	SYNOPSIS	

A comparison of Symbicort Single Inhaler Therapy (Symbicort Turbuhaler 160/4.5 μg, 1 inhalation b.i.d. plus as needed) and conventional best practice for the treatment of persistent asthma in adults - a 26-week, randomised, open-label, parallel-group, multicentre study. Study SPAIN

National co-ordinating investigators

None appointed for this study.

Study centre(s)

This study was carried out in 69 centres that included 791 patients and finally 654 were randomized. The participating centres were selected from Primary Care (30), Allergy (23) and Pneumology (16).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary objective was to compare the efficacy of Symbicort SMART therapy with the best conventional therapeutic practice in adult patients with persistent asthma.

A secondary objective was to collect safety data from adult patients with persistent asthma in both treatment groups.

Another secondary objective was to study the use of health resources and days off work related to asthma in the study patients treated with Symbicort SMART and with the best conventional medical therapy.

The primary variable was: time to first severe asthmatic exacerbation. Severe asthma exacerbation was defined as deterioration in asthma leading to at least one of the following:

1. Hospitalization/ Emergency room (or equivalent) treatment due to asthma

2. Oral GCS treatment for at least 3 days

The secondary variables were: number of severe asthma exacerbations, change in ACQ score from randomisation to the average value from visits 2-4, and mean use of as-needed medication during the treatment period, prescribed asthma medication during the treatment period, SAEs and dropouts due to AEs.

Study design

This was a 26-week, randomised, open-label, parallel group study in asthmatic patients. 654 patients were randomised to one of the following two treatment groups in a balanced (1:1) way:

- Symbicort 160/4.5 µg, 1 inhalation twice daily + as needed additional dosage if necessary (Symbicort SMART). After Visit 1, maintenance dose adjustment was allowed up until 2 inhalations twice daily or 1 inhalation twice daily, adding another class of anti-asthmatic medication based on the investigator's judgement

- The best conventional practice, active stepped and individualized treatment in accordance with both international (GINA) (1) and national (GEMA) (2) guidelines for asthma treatment

Target subject population and sample size

Female and male outpatients 18 years of age, with persistent asthma currently treated with inhaled glucocorticosteroids (ICS) combined or not with a long-acting b2-agonist (LABA). The dose of ICS had to be 400 µg/day of budesonide (or equivalents). Patients should have had a history of suboptimal asthma control within 1 month prior to enrolment, as judged by the investigator .

It was under the assumption that, at the end of the study, 11% of the patients would have experienced a severe asthma exacerbation in one treatment group compared to 6% of the patients from the other group. Using a log-rank test, a sample size of 500 patients per treatment group was required in order to detect this difference with 80% probability.

However, the study was prematurely stopped, because it was not possible to recruit the sample size required in the period of time established. For this reason, only a description of data is shown in the present report.

A pooled analysis of the data from studies D5890L00010 and D5890L00016 will be perform.

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

Investigational product was Symbicort Turbuhaler, 160/4.5 µg/dose budesonide/formoterol (delivered dose), 1 inhalation b.i.d. as maintenance treatment plus as needed, in response to symptoms (Symbicort SMART®). After Visit 1, maintenance dose adjustment was allowed up to 2 inhalations twice daily or 1 inhalation twice daily, adding another class of anti-asthmatic medication based on the investigator's judgement.

Comparator products were any conventional best practice (CBP) treatments, except Symbicort SMART and/or maintenance with oral glucocorticosteroids prescribed at the discrection of the investigator according to GINA and GEMA guidelines (1, 2)

This was an open label study and the investigator prescribed the investigational product(s). AstraZeneca did not supply the investigational product(s) to the participating sites. Instead, the patients picked up the medication at a local pharmacy, hence the batch number(s) for investigational product and comparators are not available in the study database.

Duration of treatment

The treatment period lasted for 26 weeks.

Statistical methods

Due to problems with recruitment, the number of patients in the analysis is lower than planned in the sample size calculation. This will imply lower power, the chance to detect differences has been reduced. This must be considered in the interpretation of data. Therefore the presentation of data may be viewed from a descriptive perspective only All analyses were based on the full analysis set, as defined in the ICH E9 guidelines. In the full analysis set, all randomized patients who have efficacy data post randomization were included. In this report the planned analyses is presented with treatment mean differences and associated 95% Confidence Intervals.

The time to first severe asthma exacerbation is described using Kaplan-Meier curves. The treatment groups were compared using a Cox proportional hazards model with treatment as a factor.

The mean number of severe asthma exacerbation per patient was compared using a Poisson regression model with treatment as a factor and the time in the study as a offset variable. Confidence intervals and p value were adjusted for over dispersion.

Subject population

Patient flow, demographic characteristics and analysis sets are shown in Table S1

Table S1 Patient flow

	Symbicort SMART	**CBP**	Total
Enrolled patients			**791**
Not randomized			**137**
Eligibility criteria not fulfilled			**99**
Adverse event			**4**
Patient’s voluntary withdrawal			**16**

Lost to follow-up			**14**
Other reason			**4**
Randomized	328	326	**654**
Discontinued	58	37	**95**
Incorrect inclusion	2	0	**2**
Severe protocol violation	7	4	**11**
Adverse event	3	2	**5**
Patient's voluntary withdrawal	17	7	**24**
Lost to follow-up	12	8	**20**
Patient's incorrect randomization	0	1	**1**
Other reason	17	15	**32**
Completed	270	289	**559**

Table S2 Demographic and baseline characteristics of the full data set

		Symbicort SMART (n=328)	**CBP (n=326)**	**Total (n=654)**
Sex (n and % of patient)	Male	110 (33.5)	124 (38.0)	234 (35.8)
	Female	218 (66.5)	202 (62.0)	420 (64.2)
Age	Mean (SD)	43.7 (16.4)	44.3 (16.5)	44.0 (16.5)
	Range	18-89	17-82	17-89
Race (n and % of patient)	Caucasian	322 (98.2)	322 (98.8)	644 (98.5)
	Black	3 (0.9)	-	3 (0.5)
	Oriental	1 (0.3)	-	1 (0.2)
	Other	2 (0.6)	4 (1.2)	6 (0.9)
LABA use (n and % of patient)		262 (79.9)	264 (81.0)	526 (80.4)
ICS dose/day (µg) before randomization(expressed as BDP equivalent)[a]	Mean (SD)	1028 (590)	1040 (592)	1034 (591)
	Range	200-4000	250-4000	200-4000
Median time since diagnosis (yrs)	Median	9.7	11.2	10.5
	Range	0.3-57.4	0.3-60.6	0.3-60.6
No of as needed inhalations/day	Mean (SD)	1.6 (1.2)	1.6 (1.2)	1.6 (1.2)

		Symbicort SMART (n=328)	CBP (n=326)	Total (n=654)
	Range	0.0-8.7	0.0-7.8	0.0-8.7
As needed free days (%)	Mean (SD)	24.4 (26.7)	22.3 (26.4)	23.3 (26.6)
	Range	0.0-100.0	0.0-100.0	0.0-100.0
Smoking Status (n and % of patient)	Non Smoker	209 (63.7)	210 (64.4)	419(64.1)
	Ex-Smoker	63 (19.2)	61 (18.7)	124 (18.9)
	Occasional Smoker	16 (4.9)	18 (5.5)	34 (5.2)
	Habitual Smoker	40 (12.2)	37 (11.4)	77 (11.8)
No of pack years	Mean (SD)	4.4 (4.9)	4.6 (2.8)	4.5 (4.0)
	Range	0-50	0-9	0-50
PEF(L/min) pre BD	Mean (SD)	356.3 (129.8)	355.4 (117.4)	355.9 (123.7)
	Range	100-900	100-850	100-900
PEF(L/min) post BD	Mean (SD)	385.8 (128.4)	384.4 (116.2)	385.1 (122.9)
	Range	100-900	110-780	100-900

[a] ICS dose is converted to BDP (beclomethasone dipropionate equivalent).

Table S3 Analysis sets

Analysis sets	Symbicort SMART		CBP	
Patients randomized	328		326	
Patients included in the Safety Analysis Set	326		326	
Patients excluded from Safety Analysis Set	2	No Symbicort SMART medication taken	0	No CBP medication taken
Patients included in the Full Analysis Set	328		326	
Patients excluded from the Full Analysis Set	0		0	

A total of 654 patients were included in the full analysis set (n=328 for Symbicort SMART and n=326 for CBP). The baseline data were comparable between treatments.

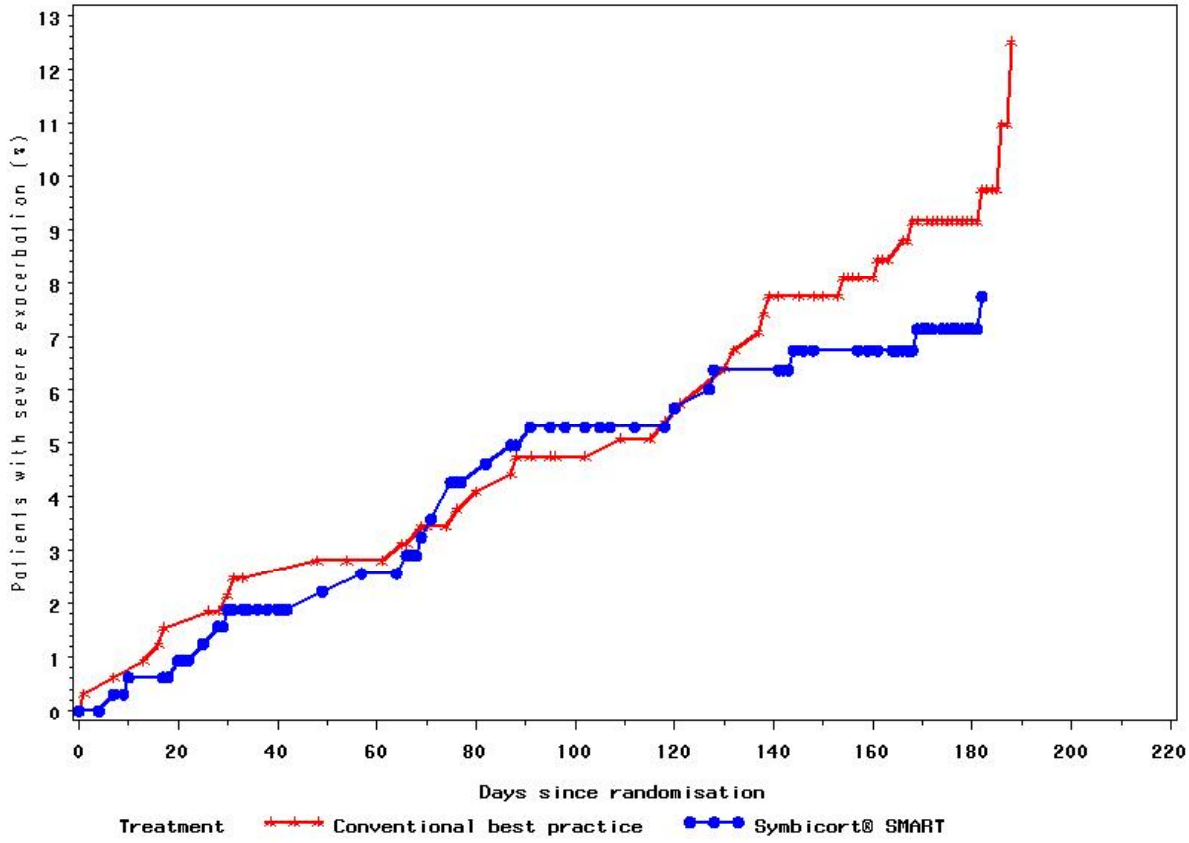
Summary of efficacy results

Tables and figures are presented in Sections 7.2 and 7.3

Primary efficacy variable

Time to first severe asthma exacerbation was described by the following Kaplan-Meier plot. The Figure S1 shows the proportion of patients with severe asthma exacerbation after the date of randomisation (days). It can be observed that the two curves were similar up to about 4 months, but with a lower proportion of patients with severe exacerbation in the Symbicort SMART group at the end of the study. A Cox PH model analysis gave a hazard ratio of 0.748 with a corresponding 95% CI of (0.43, 1.29).

Figure S1. Kaplan-Meier plot of time to first severe asthma exacerbation



Secondary efficacy variable

- There were fewer patients with severe exacerbations in the Symbicort SMART group (22, 6.7%) than in the CBP group (31, 9.5%). Only 5 patients experienced two severe asthma exacerbations (2 vs 3, respectively) and no patient had more than two severe exacerbations during the whole study period.

- ACQ score. Patients from Symbicort SMART group showed a baseline score of 1.58 points and an average value during Visits 2-4 of 0.99 points, the CBP group changed from a baseline score of 1.50 points to an average value during visits 2-4 of 1.07 points. The treatment difference for the change in ACQ score was -0.12 [95%CI: -0.23, -0.01]

- Daily use of as-needed medication. The mean number of daily inhalations in the Symbicort SMART group was 1.03 compared to 1.02 inh in the CBP group. The median of highest number of inhalations in one single day was 2 inh in both treatment groups. 4 patients in the Symbicort SMART group required more than 8 inhalations for at least one day during the study period compared to 8 patients in CBP group. In the comparison of treatments the mean difference was 0,018 [95%CI: -0.14, 0.18]

- Use of inhaled steroids. The mean daily dose of inhaled corticosteroids for each treatment group was 539 µg in the Symbicort SMART group compared to 670 µg in the CBP group. The mean daily dose IGCS use expressed as BDP (beclomethasone) equivalent was also lower in the Symbicort SMART versus the CBP arm (799 versus 1184 µg/day; this represented a 33% reduction in the mean total inhaled steroid daily dose).

Summary of safety results

Table S4 Number (%) of patients who had a serious adverse event or event leading to study discontinuation (safety analysis set)

	N (%) of patients who had an adverse event in each category[a]			
	Symbicort SMART (n=326)		CBP (n=326)	
Category of adverse event	n	(%)	n	(%)
Serious adverse events	9	(2.8%)	5	(1.5%)
Serious adverse events leading to death	0	(0.0%)	0	(0.0%)
Serious adverse events not leading to death	9	(2.8%)	5	(1.5%)
AEs leading to discontinuation of study	3	(0.9%)	2	(0.6%)
	Total number of adverse events			
Serious adverse events	11		5	
Serious adverse events leading to death	0		0	
Serious adverse events not leading to death	11		5	
AEs leading to discontinuation of study	9		2	

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

Table S5 Number (%) of patients who had at least 1 serious adverse event in any system organ class, sorted by decreasing order of frequency as summarized over all treatment groups (safety analysis set)[a]

	Symbicort SMART (n=326)		CBP (n=326)	
System organ class	**n**	**(%)**	**n**	**(%)**
Infections and infestations	3	(0.9%)	2	(0.6%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	3	(0.9%)	1	(0.3%)
Gastrointestinal disorders	2	(0.6%)	0	
Injury, poisoning and procedural complications	1	(0.3%)	0	
Congenital, familial and genetic disorders	1	(0.3%)	0	
Eye disorders	1	(0.3%)	0	
Nervous system disorders	0		1	(0.3%)
General disorders and administration site conditions	0		1	(0.3%)

a The table does not count multiple events in the same SOC for the same patient. It counts the number of unique combinations of SOC and patient.

Table S6 Number (%) of patients who had at least 1 event leading to study discontinuation in any system organ class, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set) [a]

	Symbicort SMART (n=326)		CBP (n=326)	
System organ class	**n**	**(%)**	**n**	**(%)**
Nervous system disorders	2	(0.6%)	1	(0.3%)
Vascular disorders	1	(0.3%)	0	
Skin and subcutaneous tissue disorders	1	(0.3%)	0	
Infections and infestations	1	(0.3%)	0	
General disorders and administration site conditions	1	(0.3%)	0	
Eye disorders	1	(0.3%)	0	
Cardiac disorders	1	(0.3%)	0	
Respiratory, thoracic and mediastinal disorders	0		1	(0.3%)

a The table does not count multiple events in the same SOC for the same patient. It counts the number of unique combinations of SOC and patient.

A total of 652 randomized patients were included in the safety analysis dataset. There were no fatal SAE in the study.

As seen from Table S4, there were a total of 11 serious adverse events in the Symbicort SMART arm versus 5 serious adverse events in the CBP arm. In terms of the number of AEs that led to discontinuation of the study, the number was 9 versus 2 for Symbicort SMART and CBP arm, respectively.

There were 11 randomized patients in Symbicort SMART arm and 2 randomized patients in CBP arm who experienced a serious adverse event. A total of 5 patients discontinued the study due to an AE 3 versus 2 patients, for Symbicort SMART and CBP, respectively. In this study, no clinically important differences between the two treatment groups were observed with regard to the overall pattern of reported SAEs (fatal and non-fatal) or DAEs. Both Symbicort SMART and CBP were well tolerated and no safety concerns were identified.