AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Symbicort®
Study Code	D589OC00003
Edition Number	1

A 12-Week, Double-Blind, Randomised, Multi-Centre, Parallel-Group Study Evaluating the Efficacy, Safety, and Patient Use (User Study) of Symbicort®[1] (Budesonide/Formoterol) Breath-Actuated Metered Dose Inhaler (BA MDI) 2x160/4.5 µg Twice Daily Compared with Symbicort® (Budesonide/Formoterol) AC (Actuation Counter) pMDI 2x160/4.5 µg Twice Daily and Budesonide AC pMDI 2x160 µg Twice Daily in Adult and Adolescent Asthmatics

Study dates:	First subject enrolled: 28 November 2011 Last subject last visit: 27 August 2012
Phase of development:	Therapeutic confirmatory (III)

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

[1] Symbicort® is a trademark of the AstraZeneca group of companies

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 compare the efficacy of Symbicort®[1] BA MDI 2x160/4.5 µg bid with that of Symbicort AC pMDI 2x160/4.5 µg bid by evaluation of FEV_1, 60 minutes post-dose and FEV_1, pre-dose.	Primary variables: pre-dose FEV_1 and 60 minute post-dose FEV_1. Secondary variables: mPEF and ePEF, asthma symptoms day and night, night-time awakenings due to asthma symptoms and use of rescue medication day and night.	Efficacy
To demonstrate assay sensitivity by comparing Symbicort AC pMDI to budesonide AC pMDI with regard to effect, on FEV_1 60 minutes post-dose.	60 minute post-dose FEV_1.	
Secondary	**Secondary**	
To assess patient-reported functionality of the Symbicort BA MDI device, in a clinical setting, through the use of a patient electronic Diary (eDiary) and a Patient Questionnaire.	Patient Assessment Questionnaire, Device Functionality Questions.	User Study
To assess the accuracy of the Symbicort BA MDI actuation counter by comparing actuation count, as determined by AstraZeneca on planned returned inhalers, to the change in device weight.	The secondary objectives 2 and 3 will be performed and reported under a separate CMC protocol. Specific results of this testing will be reported as an appendix to the CSR.	
To assess the BA MDI device performance after patient use, on planned returned inhalers.	The BA MDI device will be weighed before and at the end of the study by AstraZeneca R&D or designee.	
Safety	**Safety**	

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Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
To compare the safety profile of Symbicort BA MDI 2x160/4.5 µg inhalations bid, Symbicort AC pMDI 2x160/4.5 µg inhalations bid and budesonide AC pMDI 2x160 µg bid, by assessments of adverse events (AEs; nature, incidence, and severity).	AEs (nature, incidence, and severity).	Safety

AC Actuation counter; AE Adverse event; BA MDI Breath Actuated Metered Dose Inhaler; bid twice daily; CMC Chemistry Manufacturing and Control; CSR Clinical Study Report; ECG Electrocardiogram; ePEF Evening peak expiratory flow; FEV1 Forced exploratory volume in 1 second; IP Investigational product; mPEF Morning expiratory flow; pMDI pressurized Metered Dose Inhaler; PRO Patient reported outcomes; SAP Statistical analysis plan.

Study design

This was a double-blind, randomised, multi-centre, parallel-group, 12-week study evaluating the efficacy, safety and patient use (User Study) of Symbicort®[1] (budesonide/formoterol) breath actuated metered dose inhaler (BA MDI) 2x160/4.5 µg twice daily (bid) compared with Symbicort actuation counter (AC) pressurised metered dose inhaler (pMDI) 2x160/4.5 µg bid and budesonide AC pMDI 2x160 µg bid in adult and adolescent asthmatics.

The study comprised an enrollment visit, a 2 week run-in period and a 12 week treatment period. Run-in started at Visit 2 after measurement of spirometry and reversibility testing. During the run in period of 2 weeks ±3 days, patients were treated with budesonide AC pMDI 2x160 µg bid. At Visit 3 (towards the end of run in period), a second reversibility test was performed. At Visit 4, the eligible patients were randomised to one of the 3 treatments: Symbicort BA MDI 2x160/4.5 µg bid, Symbicort AC pMDI 2x160/4.5 µg bid, and budesonide AC pMDI 2x160 µg bid. Visit 5 and Visit 6 at weeks 3 and 7 respectively were follow up visits and Visit 7 at Week 12 was the last follow up/termination visit. It was followed up by a telephone call 2 weeks later to record any adverse events (AE).

Target subject population and sample size

The target population included moderate to severe asthmatics that required inhaled corticosteroid (ICS) therapy and still had reversibility after a run-in period of approximately 2 weeks (±3 days) on budesonide AC pMDI 2x160 µg bid. The population comprised males and females aged 12 years and above with documented clinical diagnosis of asthma according to the American Thoracic Society definition at least 6 months prior to Visit 2, had pre-bronchodilator forced exploratory volume in 1 second (FEV_1) ≥45% and ≤85% of predicted normal at Visit 2, and at Visit 4.

In order to achieve a power of 90% for detecting a difference between Symbicort AC pMDI and budesonide AC pMDI (ie, to demonstrate assay sensitivity) in FEV_1 60 min post-dose (mean during the treatment period), 60 patients/arm were needed assuming a true mean difference of 0.09 on the log-scale (corresponding to a difference of 9.4%) and a standard

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deviation for the change in log FEV_1 from baseline of 0.15. Assuming a 15% withdrawal rate, a total 70 patients/arm were to be randomised.

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

Symbicort BA MDI, aerosol for inhalation, 160 µg budesonide /4.5 µg formoterol, 2 actuations bid, manufactured by AstraZeneca; Batch no. 11-002924AZ and 11-001035AZ.

Placebo BA MDI, aerosol for inhalation, 2 actuations bid, manufactured by AstraZeneca; Batch no. 11-001273AZ.

budesonide AC pMDI, aerosol for inhalation, 160 µg budesonide, 2 actuations bid, manufactured by AstraZeneca; Batch no. 11-001267AZ and 11-002429AZ.

Symbicort AC pMDI, aerosol for inhalation, 160 µg budesonide/4.5 µg formoterol, 2 actuations bid, manufactured by AstraZeneca; Batch no. 11-001243AZ and 11-002381AZ.

Placebo AC pMDI, aerosol for inhalation, 2 actuations bid, manufactured by AstraZeneca; Batch no. 11-001249AZ and 11-002499AZ.

Duration of treatment

During the 2-week run-in period, patients were treated with budesonide AC pMDI. After this period, the patients were randomised to a 12-week treatment period.

Statistical methods

To demonstrate therapeutic equivalence between the 2 Symbicort treatment groups the Symbicort BA MDI was compared with the Symbicort AC pMDI. This comparison was addressed using a CI for the ratio of effects of the 2 treatments on pre-dose FEV_1 (arithmetic average during the treatment period, Visit 5 to Visit 7, expressed as a ratio of the baseline pre-dose FEV_1) and Visit 4 to Visit 7 post-dose FEV_1 as described above. The 2 treatments were to be considered therapeutically equivalent if the 95% CI for the ratio of treatment effects is contained within the equivalence limits of 80% to125%. The model used to estimate the ratio of treatment effects was the same for pre-dose FEV_1 as for post-dose FEV_1 described above, ie, a multiplicative ANCOVA with the treatment and country as factors, and baseline pre-dose FEV_1 as a covariate.

Both of the above procedures were conducted at the 5% level since both objectives had to be met in order to meet the goals of the study. It was required first that Symbicort AC pMDI be shown superior to budesonide (assay sensitivity) prior to testing therapeutic equivalence between the 2 Symbicort treatment groups.

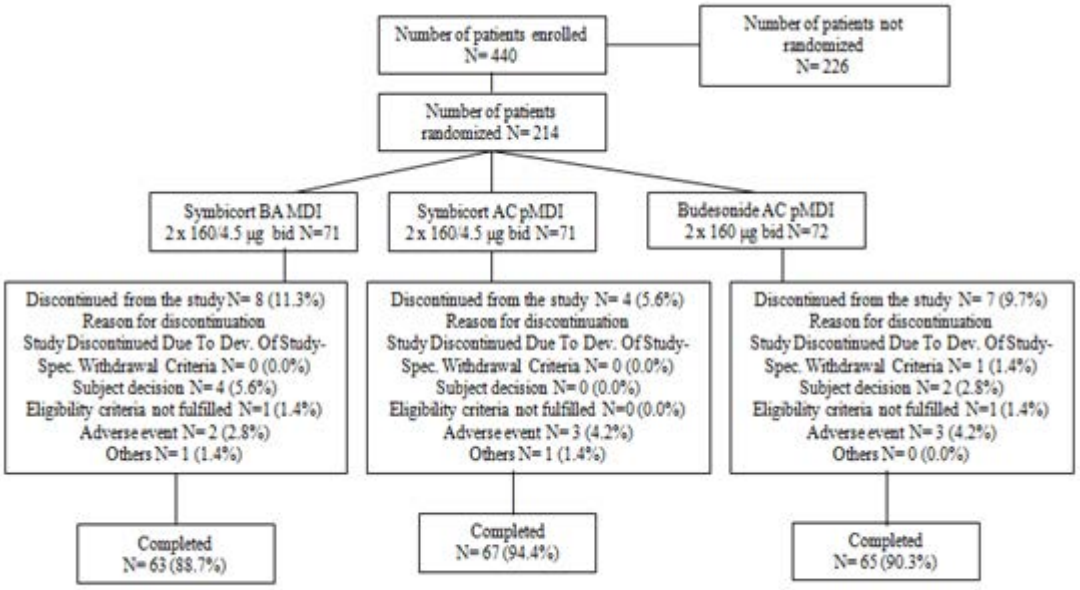
Secondary efficacy variables were analysed using ANCOVA where the change (mean during the entire treatment period) from baseline (mean of available data during run-in period) was subjected to ANCOVA with treatment and country as factors, and with the baseline value as a continuous covariate.

Comparison of Symbicort AC pMDI to budesonide AC pMDI was done for post-dose FEV_1 and the comparison of Symbicort BA MDI to Symbicort AC pMDI was done for pre- and post-dose FEV_1. The difference in post-dose FEV_1 between Symbicort AC pMDI and budesonide AC pMDI had to be statistically significant at 5% level. If this occurred, then a 95% Confidence Interval (CI) for the ratio of treatment effects was used to assess equivalence between the 2 Symbicort treatment groups. The sequence of testing was the comparison of Symbicort AC pMDI to budesonide AC pMDI (assay sensitivity) prior to testing therapeutic equivalence between the 2 Symbicort treatment groups.

Subject population

The disposition of the patients in this study is summarised in Figure S1.

Figure S1 Patient disposition



AC Actuation counter; BA MDI Breath actuated metered dose inhaler; bid Twice a day dosing; pMDI Pressurised metered dose inhaler.

A total of 214 patients were randomised to receive the study treatment (71 patients in the Symbicort AC pMDI group, 71 patients in Symbicort BA MDI group and 72 patients in the budesonide AC pMDI group). A total of 195 (91.1%) randomised patients completed the study (63 [88.7%] in the Symbicort BA MDI group, 67 [94.4%] patients in Symbicort AC pMDI group, and 65[90.3%] patients in budesonide AC pMDI group).

In all, 19 (8.9%) patients discontinued the study treatment prior to completing 12 weeks of randomised treatment. Two (2.8%) patients of Symbicort BA MDI group, 3 (4.2%) patients of Symbicort AC pMDI group, and 3 (4.2%) patients of budesonide AC pMDI group

discontinued the study due to AE, whereas 4 (5.6%) patients of Symbicort BA MDI group and 2 (2.8%) patients of budesonide AC pMDI group discontinued the study, due to subject decision.

The treatment groups were well-balanced with regard to demographics and baseline characteristics except for a larger percentage of females in the Symbicort pMDI group (66.2%) compared with the Symbicort BA MDI (52.1%) and budesonide pMDI (48.6%) groups. The majority of the patients were White and had a mean age of 42.7 years (range 12 to 81 years).

The treatment groups were similar with regards to the percentage of patients who completed the study treatment.

Summary of efficacy results

Comparison of Symbicort AC pMDI and budesonide AC pMDI for post-dose FEV_1, resulted in a statistically significant difference (Least square mean=1.10; $p<0.001$) in favour of Symbicort AC pMDI. This confirmed assay sensitivity and allowed for comparison of the 2 Symbicort treatments groups.

Comparison of the 2 Symbicort treatment groups (Symbicort BA MDI versus Symbicort AC pMDI), for post-dose FEV_1, yielded a ratio of 1.01 and a CI of 0.97 to 1.05. This established the therapeutic equivalence between the formulations for post-dose FEV_1 as the CI was entirely contained within the equivalence limits of 0.80 to 1.25.

Comparison of the 2 Symbicort treatment groups (Symbicort BA MDI versus Symbicort AC pMDI) for pre-dose FEV_1 yielded a ratio of 1.03 and a CI of 0.99 to 1.08. This established the therapeutic equivalence between the formulations for pre-dose FEV_1 as the CI was entirely contained within the equivalence limits of 0.80 to 1.25.

Table S2 and Table S3 summarise individual treatment group results and treatment comparisons, respectively, for post-dose FEV_1.

Table S2 Individual treatment group results for post-dose FEV1 (L), based on log-transformed data (FAS)

				Ratio of treatment to baseline		
		Baseline value	Treatment average		From ANCOVA	
Treatment	N	Geometric Mean (CV%)	Geometric Mean (CV%)	Geometric Mean (CV%)	LSMEAN (CV%)*	95% CI
SYM BAI	71	2.09(31.46)	2.53(30.57)	1.21(13.91)	1.24(1.56)	1.20 , 1.27
SYM pMDI	71	1.97(27.16)	2.37(26.33)	1.20(11.10)	1.22(1.57)	1.18 , 1.26

Table S2 Individual treatment group results for post-dose FEV1 (L), based on log-transformed data (FAS)

				Ratio of treatment to baseline		
		Baseline value	Treatment average		From ANCOVA	
Treatment	N	Geometric Mean (CV%)	Geometric Mean (CV%)	Geometric Mean (CV%)	LSMEAN (CV%)*	95% CI
BUD	71	2.12(26.34)	2.30(28.36)	1.09(12.10)	1.11(1.55)	1.08 , 1.15

Baseline is defined as the last pre-dose value prior to 1st dose of randomised therapy.
Trt Avg = Mean of all available valid values after randomisation.
The statistical model is Analysis of Covariance model (ANCOVA) on the log transformed outcome variable with treatment and country as factor, and log transformed baseline FEV_1 (pre-dose) as covariate.
LSMEAN: Obtained by back-transformation of the LSMEAN resulting from ANCOVA of log-transformed data.
* Coefficient of variation of the mean CV (%) =100*(sqrt (exp (SE**2)-1)).
CV (%) =100*(sqrt (exp (SD**2)-1)).
AC Actuation counter; BA MDI Breath actuated metered dose inhaler; bid Twice a day dosing; BUD Budesonide AC pMDI 2x160 µg bid; CI Confidence interval; CV Coefficient of variation; FAS Full analysis set; FEV_1 Forced exploratory volume in 1 second; pMDI Pressurised Metered dose inhaler; SE Standard error; SYM BAI Symbicort BA MDI 2x160/4.5 µg bid; SD Standard deviation; SYM pMDI Symbicort AC pMDI 2x160/4.5 µg bid.

Table S3 ANCOVA Summary - Treatment comparisons for post-dose FEV1 (L), based on log-transformed data (FAS)

	Ratio of treatment effects		
Comparison	LSMEAN(CV%)*	95% CI	p-value
SYM BAI VS BUD	1.11(1.99)	1.07 , 1.16	< 0.001
SYM pMDI VS BUD	1.10(2.00)	1.06 , 1.14	< 0.001
SYM BAI VS SYM pMDI	1.01(1.99)	0.97 , 1.05	0.547

The statistical model is Analysis of Covariance model (ANCOVA) on the log transformed outcome variable with treatment and country as factor, and log transformed baseline FEV_1 (pre-dose) as covariate.
LSMEAN: Obtained by back-transformation of the LSMEAN resulting from ANCOVA of log-transformed data.
* Coefficient of variation of the mean CV (%) =100*(sqrt (exp (SE**2)-1)).
AC Actuation counter; BA MDI Breath-actuated metered dose inhaler; bid Twice daily dosing; BUD Budesonide AC pMDI 2x160 µg bid; CI Confidence interval; CV Coefficient of variation; FAS Full analysis set; FEV_1 Forced expiratory volume in 1 second; pMDI Pressurised metered dose inhaler; SE Standard error; SYM BAI Symbicort BA MDI 2x160/4.5 µg bid; SYM pMDI Symbicort AC pMDI 2x160/4.5 µg bid.

Table S4 and Table S5 for summarise individual treatment group results and treatment comparisons, respectively, for pre-dose FEV_1.

Table S4 Individual treatment group results for pre-dose FEV1 (L) based on log-transformed data (FAS)

				Ratio of treatment to baseline		
		Baseline value	Treatment average		From ANCOVA	
Treatment	N	Geometric Mean (CV%)	Geometric Mean (CV%)	Geometric Mean (CV%)	LSMEAN (CV%)*	95% CI
SYM BAI	71	2.09(31.46)	2.34(30.95)	1.12(16.01)	1.14(1.74)	1.10 , 1.18
SYM pMDI	71	1.97(27.16)	2.15(29.15)	1.09(12.53)	1.10(1.75)	1.06 , 1.14
BUD	71	2.12(26.34)	2.23(29.36)	1.06(11.38)	1.07(1.73)	1.03 , 1.11

Baseline is defined as the last pre-dose value prior to 1st dose of randomised therapy.
Trt Avg = Mean of all available valid values after randomisation.
The statistical model is Analysis of Covariance model (ANCOVA) on the log transformed outcome variable with treatment and country as factor, and log transformed baseline FEV_1 (pre-dose) as covariate.
LSMEAN: Obtained by back-transformation of the LSMEAN resulting from ANCOVA of log-transformed data.
Coefficient of variation of the mean CV (%) =100(sqrt (exp (SE**2)-1)).
CV (%) =100*(sqrt (exp (SD**2)-1)).
AC Actuation counter; BA MDI Breath actuated metered dose inhaler; bid Twice a day dosing; BUD Budesonide AC pMDI 2x160 µg bid; CI Confidence interval; CV Coefficient of variation; FAS Full analysis set; FEV_1 Forced expiratory volume in 1 second; LS Least square; pMDI Pressurised Metered dose inhaler; SE Standard error; SYM BAI Symbicort BA MDI 2x160/4.5 µg bid; SYM pMDI Symbicort AC pMDI 2x160/4.5 µg bid.

Table S5 ANCOVA Summary - Treatment comparisons for pre-dose FEV1 (L) based on log-transformed data (FAS)

	Ratio of treatment effects		
Comparison	LSMEAN(CV%)*	95% CI	P-value
SYM BAI VS BUD	1.06(2.21)	1.02 , 1.11	0.007
SYM pMDI VS BUD	1.03(2.22)	0.98 , 1.07	0.238
SYM BAI VS SYM pMDI	1.03(2.22)	0.99 , 1.08	0.131

The statistical model is Analysis of Covariance model (ANCOVA) on the log transformed outcome variable with treatment and country as factor, and log transformed baseline FEV_1 (pre-dose) as covariate.
LSMEAN: Obtained by back-transformation of the LSMEAN resulting from ANCOVA of log-transformed data.
* Coefficient of variation of the mean CV (%) =100*(sqrt (exp (SE**2)-1)).
AC Actuation counter; BA MDI Breath-actuated metered dose inhaler; bid Twice daily dosing; BUD Budesonide AC pMDI 2x160 µg bid; CI Confidence interval; CV Coefficient of variation; FAS Full analysis set; FEV_1 Forced expiratory volume in 1 second; LS Least square; pMDI Pressurised metered dose inhaler; SE Standard error; SYM BAI Symbicort BA MDI 2x160/4.5 µg bid; SYM pMDI Symbicort AC pMDI 2x160/4.5 µg bid.

Based on p-values unadjusted for multiplicity, there were no statistically significant differences between the Symbicort treatment groups for the secondary variables (morning and evening PEF, asthma symptoms, use of rescue medication, symptom-free days, and asthma-free days) with the exception for awakening-free nights, which favoured Symbicort AC pMDI over Symbicort BA MDI.

A vast majority of patients reported that it was extremely easy or very easy to use the BA MDI device, and to determine when it was running out of the medication. Over 99% of the patients reported successful drug delivery with the BA MDI device. These results were similar to those obtained with currently marketed AC pMDI device.

Summary of safety results

There were 21 (29.6%) patients in Symbicort BA MDI group, 24 (33.8%) patients in Symbicort AC pMDI group, and 19 (26.8%) patients in budesonide AC pMDI group who experienced at least 1 AE with onset during treatment period.

There was 1 patient who had an SAE during the treatment period in the study, and that patient was in Symbicort AC pMDI group. None of the AEs resulted in death.

In total, 8 patients discontinued treatment due to AEs: 2 (2.8%) patients in Symbicort BA MDI group, 3 (4.2%) patients in Symbicort AC pMDI group, and 3 (4.2%) patients in budesonide AC pMDI group.

The highest incidence of AEs was observed in SOC infections and infestations in Symbicort AC pMDI group (17 [23.9%]), Symbicort BA MDI group (12 [16.9%]), and budesonide AC pMDI group (9 [12.7%]).

Overall, no differences in safety profiles were identified between Symbicort BA MDI, Symbicort AC pMDI, and budesonide AC pMDI in the study.