AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Budesonide/formoterol
Study Code	D5890L00032
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A randomized, double blind, parallel-group study with use of budesonide/formoterol “as needed”, or terbutaline “as needed” or regular use of budesonide + terbutaline “as needed”, in patients mild intermittent asthma and exercise-induced bronchoconstriction.

Study dates: First subject enrolled: 25 September 2009
Last subject last visit: 19 July 2010

Phase of development: Therapeutic exploratory (IIb)

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

Study centre(s)

A total of 10 study sites participated; 2 sites in Norway and 8 sites in Sweden.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To evaluate the magnitude of the protective effect of the combination of budesonide and formoterol on an as needed basis compared to the use of terbutaline as needed on exercise-induced bronchoconstriction in adults and adolescents with mild intermittent asthma	**Primary end-point:** Change in maximum post-exercise FEV_1 fall after 6 weeks	Efficacy
	Secondary end-points: Change in maximum post-exercise FEV_1 fall after 3 weeks	
	Bronchial responsiveness to mannitol	
	Concentration of exhaled nitric oxide	
Secondary	**Secondary**	
To evaluate the magnitude of the protective effect of the combination of budesonide and formoterol as needed compared to regular once daily budesonide plus terbutaline as needed on exercise-induced bronchoconstriction in adults and adolescents with mild intermittent asthma	Use of as needed medication	Efficacy
	Asthma control measured by ACQ5	
	Diary recording of asthma symptoms	
	Change in average post-exercise FEV_1 fall after 3 and 6 weeks	
	Categorical maximum percentage decrease in FEV_1 after exercise and before SABA administration	
	Time to recovery within 5% of preexercise fall in FEV_1	
	Average change from preexercise baseline in FEV_1 after SABA administration	
	Area under the curve for the first 30 minutes after exercise after 3 and 6 weeks	

Objectives	Outcome variables	Type
To evaluate safety of budesonide/formoterol as needed, terbutaline as needed and regular use of budesonide + terbutaline as needed.	Safety end-points, including Adverse Events, Serious Adverse Events, Other significant Adverse Events and Pulse and blood pressure	Safety

Study design

This was a randomized, double blind, parallel group study to assess the protective effect on exercise-induced bronchoconstriction during 6 weeks in patients with asthma.

Target subject population and sample size

The target patient population was outpatients ≥12 years with predetermined episodic exercise-induced bronchoconstriction. The planned number of randomized patients was 66.

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

The details of the investigational products and any study treatment are given in Table S2.

Table S2 Details of investigational product and any other study treatments

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
Budesonide/ formoterol Turbuhaler®	Inhalation powder, budesonide and formoterol 160 + 4.5 □g/dose	AstraZenea	2100899 / 190019554	09-000313AZ
Budesonide Turbuhaler®	Inhalation powder, budesonide 400 □g/dose	AstraZeneca	2152911 / 199411054	09-000491AZ
Terbutaline Turbuhaler®	Inhalation powder, terbutaline 0.4 mg/dose	AstraZeneca	2100082 / 191000154	09-001647AZ
Placebo Budesonide Turbuhaler®	Inhalation powder, lactose monohydrate	AstraZeneca	2152924 / 199412854	09-000493AZ

All patients in the same treatment arm received investigational product from the same batch.

Eligible patients were randomized to one of the three following treatment groups in a 1:1:1 ratio at Visit 3:

- Budesonide 400 µg once daily and terbutaline 0.4 mg before exercise and as needed
- Placebo budesonide once daily and terbutaline 0.4 mg before exercise and as needed
- Placebo budesonide once daily and budesonide/formoterol 160/4.5 µg before exercise and as needed

Duration of treatment

The treatment period was 6 weeks.

Statistical methods

A comprehensive statistical analysis plan (SAP) was prepared before clean file.

The primary objective of the study was to evaluate the magnitude of the protective effect of the combination of budesonide and formoterol on an as needed basis compared to the use of terbutaline as needed on EIB in adults and adolescents with mild intermittent asthma. The primary variable was the change in maximum decrease in post-exercise FEV_1 as percent of predicted normal calculated before and after 6 weeks of treatment.

The secondary variables were used to evaluate the protective effect of the treatments. All tests were two-sided and p-values <5% are considered as statistically significant. 95% confidence limits are given unless otherwise specified.

No adjustment of the p-values for multiple testing was done.

The H0 hypothesis was that the treatment C and treatment B are equal, e.g. (placebo x1 + budesonide/formoterol 160/4.5 BE + budesonide/formoterol 160/4.5 as needed) versus (placebo x1 + terbutaline 0,4 mg BE + terbutaline as needed).

The primary variable change in maximum decrease in post-exercise FEV_1 as percent of predicted normal calculated before and after 6 weeks of treatment, was analysed by an analysis of co-variance (ANCOVA), with treatment as factor and the baseline value before treatment of FEV_1 as covariate. If a patient was without measurements after 6 weeks, the values after 3 weeks were used instead, using the Last Observation Carried Forward (LOCF) principle. Treatment C was compared with treatment B.

The non-inferior comparison was done between treatment A and C, e.g. (budesonide 400 ug x1 + terbutaline 0,4 mg before exercise + terbutaline as needed) versus (placebo x1 + budesonide/formoterol 160/4.5 before exercise + budesonide/formoterol 160/4.5 as needed). The analysis was done as for the primary variable but in a non-inferior way. The H0 hypothesis was that the treatment C compared to treatment A was not non-inferior. The lower

limit of the one-sided 97.5% Confidence Interval should be above the –7.28% limit. The non-inferiority limit was pre-specified to 7.28% and in both cases was the lower limit of the confidence interval above this limit. The selection of the 7.28 was based on a publication by Jonasson et al, 2000, using app. 50% of the difference between the active drug and the placebo drug in their study, inside the recommended limit by FDA to be in the range of 30-80% of the difference between the active drug and the placebo drug, when designing a non-inferior study for rejecting the H0 hypothesis. If non-inferiority was proven, a descriptive superiority analysis was done using the same method.

Terbutaline as needed (treatment B) served as a control treatment. To demonstrate this, the treatment difference between treatment A and B was calculated and the treatment difference between treatment C and B was also calculated using an ANCOVA, with treatment as factor and baseline FEV_1 for primary variable.

Based on a publication by Fogel et al, 2010 (after the finalization of the study protocol), additional exploratory analyses was added and described in the statistical analysis plan. These additional analyses included area under the FEV_1 curve, average change in FEV_1, time to recovery, categorical change of FEV_1 and change in FEV_1 after terbutaline administration.

Subject population

A total of 189 patients, aged 12-67, were enrolled at 10 study sites in 2 countries: Sweden and Norway. Of 189 enrolled patients, 66 patients were randomized and allocated to study treatment at Visit 3 (7 patients in Norway and 59 patients in Sweden). The most common reasons for not being randomized on Visit 3 were failure to demonstrate at least 10% post-exercise fall in FEV_1 on Visit 2 (n=93) and baseline FEV_1 at Visit 1 not being > 80.0% of predicted normal value on Visit 1 (n=8). Twelve patients were excluded as they were on treatment for a concomitant disease that might affect the participation in or the results of the study or had other significant diseases or disorders.

A total of 59 patients completed the study, i.e. primary variable data is available on Visit 5. The last observation carried forward principle was used for the 7 patients who were missing the primary variable at Visit 5. 62 patients completed the study without major protocol deviations (i.e. PP population).

The first subject was enrolled on 25 September 2009 and the last subject finished the study on 19 July 2010.

Summary of efficacy results

The long-term protective effect on exercise-induced bronchoconstriction of the fixed combination of budesonide/formoterol used before exercise and as needed in patients with mild intermittent asthma, is superior to standard treatment with terbutaline.

The long-term protective effect on exercise-induced bronchoconstriction of budesonide/formoterol used before exercise and as needed in patients with mild intermittent

asthma, is similar to regular once daily use of budesonide together with terbutaline before exercise and as needed.

Summary of safety results

All treatments were safe and well tolerated.