AstraZeneca

BN-00S-0022

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Symbicort® Turbuhaler®

ACTIVE INGREDIENT: budesonide/formoterol

Trial title (number): A randomized double blind comparison between single doses of Symbicort Turbuhaler (budesonide/formoterol combination), formoterol, salbutamol and placebo in repeated AMP-challenges in patients with mild - to moderate asthma. Investigating the supplementary value of the budesonide component within Symbicort when tested in a model of slow onset acute asthma.

Developmental phase: IV
First subject recruited: 7 April 2004
Last subject completed: 31 October 2005
Approval date: 28 January 2008

OBJECTIVES

To investigate, whether the budesonide component within Symbicort® Turbuhaler® (the combination of formoterol and budesonide) adds to the effects of formoterol in a model of "slow onset acute asthma" , mimicking exercise and cold-air induced asthma, performed by repeated challenges with inhaled Adenosine 5'-monophosphate (AMP). The primary objective was to study the protective effect of the study treatments against subsequent provocations with inhaled AMP. A secondary objective was to investigate the onset of effect of the study treatments after inhaled AMP-induced bronchoconstriction.

Study design

A double blind, randomised, cross-over study with four single Test Days, applying double dummy techniques. The study started with a selection day (Visit 1) in which inhalation technique was practiced and an AMP provocation test was performed, with increasing AMP concentrations inhaled until a fall of ≥30% in FEV_1 was reached. Provocation with AMP was chosen since AMP induced bronchoconstriction is considered to act via mast cell degranulation, similar to exercise and cold air induced bronchoconstriction. The open treatment period on once daily budesonide/formoterol (2 doses of 160/4.5 µg once daily in the evening) was started hereafter. After at least 7 days and withdrawal of budesonide/formoterol for approximately 36 hours (Visit 2) an AMP test was performed again to confirm hyperresponsiveness to AMP. With intervals of 5 – 14 days (and approximately 36 hours of withdrawal of budesonide/formoterol) four Test Days took place (Visit 3 to Visit 6). On each Test Day three AMP tests were performed with 3 and 4 hours interval, the first approximately commencing at 09:00 hours, the second at 12:00 hours and the third at 16:00 hours, giving the same AMP doses as those at Visit 1 and Visit 2. The single dose of the double blind study medication (4 different treatments) was given on the Test Day within 1 minute after completing the first AMP provocation on that Test Day, thus at approximately a 30% fall in FEV_1. Lung function (FEV_1 and FEF_{25-75}) was measured and Borg dyspnoea score was assessed repeatedly throughout the Test Day (48 assessments). The primary outcome parameter was the maximal fall in FEV_1 in the third AMP provocation. The study was registered at the NIH / clinicaltrials.gov trial data base under number NCT00272753.

Target population and sample size

Patients (20) with mild to moderate asthma (either sex, non-smoking) were planned to be included, defined as having an age of 18 – 55 years, a FEV_1 of ≥60% of predicted, a PC_{20}-AMP ≤160 mg/ml and a documented fall in FEV_1 of ≥30% upon continuation of the AMP provocation test. The smoking history had to be ≤10 PackYears.

Investigational product and comparators: dosage, mode of administration and batch numbers

Maintenance treatment from Visit 1 to Visit 6 consisted of a once daily dosing of budesonide/formoterol (via Turbuhaler, 160 µg and 4.5 µg as delivered dose, equivalent to 200 µg and 6 µg per metered dose): two inhalations in the evening (total daily dose 320/9 µg). Concomitant treatment consisted of inhaled terbutaline (Bricanyl® Turbuhaler, 250 µg per delivered dose), to be used "as needed".
Study treatments on the 4 Test Days of Visit 3 to Visit 6 (after abstaining from the maintenance budesonide/formoterol treatment for approximately 36 hours and inhaled terbutaline for >8 hours) treatment consisted (in a randomized, cross-over manner) of a single inhaled dose, inhaled within one minute of completing the first AMP provocation on that Test Day, of budesonide/formoterol (via Turbuhaler, one dose of 160/4.5 µg), formoterol (via Turbuhaler, one dose of 4.5 µg), salbutamol (via pressurized Metered Dose Inhaler (pMDI), 2 doses of 100 µg), or placebo. The pMDI was used with a Volumatic® plastic spacer.
Batch numbers: budesonide/formoterol: EB373, EL252, EB31, FE36; formoterol: EB20, FH27; placebo Turbuhaler EG16, FH18, FH39; terbutaline: 3221039, 3220002B; salbutamol: P6907, 6997; placebo pMDI: CE15; Volumatic spacer: 09C894931.

Duration of treatment

Maintenance treatment with budesonide/formoterol once daily was to be used for approximately two months. Double blind treatment on the Test Days of Visit 3, 4, 5 and 6 was given as a single dose.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

The primary aim of the study was to investigate the protective effects of the study treatments.
The main efficacy parameter was the lung function parameter FEV_1, which was measured throughout the test day (48 assessments), secondary parameters were the lung function parameter FEF_{25-75} and the subjective Borg dyspnoea score, both assessed simultaneously with FEV_1. These three parameters were assessed prior and during each AMP provocation, with short intervals in the first hour after the AMP provocations and additionally each hour in between AMP provocations.
The primary parameter in assessing the protective effect of the study treatments was the maximum % fall in FEV_1 observed in the third AMP provocation, expressed relative to the baseline FEV_1 measured immediately prior to this third AMP provocation.
Secondary parameters in assessing the protective effects were the maximum % fall in FEV_1 observed in the second AMP provocation; the calculated Area Under the Curve (AUC) for FEV_1 in the first 60 minutes after the third AMP provocation; the AUC for FEV_1, FEF_{25-75} and Borg score over the entire Test Day and the recovery time (time needed for FEV_1 to return to exact 90% of the FEV_1 prior to the third challenge) in the third AMP provocation.
For the secondary objective of the study (the onset of effect) the change in FEV_1, as % of baseline, from 0 to 3 minutes after inhalation of the study medication was calculated and the Recovery Time after the first AMP provocation was calculated.
There were no pharmacokinetic parameters assessed.

Safety

Adverse events, reported spontaneously or in response of the standard question at the start and the end of Visit 2 to Visit 6.

Statistical methods

The primary efficacy parameter was the maximum % fall in FEV_1 after the third AMP provocation. The % fall was calculated relative to the FEV_1, measured at start of this third AMP provocation. It was analysed by ANOVA using an additive model with the factors subject, period and treatment. The Test Day's baseline FEV_1 as % of predicted was used as a covariate. No tests for possible carry-over effects of one Visit to a next Visit was performed because of the long intervals between the single doses of study treatment. The primary analysis was aimed at studying superiority of budesonide/formoterol over formoterol and salbutamol. For the analysis of this primary parameter all 6 possible comparisons were investigated.
The secondary efficacy parameters were analysed in an identical way as the primary parameter, but for the secondary parameters a limited number of comparisons (only budesonide/formoterol versus the other treatments) was investigated for reasons of multiplicity.
Data is shown below as Least Square Means from the ANOVA analyses.

Subject population

A total of 35 patients was enrolled in the study, 6 patients were enrolled twice. In total 18 patients were randomised (14 from centre 1 and 4 from centre 2), 17 patients received at least one dose of blind treatment.

Table S1 Subject population and disposition

		Subjects		
Population				
N randomised (% of planned)		18	(90%)	
N treated[a] (% of planned)		17	(85%)	
Demographic characteristics (treated subjects)				
Sex (N and %)	Male	6	(35%)	
	Female	11	(65%)	
Age (years)	Mean (SD) Range	37.2	(10.4)	20 to 53
Race (N and %)	Caucasian	17	(100%)	
	Other	0	(0%)	
Baseline characteristics				
FEV_1 (L) Mean (SD) Range		3.26	(0.80)	2.11 to 4.69
FEV_1 (% of predicted) Mean (SD) Range		94.6	(16.3)	62.6 to 126
PC_{20} – AMP (mg/ml) GMean (median) Range		2.64	(3.96)	0.08 to 124.62
Disposition				
N (%) of subjects who	Completed	15	(88%)	
	Discontinued	2	(12%)	
N analysed for safety[a]		17	(100%)	
N analysed for efficacy		17	(100%)	

[a] Number of subjects who took at least 1 dose of double blind study treatment; N = Number; GMean: geometric mean.

Efficacy and pharmacokinetic results

The study was interrupted before reaching the required number of 20 completed patients but with 18 randomised patients due to the enrolment period lasting longer than expected and expiring study medication. Of these 18 patients, 17 received at least one dose of randomised treatment,

the 18th patient did not fulfil the lung function criteria on stable baseline lung function at the start of the first Test Day and was therefore withdrawn prior to receiving study treatment. Of the 17 patients, 15 completed all four Test Days, 1 patient received three treatments and 1 patient received two treatments. These two discontinued randomised patients were withdrawn because of expiring study medication. No additional bronchodilators were taken during the Test Days.

The primary study objective was investigating protective effects against subsequently inhaled AMP.

The primary parameter: the % fall in FEV_1 in the third AMP provocation, at 7 hours after inhalation amounted **15.7%** after budesonide/formoterol, **20.1%** after formoterol, **29.8%** after salbutamol and **31.9%** after placebo (least square mean data from ANOVA). The difference between budesonide/formoterol and formoterol was not statistically significant (p=0.24), the difference between budesonide /formoterol and salbutamol was statistically significant (p=0.0005) as was the difference between budesonide/formoterol and placebo (p<0.0001). The difference between formoterol and placebo was significant (p=0.0025), as was the difference between formoterol and salbutamol (p=0.0138). The difference between salbutamol and placebo was not significant (p=0.5662).

Secondary parameters:

The % fall in FEV_1 in the second AMP provocation, 4 hours after inhalation, amounted **8.8%** after budesonide/formoterol, **17.0%** after formoterol, **20.2%** after salbutamol and **27.1%** after placebo. The difference between budesonide/formoterol and formoterol was significant (p=0.0232), the difference between budesonide /formoterol and salbutamol was statistically significant (p=0.0028) as was the difference between budesonide/formoterol and placebo (p<0.0001).

The calculated Area Under the Curve ($AUC_{0\text{-}60}$, expressed in hour x % of baseline) for FEV_1 in the 60 minutes after the third AMP provocation was –4.2 h.% for budesonide/formoterol, –10.7 h.% for formoterol, –17.9 h.% for salbutamol and –19.9 h.% for placebo. The AUC after budesonide/formoterol differed significantly from that after formoterol (p=0.0454), from salbutamol (p=0.0001) and from placebo (p<0.0001).

The AUC for FEV_1 over the entire test day ($AUC_{9\text{-}17h}$, expressed in hours x % of baseline) was 20.9 h.% for budesonide/formoterol, –6.4 h.% for formoterol, –23.6 h.% for salbutamol and –61.0 h.% for placebo. The AUC after budesonide/formoterol differed significantly from that after formoterol (p=0.0329), from salbutamol (p=0.0011) and from placebo (p<0.0001).

The AUC for $FEF_{25\text{-}75}$ over the entire test day ($AUC_{9\text{-}17}$, expressed in hours x % of baseline) was 134.0 h.% for budesonide/formoterol, 47.8 h.% for formoterol, –44.6 h.% for salbutamol and –66.2 h.% for placebo. The AUC after budesonide/formoterol did not differ significantly from that after formoterol (p=0.0699), but differed from salbutamol (p=0.0005) and from placebo (p<0.0001).

The AUC for Borg score over the entire test day ($AUC_{9\text{-}17}$, expressed in hours x arbitrary units) was 0.21 for budesonide/formoterol, –0.55 for formoterol, 1.47 for salbutamol and 4.20 for placebo. This AUC after budesonide/formoterol did not differ significantly from that after formoterol (p=0.5699), neither from that after salbutamol (p=0.3657), but differed from that after placebo (p=0.0039).

The Recovery Time (time needed for FEV_1 to return to exact 90% of the FEV_1 prior to the third challenge) in the third AMP provocation was (median values) 4.0 minutes for budesonide/formoterol, 12.9 minutes for formoterol, 13.0 minutes for salbutamol and 28 minutes for placebo. In 6 of the 65 Test Days the Recovery Time was censored to 0 minutes, since FEV_1 did not fall more than 90% at all, complicating analysis. The Recovery Time after budesonide/formoterol did not differ significantly from that after formoterol (p=0.6829), neither from that after salbutamol (p=0.6035), nor from that after placebo (p=0.2284) in the Cox Proportional Hazard analysis.

The above mentioned data on efficacy concerning protective effect is summarized in the Table S2 below.

Table S2 Summary of efficacy data on protective effect

	budesonide/ formoterol	formoterol	salbutamol	placebo
Max fall in FEV_1 in third AMP test (%)	15.7	20.1	**29.8***	**31.9***
AUC_{0-60}-FEV_1 in third AMP test (h.%)	– 4.2	**– 10.7***	**– 17.9***	**– 19.9***
Max fall in FEV_1 in second AMP test (%)	8.8	**17.0***	**20.2***	**27.1***
AUC_{9-17h}-FEV_1 over Test Day (h.%)	20.9	**– 6.4***	**– 23.6***	**– 61.0***
AUC_{9-17h}-FEV_{25-75} over Test Day (h.%)	134.0	47.8	**– 44.6***	**– 66.2***
Recovery in FEV_1 in third AMP test (min)	4.0	12.9	13.0	28.0
AUC_{9-17h}-Borg Score over Test Day (h.U)	0.21	– 0.55	1.47	**4.20***

***** denotes a statistically significant difference compared to budesonide/formoterol

The secondary objective of the study was investigating the onset of effect, since the study treatments were administered at the moment of an approximately 30% decreased FEV_1 due to the inhaled AMP.
The increase in FEV_1 in the first AMP provocation, from 0 to 3 minutes after inhalation (as % of baseline) was 15.3 % for budesonide/formoterol, 13.2 % for formoterol, 21.5 % for salbutamol and 1.7 % for placebo. The increase in FEV_1 after budesonide/formoterol did not differ significantly from that after formoterol ($p=0.4401$), but differed significantly from salbutamol ($p=0.0225$) and from placebo ($p<0.0001$). In this respect, the budesonide/ formoterol treatment performed worse than the salbutamol treatment and better than placebo.
The median Recovery Time for AUC for FEV_1 in the first AMP provocation (time until recovery to 90% of baseline) was 8.7 minutes for budesonide/formoterol, 6.3 minutes for formoterol, 3.4 minutes for salbutamol and 27.5 minutes for placebo. The Recovery Time after budesonide/formoterol differed significantly from placebo ($p=0.0025$) but not from formoterol ($p=0.5688$) or salbutamol ($p=0.9036$) in a Cox Proportional Hazards analysis.

Safety results

There were no Serious Adverse Events reported in this study. Adverse Events are reported in the Tables S3 and S4 below solely for the 17 patients who received at least one dose of the double blind study treatments. There was one additional patient who received budesonide/formoterol maintenance medication but he was withdrawn prior to receiving blinded study treatment due to non-fulfilment of the inclusion criteria. This patient had one Adverse Event (moderate common cold for the five days preceding Visit 3). One other patient was discontinued on the enrolment Visit 1 due to development of migraine on the visit day, she was discontinued prior to receiving maintenance study The study treatments were given as single doses, the Adverse Events below describe the Events reported on the specific Test Day and in the period until the next Test Day. An Adverse Event which persisted for more than one Test Day is listed in two or more treatments. Adverse Events reported in the run-in period are excluded from this summary.

Table S3 **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	N (%) of subjects who had an adverse event in each category			
	bud/for (n=17)	formoterol (n=15)	salbutamol (n=16)	placebo (n=17)
Any Adverse Events	6 (35%)	4 (27%)	7 (44%)	5(29%)
Serious Adverse Events	0	0	0	0
Serious Adverse Events leading to death	0	0	0	0
Serious Adverse Events not leading to death	0	0	0	0
Discontinuations of study treatment due to Adverse Events	0	0	0	0
Other significant Adverse Events	0	0	0	0
	Total number of adverse events			
Adverse Events	8	5	9	8
Mild	7	5	9	8
Moderate	1	0	0	0
Severe	0	0	0	0
Maximum number Adverse Events per patient	2	2	2	3
Serious Adverse Events	0	0	0	0
Other significant Adverse Events	0	0	0	0

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; events persisting over multiple periods are counted in each period; bud/for: budesonide/formoterol.

Table S4 **Number (%) of subjects with the reported adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)**

Adverse event (preferred term)	Number (%) of patients who had an adverse event				
	bud/for (n=17)	formoterol (n=15)	salbutamol (n=16)	placebo (n=17)	Total (n=17)
Headache	3 (18%)	2 (20%)	3 (19%)	2 (12%)	5 (29%)
Nasopharyngitis	2 (12%)	0 (0%)	3(19%)	3 (18%)	4 (25%)
Pharyngolaryngeal pain	1 (6%)	0 (0%)	1 (6%)	0 (0%)	2 (12%)
Bursitis	1 (6%)	1 (7%)	0 (0%)	0 (0%)	2 (12%)
Cough	1 (6%)	1 (7%)	1 (6%)	1 (6)	1 (6%)
Cystitis	0 (0%)	0 (0%)	1 (6%)	1 (6%)	1 (6%)
Diarrhoea	0 (0%)	0 (0%)	0 (0%)	1 (6%)	1 (6%)

All Adverse Events reported after randomisation are included in this table; events persisting over multiple periods are counted in each period but not added in the Total column; bud/for: budesonide/formoterol

A small number of Adverse Events was noted, of which none constituted a Serious Adverse Events. Only one Adverse Event was coded as being of moderate intensity (a case of headache), the other adverse events were all coded as mild. The study procedures, including 48 assessments of lung function per Test Day and the study treatments were well tolerated.

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Seroquel™ (quetiapine), Healthcare Professionals should view their specific country information.