

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

Formoterol (Oxis®) Turbuhaler® (12 μg formoterol per dose, batch numbers DK28, EH29), placebo Turbuhaler (batch numbers DB30, DI32, EH37), formoterol (Foradil®) pMDI (12 μg formoterol per dose, batch numbers X1471, X1497, X1530, X1542, X1561, S0008) and placebo pMDI (batch numbers P6351, P6349, P6491, P6547, P6985). The pMDI's were used together with the Aerochamber® spacer device (batch numbers X1472, X1498, X1540, X1562).

Duration of treatment

Two single doses, separated by 30 minutes. The total observation time of the study was one hour, but Severe Adverse Events were followed for one day making a total duration of the study of one day (approximately 24 hours).

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

Primary variable:

The main efficacy parameter was the lung function parameter FEV_1, which was measured five times on the test day (immediate before and at 5, 15, 30, 45 and 60 minutes after the first inhalation). For the statistical analysis the primary outcome

variable was the increase in FEV_1 in % from zero to 60 minutes (T = 0 to T = 60), expressed as ratio FEV_1 at 60 minutes / FEV_1 at 0 minutes.

Secondary variables:

The secondary efficacy parameters were other lung function parameters measured in parallel with FEV_1, like FVC and FEF_{25-75}, the Borg dyspnoea score, and subjective scores on the inhalers. PIF was measured at baseline.

For the statistical analysis, the secondary outcome variables were the change in FEV_1, FVC, FEF_{25-75} and Borg score at specific time points; the calculated Area Under the Curve (AUC) for the change in FEV_1, FVC, FEF_{25-75} and Borg score in the entire 60 minutes of observation; Time to Response in FEV_1, i.e. an increase in FEV_1 of 10% predicted; Time to Response in Borg score, i.e. a 50% reduction in Borg Score; the proportion of patients "responding" with an increase in FEV_1 of ≥10% predicted or a reduction of ≥50% in Borg score, and the proportion of patients requiring additional bronchodilator treatment in the 60 minutes of observation ("treatment failure").

No pharmacokinetic data were collected.

Safety

Adverse events, reported spontaneously or in response of the standard question at the end of the one hour lasting study. Due to the character of the study, hospitalisations for further treatment of the dyspnoea were not considered to be a Serious Adverse Event.

Statistical methods

The primary analysis was aimed at studying non-inferiority. The new treatment (formoterol via Turbuhaler, TBH) was assumed to be equivalent to the standard treatment (formoterol via pMDI), when the entire one-sided 95% confidence interval of the observed ratio of the two treatments (TBH / pMDI) of the mean increase in FEV_1 at 60 minutes is above 0.85, i.e. the treatment effect after formoterol via TBH should be more than 85% of the effect following formoterol via pMDI. The analysis was performed by ANOVA using a multiplicative model with the factor treatment and log-transformed baseline FEV_1 as % of predicted as a covariate. The Least-Squared Means resulting from this model were used to calculate the one-sided 95% confidence interval for the log-transformed differences between the treatments: log (TBH) minus log (pMDI). The one-sided 95% confidence interval of the ratio (TBH / pMDI) was calculated from this by taking the anti-logs. Data of all patients were used in the statistical analysis. The data were additionally described separately for the subgroup with "proven COPD", though without statistical comparisons for the two treatments within separate diagnoses.

Assuming a real ratio of TBH / pMDI of minimally 0.95, 37 patients per treatment group were needed in order to be able to state non-inferiority with a one sided significance level of 5% and a power of 80%.

Subject population

The study population consisted of predominantly male patients in their sixth or seventh decade, with COPD as most frequent diagnosis. Of these 77 patients, 47 were 65 years of age or older.

Table S1 Subject population and disposition

		Turbuhaler		pMDI		Total	
Population							
N randomised (N planned)		39	(37)	38	(37)	77	(74)
Demographic characteristics							
Sex (n and % of subjects)	Male	25	(64%)	26	(68%)	51	(66%)
	Female	14	(36%)	12%	(32%)	26	(34%)
Age (years)	Mean (SD)	67.1	(13.3)	65.3	(10.8)	66.2	(12.1)
	Range	29 to 84		41 to 82		29 to 84	
Pack-Years smoked	Median	30		33		32	
(Ex- or current-smokers)	Range	1 – 120		1 – 133		1 – 133	
Race (n and % of subjects)	Caucasian	38	(97%)	37	(97%)	75	(97%)
	Oriental	1	(3%)	1	(3%)	2	(3%)
Diagnosis (n and %)	COPD	25	(64%)	24	(63%)	49	(64%)
	Asthma	4	(10%)	2	(5%)	6	(8%)
	Mixture	10	(26%)	12	(32%)	22	(29%)
FEV_1 previous 12 months (L)	Mean (SD)	1.43	(0.64)	1.42	(0.67)	1.43	(0.65)
Baseline characteristics							
Mean (SD) FEV_1 (L)		0.98	(0.34)	1.09	(0.46)	1.03	(0.40)
Mean (SD) FEV_1 (% predicted)		38.3	(12.5)	40.3	(17.8)	39.3	(15.3)
Median Borg Score (range)		5	(1-10)	5	(1-9)	5	(1-10)
Disposition							
N (%) of subjects who	Completed	39	(100%)	36	(95%)	75	(97%)
	discontinued	0		2	(5%)	2	(3%)
N analysed for safety[a]		39		38		77	
N analysed for efficacy (ITT)		39		38		77	

[a] Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing
ITT=Intention to treat; N=Number

Efficacy and pharmacokinetic results

The primary parameter was the change in FEV_1 in % from enrolment (T = 0 minutes) to end of treatment (T = 60 minutes), expressed as ratio (FEV_1 at T = 60 / T = 0), this ratio was for formoterol TBH 1.175 (95% C.I. 1.092 – 1.265) and for formoterol pMDI 1.248 (95% C.I. 1.144 – 1.362), equivalent with 17.5% and 24.8% improvement respectively. The relative ratio of the effects after formoterol TBH / formoterol pMDI (adjusted for differences in baseline FEV_1) was 0.94 and the lower limit of the 95% C.I. was 0.86, which was above the predefined level of 0.85. Hereby a statistically significant "non-inferiority" was concluded (p=0.037) with the effect of formoterol TBH being 94% of the effect of formoterol pMDI. The test on the difference between the two treatments was not significant (relative ratio 0.94, 95% C.I. 0.84 – 1.05, p=0.29). Within the subgroup of 49 patients with COPD the effect of formoterol TBH at 60 minutes was 98% of the effect of formoterol pMDI (ratios 1.10 and 1.13, relative ratio 0.98, 95% C.I. 0.89 – 1.07).

Concerning secondary parameters, the ratio for FEV_1 at 5 minutes / 0 minutes was 1.11 for formoterol TBH (95% C.I. 1.06 – 1.16) and 1.18 (1.12 – 1.25) for formoterol pMDI, the relative effect formoterol TBH / pMDI was 0.94 and the lower limit of the 95% C.I. was 0.88, indicating statistically significant "non-inferiority" (p=0.004). The difference between the two treatments was not significant (p=0.079). Within the "proven COPD" subgroup the ratio for formoterol TBH was 1.07 and for formoterol pMDI 1.09 with for both the 95% C.I. above 1 (significance not tested) and the relative ratio was 0.98 (95% C.I. 0.93 – 1.04).

The ratio for FEV_1 at 30 minutes / 0 minutes was 1.12 for formoterol TBH (95% C.I. 1.04 – 1.20) and 1.16 for formoterol pMDI (1.07 – 1.26), the relative effect formoterol TBH / pMDI was 0.96 and the lower limit of the 95% C.I. was 0.88, indicating statistically significant "non-inferiority" (p=0.013). The difference between the two treatments was not significant (p=0.48). Within the "proven COPD" subgroup the ratio for formoterol TBH was 1.10 and for formoterol pMDI 1.08 and the relative ratio was 1.03 (95% C.I. 0.94 – 1.13).

The other secondary parameters showed similar effects for the two treatments. The effects on FVC, FEF_{25-75} and Borg Score at the pre-specified time-points of analyses did not differ significantly. On lung function parameters the effects of formoterol TBH were slightly smaller and on Borg Score slightly larger than the effects of formoterol pMDI. The effects on AUC-FEV_1, AUC-FVC and AUC-Borg did not differ either but AUC-FEF_{25-75} differed significantly in favour of formoterol pMDI (p=0.037). The Time to Response in FEV_1 and the Time to Response in Borg Score did not differ, though only 21 of all 74 patients with FEV_1 data showed the required improvement of 10% predicted and 16 of all 75 patients with Borg Score data showed a 50% decrease in Borg Score. The subjective scores, given to the two inhalers did not differ between the two inhalers and there were no Treatment Failures.

Safety results

There were no Serous Adverse Events or Discontinuations due to Adverse Events.

There were 4 Adverse Events reported (all of Mild intensity) in 4 patients, all 4 under formoterol pMDI treatment.

Table S2 Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)

Category of adverse event	Turbuhaler (39)	pMDI (38)	Total (77)
	N of subjects who had an adverse event in each category[a]		
Any adverse events	0	4	4
Serious adverse events	0	0	0
Serious adverse events leading to death	0	0	0
Serious adverse events not leading to death	0	0	0
Discontinuations of study treatment due to adverse events	0	0	0
Other significant adverse events	0	0	0
	Total number of adverse events		
Adverse events	0	4	4
Serious adverse events	0	0	0
Other significant adverse events	0	0	0

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

Table S3 Number (%) of subjects with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)

Adverse event (preferred term)	Number (%) of subjects who had an adverse event				
	Turbuhaler (n=39)	pMDI (n=38)		Total (n=77)	
Hypertension worse	0	1	(3%)	1	(1%)
Chills	0	1	(3%)	1	(1%)
Hypertension	0	1	(3%)	1	(1%)
Rales	0	1	(3%)	1	(1%)

[a] All Events are included in this table.