Drug product:	Symbicort®	**SYNOPSIS**	
Drug substance(s):	Budesonide/formoterol		
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Real life effectiveness in asthma of Symbicort® Single Inhaler Therapy (RELEASE)

Study centre(s)

This multicentre study was conducted at 78 primary care centres in the UK. Sixty-six of the 78 centres enrolled patients into the study.

Publications

There were no publications based on this study prior to the date of the report.

Study dates		**Phase of development**
First patient enrolled	27 September 2005	Therapeutic confirmatory (III)
Last patient completed	18 December 2006	

Objectives

The primary objective of the study was to compare Symbicort® (budesonide 160 µg/inhalation and formoterol fumarate dihydrate 4.5 µg/inhalation) as single inhaler therapy, with a subject's previous therapy (including low dose inhaled corticosteroids), by assessment of the changes in the Asthma Control Questionnaire (ACQ) in uncontrolled asthmatic subjects.

No secondary objectives were specified in the clinical study protocol.

Study design

This was an open, multicentre study with a 4-week run-in period and a 26-week treatment period when patients with not optimally controlled asthma (RCP-3 score>0) received Symbicort as single inhaler therapy. Patients attended a screening visit 4 weeks before

initiation of study treatment, an initiation of study treatment visit at 0 weeks and 3 further visits at 4, 18 and 26 weeks. They were also contacted by telephone on 2 occasions at 8 and 12 weeks.

Target patient population and sample size

The target patient population was patients with confirmed mild to moderate asthma (minimum of 6 months documented history prior to enrolment), who had at least one positive answer on the Royal College of Physicians 3 questions (RCP-3) questionnaire at baseline (visit 2). Patients were also currently receiving a daily dose of 200 to 1000 µg of beclomethasone dipropionate (BDP) or 100 to 500 µg of fluticasone or 200 to 800 µg of budesonide or equivalent (in addition to reliever and other medication, such as a long-acting β_2-agonist [LABA]) for at least 2 weeks prior to enrolment.

Sample size calculations estimated that approximately 50 patients would be sufficient to detect a clinically relevant change in the primary outcome variable, ACQ. However, a sample size of 500 patients was initially considered appropriate to assess the impact of the single inhaler therapy management option within clinical practice. The sample size was increased to approximately 600 following protocol amendment 3 dated 3 July 2006.

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

Symbicort® (budesonide/formoterol) Turbohaler® 160/4.5 µg delivered dose, twice daily (one inhalation in the morning and one inhalation in the evening) and as required in response to symptoms (prn). Patients were instructed to follow an asthma management plan and to contact the doctor/nurse, if using 9-12 doses in total every day for more than 2 weeks, or more than 12 doses taken in total on any day were used. Batch numbers: GD945/1, GL1161 and GM1177 were used.

Duration of treatment

26 weeks

Criteria for evaluation (main variables)

The baseline value for the outcome variables was the value recorded following the run-in period and prior to initiation of study treatment.

Patient reported outcomes (PROs)

- Primary variable:
  - Change in ACQ score from baseline
- Secondary variables:
  - Change in Asthma Quality of Life Questionnaire (standardised version) (AQLQ(S)) domain and overall scores from baseline

- Change in Satisfaction with Asthma Treatment Questionnaire (SATQ) scores from baseline
- Change in the individual and total RCP-3 scores from baseline
- Study medication use including mean number of total and as-needed inhalations per day, number (%) of patients taking more than a total of 12 inhalations on at least 1 day and number (%) of patients taking at least 9 inhalations in total every day for more than 2 weeks

Efficacy

- Secondary variables:
  - Change in forced expiratory volume in one second (FEV_1) from baseline
  - Change in peak expiratory flow (PEF) from baseline

Safety

- Safety variables:
  - The nature, incidence and severity of adverse events (AEs), including serious AEs (SAEs) and discontinuations due to AEs (DAEs)

Statistical methods

The primary and secondary efficacy and PRO variables were analysed using a full analysis set, which comprised of all patients with at least one assessment of efficacy after initiation of study treatment,

Primary variable: The difference in ACQ between baseline and the average of available data for 4, 18 and 26 weeks was analysed by a paired t-test. A difference of 0.5 was deemed to represent clinical significance. In addition, the difference in ACQ between baseline and 4 weeks was analysed by a paired t-test, to assess whether Symbicort single inhaler therapy provided an early onset of action.

Secondary variables: The changes in AQLQ(S), SATQ, FEV_1 and PEF were analysed using the paired test. The changes in RCP-3 from baseline were analysed using the Wilcoxon signed rank test. Study medication use was summarised using standard summary statistics.

Patient population

The patient population and disposition are shown in Table S1. In total, 639 patients from 66 centres were enrolled in the study and entered the run-in period. Of these, 573 patients entered the treatment period and 571 patients received Symbicort as single inhaler therapy. Seventy-five (13.1%) patients were discontinued after entering the treatment period, 19 (3.3%) patients due to adverse event.

Table S1 Patient population and disposition

	Number (%)[c] of patients	
Population		
Number enrolled	639	
Number entered in treatment period	573	
Disposition		
Number discontinued	75	(13.1)
Number discontinued due to:		
Adverse event [a]	19	(3.3)
Voluntary discontinuation by patient	21	(3.7)
Lost to follow up	21	(3.7)
Severe non-compliance with protocol	7	(1.2)
Other	7	(1.2)
Number of completers	498	(86.9)
Analysis sets		
Number analysed for safety [b]	571	(99.7)
Number analysed for PRO and efficacy (Full analysis set)	564	(98.4)

[a] One patient entered the treatment period and was discontinued due to adverse event, but was not treated. Another patient completed the study, but was also recorded as treatment discontinued due to adverse event. A further patient classed as 'severe non-compliance' as the main reason for discontinuation had a discontinuation due to adverse event. This accounts for the 20 patients classed as discontinuations due to adverse event in Table 36.

[b] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing

[c] Percentages are based on number of patients entered in study treatment period

The patient demographic and baseline disease characteristics are given in Table S2. The mean age of the population was 48 years (range 18 to 89 years) and 98% of the study population were of Caucasian origin. All patients had a diagnosis of asthma for at least 6 months and were receiving maintenance inhaled corticosteroid treatment, either alone (349, 62%), with an additional LABA (28, 5%) or as part of an inhaled corticosteroid/LABA combination (187, 33%) before the study.

Table S2 Demographic and baseline characteristics

	Total	
Demographic characteristics		
Sex (n and % of patients)		
Male	242	(42.9)
Female	322	(57.1)
Age (years)		
Mean (range)	48.4	(18 to 89)
Ethnic origin (n and % of patients)		
Caucasian	553	(98.0)
Black	4	(0.7)
Oriental	0	
Other	7	(1.2)
Disease characteristics		
Time since asthma first diagnosed (years)		
Mean (range)	16.65	(0.5 to 66.2)
FEV_1 (L)		
Mean (range)	2.662	(0.88 to 5.07)
Asthma control questionnaire score		
Mean (range)	1.72	(0 to 5)
RCP-3 score		
Mean (range)	1.8	(0 to 3) [a]
Inhaled corticosteroid dose at entry (µg)		
Mean (range)	487.0	(100-1000)
Previous inhaled corticosteroid (n and % of patients)		
Inhaled corticosteroid only	349	(61.9)
Inhaled corticosteroid + LABA (as monoproducts)	28	(5.0)
Inhaled corticosteroid/LABA combination	187	(33.2)

[a] One patient with no positive RCP-3 answer was incorrectly included in the treatment period

Patient reported outcome (PRO) results

Primary variable: Change in ACQ score from baseline

Treatment with Symbicort single inhaler therapy resulted in statistically significant and clinically relevant improvements in asthma control compared with their previous asthma therapy, as indicated by the change in ACQ score from baseline (mean change from baseline -0.54, p<0.0001, Table S3).

The asthma control of the patients also significantly improved following treatment with Symbicort single inhaler therapy, irrespective of whether the patients had previously received ICS alone, or with a LABA, either additionally or as a combination product (Table S3).

Table S3 Statistical analysis of changes in ACQ scores from baseline to treatment period, full analysis set

	Baseline ACQ [a]		**Change from baseline** [b]		**95% CI**	**P-value**
	Mean	Range	Mean	Range		
All patients (n=556)	1.72	0.0 to 5.0	-0.54	-4.4 to 3.2	-0.62, -0.46	<0.0001
Pre-study treatment						
ICS only (n=342)	1.72	0.0 to 5.0	-0.64	-4.4 to 3.2	-0.74, -0.54	<0.0001
ICS + LABA (n=28)	1.90	0.0 to 5.0	-0.42	-2.4 to 2.2	-0.80, -0.04	0.0314
ICS/LABA combination (n=186)	1.70	0.0 to 4.6	-0.37	-3.9 to 3.0	-0.50, -0.25	<0.0001

[a] The overall ACQ score can take a range from 0 to 6. A lower score indicates a greater level of control.
[b] Derived as (average ACQ score at visits 3-5) – (baseline ACQ score). A negative change of ≤-0.5 from baseline was considered a clinically relevant improvement in asthma control.

Fast control of asthma symptoms was achieved within 4 weeks with Symbicort single inhaler therapy (mean change from baseline –0.47, p<0.0001).

Change in AQLQ(S) from baseline

The AQLQ(S) was used to assess quality of life in this 6-month study. Symbicort single inhaler therapy treatment increased the overall and domain scores statistically significantly compared to baseline (Table S4). The changes in overall, symptom, environment and emotional domain scores were also considered clinically relevant.

Table S4 Statistical analysis of changes in AQLQ (S) from baseline to treatment period, full analysis set

	Baseline AQLQ(S) [a]		Change from baseline [b]		95% CI	P-value
	Mean	Range	Mean	Range		
All patients						
Overall (n=553)	5.16	1.6 to 6.9	0.56	-3.1 to 3.8	(0.48, 0.63)	<0.0001
Symptom (n=556)	5.02	1.3 to 7.0	0.64	-3.9 to 4.7	(0.55, 0.73)	<0.0001
Activity (n=555)	5.43	1.7 to 7.0	0.43	-3.5 to 3.2	(0.35, 0.50)	<0.0001
Emotional (n=555)	5.21	1.0 to 7.0	0.57	-3.6 to 4.4	(0.48, 0.67)	<0.0001
Environment (n=556)	4.85	1.0 to 7.0	0.60	-2.8 to 4.3	(0.52, 0.69)	<0.0001
Pre-study treatment						
ICS only						
Overall (n=343)	5.18	2.2 to 6.9	0.64	-2.1 to 3.6	(0.55, 0.73)	<0.0001
ICS + LABA						
Overall (n=28)	4.99	2.0 to 6.9	0.50	-2.9 to 3.1	(0.08, 0.93)	0.0208
ICS/LABA combination						
Overall (n=182)	5.16	1.6 to 6.9	0.41	-3.1 to 3.8	(0.27, 0.54)	<0.0001

[a] The overall and domain scores can take a range from 1 to 7. A higher score indicates a greater level of quality of life.

[b] Derived as (average AQLQ(S) score at visits 3-5) – (baseline AQLQ(S) score). A positive change of ≥0.5 from baseline was considered a clinically relevant improvement in quality of life.

Change in SATQ from baseline

Patients were more satisfied with Symbicort single inhaler therapy than their previous asthma therapy in all respects with significant changes in SATQ overall and domain scores for effectiveness, ease of use, burden of asthma medication, and side effects and worries (all p<0.0001).

Change in RCP-3 from baseline

Asthma control, as assessed by the total RCP-3 score significantly improved on Symbicort single inhaler therapy compared to previous asthma therapy (mean change -0.9, p<0.0001).

Use of Symbicort

The total use of Symbicort during the treatment period, as derived from diary card data is shown in Table S5. The mean number of total inhalations per day was 2.74 and more than 2

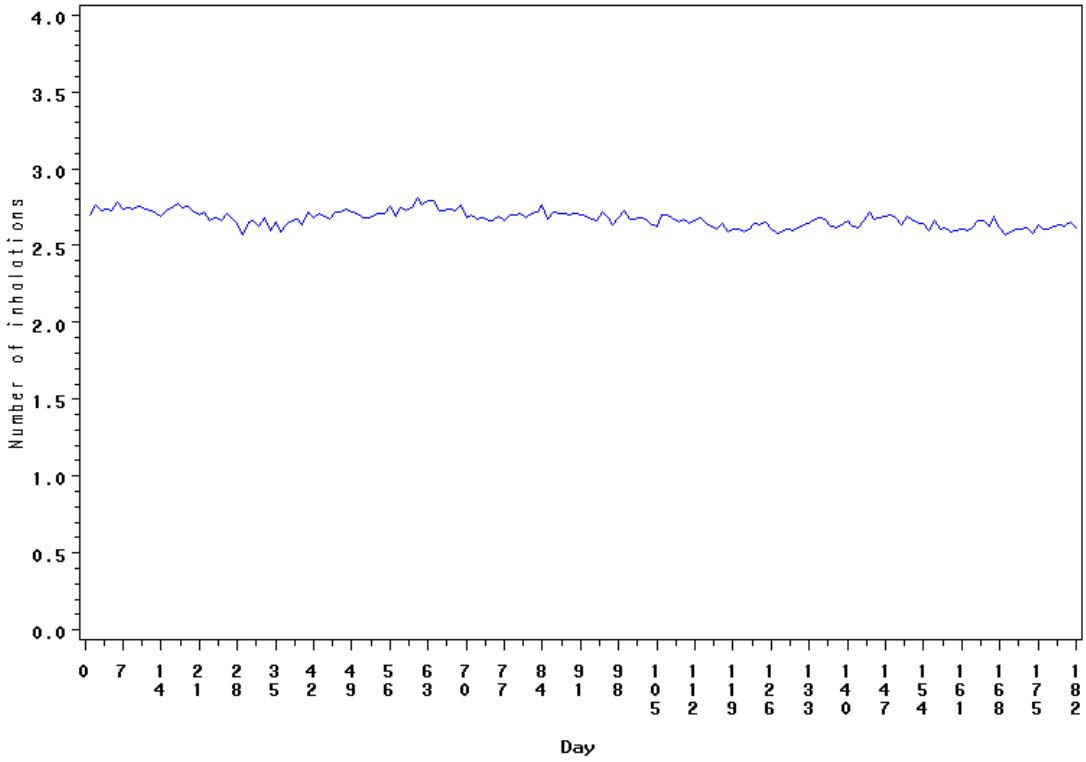
inhalations per day were only used on 36% of days. The use of Symbicort was fairly consistent throughout the study (Figure S1).

Symbicort single inhaler therapy allows temporary use of high as-needed doses of Symbicort in response to an increase in symptoms. There was little evidence of overuse in this study as on only 0.9% of days were ≥9 inhalations used. Four (0.7%) patients took >12 inhalations on at least 1 day and 6 (1.1%) patients took at least 9 inhalations every day for more than 2 weeks. Seven patients in total were in one or both of these high use categories, for which they were instructed to visit the doctor/nurse according to the asthma management plan.

Table S5 Total use of Symbicort (maintenance dose and as-needed) during the treatment period, full analysis set

	Mean	**SD**	**Range**
Number of patients n=555			
Mean number of inhalations per day	2.74	1.19	1.0 to 10.8
Percentage of days using ≥3 inhalations	35.66	34.00	0 to 100.0
Percentage of days using ≥5 inhalations	8.39	20.23	0 to 100.0
Percentage of days using ≥9 inhalations	0.87	5.42	0 to 85.0

Figure S1 Mean total number of inhalations of Symbicort per day (maintenance dose and as-needed)



Efficacy results

The lung function of patients significantly improved following treatment with Symbicort single inhaler therapy (mean increase in PEF 11.9 L/min, $p<0.0001$; mean increase in FEV_1 0.04 L, $p=0.001$) compared with previous therapy.

Safety results

The mean exposure to Symbicort single inhaler therapy was 170 days with a median exposure of 183 days.

A summary of AEs in each category is shown in Table S6. There were no deaths during the study and the incidence of non-fatal SAEs and discontinuations due to AE were low. None of the SAEs were considered causally related to Symbicort single inhaler therapy. Nine (1.6%) patients discontinued the study due to drug related AEs such as headache, palpitations, oral pain, pharyngolaryngeal pain, dry mouth and dysphonia. Nine (1.6%) patients who discontinued due to AE had AEs related to the disease under study (asthma, wheezing, dyspnoea, cough).

Table S6 Number (%) of patients who had at least 1 treatment-emergent adverse event in any category, safety analysis set

Category of adverse event	Number (%) of patients who had an adverse event in each category [a] (n=571)	
Any adverse events	397	(69.5)
Serious adverse events		
Serious adverse events leading to death	0	
Serious adverse events not leading to death	16	(2.8)
Discontinuations of study treatment due to adverse events	20	(3.5)
Other significant adverse events	0	(0)
Causally related AEs	42	(7.4)
Causally related SAEs	0	

[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.

The most commonly reported AEs were lower respiratory tract infection, upper respiratory tract infection, nasopharyngitis and back pain (≥5%). The system organ class in which most AEs were reported was infections and infestations, reported by 43% of patients.

The incidence of common steroid associated AEs, such as oral candidiasis (2.6%) in patients treated with Symbicort single inhaler therapy was low. Patients had been instructed to rinse out their mouth with water after inhalation of the maintenance doses of Symbicort. There was no indication of any systemic steroid related side effects, such as adrenal suppression or growth impairment.