Rapporteur's Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

Budesonide + Formoterol

Symbicort® Turbohaler® 80/4.5 µg, 160/4.5 µg, 320/9 µg

DE/W/046/pdWS/001

Rapporteur:	Germany
Finalisation procedure:	07.11.2012
Date of finalisation of PAR:	07.12.2012

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Symbicort® Turbohaler® 80/4.5 µg, 160/4.5 µg, 320/9 µg
INN (or common name) of the active substance(s):	Budesonide + Formoterol
MAH (s):	Astra Zeneca
Pharmaco-therapeutic group (ATC Code):	R03AK07
Pharmaceutical form(s) and strength(s):	Symbicort® Turbohaler® 80/4.5 µg, 160/4.5 µg, 320/9 µg dry powder for inhalation

I. EXECUTIVE SUMMARY

An update of the paediatric information in Section 4.2 and 5.1 of the SmPC is proposed.

Summary of outcome

☐ No change

X Change

X New study data: section 5.1

☐ New safety information: <section(s) xxxx, xxxx>

☐ Paediatric information clarified: <section xxxx>

☐ New indication: <section(s) xxxx, xxxx>

II. RECOMMENDATION

Based on the clincial data submitted by the applicant an update of the paediatric information in Sections 4.2 and 5.1 of the SPC is proposed.

III. INTRODUCTION

Astra Zeneca submitted 39 completed paediatric studies for the combination of budesonide and formoterol, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Symbicort Turbuhaler and that there is no consequential regulatory action

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical studies

The licensed formulation in the EU is Symbicort Turbuhaler. Symbicort pMDI is licensed in the US for asthma patients 12 years of age and older. According to the applicant a clinical development program for children 6 to 11 years of age is ongoing. Symbicort pMDI studies are also included in this document.

IV.2 Non-clinical aspects

This section is not applicable, because no non-clinical studies have been submitted.

IV.3 Clinical aspects

1. Introduction

Symbicort Turbuhaler, a fixed combination dry powder inhaler containing budesonide and formoterol was first approved in the EU in 2000 via a MRP with Sweden as reference member state. Symbicort is indicated for the maintenance treatment of asthma in adults and children aged 6 years and above, where the combination of an inhaled corticosteroid and a long-acting beta 2- agonist is appropriate. The higher strengths (160/4.5 µg and 320/9µg) also hold a COPD indication.
Symbicort Turbuhaler 320/9 µg is not licensed for children below the age of 12.
The applicant claims that Symbicort Turbuhaler has a harmonised SPC in all member states.

Symbicort MDI is not approved in the EU. Any how, the applicant has included studies on the MDI which are also discussed below.

The MAH submitted report(s)/ extended synopsis for the studies displayed in the table below:

Listing of studies, not previously submitted, with paediatric patients

Study code	Country/region	Target pop (years)	N of patients[a]	
			Total	<18 years
Symbicort maintenance therapy studies (Symbicort Turbuhaler and Symbicort pMDI)				
SD-039-0353	Multi-national	4-17	286	286
SD-039-0688	Europe	4-11	630	630
SD-039-0714	UK	12-17	271	271
CN-039-0001	China	12-80	320	3
SD-039-0681	Multi-national	≥12	680	109
SD-039-0682	Multi-national	6-11	622	622
SD-039-0715	Multi-national	≥12	673	89
D5896C00001	US	≥12	618	97
SD-039-0716	US	≥6	511	106
SD-039-0717	US	≥12	596	43
SD-039-0718	US	6-15	411	411
SD-039-0719	US	6-11	186	186
SD-039-0725	US	6-15	521	521
SD-039-0726	US	≥16	751	28
SD-039-0728	US	≥12	708	90
SD-039-0689	Europe	≥12	456	13
D5890C00010	Japan	≥16	348	1
Symbicort adjustable maintenance dosing studies (Symbicort Turbuhaler and Symbicort pMDI)				
SD-039-0686	Europe	≥12	658	15
BS-039-0002	Switzerland	≥12	142	5
CF-039-0001	France	≥12	873	50
CF-039-0002	France	≥12	2068	77
CI-SYM-0001	Italy	≥6	2358	149
DC-039-0001	Canada	≥12	995	66
LD-039-0001	Sweden	≥12	1034	75
MA-SYM-0001	Multi-national	≥12	537	33
D5896C00005	US	≥12	1222	173
Symbicort maintenance and reliever therapy (Symbicort Turbuhaler only)				
SD-039-0667	Multi-national	12-80	697	109
SD-039-0668	Multi-national	12-80	1890	121
SD-039-0673	Multi-national	4-80	2760	657
SD-039-0691	Multi-national	≥12	2143	76
SD-039-0734	Multi-national	≥12	3394	354

Listing of studies, not previously submitted, with paediatric patients

Study code	Country/region	Target pop (years)	N of patients[a]	
			Total	<18 years
SD-039-0735	Multi-national	≥12	3335	623
LD-039-0003	Sweden	≥6	491	109
D5890L00004	Canada	≥12	1538	91
D5890C00002	Multi-national	≥12	2309	324
Symbicort as a single dose for the relief of acute bronchoconstriction (Symbicort Turbuhaler only)				
SD-039-0693	Multi-national	≥12	115	5
SD-039-0702	Multi-national	≥12	104	3
Symbicort used as needed only (Symbicort Turbuhaler only)				
AF-039-0001	Finland/Sweden	6-65	92	2
Clinical pharmacology study				
D5896C00013	US	6-11	24	24

[a] Safety population for following locally-run (marketing company) studies: BS-039-0002, CF-039-0001, CF-039-0002, CI-SYM-0001, DC-039-0001, LD-039-0001, MA-SYM-0001 and AF-039-0001; randomised patients for other studies.

2. Clinical studies

Symbicort maintenance therapy:
Symbicort Turbuhaler studies:

SD-039-0353 (1998-1999) Efficacy and safety of budesonide/formoterol Turbuhaler® in a fixed combination in steroid-using asthmatic children - COMIC .

Objective(s): The primary objective was to compare the efficacy of the fixed combination budesonide/ formoterol Turbuhaler® with that of budesonide Turbuhaler.

Study design: This was a 12 week, double-blind, double-dummy, randomised, active-controlled, parallel-group, multi-centre (43 centres in Hungary, the Czech Republic, South Afrika, the UK, Spain , Belgium and Israel) study.

Study population /Sample size:
Male and female asthma patients 4-17 years of age with a baseline FEV1 40 - 90% of predicted normal value and a fixed dose of inhaled GCS at least 6 weeks prior to visit 1. (daily dose:≥ 400 µg budesonide Turbuhaler, ≥ 600 µg budesonide pMDI, ≥ 375 µg fluticasone propionate in any device, ≥ 600 µg beclomethasone dipropionate in any device).
With 100 patients per treatment group, and a standard deviation of 30 L/min in change in morning PEF, it was estimated that a difference in change in PEF of 12 L/min between treatments could be found with 80% power at a 5% significance level using pair-wise comparisons.

Treatments:
Fixed combination of Budesonide/formoterol 2 x 80/4.5 g b.i.d.

Or
Budesonide 2 x 100 g b.i.d.

Outcomes/endpoints

Primary endpoint: change from baseline in morning PEF

Statistical Methods
The primary analysis was an intention-to-treat analysis. For the primary efficacy variable averages were calculated for the last 10 days of the run-in period and for the whole of the treatment period. The change from run-in to the treatment period in these averages was analysed using an ANOVA model with factors treatment, country, age class, and with the run-in average as covariate.

Results

Recruitment/ Number analysed
286 patients were randomised, received active treatment and were analysed for efficacy and safety. 268 patients completed the study. 9 patients in each group discontinued the study.

Efficacy results:
The primary variable increased by 23 L/min in the fixed combination group and 11 L/min in the budesonide group. The difference between the groups was statistically significant ($p<0.001$). Statistically significant difference ($p<0.001$) was also demonstrated for evening PEF where the fixed combination increased by 20 L/min whereas the budesonide group only increased by 8 L/min. In addition, FEV1 measurements and repeated FEV1 measurements over 12 hours, were improved on the 5 % significance level by the fixed combination compared to budesonide alone.

Safety results:
73 patients in the combination group compared to 68 patients in the budesonide group experienced at least one AE. Pharyngitis, respiratory infection and rhinitis were the most frequently reported AEs. 9 patients in each group discontinued the study. 7 patients in the combination group compared to no patient in the budesonide group reported a SAE (5 asthma excerbation/aggrevation). The investigator rated these SAEs not causally related to the study treatment.

Conclusion:
Morning PEF increased significantly more in the combination compared to the budesonide group. Although, generally the treatments were well tolerated, only patients in the combination group reported SAEs. Most of these SAEs were related to deterioration of asthma.

Assessor's comment: This study showed improved lung function as measured as mPEF compared to ICS monotherapy. The higher rate of asthma related SAEs is of concern, although this finding might also be mere chance. According to a histogram in the study report around 15% of the patients were 4-6 years old. This number seems to be to low to draw meaningful conclusions. This study supported the initial approval of the paediatric indication in the EU, which resulted in a license from 6 years of age.

SD-039-0688 (2002-2003): Efficacy and safety of Symbicort® (budesonide/formoterol 80/4.5 µg, 2 inhal. b.i.d.) compared to Pulmicort® (budesonide 100 µg, 2 inhal. b.i.d.) and Pulmicort (budesonide 100 µg, 2 inhal. b.i.d.) plus Oxis® (formoterol 4.5 µg, 2 inhal. b.i.d.) all delivered via Turbuhaler® in steroid using asthmatic children. A double-blind, double-dummy, randomised, parallel-group, phase III, multicentre 12-week study.

Objective(s): primary: to show superior efficacy compared to Pulmicort Turbuhaler.

Study design: randomised, double blind, double dummy, parallel group active controlled, multicentre (80 centres in Europe) 12-week study.

Study population /Sample size:
630 symptomatic male and female asthmatic patients aged 4-11 years treated with 375-1000 µg/d of ICS with a mean morning PEF during the 7 last days of the run-in period of 50-85% of the postbronchodilatory PEF obtained at Visit 1. In order to have 540 evaluable patients (180 patients in each treatment arm), 600 patients were needed to be randomised.

Treatments:
Symbicort Turbuhaler 80/4.5 µg 2 inhalations bid
or
Pulmicort Turbuhaler 100 µg 2 inhalations bid
or
Pulmicort Turbuhaler 100 µg plus Oxis 4.5 µg, each 2 inhalations bid

Outcomes/endpoints
Primary endpoint: Change from baseline to treatment (average of the 12 weeks treatment period) in morning PEF.

Statistical Methods
The statistical analysis was based on the full analysis set. The primary objective was achieved using a t-test under the assumed analysis of variance model. All hypotheses testing was done with two-sided alternative hypotheses and p-values less than 5% were considered statistically significant.

Results

Recruitment/ Number analysed
630 patients were randomised and analysed. 592 completed the study. The main reason for discontinuation in each group (Symbicort: 14, Pulmicort: 13, Pulmicort + Oxis: 11) was that the eligibility criteria were not fulfilled.
The groups were balanced with regard to baseline data.

Efficacy results
Symbicort significantly improved lung function (morning PEF, evening PEF, FEV1) compared to Pulmicort (mPEF (L/min): Symbicort: +27.3, Pulmicort: +16.4, Δ:10.9, p<0,001). The comparison of Symbicort and Pulmicort plus Oxis was not statistically significant (mPEF (L/min): Symbicort +27.3, Pulmicort+ Oxis:+31.5, Δ: -4.2, p= 0.14 . Comparisons for asthma symptoms, asthma control and use of rescues medication between Symbicort and Pulmicort were not significant.

Safety results
39% of the patients in the Symbicort group compared to 40%patients in the Pulmicort group and 37%patients in the Pulmicort+ Oxis group reported at least one AE. Respiratory infection and rhinitis were the most common AEs. 3 patients in the Symbicort group and in the Pulmicort group, respectively, and 5 patients in the Pulmicort+Oxis group experienced a SAE. 1 patient in the Pulmicort group and 2 patients in the Pulmicort+Oxis group discontinued the study due to an AE. Regarding vital signs and laboratory measurements (morning p-cortisol and 24-hour U-cortisol) no clinically important differences between the treatments were observed.

Conclusion: In symptomatic children 4-11 years with asthma Symbicort significantly improved lung function compared to Pulmicort mono-therapy but did not show a benefit over Pulmicort regarding asthma symptoms. No difference in the effect on lung function was found compared to the combination of Pulmicort and Oxis.

Assessor's comment: Rather large improvements with regard to mPEF were seen in all groups. Symbicort was proven to be significantly superior to Pulmicort with this regard. However this did not translate into a benefit with regard to asthma symptoms or asthma control. According to a histogram in the study report around 12% of the patients were 4-5 years old.

SD-039-0714 (2001-2002) Efficacy and safety of budesonide/formoterol Turbuhaler® (160/4.5 µg b.i.d. delivered dose) compared to budesonide Turbuhaler® (200 µg b.i.d. metered dose) in steroid-using asthmatic adolescent patients. A double blind, double-dummy, randomised, parallel group, phase III, multicentre study. (ATTAIN STUDY)

Objective(s):
Primary: to compare the efficacy of formoterol/budesonide Turbuhaler (160/4.5 µg delivered dose bid) with budesonide Turbuhaler (200µg metered dose bid).

Study design
12 weeks, double blind, randomised, parallel group, multi-centre (122 centres in the UK) study.

Study population /Sample size
Symptomatic male and female asthma patients aged 12-17 years, receiving ICS with baseline FEV1 values of 40-90% predicted normal.
A sample size of 150 per group was estimated to have 90% power to detect a difference in mean change in morning PEF of 15 L/min.

Treatments
Symbicort Turbuhaler 160/4.5 µg delivered dose one inhalation bid
or
Pulmicort Turbuhaler 200 µg metered dose one inhalation bid

Outcomes/endpoints
Primary endpoint: change from baseline to the treatment in morning PEF

Statistical Methods
The statistical analysis was based on the intention to treat population. The primary variable was analysed using an analysis of covariance model with treatment and centre as fixed factors and the baseline value as a covariate. All hypotheses testing was done with two-sided alternative hypotheses and p-values less than 5% were considered statistically significant.

Results

Recruitment/ Number analysed
271 patients were randomised to treatment. 219 patients completed the study. 25 patients in the Symbicort group and 27 patients in the Pulmicort group discontinued the study. 270 patients were analysed for safety and 264 patients were analysed for efficacy.

Baseline data
Reversibility, mPEF and ePEF were slightly higher in the Symbicort group.

Efficacy results
Both groups showed an improvement in morning PEF from baseline. The increase was numerically higher in the Symbicort group (Symbicort: +14.9 L/min, Pulmicort: +10.2 L/min). However, the comparison to the Pulmicort group did not result in a significant difference (p=0.286). Except for FEV1 measured at clinics which showed a significant benefit of Symbicort (p=0.01), all other secondary variables improved from baseline but failed to show a significant difference between both treatments.

Safety results
The incidence of AEs was comparable between groups (Symbicort 49.3%, Pulmicort 48,5%). Respiratory infection and pharyngitis were the most common AEs. 6% of the patients discontinued the study due to an AE in the Pulmicort group compared to 2.9% in the Symbicort group. The most common reason was deterioration of asthma. Only two SAEs, one in each group, occurred.

Conclusion:
Both treatment groups were not significantly different with regard to the primary parameter. No safety concern arose.

Assessor's comment: This lower dose study failed to show a significant benefit of Symbicort compared to Pulmicort in increase in mPEF. However a significant difference was seen with regard to FEV1 which might have been the primary parameter of choice.

CN-039-0001 (2003) An open, randomised, active-controlled, multicentre study with a parallel design to assess the efficacy and safety of Symbicort (Budesonide/Formoterol) Turbuhaler® in inhaled steroid-using asthmatic patients

Objective(s):
Primary: to compare the efficacy of formoterol/budesonide Turbuhaler (160/4.5 µg delivered dose) 2 inhalations bid with Budesonide (200µg /dose) + Formoterol (4.5 µg/ dose) two inhalations.

Study design
12 week, open-label, randomised, active controlled, parallel group, multi-centre (9 centres in China) study.

Study population /Sample size
Male and female asthma patients aged 12-80 years, daily use of ICS with baseline FEV1 values of 40-95% predicted normal were enrolled.
100 evaluable subjects were required per group upon SFDA (China State Food and Drug Administration) clinical trial guideline.

Treatments
Budesonide/ Formoterol Turbuhaler 160/4.5 µg two inhalations bid
or
Budesonide Turbuhaler 160µg two inhalations bid plus Formoterol Turbuhaler 4.5 µg two inhalations bid.

Outcomes/endpoints
Primary endpoint: morning PEF

Statistical Methods
The statistical analyses were based on the intention to treat population as well as the per protocol population. Treatment groups were compared using inferential statistics. All hypotheses testing was done with two-sided alternative hypotheses and p-values less than 5% were considered statistically significant.
The primary variable was analysed using an analysis of variance model for factors of treatment, centre, age and baseline average morning PEF.

Results

Recruitment/ Number analysed
320 patients were randomised. 296 patients completed the study. The safety population and the ITT population encompassed 317 patients. The per-protocol populations consisted of 279 patients. Only 3 subjects were in the age range of 12-≤18 years of age.

Baseline data
There were imbalances with more males and more younger subjects in the fixed combination group.

Efficacy results
The efficacy results were consistent between the ITT and the PP population.
Both groups showed an improvement from baseline in morning PEF as well as the other parameters. No significant difference was detected between groups.

Safety results
The incidence of AEs was comparable between groups (fixed combination 11,5%, free combination 10,6%). 1.9% of the patients discontinued due to AEs in the fixed combination group compared to 1.3% in the Symbicort group. The most common reason was deterioration of asthma. Only one SAE occurred, in the fixed combination group.

Conclusion:
Efficacy parameters were not significantly different between groups. Both treatments were well tolerated.

Assessor's comment: This study assesses the effect of Symbicort Turbuhaler in a Chinese population at the higher dose. It is of limited value to this assessment, because only 3 adolescent subjects were enrolled.

SD-039-0689 (2001-2002)Efficacy and safety of Symbicort® (budesonide/formoterol) 1280/36 µg daily delivered dose compared to Pulmicort® (budesonide) 1600 µg metered dose and Pulmicort (budesonide) 1600 µg metered dose plus Oxis® (formoterol) 36 µg delivered dose all delivered via Turbuhaler® in steroid-using asthmatic adolescents and adults. A double-blind, double-dummy, randomized, parallel group, phase III, multicentre study.

Objective(s): The primary objective was to compare the efficacy of Symbicort (budesonide/formoterol) with that of Pulmicort (budesonide) in steroid-using asthmatic adolescent and adult subjects during 12 weeks of treatment.

Study design: The study was a 24-week, double-blind, double-dummy, randomized, reference-controlled, parallel-group, multicentre (54 centres in Australia and Europe) study.

The subjects in the Symbicort and Pulmicort + Oxis group received their treatment for 24 weeks. The subjects in the Pulmicort group were switched after 12 weeks of treatment to either Symbicort or Pulmicort + Oxis for an additional 12 weeks of treatment.

Study population /Sample size:
Male and female asthma patients, ages 12 and above, treated with ≥ 750 µg per day of ICS, and with a pre-bronchodilator FEV1 ≥ 40% and ≤ 85% of predicted were enrolled.
A two group t-test with a 5% two-sided significance level would have 90% power to detect a difference in change in morning PEF of 18 L/min when the sample sizes in these two groups (Pulmicort and Symbicort) were 100 and 200, respectively.

Treatments:
Symbicort® (budesonide/formoterol) Turbuhaler® 320/9 µg per inhalation, 2 inhalations bid
or
Pulmicort® (budesonide) Turbuhaler® 400 µg per inhalation, 2 inhalations bid
or
Pulmicort Turbuhaler 400µg/ inhalation 2 inhalations bid+Oxis® (formoterol) Turbuhaler® 9 µg per inhalation, 2 inhalations bid

Outcomes/endpoints

Primary endpoint: change from baseline to 12 weeks in morning PEF

Statistical Methods
An intention to treat (ITT) analysis was used. The change from baseline to the treatment period in the primary variable, morning PEF, was analysed using an analysis of variance (ANOVA) model with treatment and country as fixed factors and the baseline value as a covariate.

Results

Recruitment/ Number analysed
456 patients (Symbicort: 226, Pulmicort+Oxis:115, Pulmicort/Symbicort: 61, Pulmicort/Pulmicort+Oxis:54) were enrolled and analysed for efficacy and safety, 400 completed the study. 13 patients were < 18 years of age.The number of patients who discontinued the study was comparable between groups. Treatment groups were balanced for most parameters at baseline. However, patients in the Pulmicort/Pulmicort+Oxis group had the lowest number of asthma control days, symptom-free days and rescue free days.

Efficacy results :
Symbicort 320/9 µg 2 inhalations twice daily (1280/36 µg total daily delivered dose) was more effective than Pulmicort 400 µg 2 inhalations twice daily (1600 µg total daily metered dose) in increasing morning PEF, the primary variable of the study, over 12 weeks of treatment in asthmatic subjects not well controlled on inhaled ICS. The mean difference was 32.9 L/min ($p<0.001$). Similar improvements were observed in the Pulmicort + Oxis group as in the Symbicort group. The 95% confidence interval for the difference between Symbicort and the free combination (Pulmicort + Oxis) was entirely within the generally accepted equivalence limits for PEF (± 15 L/min). Results for secondary variables supported those for the primary variable with statistically significant improvements in favour of Symbicort over Pulmicort for evening PEF, total asthma symptom score, daytime asthma symptoms, symptom free days, use of rescue medication/ 24 hours, rescue free days, asthma control days, time to first mild exacerbation, and FEV1. There was no statistically significant difference between Symbicort and Pulmicort + Oxis for any variable.

Safety results:
The main focus of the safety evaluation was the two groups for which treatment was unchanged during the 24-week study: the Symbicort and the Pulmicort + Oxis groups. The proportion of subjects reporting AEs was similar in the two treatment groups, Symbicort (51%) and Pulm+Oxis (55%). The most frequently reported AE in all treatment groups was Respiratory infection. One subject died from Pulmonary embolism after 17 weeks and two days of treatment with Symbicort. The proportion of subjects reporting SAEs, other than death, was similar in the Symbicort and Pulm+Oxis treatment groups (3% for both). The proportion of subjects reporting DAEs was 4% in the Symbicort treatment group and 5% in the Pulm+Oxis treatment group. No clinically important differences as regards s-potassium, s-glucose, vital signs, or ECG variables were identified between the Symbicort and the Pulm+Oxis treatment groups or within these groups over time. There were no statistically significant differences between the Symbicort and the Pulmicort + Oxis treatment groups regarding morning plasma cortisol or stimulated cortisol. Although mean plasma cortisol decreased slightly over time in all groups, 93% of the subjects in the Symbicort group and 89% of the subjects in the Pulmicort + Oxis group still had a normal response to ACTH stimulation at the end of the study.

Conclusion:
Symbicort Turbuhaler 320/9 µg 2 inhalations bid was more effective in improving morning PEF than a corresponding dose of budesonide administered as Pulmicort Turbuhaler 400 µg 2 inhalations bid. Similar outcomes were observed between the Symbicort and the Pulmicort + Oxis group. No new safety concerns were identified and similar safety profiles were observed between the Symbicort and Pulmicort + Oxis treatment groups.

Assessor's comment: The dose administered here exceeds the dose licensed for the adolescent population. However due to the lower number of adolescents, no final conclusions can be drawn

D5890C00010 (2005-2006) An 8-week, randomised, double blind, parallel-group, multi-centre, phase III study comparing the efficacy and safety of Symbicort® Turbuhaler® 160/4.5 µg twice daily and Pulmicort® Turbuhaler® 200 µg twice daily + Theolong® tablet 200 mg twice daily in Japanese patients with asthma

Objective(s): The primary objective of this study was to confirm the efficacy (superiority) of Symbicort® Turbuhaler® 160/4.5µg (D.D.: delivered dose) twice daily for 8 weeks in comparison to Pulmicort® Turbuhaler® 200 µg (M.D.: metered dose) twice daily + Theolong® tablet 200 mg twice daily.

Study design: This was a 8 weeks, randomised, double-blind, parallel group, multicentre (57 centres in Japan) study

Study population /Sample size:
Outpatients aged 16 years or older with asthma whose forced expiratory volume in one second (FEV1) was ≥50% of predicted normal, and who were treated with inhaled corticosteroid and theophylline SR tablet as a basic asthma treatment.

Treatments:
Symbicort® Turbuhaler® 160/4.5µg one inhalation bid
Or
Pulmicort® Turbuhaler® 200 µg + Theolong® tablet 200 mg

Outcomes/endpoints

Primary endpoint: Change in average morning peak expiratory flow (mPEF) from the run-in to the treatment period.

Statistical Methods
The period averages of the primary parameter were calculated for the last 10 days of the run-in period and for the whole of the treatment period. Comparison between the treatments was performed using an analysis of covariance model (an additive model) including treatment as a fixed factor and the run-in period average as a covariate. The mean treatment difference was estimated from the model, and 95% confidence interval and p-value were calculated. The primary analysis set for efficacy was the Full Analysis Set.

Results

Recruitment/ Number analysed
348 (1 patient < 18 years of age) patients were randomised to either of the two treatment groups (Symbicort group: n=178, Pulmicort +Theolong group: n=170).
The number of analysed patients was 346 (Symbicort group: n=176, Pulmicort + Theolong group: n=170) in the FAS and safety analysis set. 11 patients in the Symbicort group and 6 patients in the Pulmicort +Theolong group discontinued the study. The treatment groups were well-balanced as regards demography and other baseline characteristics.

Efficacy results :
The increase in mPEF as primary variable was statistically significant greater in the Symbicort group than in the Pulmicort + Theolong group (Symbicort: +15.24 L/min, Pulmicort+Theolong: +6.47 L/min, p=0.0051: ANCOVA).

Safety results:
Nasopharyngitis and headache were the most common adverse events in both treatment groups. The number of drug-related AEs (all nonserious) was numerically higher in the Symbicort group (Symbicort group: 19 events in 14 patients, Pulmicort + Theolong group: 11 events in 7 patients), mainly caused by reports of class-related AEs for β2-agonists, such as headache and muscle spasms. The incidence of SAEs was low in the both treatment groups (Symbicort group: 1 event in 1 patient, Pulmicort + Theolong group: 2 events in 1 patient). The incidence of DAEs was similar between the two groups (Symbicort group: 6 events in 6 patients, Pulmicort+Theolong group: 5 events in 5 patients). There were no clear differences in clinical laboratory values, vital signs or ECG between treatments.

Conclusion: Symbicort Turbuhaler 160/4.5 µg 1 inhalation twice daily was more effective than Pulmicort Turbuhaler 200 µg 1 inhalation twice daily + Theolong 200 mg twice daily regarding effect on morning PEF. No new safety signal was detected.

Assessor's comment: This study evaluates the safety and efficacy of Symbicort compared to Pulmicort +theophylline. This kind of therapy is not used very often to treat asthma in children (at least in Germany).Moreover, only one patient < 18 years has been enrolled. There were no new relevant findings.

Assessor's overall conclusion on Symbicort Turbuhaler maintenance studies: *The applicant submitted six studies which investigated Symbicort Turbuhaler in asthma maintenance therapy. Symbicort Turbuhaler is licensed from 6 years of age for this indication. Study SD-039-0353 (study has also been submitted during paediatric licensing procedure) as well as SD-039-0688 enrolled patients from 4 years of age. Anyhow no sub-group analysis of this younger age*

group has been provided and the number of these patients seems to be too low to draw meaningful conclusions or warrant a change to the SPC.
Study SD-039-0714 was negative as regards the primary endpoint. Studies CN-039-000, SD-039-0689 and D5890C00010 only enrolled a very low number of adolescents.
No new safety signal was detected in the submitted studies.
In section 5.1 the SPC of Symbicort Turbuhaler contains information on paediatric studies. This information should be updated to give a picture of the available paediatric data. No other changes are deemed necessary.

Symbicort pMDI studies:

***SD-039-0681 (2002-2003):* A randomised, double-blind, parallel-group, multicentre phase-III study to compare the efficacy and safety of Symbicort® pMDI (HFA, budesonide/formoterol 160/4.5 µg 2 actuations b.i.d., delivered dose) with that of Pulmicort® pMDI (budesonide 200 µg 2 actuations b.i.d., metered dose) and Symbicort Turbuhaler® (budesonide/formoterol 160/4.5 µg 2 inhalations b.i.d., delivered dose) in adolescents and adults with asthma**

Objective(s) : primary: to show superior efficacy of Symbicort pMDI 160/4.5 µg at 2 inhalations bid compared to Pulmicort pMDI 200µg 2 inhalations bid.

Study design: randomised, double blind, parallel group, active controlled, multicentre (62 centres in Brazil, Bulgaria, Canada, Hungary, Mexico, the Phillipines, Thailand and the US) 12-week study.

Study population /Sample size: Male and female asthmatic patients aged > 12 years, not adequately controlled on ICS monotherapy with a FEV1 ≥ 50% and ≤ 90%of predicted normal. 660 patients needed to be randomised to reach 600 evaluable subjects for having a 90% chance of detecting a true difference in morning PEF of 13 L/min between treatments.

Treatments:
Symbicort pMDI (HFA) 160/4,5 µg (delivered dose) 2 actuations bid
or
Pulmicort pMDI (CFC)200 µg(metered dose) 2 actuations bid
or
Symbicort Turbuhaler 160/4.5 µg (delivered dose) 2 inhalations bid

Outcomes/endpoints
Primary endpoint: Change from baseline to treatment in morning PEF.

Statistical Methods
The statistical analysis was based on the full analysis set. The primary variable was analysed using an analysis of variance model with treatment and country as fixed factors, and the mean run-in value as a covariate. All hypotheses testing was done with two-sided alternative hypotheses and p-values less than 5% were considered statistically significant.
For the secondary objective the upper and lower limits of the 95% confidence interval for the difference in morning PEF between Symbicort pMDI and Symbicort Turbuhaler was compared with the equivalence limits -15 L/min and 15 L/min.

Results

Recruitment/ Number analysed

680 patients were randomised and analysed for efficacy. 109 patients were in the age range 12-17 years of age. 27 patients in the Symbicort pMDI group, 29 patients in the Pulmicort group and 23 patients in the Symbicort Turbuhaler group discontinued the study.
The groups were comparable at baseline.

Efficacy results
Symbicort pMDI was shown to be superior with regard to the primary variable (Symbicort pMDI: +29.3 L/min, Pulmicort :+0.6 L/min, p<0.001). The analyses of the secondary variables supported this finding. Therapeutic equivalence between Symbicort pMDI and Symbicort Turbuhaler was established (mPEF (L/min): Symbicort pMDI: +29.3, Symbicort DPI: +32.0, p= 0.48, 95% CI: (-10.4; 4.9).

Safety results
30% of the patients in the Symbicort pMDI group, 38% of the patients in the Pulmicort group and 29% of the patienst in the Symbicort Turbuhaler group reported at least one AE. The most frequently reported AE was nasopharyngitis. 30 subjects (11 Symbicort pMDI, 15 Pulmicort, 4 Symbicort Turbuhaler) discontinued the study due to an AE. 2 patients in the Symbicort pMDI group as well as the Pulmicort group experienced SAEs.

Conclusion: Symbicort pMDI was shown to be superior to Pulmicort pMDI and non-inferior to Symbicort Turbuhaler with regard to morning PEF. Safety parameters were comparable between groups.

SD-039-682*: A 12-week randomised, double-blind, parallel-group, multicentre phase-III study to compare the efficacy and safety of Symbicort® pMDI (budesonide/formoterol 80/4.5 µg 2 actuations b.i.d., delivered dose) with that of Pulmicort® pMDI (budesonide 100 µg 2 actuations b.i.d., metered dose) and Symbicort Turbuhaler® (budesonide/formoterol 80/4.5 µg 2 actuations b.i.d., delivered dose) in children with asthma (2002-2003)*

Objective(s) : primary: to show superior efficacy of Symbicort pMDI 80/4.5 µg at 2 inhalations bid compared to Pulmicort pMDI 100µg 2 inhalations bid.

Study design: randomised, double blind, double dummy, parallel group, active controlled, multicentre (53 centres in Argentinia, Brazil, Denmark, Hongkong, Mexico, Poland, Slovakia and Taiwan) 12-weeks study comparing the efficacy and safety of Symbicort pMDI with that of Symbicort Turbuhaler and Pulmicort Turbuhaler.

Study population /Sample size: Male and female asthmatic patients aged 6- 11 years, treated with ICS, with a history of clinically important exercise induced bronchoconstriction and a PEF ≥ 50% of predicted normal.
540 patients needed to be randomised to reach 450 evaluable subjects for having a 90% chance of detecting a true difference in morning PEF of 11.3 L/min between treatments.

Treatments:
Symbicort pMDI (HFA) 80/4,5 µg (delivered dose) 2 actuations bid
or
Pulmicort pMDI (CFC)100 µg(metered dose) 2 actuations bid
or
Symbicort Turbuhaler 80/4.5 µg (delivered dose) 2 inhalations bid

Outcomes/endpoints
Primary endpoint: Change from baseline to treatment in morning PEF.

Statistical Methods
The statistical analysis was based on the full analysis set. The primary variable was analysed using an analysis of variance model with treatment and country as fixed factors, and the mean run-in value as a covariate. All hypotheses testing was done with two-sided alternative hypotheses and p-values less than 5% were considered statistically significant.
For the secondary objective the upper and lower limits of the 95% confidence interval for the difference in morning PEF between Symbicort pMDI and Symbicort Turbuhaler was compared with the equivalence limits -15 L/min and 15 L/min.

Results

Recruitment/ Number analysed
622 patients were randomised and 621 patients were analysed for efficacy. Discontinuation rate was similar between groups.14 patients each in the Symbicort pMDI group and in the Pulmicort group, respectively and 11 patients in the Symbicort Turbuhaler group discontinued the study. The groups were comparable at baseline.

Efficacy results
Symbicort pMDI was shown to be superior with regard to the primary variable (mPEF (L/min): Symbicort pMDI:+29.5 , Pulmicort:+19.9 p<0.001). Some analyses of the secondary variables concerning lung functions parameters supported this finding. Variables with regard to asthma symptoms and asthma control were not significantly different between the two groups. Therapeutic equivalence between Symbicort pMDI and Symbicort Turbuhaler was established (mPEF (L/min): Symbicort pMDI: +29.5, Symbicort Turbuhaler: +30.2, p=0.78, 95% CI: (-6.0, 4.6).

Safety results
45% of the patients in the Symbicort pMDi group, 47% of the patients in the Symbicort Turbuhaler group and 39% of the patients in the Pulmicort pMDI group reported at least one AE. The most frequently reported AE was nasopharyngitis. Only 5 SAEs were reported in the study; 3 in the Pulmicort pMDI group and 2 in the Symbicort Turbuhaler group. The proportion of subjects who discontinued the study due to AEs was relatively low, in total 11 subjects; 3 (1%) in the Symbicort pMDI group, 7 (3%) in the Pulmicort pMDI group, and 1 (< 0.5%) in the Symbicort Turbuhaler group. At the end of treatment, there were no statistically significant differences in P-cortisol between Symbicort pMDI and Symbicort Turbuhaler. However, there was a statistically significant difference between Symbicort pMDI and Symbicort Turbuhaler regarding 24-hour U-cortisol but not in P-cortisol. This difference in 24 hour U-cortisol, with the adjustment for baseline, implies higher values in the Symbicort pMDI group.

Conclusion: Symbicort pMDI was shown to be superior to Pulmicort pMDI and non-inferior to Symbicort Turbuhaler with regard to morning PEF. No safety signal was detected.

SD-039-715(2002-2003): ***An open, parallel-group, randomised, multi-centre phase III study to compare the long-term (52-week) safety of Symbicort® (budesonide/ formoterol) pMDI 160/4.5 µg 2 actuations b.i.d. with that of Symbicort Turbuhaler® 160/4.5 µg 2 inhalations b.i.d. in adults and adolescents with asthma***

Objective(s) : primary: to compare the long-term safety profile superior efficacy of Symbicort pMDI 160/4.5 µg at 2 inhalations bid and Symbicort DPI 160/4.5 µg 2 inhalations bid.

Study design: randomised, open, parallel group, active controlled, multicentre (60 centres in Australia, France, the Philippines, Slovakia, South Africa and Thailand) 52-week study.

Study population /Sample size: Male and female asthmatic patients aged ≥12 years with daily use of ICS and need for additional therapy with LABA, and a FEV1 ≥ 50% of predicted normal. 650 patients were planned to be randomised to have 300 evaluable patients in the Symbicort pMDI group and 150 evaluable patients in the Symbicort DPI group.

Treatments:
Symbicort pMDI 160/4,5 µg (delivered dose) 2 actuations bid
or
Symbicort Turbuhaler 160/4.5 µg (delivered dose) 2 inhalations bid

Outcomes/endpoints
Primary endpoint: safety parameters: AEs, lab chemistry including 24-h U-cortisol (sub-group), vital signs and ECG. No single parameter was considered as primary.
In addition, efficacy was assessed using "Change from Visit 1 to the average of the 52-week treatment period (Visit 2 to Visit 6)" for FEV1, FVC, and time to first severe asthma exacerbation as parameters.

Statistical Methods/ sample size calculation: With the exceptions of P-cortisol and 24-h U-cortisol the results are described descriptively. The P-cortisol and 24-h U-cortisol data was analysed in a multiplicative analysis of variance model.
The efficacy analysis was based on the full analysis set. The change from Visit 1 to the average of the treatment period was analysed using an analysis of variance model with treatment and country as fixed factors, and the baseline value as a covariate. For time to first severe asthma exacerbation a logrank test was performed and further analyses were made in a Cox regression model. All hypotheses testing were done with two-sided alternative hypotheses and p-values less than 5% were considered statistically significant.
About 650 subjects were planned to be randomised in order to reach 480 evaluable subjects after 26 weeks (320 in the Symbicort pMDI arm and 160 in the Symbicort Turbuhaler arm), and 450 evaluable subjects after 52 weeks (300 in the Symbicort pMDI arm and 150 in the Symbicort Turbuhaler arm). The sample size was primarily based on safety and chosen large enough to document the AE profile of Symbicort pMDI.

Results

Recruitment/ Number analysed
673 patients (89 adolescents) were randomised (Symbicort pMDI: 446, Symbicort Turbuhaler: 227). 54 patients in the Symbicort pMDI group and 21 patients in the Symbicort Turbuhaler group discontinued the study.
Patients groups were comparable at baseline.

Safety results:
The proportion of subjects reporting one or more AE during the treatment period was 74% in the Symbicort pMDI group and 77% in the Symbicort Turbuhaler group.
The most common AE was upper respiratory infection nos. 14 patients (12 in the Symbicort MDI and 2 in the Symbicort Turbuhaler group) discontinued the study due to AEs. The most common reason was hoarseness. The incidence of hoarseness, oral candidiasis and palpitations was slightly higher in the Symbicort pMDI group. In contrast to 24-h urinary cortisol significant differences were found for P-cortisol and P-glucose. P-cortisol as mean change of baseline to end of treatment showed higher values in the Symbicort pMDI group. P-glucose showed higher

values in the Symbicort Turbuhaler group. This was attributed to a higher number of diabetic patients in this group.

Efficacy results
No differences were detected with regard to FEV1, FVC, and time to first severe asthma exacerbation.

Conclusion: It was concluded that no clinically relevant differences were detected between Symbicort pMDI and Symbicort Turbuhaler therapy.

D5896C00001 (2003-2005): A randomized, double-blind, active-controlled, parallel-group, singledummy, multicenter, 12 week study to assess the efficacy and safety of SYMBICORT® pMDI 160/4.5 µg x 2 actuations once-daily (qd) compared to SYMBICORT pMDI 80/4.5 µg x 2 actuations qd, SYMBICORT pMDI 80/4.5 µg x 2 actuations twice-daily (bid) and to budesonide pMDI 160 µg x 2 actuations qd in asthmatic subjects 12 years of age and older

Objective(s): primary: to demonstrate the efficacy of Symbicort pMDI 160/4.5 µg 2 actuations once daily in asthmatic adults and adolescents previously treated with Symbicort pMDI 80/4.5 µg 2 inhalations bid by assessment of lung function, symptoms and physician/patient reported outcomes.

Study design: randomised, double-blind, parallel group, active controlled, single-dummy, multicentre (143 centres in the US) 12-week study investigating the efficacy, impact on health related quality of life and safety of Symbicort pMDI qd as maintenance.

Study population /Sample size:
Stable male and female asthmatic patients aged ≥12 years with a FEV1 ≥ 60% and ≤ 90% of predicted normal.
In order to detect a true mean difference between any pair of treatments of 0.20 L in the primary efficacy variable of change from baseline in evening predose FEV1, assuming a common true population standard deviation of 0.5 L, 133 evaluable subjects per treatment group would provide at least 90% power for a 2-sided group t-test with a 5% significance level. Under the same assumed standard deviation, 130 evaluable subjects per treatment group would provide 80% power for a 2-sided test with a 5% level of significance to detect a true difference between any pair of treatments of 0.175 L in evening predose FEV1. It was assumed up to 10% of randomized subjects would be unevaluable for the primary efficacy analysis of evening predose FEV1; therefore, approximately 150 subjects per treatment group (or approximately 600 subjects overall) should have been randomized to provide adequate power to achieve the primary objective of this study.

Treatments:
All patients received Symbicort pMDI 80/4.5 µg 2 actuations bid during the run-in
During the treatment phase the following products were administered:

Symbicort pMDI 160/4,5 µg (delivered dose) 2 actuations qd in the evening (Symbicort pMDI 320/9 qd group)
or
Symbicort pMDI 80/4.5 µg 2 actuations qd in the evening (Symbicort pMDI 160/9 qd group)
or
Symbicort pMDI 80/4.5 µg 2 actuations bid (Symbicort 320/9 bid group)
or

Budesonide pMDI 160 µg 2 actuations qd in the evening (Budesonide 320 group)

Outcomes/endpoints
Primary endpoint: evening pre-dose FEV1 (collected from spirometry assessments during scheduled study visits).

Statistical Methods
The efficacy analysis set (EAS), defined as all randomized subjects who took at least 1 dose of double-blind treatment and for whom the primary efficacy endpoint could be calculated, was used in the primary analysis of efficacy.
The primary efficacy endpoint was analyzed using an analysis of covariance (ANCOVA) model with treatment and center as fixed factors and baseline evening predose FEV1 as a covariate.
The primary comparison was between SYMBICORT pMDI 320/9 qd and budesonide pMDI 320 qd, using a contrast from this ANCOVA model at the 5% significance level (2-sided).

Results

Recruitment/ Number analysed
618 subjects (97 patients 12-<18 years of age) were randomized and received treatment. 535 patients completed the study. The overall withdrawal rate was highest in the SYMBICORT pMDI 160/9 qd treatment group (17.1%); the percentages of subjects withdrawn in the other 3 treatment groups were similar and slightly lower (ranging from 11.8% to 12.4%). 618 patients were analysed for safety. 606 patients were analysed for efficacy.
Treatment groups were similar at baseline with respect to most demographic and disease severity characteristics.

Efficacy results:
Primary variable:
SYMBICORT pMDI 320/9 qd was shown to be superior to budesonide 320 qd ($p<0.001$).
SYMBICORT pMDI 160/9 qd was shown to be superior to budesonide 320 qd ($p=0.016$).
SYMBICORT pMDI 160/9 bid was shown to be superior to budesonide 320 qd ($p<0.001$).
The SYMBICORT pMDI 160/9 bid treatment group maintained the mean level of pulmonary function (as assessed by evening predose FEV1) that was established during the run-in baseline period (during which all subjects were treated with SYMBICORT pMDI 160/9 bid), without experiencing a loss of efficacy during double-blind treatment. In contrast, decreases from baseline during double-blind treatment were seen for both of the SYMBICORT pMDI once-daily treatment groups compared to the SYMBICORT pMDI 160/9 bid group (LS mean difference 0.09 L, 95% CI: 0.04 to 0.13 L for SYMBICORT pMDI 160/9 bid minus SYMBICORT pMDI 320/9 qd; LS mean difference 0.14 L, 95% CI: 0.09 to 0.19 L for SYMBICORT pMDI 160/9 bid minus SYMBICORT pMDI 160/9 qd; $p<0.001$ for each).
Treatment differences were seen favoring SYMBICORT pMDI 320/9 qd compared to SYMBICORT pMDI 160/9 qd (LS mean difference 0.05 L, 95% CI: 0.00 to 0.10 L; $p=0.031$).
Results of the secondary efficacy endpoints were supportive of these primary findings.

Safety results:
The number of patients with any AE was the lowest in the Symbicort 320/9 qd group (43.1%) and the highest in the budesonide 320 qd group (54.9%). The most common AEs were headache and nasopharyngitis. No consistent pattern with respect to budesonide or formoterol total daily dose was seen in the incidence of these events across treatment groups, except for nasopharyngitis and vomiting, each of which was slightly higher on SYMBICORT pMDI160/9 bid compared to the other treatment groups.
Five subjects experienced serious adverse events (SAE) during the double-blind treatment period: 2 (1.3%) in SYMBICORT pMDI 160/9 bid group and 3 (1.9%) in the SYMBICORT pMDI

160 qd group. The percentage of subjects who had AEs that led to discontinuation (DAE) with onset during randomized treatment was low and similar across treatment groups (1.3% for SYMBICORT pMDI 160/9 bid, 1.3% for SYMBICORT pMDI 320/9 qd, 2.5% for SYMBICORT pMDI 160/9 qd, and 0.7% for budesonide 320 qd). One notable additional subject (SYMBICORT pMDI 160/9 bid) had a DAE 1 day following discontinuation of randomized treatment; this event (myocardial infarction) was also an SAE but was not considered related to study drug by the investigator. No clinically meaningful changes or treatment group differences were observed in clinical laboratory, vital signs (heart rate, diastolic and systolic blood pressure), or physical exam findings

Conclusion: SYMBICORT pMDI administered once daily at a total daily dose of 320/9 µg or 160/9 µg or twice daily at a total daily dose of 320/18 µg showed superiority over once-daily budesonide 320 µg in most measures of lung function and asthma control. Both once-daily SYMBICORT treatments were less effective in maintaining asthma control and lung function than SYMBICORT pMDI treatment administered twice-daily at a total daily dose of 320/18 µg.

SD-039-0716 (2002-2003): A Twelve-Week, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Trial of SYMBICORT® pMDI (80/4.5 µg) versus its Monoproducts (budesonide and formoterol) in Children (≥6 Years of Age) and Adults with Asthma – SPRUCE 80/4.5

Objective(s):

Primary: To compare the safety and efficacy of SYMBICORT® pMDI 80/4.5 µg to budesonide 80 µg per puff and formoterol 4.5 µg per inhalation. All administered as 2 inhalations twice daily, in subjects ≥ 6 years of age with asthma.

Secondary: To compare the safety, efficacy and onset of effect of all 3 active products alone relative to placebo in subjects with asthma.

Study design: randomized, double-blind, double-dummy, placebo-controlled 12 weeks trial comparing the efficacy and safety of SYMBICORT® pMDI with those of its mono-products.

Study population /Sample size:
Male and female subjects with asthma ≥ 6 years of age, chronically treated with a low to medium dose of inhaled corticosteroid, with FEV1 between 60% to 90% of predicted normal for subjects ≥12 and ≥75% of predicted normal for subjects <12.
To detect a true mean difference between treatment groups of 0.25 L for the co-primary efficacy variables 105 evaluable subjects ≥ 12 years of age per treatment group were required. In addition, the protocol allowed for up to 92 subjects 6 to <12 years of age to be randomized, for a potential grand total of 540 subjects ages 6 years and older to be randomized.

Treatments:
SYMBICORT pMDI 80/4.5 µg, 2 actuations bid
or
Budesonide pMDI 80 µg, 2 actuations bid,
or
Formoterol Turbuhaler 4.5 µg, 2 inhalations bid
or
Placebo

Outcomes/endpoints

Co-primary endpoints: baseline-adjusted average 12-hour FEV1 and pre-dose FEV1

Statistical Methods
The efficacy analysis set (EAS) was defined as all randomized subjects who took at least 1 dose of study medication and contributed sufficient data for at least 1 co-primary endpoint. Primary efficacy analyses are based on subjects from the EAS population who were ≥12 years of age. Secondary efficacy analyses were performed using the EAS (all ages) and per-protocol (PP) analysis sets. The co-primary variables – baseline-adjusted average 12-hour FEV1 and predose FEV1 – were each analyzed by formulating contrasts within an analysis of covariance (ANCOVA) model, adjusting for the fixed factors of center and treatment and for the covariate of baseline FEV1.
Baseline-adjusted average 12-hour FEV1 was analyzed at Week 2, last observation carried forward (LOCF) as the primary timepoint and was used to compare SYMBICORT pMDI to budesonide. Predose FEV1 was analyzed as a change from baseline to the average over the double-blind treatment period as the primary timepoint and was used to compare SYMBICORT pMDI to formoterol.

Results

Recruitment/ Number analysed
511 patients were randomized and analyses for efficacy and safety. 31 patients were 6 -< 12 years of age.106 subjects were < 18 years of age. Treatment groups were comparable at baseline.
The overall withdrawal rate was highest in the placebo group (51%), followed by the formoterol group (32%). The percentage of subjects withdrawn in the SYMBICORT pMDI and budesonide groups was similar and lower than that (15%). The most common reason for withdrawal was due to study-specific discontinuation criteria (ie, withdrawals due to pre-defined asthma events), which occurred in a higher percentage of subjects in the placebo and formoterol groups (33.6% and 20.3%, respectively) than in the SYMBICORT pMDI and budesonide groups (7.7% and 6.3%, respectively).

Efficacy results
The mean baseline-adjusted average 12-hour FEV1 was significantly greater for SYMBICORT pMDI compared to budesonide ($p<0.001$). The mean baseline-adjusted average 12-hour FEV1 was significantly greater for formoterol compared to placebo ($p<0.001$). SYMBICORT pMDI demonstrated clinically significant improvement in lung function that was maintained over 12 hours, and there was no diminution of the 12-hour bronchodilatory effect of SYMBICORT pMDI observed over time, as assessed by comparison of the 12-hour FEV1 profiles after the first dose and after 2 weeks and 12 weeks of therapy.
A significantly greater mean increase from baseline in predose FEV1 was seen for SYMBICORT pMDI versus formoterol ($p=0.001$). A significantly greater mean increase from baseline in predose FEV1 was seen for budesonide versus placebo ($p<0.001$).
Following the initial dose of SYMBICORT pMDI, predose FEV1 improved markedly during the first 2 weeks of treatment, continued to show improvement at the Week 6 assessment, and showed no diminution of effect at Week 12.

Safety results
The overall percentage of subjects with at least 1 AE during double-blind treatment was slightly lower in the formoterol (54.5%) and placebo (58.8%) groups than in the SYMBICORT pMDI (64.6%) and budesonide (60.6%) groups; this pattern is consistent with the duration of exposure across treatment groups. The incidence of serious adverse events (SAEs) during the double-blind treatment period was very low (2 subjects in each of the SYMBICORT pMDI [lobar

pneumonia, facial bones fracture] and placebo [abdominal pain, intestinal obstruction] groups). The percentage of subjects with adverse events leading to discontinuation (DAEs) was lower in the SYMBICORT pMDI, budesonide, and formoterol groups compared to the placebo group. Asthma was the most commonly observed DAE (8 subjects), with all occurrences in the placebo (6 [4.6%]) and budesonide (2 [1.6%]) groups. The most common AEs were headache and nasopharyngitis.
Twelve-lead ECG and chemistry (glucose and potassium) assessments generally did not reveal meaningful differences between treatment groups. Other than a higher incidence of abnormal lung exams in formoterol and placebo subjects, no significant findings in clinical chemistry and hematology parameters, physical examination, or vital signs were noted among active treatment groups.

Conclusion:
For the co-primary efficacy endpoints, SYMBICORT pMDI showed superiority over its mono-products. No new safety issues were detected.

SD-039-0717 (2002-2004): A Twelve-Week, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Trial of SYMBICORT® (160/4.5 µg) versus its Mono-products (budesonide and formoterol) in Adolescents (≥12 Years of Age) and Adults with Asthma – SPRUCE 160/4.5

- **Objective(s) :**

Primary: To compare the safety and efficacy of SYMBICORT® pMDI 160/4.5 µg to budesonide 160 µg per puff (MDI) and formoterol 4.5 µg per inhalation (DPI). All administered as 2 inhalations twice daily, in subjects ≥ 12 years of age with asthma.

Study design: randomized, double-blind, double-dummy, placebo-controlled 12 weeks trial comparing the efficacy and safety of SYMBICORT® pMDI with those of its mono-products. The study was conducted in 84 centres in the US.

Study population /Sample size:
Male and female subjects with asthma ≥ 12 years of age, chronically treated with a medium to high dose of inhaled corticosteroid, with FEV1 between 45% to 85% of predicted normal.
To detect a true mean difference between treatment groups of 0.25 L for the co-primary efficacy variables with 95% power for each variable (assuming a population standard deviation of 0.50 L, a 2-group t-test, and a 5% two-sided significance level for each test), 105 evaluable subjects per treatment group were required. Allowing for up to 5% of randomized subjects to be unevaluable for efficacy, 112 randomized subjects per treatment group (560 subjects overall) were sought to meet the primary objective.

Treatments:
SYMBICORT pMDI 160/4.5 µg, 2 actuations bid
or
Budesonide pMDI 160 µg, 2 actuations bid,
or
Formoterol Turbuhaler 4.5 µg, 2 inhalations bid
or
Budesonide pMDI 160 µg, 2 actuations bid in combination with Formoterol Turbuhaler 4.5 µg, 2 inhalations bid
or
Placebo

Outcomes/endpoints

Co-primary endpoints: baseline-adjusted average 12-hour FEV1 and pre-dose FEV1

Statistical Methods
The efficacy analysis set (EAS) was defined as all randomized subjects who took at least 1 dose of study medication and who contributed sufficient data for at least 1 co-primary endpoint.
The co-primary variables – baseline-adjusted average 12-hour FEV1 and predose FEV1 – were each analyzed by formulating contrasts within an analysis of covariance (ANCOVA) model adjusting for the fixed factors of center, ICS dose strata at entry and treatment and for the covariate of baseline FEV1.
Baseline-adjusted average 12-hour FEV1 was analyzed at Week 2. Last observation carried forward (LOCF) as the primary timepoint and was used to compare SYMBICORT pMDI to budesonide. Predose FEV1 was analyzed as a change from baseline to the average over the double-blind treatment period as the primary timepoint and was used to compare SYMBICORT pMDI to formoterol.

Results

Recruitment/ Number analysed
596 patients were randomized and analysed for efficacy and safety. 43 patients were in the age group 12-< 18 years of age.
Treatment groups were comparable at baseline with respect to most demographic and disease severity characteristics.
The overall withdrawal rate was highest in the placebo group (60%), followed by the formoterol group (51.2%). The percentage of subjects withdrawn in the SYMBICORT pMDI and budesonide and budesonide plus formoterol groups was lower (21.8%, 28.4% and 25.2%). The most common reason for withdrawal was due to study-specific discontinuation criteria (ie, withdrawals due to pre-defined asthma events), which occurred in a higher percentage of subjects in the budesonide and formoterol and placebo groups (20.2%, 35.8% and 49.6%, respectively) than in the SYMBICORT pMDI and budesonide plus formoterol groups (10.5% and 11.3%, respectively).

Efficacy results
The mean baseline-adjusted average 12-hour FEV1 was significantly greater for SYMBICORT pMDI compared to budesonide ($p<0.001$). A significantly greater mean increase from baseline in predose FEV1 was seen for SYMBICORT pMDI versus formoterol ($p=0.001$). For the co-primary variables at every protocol-specified timepoint, there were no clinically relevant or statistically significant differences between the fixed combination of budesonide and formoterol administered as SYMBICORT pMDI and the free combination of budesonide administered with a pMDI device plus formoterol administered with a TBH device.
With regard to key secondary endpoints (percentage of subjects who had a predefined asthma event; asthma symptoms as measured by percentage of symptom-free days; and overall AQLQ[S]score) SYMBICORT pMDI was statistically superior to placebo ($p<0.001$ for all endpoints). For all 3 key secondary endpoints, SYMBICORT pMDI also demonstrated a significant difference over each of its monoproducts.
For all secondary variables at every protocol-specified timepoint, there were no clinically relevant or statistically significant differences between the fixed combination of budesonide and formoterol administered as SYMBICORT pMDI and the free combination of budesonide administered with a pMDI device plus formoterol administered with a TBH device.
Although there were some methodical problems, PK results (sub-group) indicated comparable budesonide exposure between the fixed combination, the mono-substances and the free

combination, respectively. Formoterol exposure also was comparable between groups. Cmax was the lowest in the Symbicort group.

Safety results
The overall percentage of subjects with at least 1 AE during double-blind treatment was lower in the placebo group than in the active treatment groups (Symbicort::61.3%, Budesonide: 58.7% Formoterol: 62.6%, free combination: 63.5%, placebo: 43.2%) Incidence of SAEs during the double-blind treatment period was low (4 subjects in the SYMBICORT pMDI group, 2 patients in the formoterol group, 3 patients in the free combination group). One SAE (ECG T wave inversion) in the SYMBICORT pMDI group was considered to be drug-related. AEs leading to discontinuation were slightly higher in the combination groups.
Asthma was the most commonly observed DAE (n=8) (SYMBICORT: 3, budsonide: 1, formoterol: 3, budesonide plus formoterol: 0, placebo: 1).
The most common AEs were headache, upper respiratory tract infection and nasopharyngitis.
Twelve-lead ECG and chemistry (glucose and potassium) assessments generally did not reveal clinically meaningful differences between treatment groups, although a slightly higher number of SYMBICORT pMDI subjects were noted to have ST-T wave changes on ECGs. Other than a higher incidence of abnormal lung exams in formoterol and placebo subjects, no significant findings in clinical chemistry and hematology parameters, physical examination, or vital signs were noted among active treatment groups.

Conclusion:
For the co-primary efficacy endpoints, SYMBICORT pMDI showed superiority over its mono-products. No safety signal was detected.

SD-039-0718 (2002-2003) A Twelve-Week, Randomized, Double-Blind, Double-Dummy Trial of Symbicort® (40/4.5 mcg) versus its Mono-Products (budesonide and formoterol) in Asthmatic Children Aged Six to Fifteen Years – SEEDLING 40/4.5

Objective(s):
Primary: To compare the safety and efficacy of SYMBICORT® pMDI 40/4.5 µg to budesonide 40 µg per puff (MDI) and formoterol 4.5 µg per inhalation (DPI). All administered as 2 inhalations twice daily, in subjects aged 6 – 15 years with asthma.

Study design: randomized, double-blind, double-dummy, active-controlled 12 weeks trial. The study was conducted in 52 centres in the US.

Study population /Sample size:
Male and female subjects with asthma aged 6 -15 years, chronically treated with a low to medium dose of inhaled corticosteroid, with FEV1 ≥ 50% of predicted normal.
It was determined that a sample size of 133 subjects per treatment group would provide 90% power to detect a mean difference in change in morning PEF of 12 L/min between the SYMBICORT pMDI group and either of the other two groups, assuming that the common standard deviation was 30 L/min.

Treatments:
SYMBICORT pMDI 40/4.5 µg, 2 actuations bid
or
Budesonide pMDI 40 µg, 2 actuations bid,
or
Formoterol Turbuhaler 4.5 µg, 2 inhalations bid

Outcomes/endpoints

Primary endpoint: Morning peak expiratory flow (PEF)

Statistical Methods
The efficacy analysis set (EAS) was defined as all randomized subjects who took at least 1 dose of study medication and contributed at least 1 PEF value to the primary endpoint. Primary efficacy analyses were based on subjects from the EAS population. The primary variable, morning PEF, was analyzed by formulating contrasts within an analysis of covariance (ANCOVA) model, adjusting for the fixed factors of center, age strata, and treatment and for the covariate of baseline morning PEF. Morning PEF was analyzed as the change from baseline to the average over the treatment period as the primary endpoint and was used to compare SYMBICORT pMDI to budesonide and SYMBICORT pMDI to formoterol.

Results

Recruitment/ Number analysed
411 patients were randomized and analysed for efficacy and safety.
Treatment groups were comparable at baseline with respect to most demographic and disease severity characteristics.
The overall withdrawal rate was lowest in the Symbicort group (28%). It was similar and slightly higher in the mono-therapy groups (35%). The most common reason for withdrawal was due to study-specific discontinuation criteria (ie, withdrawals due to pre-defined asthma events), which was similar across treatment groups (20% for SYMBICORT pMDI, 24% for budesonide, 23% for formoterol).

Efficacy results
A significantly greater increase from baseline in morning PEF was seen for SYMBICORT pMDI compared with budesonide and with formoterol during the double-blind treatment period (Symbicort: +23.56 L/min, Budesonide: +7.95 L/min, Formoterol: + 8.55 L/min, $p<0.001$ for each comparison of Symbicort ot the mono-products).
There were no statistically significant treatment differences observed with regard to patient reported outcomes, as assessed by PAQLQ(S) and PACQLQ; however, improvements from baseline in these measures were seen in all treatment groups.
Pharmacokinetic results (AUC0-6 and Cmax) indicated that the systemic exposure to budesonide was comparable between the SYMBICORT pMDI and budesonide groups, as indicated by AUC0-6 and Cmax mean treatment ratios of 0.88 (90% CI 0.680, 1.146) and 0.90 (90% CI 0.603, 1.332), respectively. Analysis of formoterol data indicated that systemic exposure to formoterol (AUC0-6) was comparable in the 2 treatment groups as indicated by a mean treatment ratio of 0.875 (90% CI 0.692, 1.107). However, Cmax was significantly lower in the SYMBICORT pMDI treatment group as indicated by a mean treatment ratio of 0.611 (90% CI 0.466, 0.801).

Safety results
The overall percentage of subjects with at least one AE was similar in the SYMBICORT pMDI and formoterol groups (70.3%) and slightly lower in the budesonide group (63.4 %). The only serious adverse event (SAE; asthma) reported during the double-blind treatment period occurred in the formoterol group and led to the discontinuation of the subject from treatment. The most common AEs were headache pharyngolaryngeal pain and nasopharyngitis. Hematology and chemistry assessments, including glucose and potassium timed to coincide with peak sustained pharmacodynamic activity, did not generally reveal meaningful differences

in mean changes from baseline within or between treatment groups. Individual clinically important findings in chemistry and hematology variables were infrequent with no meaningful differences between treatment groups.
Twelve-lead ECGs timed to coincide with peak sustained pharmacodynamic activity did not reveal meaningful differences in mean changes from baseline between treatment groups. Mean changes from baseline in heart rate and in QTc (Bazett's and Fridericia's correction) noted in SYMBICORT pMDI and formoterol groups compared to the budesonide group were small and not clinically meaningful. No consistent association was seen between individual clinically important changes in glucose or potassium and changes in ECG parameters. No significant physical examination or vital sign findings were noted among treatment groups.

Conclusion:
For the primary efficacy endpoint, morning PEF, SYMBICORT pMDI showed superiority over both of its mono-products. No new safety signal was detected.

SD-039-0719 (2002-2003) A Six-Month, Randomized, Open-Label Safety Study of SYMBICORT® (160/4.5 µg) Compared to PULMICORT Turbuhaler® in Asthmatic Children Aged 6 to 11 Years—SAPLING

Objective(s):
Primary: to compare the long-term safety profile of SYMBICORT®, 160/4.5µg to that of PULMICORT®, 200µg both administered as 2 inhalations twice daily, in asthmatic children aged 6 to 11 years over a period of 26 weeks.

Study design: This was a 26-week, randomized, open-label, safety study of SYMBICORT® pressurized metered-dose inhaler compared with PULMICORT Turbuhaler® in children 6 to <12 years of age with asthma. The study was conducted in 29 centres in the US.

Study population /Sample size:
The subject population comprised male and female subjects 6 to <12 years of age with ICS-dependent asthma. Subjects must have demonstrated forced expiratory volume in 1 second ≥50% of predicted normal. Approximately 175 to 180 children were to be randomized into this study in a 2:1 ratio (SYMBICORT pMDI/PULMICORT TBH). The sample size for this study was not based on any formal statistical criteria. Rather, it was chosen to achieve at least 100 study completers in the SYMBICORT pMDI treatment group, assuming a 15% early withdrawal rate.

Treatments:
SYMBICORT pMDI (budesonide/formoterol) 160/4.5 µg per actuation, 2 actuations bid
or
PULMICORT TBH 200 µg (budesonide) per inhalation, 2 inhalations bid.

Outcomes/endpoints
Primary endpoint: No single variable was considered to be primary. The primary objective of the study was to assess long-term safety.

Statistical Methods
The safety analysis set was defined as all randomized subjects who took at least 1 dose of study medication. The safety analysis set was used for the analyses of efficacy, health economic, and safety variables. The PK analysis set included all subjects who consented to PK testing and who had at least 1 blood draw for PK testing performed during treatment. The patient reported outcome analysis set contained all subjects who were ≥7 years of age. Predose FEV1 was analyzed by formulating contrasts within an analysis of covariance (ANCOVA) model, adjusting

for fixed factors of center and treatment and for the covariate of baseline FEV1. Patient reported outcome variables were compared between treatment groups using analyses similar to those specified for predose FEV1. Data from Global Assessments were analyzed using chi-square tests; positive responses were pooled in the primary method. For measures of direct medical and indirect resource utilization, event rate data were analyzed with Poisson regression and numbers of subjects were compared using Fisher's exact test. Pharmacokinetic parameters for budesonide and formoterol were summarized with descriptive statistics. Cmax and AUC0-6 for budesonide were compared between treatment groups using a multiplicative ANOVA model. Safety variables were analyzed with descriptive statistics, shift tables, and ANCOVA models.

Results

Recruitment/ Number analysed

186 subjects received study medication and were included in the safety analysis set.
Treatment groups were comparable at baseline with respect to demographic and disease severity characteristics.
Among randomized subjects, the overall withdrawal rate was low (12.3%) and slightly lower in the SYMBICORT pMDI group (10.5%, 13/124) compared with the PULMICORT TBH group (15.9%, 10/63). The most common reason for discontinuation was withdrawal of consent (4.8% overall). A total of 164 (87.7%) subjects completed the study.

Efficacy results

Compared with baseline, both SYMBICORT pMDI and PULMICORT TBH 200 improved the lung function and quality of life of paediatric subjects with asthma. Mean improvements from baseline in predose FEV1 were significantly greater for SYMBICORT pMDI compared with PULMICORT TBH for the average of all FEV1 values across all on-treatment visits as well as at the end of treatment ($p \leq 0.009$ and $p < 0.001$, respectively). Primary analysis of the physician Global Assessment indicated no statistically significant differences between treatment groups. Analysis of the caregiver Global Assessment indicated a significantly ($p \leq 0.048$ for both questions) higher rate of positive responses for SYMBICORT pMDI subjects compared with PULMICORT TBH subjects at end of treatment.
Improvements from baseline for all PAQLQ(S) scores were significantly ($p \leq 0.012$ for overall score and each domain score) greater for SYMBICORT pMDI versus PULMICORT TBH, but the differences between groups did not reach a minimally important difference (defined as a mean difference between groups of ≥0.5 point). Improvements from baseline in PACQLQ were significantly greater for SYMBICORT pMDI versus PULMICORT TBH for overall ($p=0.006$) and emotional function ($p=0.001$) scores.
There were fewer visits to urgent care facilities made by subjects in the SYMBICORT pMDI group (0.069 visits per subject-treatment year) compared with the PULMICORT TBH group (0.314 visits per subject-treatment year; $p=0.012$ for the difference between groups). There were no differences between treatment groups in the number of either unscheduled health care provider visits or phone calls to health care providers due to asthma or breathing problems. Discrepancies were found between SAE narratives and IVRS data for ER visits and hospital admissions. Therefore, no formal treatment comparisons were performed for these direct medical resources because the data were deemed to be unreliable.
Results obtained from measures of indirect resource utilization indicated the following. There were fewer days that the caregiver was absent from work due to the subject's asthma or breathing problems for the SYMBICORT pMDI group (0.503 days per subject-treatment year) compared with the PULMICORT TBH group (1.011 days per subject-treatment year; $p=0.008$ for the difference between groups). However, there was no difference between treatment groups in the percentage of subjects with caregivers who reported at least 1 such day. There were fewer days ($p<0.001$ for the difference between groups) that the child was unable to

participate in daily activities due to asthma or breathing problems and fewer children (p=0.050 for the difference between groups) reporting at least 1 such day for the SYMBICORT pMDI group (1.752 days per subject-treatment year, 29.3% of subjects) compared with the PULMICORT TBH group (3.662 days per subject-treatment year, 44.4%of subjects). Systemic exposure to budesonide was comparable between the SYMBICORT pMDI and PULMICORT TBH treatment groups with regard to the point estimate but a rather wide 90% CI, as indicated by AUC0-6 and Cmax mean (90% confidence interval) treatment ratios of 1.080 (0.442, 2.641) and 0.956 (0.368, 2.481), respectively (11 subjects in total).

Safety results
The overall percentage of subjects with at least 1 AE was similar between the SYMBICORT pMDI (84.6%) and PULMICORT TBH (85.7%) groups. Two serious adverse events (asthma, pneumonia) reported during the randomized treatment period occurred in the SYMBICORT pMDI group and 1 SAE (sickle cell anemia) occurred in the PULMICORT TBH group. Four subjects (2 in each treatment group) experienced AEs leading to discontinuation from study treatment during the randomized treatment period. Asthma DAEs occurred in 2 subjects, 1 in each treatment group.
The most frequently occurring AEs were headache, upper respiratory tract infection, nasopharyngitis, upper abdominal pain, asthma, pharyngolaryngeal pain, and cough. While the incidence of these events was generally similar across treatment groups, the percentages of subjects with asthma, pharyngolaryngeal pain, and cough were slightly higher in the SYMBICORT pMDI group. The musculoskeletal and connective tissue disorders SOC revealed a higher incidence of AEs in the SYMBICORT pMDI group (n= 16, Pulmicort: n=4) (due mostly to slightly higher incidences of myalgia, extremity pain, and arthralgia AEs). Increased duration of exposure to SYMBICORT pMDI or PULMICORT TBH was not associated with a change in the profile of adverse events reported.
Generally, clinical laboratory assessments and assessments of vital signs and ECGs did not reveal relevant or unexpected differences to the disadvantage of Symbicort pMDI.

Conclusion:
No new safety signal was detected. SYMBICORT pMDI demonstrated improvements from baseline in the control of asthma and the management of asthma as well as advantages in direct medical and indirect resource use.

SD-039-0725 (2002-2003) A Twelve-Week, Randomized, Double-blind, Double-Dummy, Active-Controlled Study of SYMBICORT® pMDI Administered Once Daily in Children and Adolescents 6 to 15 Years of Age with Asthma – SPROUT

Objective(s):
Primary: To demonstrate the efficacy of SYMBICORT pMDI 80/4.5 µg, 2 actuations once daily (qd), compared to budesonide pMDI 80 µg, 2 actuations qd, in asthmatic children and adolescents previously stable on SYMBICORT pMDI 40/4.5 µg, 2 actuations twice daily (bid).

Study design: This was a 12-week, multicenter (128 centres in the US), randomized, double-blind, parallel group, active-controlled, Phase 3 study. The randomization was stratified based on the age of the subject at Visit 1(6 to 11 years of age versus 12 to 15 years of age).

Study population /Sample size:
The target subject population included male and female subjects with stable asthma on ICS who were 6 to 15 years of age inclusive, at the time of screening. Subjects were required to have an FEV1 of between 60%-90% of predicted normal. Subjects with an FEV1 between 90-95% predicted could be included if they had an FEV1/FVC ratio measured on screening spirometry of <80%.

To detect a true difference in mean change in evening PEF of 10 L/min, assuming a common standard deviation of 30.0 L/min, a 2-group t-test with a 5% two-sided significance level and 88% power required a sample size of 180 subjects per treatment arm. Assuming that a negligible number of randomized subjects would be unevaluable for the primary efficacy analysis it was decided to randomize approximately 180 subjects per treatment group.

Treatments:
SYMBICORT pMDI 80/4.5 µg, 2 actuations qd (total daily dose: 160/9.0 µg);
or
SYMBICORT pMDI 40/4.5 µg, 2 actuations bid (total daily dose: 160/18.0 µg)
or
Budesonide pMDI 80 µg, 2 actuations qd (total daily dose: 160 µg).

Outcomes/endpoints

Primary endpoint: change from baseline to the mean over the double-blind treatment period in evening PEF

Statistical Methods
The efficacy analysis set (EAS), defined as all randomized subjects who took at least 1 dose of double-blind treatment and who contributed at least 1 evening PEF diary entry after receiving double-blind medication, was used in the primary analysis. Change from baseline in evening PEF was analyzed with an analysis of covariance (ANCOVA) model, adjusting for the fixed factors of center, age strata, and treatment, and for the covariate of baseline evening PEF. Pairwise comparisons between treatments were made by formulating contrasts within the context of this model. The primary comparison was between SYMBICORT 80 qd and budesonide 80 qd. SYMBICORT 40 bid was compared to budesonide 80 qd to support the secondary objectives. In addition, the SYMBICORT pMDI once-daily group and the SYMBICORT pMDI twice-daily group were compared to each other using two-sided 95% confidence intervals obtained from the same ANCOVA model described above; this comparison was on a descriptive level and was not associated with a decision rule.

Results

Recruitment/ Number analysed
522 subjects were subsequently randomized. Randomization was stratified by age (6 to 11 years of age versus 12 to 15 years of age) at the time of screening, to ensure an approximately uniform distribution of subjects across treatment groups within each of these 2 strata; the primary analysis included all subjects from both strata. The safety analysis set is comprised of all randomized subjects, except 1 subject who did not receive double-blind treatment. Two of the remaining 521 randomized subjects were excluded from the efficacy analysis set (EAS) because of insufficient efficacy data. There were no apparent differences between treatment groups with respect to demographic and disease severity characteristics.
Among randomized subjects, the overall withdrawal rate was highest in the SYMBICORT 80 qd group (22.0%), followed by the budesonide 80 qd group (19.4%) and the SYMBICORT 40 bid group (11.4%). The most common reason for withdrawal was development of study-specific discontinuation criteria (ie, withdrawals due to predefined asthma events). The percentage of subjects who withdrew because of a predefined asthma event was 16.7% in the SYMBICORT 80 qd group, 14.9% in the budesonide 80 qd group, and 7.1% in the SYMBICORT 40 bid group.

Efficacy results :
Key findings for the primary efficacy endpoint are as follows:

Change from baseline in evening PEF was 6.69, 0.45 and -5.84 L/min for SYMBICORT 40bid, SYMBICORT 80qd and Budesonide, respectively.
• SYMBICORT 80 qd was shown to be superior to budesonide 80 qd (p=0.027).
• SYMBICORT 40 bid was shown to be superior to budesonide 80 qd (p<0.001).
• There was no clinically relevant difference in mean response between the SYMBICORT 40 bid group and the SYMBICORT 80 qd group (LS mean difference 4.55 L/min, 95% CI: -2.75 to 11.84 L/min, p=0.222).
Evening predose FEV1 was measured in the clinic at the end of both the once-daily and twice-daily dosing intervals and was prospectively designated as the primary spirometry endpoint. Results for this endpoint are as follows:
• SYMBICORT 80 qd was not statistically different from budesonide 80 qd (p=0.183). SYMBICORT 40 bid was superior to budesonide 80 qd (p<0.001). There was also a treatment difference favoring SYMBICORT 40 bid compared with SYMBICORT 80 qd (LS mean difference 0.06 L, 95% CI: 0.01 to 0.10 L, p=0.011).

Safety results
The percentage of subjects with at least 1 AE with onset during double-blind treatment was 65.2% for the SYMBICORT 40 bid group, 61.9% for the SYMBICORT 80 qd group and 59.2% for the Budsonide group.
6 subjects had an SAE with onset during the double-blind treatment period: 2 subjects in the SYMBICORT 40 bid group (abdominal pain, asthma), 3 subjects in the SYMBICORT 80 qd group (influenza, asthma [2 subjects]), and 1 subject in the budesonide 80 qd group (asthma). 8 subjects had at least 1 AE with onset during double-blind treatment that led to discontinuation during the treatment period (3 subjects in the SYMBICORT 40 bid group, 4 subjects in the SYMBICORT 80 qd group, and 1 subject in the budesonide 80 qd group). The most common DAE with onset during double-blind treatment was asthma; this occurred in 5 subjects: 2 SYMBICORT 40 bid, 2 SYMBICORT 80 qd, and 1 budesonide 80 qd.
Among the most common AEs, some (eg, pharyngolaryngeal pain, viral upper respiratory tract infection) were reported more frequently for SYMBICORT pMDI than for budesonide. There were no notable differences between the SYMBICORT pMDI bid and qd treatment regimens with respect to the profile of commonly reported AEs.
The SYMBICORT pMDI groups did not demonstrate any clinically relevant changes in laboratory values, vital signs or ECGs compared with the budesonide group.

Conclusion:
SYMBICORT pMDI administered once daily at a total daily dose of 160/9 µg showed small but statistically significant superiority over once-daily budesonide 160 µg as measured by evening PEF. However, both once-daily SYMBICORT pMDI and once-daily budesonide were less effective in maintaining asthma control and lung function than SYMBICORT pMDI treatment administered twice daily at a total daily dose of 160/18 µg. No new safety signal was detected.

SD-039-0726 (2003-2004) A Twelve-Week, Randomized, Double-Blind, Double-Dummy, Placebo- and Active-Controlled Study of SYMBICORT pMDI Administered Once Daily in Adults and Adolescents with Asthma – STEM

Objective(s):

Primary: To demonstrate the efficacy of SYMBICORT pMDI 160/4.5 µg, 2 actuations once daily (qd), compared to placebo and to budesonide pMDI 160 µg, 2 actuations qd, in asthmatic adults and adolescents previously stable on SYMBICORT pMDI 80/4.5 µg, 2 actuations twice daily (bid), by assessment of lung function and patient- and physician reported outcomes.

Study design: This was a 12-week, multicenter (151 centres in the US), randomized, double-blind, parallel group, placebo and active-controlled, Phase 3 study.

Study population /Sample size:
Male and female subjects, 16-years of age and older with stable asthma on low to medium dose ICSs with a FEV1 between 60-90% were eligible for this study.
A sample size of 150 subjects per treatment arm would provide 84% power to detect a true difference in mean change in evening PEF of 12 L/min and 95% power to detect a true difference in mean change in evening PEF of 15 L/min.

Treatments:
SYMBICORT pMDI (budesonide/formoterol) 160/4.5 µg per actuation,
2 actuations administered qd (hereafter called the SYMBICORT 160 qd treatment group)
or
SYMBICORT pMDI (budesonide/formoterol) 80/4.5 µg per actuation, 2 actuations administered qd (hereafter called the SYMBICORT 80 qd treatment group)
or
SYMBICORT pMDI (budesonide/formoterol) 80/4.5 µg per actuation, 2 actuations administered bid (hereafter called the SYMBICORT 80 bid treatment group), this treatment was also given during run-in.
or
Budesonide pMDI 160 µg per actuation, 2 actuations administered qd (hereafter called the budesonide 160 qd treatment group)
or
Placebo pMDI, 2 actuations administered bid (hereafter called the placebo treatment group)

Outcomes/endpoints

Primary endpoint: evening PEF (from daily diary)

Statistical Methods
The efficacy analysis set (EAS), defined as all randomized subjects who took at least 1 dose of double-blind treatment and who contributed at least 1 evening PEF diary entry after receiving double-blind medication, was used in the primary analysis. The primary analysis for this study was the change from baseline to the mean over the double-blind treatment period in evening PEF. The primary comparison consisted of a sequential testing procedure: First, SYMBICORT 160 qd was compared to placebo. If this comparison was found to be statistically significant at the 5% significance level, then SYMBICORT 160 qd was compared to budesonide 160 qd, also at the 5% significance level. Change from baseline in evening PEF was analyzed with an analysis of covariance (ANCOVA) model, adjusting for the fixed factors of center and treatment, and for the covariate of baseline evening PEF.
Secondary analyses were performed to compare SYMBICORT 80 bid to placebo and budesonide 160 qd, and to compare SYMBICORT 80 qd to placebo and budesonide 160 qd. Budesonide 160 qd, was also compared to placebo. Differences between the 2 once-daily SYMBICORT pMDI groups and between these groups and the SYMBICORT pMDI twice daily group are presented primarily at a descriptive level, using 2-sided 95% confidence intervals. All of these secondary comparisons were performed within the context of the same ANCOVA model used for the primary analysis.

Results
Recruitment/ Number analysed
752 subjects were randomized. 751 subjects (28 < 18 years of age) received double-blind treatment and all but 7 subjects provided at least 1 efficacy observation.

Treatment groups were similar at baseline with respect to most demographic and disease severity characteristics.
Among randomized subjects, the overall withdrawal rate was highest in the placebo treatment group (41.5%) while the percentages of subjects withdrawn in the active treatment groups (3 SYMBICORT pMDI groups and the budesonide 160 qd group) were similar and notably lower (ranging from 12.4% to 19.3%). The most common reason for withdrawal was due to study-specific discontinuation criteria (ie, withdrawals due to predefined asthma events). The percentage of subjects who withdrew because of a predefined asthma event was notably lower in the SYMBICORT 80 bid (2.6%), SYMBICORT 160 qd (6.8%), and SYMBICORT 80 qd (4.6%) groups than in the placebo (35.9%) and budesonide 160 qd (12.4%) groups.

Efficacy results:
Change from baseline in evening PEF was 1.14, -14.28,-13.98, -31.88 and -38.95 L/min for SYMBICORT 80 bid, SYMBICORT 160qd, SYMBICORT 80qd, Budesonide 160qd and placebo, respectively.
• SYMBICORT 160 qd was shown to be superior to both placebo and budesonide 160 qd ($p<0.001$ for each).
• SYMBICORT 80 bid was shown to be superior to all other treatments ($p<0.001$ for each)
• SYMBICORT 80 qd was shown to be superior to both placebo and budesonide 160 qd ($p<0.001$ for each)
• The SYMBICORT 80 bid treatment group maintained the mean level of pulmonary function (as assessed by evening PEF) that was established during the run-in baseline period, without experiencing a loss of efficacy during double-blind treatment. In contrast, decreases from baseline during double-blind treatment were seen for both of the SYMBICORT once-daily treatment groups compared to the SYMBICORT 80 bid group (LS mean difference for SYMBICORT 80 bid minus SYMBICORT 160 qd equals 16.43 L/min, 95% CI: 8.81 to 24.05 L/min; LS mean difference for SYMBICORT 80 bid minus SYMBICORT 80 qd equals 17.94 L/min, 95% CI: 10.32 to 25.55 L/min; $p<0.001$ for each).
• There was no clinically relevant difference between the mean response seen in the SYMBICORT 160 qd group and in the SYMBICORT 80 qd group (LS mean difference 1.51 L/min, 95% CI: -6.14 to 9.15 L/min, $p=0.699$).
•Evening predose FEV1 was measured in the clinic at the end of the once-daily dosing interval and prospectively designated as the primary spirometry endpoint. The once-daily SYMBICORT pMDI groups demonstrated statistically significantly greater efficacy than placebo. However, unlike the evening PEF results, the comparisons between SYMBICORT 160 qd and budesonide 160 qd and between SYMBICORT 80 qd and budesonide 160 qd were not statistically significant during double-blind treatment ($p=0.158$ and $p=0.250$, respectively).

Safety results
A total of 751 of 752 subjects who were randomized into the study received at least 1 dose of study drug and were included in the safety analysis set.
The overall percentage of subjects with at least 1 adverse event was 58.4% in the SYMBICORT 80 bid group, 51.0% in the SYMBICORT 160 qd group, 55.3% in the SYMBICORT 80 qd group, 52.4% in the Budesonide 160 qd group and 49.0% in the placebo group. 5 subjects experienced a SAE during the double blind treatment period (3 subjects in SYMBICORT 80 bid group (breast cancer in situ, road traffic accident, musculoskeletal chest pain), 1 subject in the SYMBICORT 160 qd group (prostate cancer), and 1 subject in the budesonide 160 qd group (tension headache)). 19 subjects in the safety analysis set (6 subjects in SYMBICORT 80 bid group, 5 subjects in the SYMBICORT 160 qd group, 2 subjects in the SYMBICORT 80 qd group, 3 subjects in the budesonide 160 qd group, and 3 subjects in the placebo group) had at least 1 AE with onset during double-blind treatment leading to discontinuation during the double-blind treatment period.

The most frequently occurring AEs were nasopharyngitis, upper respiratory tract infection, headache, pharyngolaryngeal pain, sinusitis, viral upper respiratory tract infection, influenza, nasal congestion, and back pain. The incidence of these events was generally similar across the treatment groups. There was no clear evidence of a dose response for adverse events when the SYMBICORT bid and qd treatment groups were compared.
For all hematology and clinical chemistry parameters, including serum glucose and potassium, there were no clinically meaningful changes from baseline or differences across treatment groups at any visit. There was a slight mean decrease in 24-hour urinary cortisol and cortisol/creatinine ratio for both SYMBICORT 160 qd and budesonide 160 qd compared to the other groups.
With respect to objective measures of cardiac safety, for heart rate, QRS, and PR intervals there were no clinically relevant treatment group differences in change from baseline or shifts to abnormal at any analyzable timepoint. There were 7 DAEs (2 SYMBICORT 80 bid, 3 SYMBICORT 160 qd, 1 SYMBICORT 80 qd, and 1 placebo) associated with Holter findings; 5 of these subjects met Holter withdrawal criteria. No clinically meaningful changes or treatment group differences were observed in vital signs (pulse, diastolic and systolic blood pressure) and physical exam findings.

Conclusion:
Overall, SYMBICORT pMDI administered once daily at a total daily dose of 320/9 µg or 160/9 µg showed superiority over placebo and once-daily budesonide 320 µg, as measured by lung function and asthma control. However, both once-daily SYMBICORT treatments were less effective in maintaining asthma control and lung function than SYMBICORT pMDI treatment administered twice-daily at a total daily dose of 320/18 µg. No new safety signal was detected.

SD-039-0728 (2003-2005) A 52-week, randomized, double-blind, single-dummy, parallel-group, multicenter Phase III study comparing the long-term safety of SYMBICORT® pMDI 160/4.5 µg x 4 actuations twice daily to SYMBICORT® pMDI 160/4.5 µg x 2 actuations twice daily and budesonide HFA pMDI 160 µg x 4 actuations twice daily in adult and adolescent subjects with asthma

Objective(s):
Primary: to assess the long-term safety profile of SYMBICORT pMDI 160/4.5 µg x 4 actuations twice daily (bid) as compared to that of SYMBICORT pMDI 160/4.5 µg x 2 actuations bid and budesonide HFA pMDI 160 µg x 4 actuations bid, over 52-weeks.

Study design: This was a 52-week, randomized, double-blind, single-dummy, parallel-group, multicenter Phase III study. The study was conducted in 77 centres in the US.

Study population /Sample size:
The target population included male and female subjects ≥12 years of age with moderate to severe asthma stable on ICSs. Subjects were required to have an FEV1 of ≥45% of predicted normal. Approximately 570 subjects were targeted for randomization in an overall ratio of approximately 350:110:110 (SYMBICORT pMDI 160/4.5 µg x 4 actuations bid: SYMBICORT pMDI 160/4.5 µg x 2 actuations bid: budesonide 160 µg x 4 actuations bid, respectively).

Treatments:
SYMBICORT pMDI (budesonide/formoterol) 160/4.5 µg x 4 actuations bid;
or
SYMBICORT pMDI (budesonide/formoterol) 160/4.5 µg x 2 actuations bid;
or
Budesonide HFA pMDI 160 µg x 4 actuations bid

Outcomes/endpoints

Primary endpoint: No single variable was considered primary. Evalautions included: asthma exacerbations, electrocardiograms (ECGs) and Holter monitors, forced expiratory volume in the 1st second (FEV1), morning peak expiratory flow (AM PEF), adverse events, laboratory parameters including 24-hour urinary cortisol, use of adjunctive asthma therapy due to worsening of asthma, and physical examinations.

Statistical Methods
No single variable was considered the primary variable. In addition to the safety analysis set, consisting of all randomized subjects who received at least 1 dose of randomized study drug, the postdose analysis set, consisting of all subjects who had clinic visit safety assessments measured 1-2 hours after randomized treatment at all visits, was also used in the analysis of some safety data.
Continuous variables were analyzed with linear models. Event data, such as asthma exacerbations and direct and indirect resource utilization variables, were presented as follows: (1) the number and percent of subjects, analyzed using a chi-square test, and (2) event data, expressed in days per subject-treatment year and, when applicable, analyzed using Poisson regression. For asthma exacerbations, time to 1st event was additionally analyzed using survival techniques. P-values and 95% confidence intervals using 2-sided alternatives, unadjusted for multiplicity, are presented for all pairwise comparisons; however, these were considered descriptive in nature to aid in data interpretation, and this output from statistical analyses was not associated with a decision rule.

Results

Recruitment/ Number analysed
708 subjects (90 patients 12-< 18 years of age) were randomized (443 in the SYMBICORT pMDI 640/18 bid group, 132 in the SYMBICORT pMDI 320/9 bid group, and 133 in the budesonide 640 bid group). Treatment groups were similar at baseline with respect to most demographic and disease severity characteristics. The overall discontinuation rate was highest in the budesonide 640 bid group (19.5%), compared with 18.5% in the SYMBICORT pMDI 640/18 bid group and 15.9% in the SYMBICORT pMDI 320/9 bid group. The most common reason for discontinuation among randomized subjects was adverse events (50 subjects, 7.1%).

Efficacy results:
Improvements in mean predose FEV1 and mean 2-hour postdose FEV1 relative to baseline were seen with all 3 treatments at all timepoints (change from baseline in pre-dose FEV1: SYMBICORT 640: 0.18 L, SYMBICORT 320: 0.16L, Budesonide: 0.08L). Compared with budesonide 640 bid, SYMBICORT pMDI 640/18 bid and SYMBICORT pMDI 320/9 bid resulted in significantly greater improvement in both of these spirometry endpoints. For diary-based measures of asthma control, including morning PEF, symptom-free days, rescue medication-free days, asthma-control days, and daily use of rescue medication, SYMBICORT pMDI 640/18 bid and SYMBICORT pMDI 320/9 bid also resulted in significantly greater improvement over budesonide 640 bid. Improvements in mean predose FEV1, mean 2-hour postdose FEV1, mean morning PEF, and measures for mean rescue medication use (ie, rescue medication-free days and total daily rescue use) for SYMBICORT pMDI 640/18 bid were numerically, but not statistically significantly larger than improvements in the SYMBICORT pMDI 320/9 bid group.
A significantly lower percentage of subjects in the SYMBICORT pMDI 640/18 bid group (12.2%) experienced an asthma exacerbation compared with subjects in the budesonide 640 bid group (21.8%). Time to 1st asthma exacerbation in the SYMBICORT pMDI 640/18 bid group was also significantly longer compared with the budesonide group, based on results from survival analysis. In addition, subjects in each SYMBICORT pMDI group had a significantly lower total

number of asthma exacerbations per subject-treatment year (0.174) compared with the budesonide group (0.315). There were no statistically significant differences between the SYMBICORT pMDI groups for these variables. Analysis of patterns of deterioration and recovery associated with asthma exacerbations, as measured by mean morning PEF, mean number of puffs/day of rescue medication use, and mean percentage of subjects with symptom-free days during the period extending from 30 days before to 30 days after asthma exacerbation indicated no deleterious impact of formoterol on the course of an exacerbation. The number of hospitalizations and emergency/urgent care visits due to asthma were numerically, but not statistically significantly, higher in the SYMBICORT pMDI groups compared with the budesonide group; these findings for SYMBICORT pMDI were not dose-ordered.
MART(Maximal achievable response testing) was performed to evaluate the postalbuterol maximal FEV1 obtained during randomized treatment compared to the baseline postalbuterol maximal FEV1 obtained prior to initiation of randomized treatment. Subjects in the SYMBICORT pMDI groups experienced small but statistically significant decreases from baseline in postalbuterol maximum FEV1 at Week 6, end of Month 6, and for treatment average, compared with subjects in the budesonide group, although the mean maximum FEV1 values achieved were generally higher for each SYMBICORT pMDI group than for the budesonide group. The largest difference for SYMBICORT pMDI 640/18 bid minus budesonide 640 bid occurred at end of Month 6 (LS mean difference [95% CI]=-0.12 L [-0.20, -0.04]), and the largest difference for SYMBICORT pMDI 320/9 bid minus budesonide 640 bid occurred at Week 6 (LS mean difference=-0.10 L [-0.18, -0.02]) and at end of Month 6 (LS mean difference= -0.10 L [-0.18, -0.01]). Results at Month 12 and at end of treatment were generally similar to those at earlier timepoints; however, differences between the SYMBICORT pMDI groups and the budesonide group were smaller and not statistically significant. There were no significant differences between the SYMBICORT pMDI groups at any timepoint analyzed. For measures of direct medical and indirect resource utilization, subjects in the SYMBICORT pMDI 640/18 bid group and the SYMBICORT pMDI 320/9 bid group used significantly less rescue medication and oral steroids, and experienced significantly fewer days of interrupted activities due to asthma (8.331 and 8.339 days interrupted per subject-treatment year, respectively) than subjects in the budesonide group (17.763 days interrupted per subject-treatment year, $p<0.001$ for comparisons between each SYMBICORT pMDI group and the budesonide group). Differences between treatment groups for other measures of direct medical and indirect resource utilization were not statistically significant. There were no significant differences between the SYMBICORT pMDI groups for these variables. Systemic exposure to budesonide was comparable for the SYMBICORT pMDI 640/18 bid and budesonide 640 bid treatment groups, as indicated by mean AUC0-12 and Cmax treatment ratios (90% confidence interval) of 1.081 (0.834, 1.400) and 0.925 (0.732, 1.169), respectively. For budesonide 640 bid versus SYMBICORT pMDI 320/9 bid, mean dose-adjusted AUC0-12 and Cmax treatment ratios for plasma budesonide were 0.745 (0.578, 0.962) and 0.858 (0.682, 1.081), respectively, indicating a slightly less than proportional increase in budesonide exposure in the budesonide group, compared with the SYMBICORT pMDI 320/9 bid group. For SYMBICORT pMDI 640/18 bid versus SYMBICORT pMDI 320/9 bid, mean dose-adjusted AUC0-12 and Cmax treatment ratios for plasma budesonide were 0.805 (0.619, 1.048) and 0.794 (0.626, 1.007), respectively, indicating a slightly less than proportional increase in budesonide exposure in the SYMBICORT pMDI 640/18 bid group, compared with the SYMBICORT pMDI 320/9 bid group. Median Tmax for budesonide was approximately 20 minutes in the SYMBICORT pMDI 640/18 bid and SYMBICORT pMDI 320/9 bid groups (0.358 hours and 0.331 hours, respectively), compared with approximately 40 minutes (0.658 hours) in the budesonide group.
Mean dose-adjusted AUC0-12 and Cmax treatment ratios for plasma formoterol were 1.096 (0.906, 1.325) and 1.128 (0.944, 1.346), respectively, for SYMBICORT pMDI 640/18 bid versus SYMBICORT pMDI 320/9 bid, indicating an approximately proportional increase in formoterol exposure with the doubling of formoterol dose. Median Tmax values for formoterol were

generally similar for the SYMBICORT pMDI 320/9 bid group (0.832 hours) and the SYMBICORT pMDI 640/18 bid group (0.657 hours).

Safety results

All 708 randomized subjects received at least 1 dose of randomized study drug and were included in the safety analysis set.

The percentage of subjects with study drug-related AEs as judged by the investigator was higher in the SYMBICORT pMDI 640/18 bid group (28.0%) than in the budesonide 640 bid group (19.5%), while the percentage in the SYMBICORT pMDI 320/9 bid group was the lowest (15.2%). The overall percentage of subjects with serious adverse events (SAEs) during randomized treatment was higher in the SYMBICORT pMDI 320/9 bid group (9.1%) than in the SYMBICORT pMDI 640/18 bid (4.7%) and budesonide 640 bid (3.8%) groups. There were 4 subjects with SAEs related to cholecystitis, all in the SYMBICORT pMDI 640/18 bid group; however, all were judged to be unrelated to study drug by the investigatorr. The overall incidence of discontinuations due to AEs (DAEs) was slightly higher in the SYMBICORT pMDI groups than in the budesonide group (Symbicort 640/18 bid: 7.4%, Symbicort 320/9 bid: 6.1%, Budesonide 640 bid: 4.5%) .

Overall, an association between budesonide dose and AE incidence was most clearly evident for pharyngolaryngeal pain. A dose-ordered relationship with respect to formoterol dose was observed for several PTs typically associated with β2-agonist effects (specifically tremor and muscle cramp). The overall incidence of AEs in the cardiac SOC and the incidence of individual cardiac-related PTs in the cardiac and investigations SOCs were slightly higher in the SYMBICORT pMDI treatment groups than in the budesonide group; the majority of individual events were related to abnormalities detected during ECG and Holter monitoring and did not result in subject discontinuation. For cardiac and cardiac-related AEs, there were no consistent differences noted between the 2 SYMBICORT pMDI groups. There were no significant patterns of AEs emerging after longer periods of treatment for any of the treatmentgroups. Overall, there were no clinically relevant findings in hematology or clinical chemistry assessments for the SYMBICORT pMDI 640/18 bid or SYMBICORT pMDI 320/9 bid treatment group, compared with budesonide. For serum otassium, small mean decreases from baseline for each SYMBICORT pMDI group were more pronounced than those for budesonide, and a dose-ordered relationship was noted btween the SYMBICORT pMDI doses.

Treatment group omparisons showed evidence of lower mean values of 24-hour urinary cortisol for both the YMBICORT pMDI 640/18 bid and budesonide 640 bid groups compared with the SYMBICORT pMDI 320/9 bid group, starting at 6 months following randomization and persisting thereafter.

For ECG heart rate in the postdose analysis set, small mean increases were greater in the SYMBICORT pMDI groups than in the budesonide group. The increases were dose-ordered for the 2 SYMBICORT pMDI groups. For both the postdose and safety analysis sets, QT, QTc (Baz), and QTc (Frid) least squares (LS) mean changes from baseline and differences between the SYMBICORT pMDI and budesonide groups were generally small across most timepoints, with the most prominent differences observed for QTc (Baz). For the postdose analysis set, the largest difference for QTc (Baz) for SYMBICORT pMDI 640/18 bid minus budesonide 640 bid occurred at end of Month 6: LS mean difference (95% CI)=8.0 msec (3.22, 12.81), and the largest difference for the SYMBICORT pMDI 320/9 bid minus budesonide 640 bid comparison occurred at Week 6: LS mean difference=9.2 msec (3.44, 15.05). For QTc (Frid), similar patterns were observed, though with differences of smaller magnitude. For the subjects identified with potentially significant values for QT, QTc (Baz), and QTc (Frid) (ie, crossed the high threshold [450 msec] or with changes ≥30 msec), the majority of these subjects manifested only a change ≥30 msec; for QTc (Baz) and QTc (Frid), the percentage of these subjects was highest in the SYMBICORT pMDI groups, with evidence of a formoterol dose-ordered relationship. Overall, the percentage of subjects with values crossing the 450-msec threshold was similar across treatment groups with no formoterol dose-ordered relationship noted for QTc (Baz) and QTc

(Frid). Three SYMBICORT pMDI subjects had values that crossed the extremely high reference threshold of ≥500 msec for QT or for QTc (Baz) interval: 2 subjects in the SYMBICORT pMDI 640/18 bid group and 1 subject in the SYMBICORT pMDI 320/9 bid group. All 3 of these subjects also had at least 1 pre-randomization QT or QTc (Baz) interval value ≥450 msec. No subject had a QTc (Frid) ≥500 msec. Analysis of the overall ECG evaluation (made by an independent cardiologist) indicated that the most prevalent abnormality observed across treatment groups was ST-T wave changes, which had a higher incidence in the SYMBICORT pMDI groups than in the budesonide group, but was not dose-ordered between the 2 SYMBICORT pMDI groups. For Holter assessments of average heart rate, minimum heart rate, and percent duration of tachycardia (heart rate >100 bpm), small mean increases were seen for the 2 SYMBICORT pMDI treatment groups compared to budesonide; however, these differences were not considered clinically meaningful and were not consistently formoterol dose-ordered. Shift table analyses performed on Holter monitor data similarly revealed no consistent dose-ordered effects of formoterol or important differences in the percentages of subjects shifting from normal to abnormal for Holter assessments, including average heart rate, minimum heart rate, sinus pause, ventricular runs, total ventricular and supraventricular ectopic beats, and overall Holter interpretation. The number of subjects with potentially clinically important Holter findings identified on treatment was generally low in all treatment groups.
No clinically meaningful changes or treatment group differences were observed in vital signs (pulse rate, diastolic and systolic blood pressure) or physical exam findings during the conduct of the study.

Conclusion:
No new safety signal was detected.
For measures of lung function and asthma control, SYMBICORT pMDI 640/18 bid and SYMBICORT pMDI 320/9 bid showed greater improvement compared with budesonide 640 bid.

Assessor's comment on Symbicort pMDI studies: Symbicort pMDI is not licensed in the EU.The applicant considered these studies relevant to this procedure, because both products have the same active substances.
The inhaler device plays a very important role as regards drug delivery and it is very difficult to draw conclusions from studies which have been conducted with different inhalers.
No new relevant substance specific information which warrant changes to the SPC of Symbicort TBH can be derived here.
As a general remark, we would like to add that the use of formoterol as monotherapy has been linked to safety problems. It is not in accordance with the current licensing status in the EU and is therefore not supported.

Symbicort adjustable maintenance dosing studies:

Symbicort Turbuhaler:

SD-039-0686 (2001-2002) A randomized, double-dummy, double-blind/open, parallel-group, phase-III, multicentre, 7-month study to assess the efficacy and safety of Symbicort® Turbuhaler® (budesonide/formoterol; 160/4.5 µg delivered dose) given either as standard therapy (2 inhal. b.i.d.) or with an adjustable dosing regimen (1, 2 or 4 inhal. b.i.d.) versus Seretide Diskus (salmeterol/fluticasone; 50/250 µg metered dose) given as standard therapy (1 inhal. b.i.d.) in adult and adolescent asthmatic patients

Objective(s):

Primary: to compare the efficacy of Symbicort Turbuhaler, given as a standard therapy or with an adjustable dosing regimen, with that of Seretide Diskus given as a standard therapy in asthmatic adults and adolescents.

Study design: This was a randomized, double-dummy, double-blind/open, parallel-group, multicentre, 7-month study. The study was conducted in 93 centres in Denmark, Finland, The Netherlands, Germany, Norway, and Sweden.

Study population /Sample size:
Symptomatic male or female subjects aged ≥12 years with a diagnosis of perennial asthma, using ≥500 - ≤1200 µg daily of inhaled GCS, with a forced expiratory volume in one second (FEV1) ≥50% of predicted normal.
Based on a previous study, with 200 completed subjects per treatment group, an actual difference of 8.5% between two groups could be detected with 80% power (assuming a significance level of 5% and a 2-sided alternative hypothesis).

Treatments:
Seretide Diskus (salmeterol/fluticasone), 50/250 µg per inhalation, 1 inhalation morning and evening
or
Symbicort Turbuhaler (budesonide/formoterol), 160/4.5 µg per inhalation, 2 inhalations morning and evening
or
Symbicort Turbuhaler Adjustable Dosing (Symbicort AD), 160/4.5 µg per inhalation, 2 inhalations morning and evening during the first part (1 month; Treatment period I) of the study and thereafter either 1 or 2 inhalations morning and evening (with an increase to 4 inhalations morning and evening for 7-14 days in case of asthma worsening) during the second part (6 months; Treatment period II) of the study.

Outcomes/endpoints

Primary endpoint: The primary efficacy endpoint was the odds of having a well-controlled asthma week during the randomized treatment period.

Statistical Methods
The full analysis set was used in all efficacy and safety analyses. The incidence of well-controlled asthma weeks during the treatment period was considered as a series of correlated binary variables. A generalized estimating equation (GEE) with a logistic link function, the dependency model as exchangeable observations, treatment, country and asthma control the last week before randomization (well-controlled or not) as factors and subject as cluster were used to estimate the odds of having a well-controlled asthma week and to compare the treatments. Number of exacerbations were analysed in a Poisson regression model and time to first exacerbation was analysed in a COX proportional hazards model. Period means of diary card variables and FEV1 were analysed in ANOVA models adjusting for run-in and country.

Results

Recruitment/ Number analysed
658 subjects (15 patients 12-17 years of age) were randomized. Treatment groups were similar at baseline with respect to most demographic and disease severity characteristics. The overall discontinuation rate was highest in the Symbicort Turbuhaler group (14.4%), compared with 11.2%% in the Seretide group and 12.3% in the SYMBICORT adjustable dose group.

Efficacy results:
No difference between treatments was seen for the primary variable. With regard to secondary endpoints the comparison of Seretide versus the SYMBICORT adjustable dose group show a significant reduction of events in the SYMBICORT adjustable dose group (p=0.018). FEV1 increased significantly more in the SYMBICORT compared to the Seretide group (difference: 58ml, p= 0.041). Seretide was significantly better compared to the SYMBICORT adjustable dose group in increasing evening PEF (difference: 7.9l/min, p=0.025). SYMBICORT adjustable dose was significantly bettering reducing rescue medication use compared to Seretide (difference 0.25 rescue occ./24h, p=0.0064).

Safety results
Overall, the proportions of subjects reporting any AE were similar across the treatment groups; Symbicort 58%, Symbicort AD 57%, and Seretide 66%. The system organ class (SOC) in which most AEs were reported was Respiratory system disorders and in this SOC, Respiratory infection was the most frequently reported AE with a similar incidence across treatments. The incidence of dysphonia was slightly higher in the Seretide group compared to Symbicort treatment group and Symbicort AD group. The number of serious adverse events (SAEs) was similar in the treatment groups (Seretide: 8, Symbicort:13, Symbicort AD: 9). The frequency of DAEs was similar (3-5%) between groups.

Conclusion:
No difference was detected between the treatment groups in the primary variable well-controlled asthma weeks. No new safety concerns were identified.

Assessor's comment: This study enrolled a low number of adolescents. It was inconclusive as regards the primary endpoint and did not evaluate standard safety parameters, e.g. lab chemistry, ECGs. In general stepping-up and down depending on the level of asthma control is in accordance with the recommendations of the GINA Guideline. This practice is covered by the current marketing authorization of Symbicort Turbuhaler to some extent. The highest dose licensed in the adolescent population is 2 inhalations of Symbicort Turbuhaler 160/4.5 bid. Therefore the highest dose used in this study is not covered.

BS-039-0002 The effectiveness and safety of an individualised Symbicort Turbuhaler maintenance dosing regimen (Symbicort Asthma Control Plan) versus Symbicort Turbuhaler given as standard regular twice daily therapy

Please note that this phase IV study has only been submitted as a publication (Leuppi et al, Swiss Med wkly 2003, 133: 302-309). Therefore only a brief summary is given here

Summary: the open-label, parallel-group, multicentre study enrolled 127 asthmatic patients ≥ 12 years of age (5 adolescents), well –controlled on ICS+LABA therapy. After a 4 –weeks run-in on Symbicort Turbuhaler 160/4.5 µg 2 inhalations bid, they were randomised to either stay on the therapy received during run-in or to switch to Symbicort adjustable dose therapy (1 inhalation bid or 2 inhalations at night with interim step-ups to two inhalations bid up to 4 inhalations bid for 14 days). Study duration on active treatment was 12 weeks. >50% of the patients in the adjustable dose group used a decreased maintenance dose on > 50% of the days. 18.8% never reduced their dose and 5.8% stepped their dose up. Symptom severity (NHLBI severity grade) decreased in both groups, with a significant decrease (p= 0.004) in the adjustable dose group. Treatment failures occurred in 17% and 24% of patients (adjustable and fixed dosing , respectively p=0.35) (number of treatment successes and treatment failures were the primary endpoints in this study). Nocturnal awakenings and rescue medication use were significantly less frequent in the

adjustable dose group and the average daily medication dose was also significantly reduced. Lung function parameters were not significantly different between groups.

Assessor's comment: This study was only submitted as a publication. It enrolled only 5 adolescents. Therefore, it is of limited value to this assessment.

CF-039-001(2001-2002) Comparison of SYMBICORT Turbuhaler 200/6 µg at fixed doses versus SYMBICORT Turbuhaler 200/6µg at doses adjusted to asthma control for 16 weeks of treatment

Please note that only the study synopsis has been provided in English (in accordance with the request by the EMA) and is discussed here.

Objective(s): to compare the efficacy and safety of two SYMBICORT maintenance strategies over a period of 16 weeks.

Study design: this was a multi-centre (353 centres in France), open-label, parallel-group, 16 week, Phase IV study.

Study population /Sample size: Male and female asthma patients > 12 years of age stable on a ICS +LABA combination therapy or insufficiently controlled on ICS mono-therapy in combination with SABAs were to be enrolled. It was planned to randomize1960 patients.

Treatments:
SYMBICORT Turbuhaler 200/6 µg 2 inhalations bid
or
SYMBICORT Turbuhaler 200/6 µg 2 inhalations in one or two doses or 2 inhalations bid (adjustable dose group)

Outcomes/endpoints
Primary endpoint: Number of severe asthma exacerbations

Statistical Methods
The primary variable was compared between groups by a Chi-square test with calculations of the relative risk and 95% confidence intervals.

Results

Recruitment/ Number analysed
873 subjects (50< 18 years of age) were randomized.126 patients discontinued prematurely.

Efficacy results:
There was no significant difference between groups with regard to severe asthma exacerbations (fixed dose: 6.7%, adjusted dose: 9.3%). The percentage of days without asthma symptoms was >90% for both groups during run-in as well as during the randomized period. The change in this criterion between the 2 periods was significantly different between the two groups, in favour of the fixed dose group. Otherwise no significant differences were observed between groups.

Safety results:
The proportion of patients experiencing at least one AE during the randomized period was 45.3% in the fixed dose group and 48.6% in the adjustable dose group.

Conclusion:
No differences regarding safety and efficacy of both treatments were observed.

Assessor's comment: Information on this study is rather sparse. Anyhow, it was inconclusive as regards the primary parameter. Furthermore standard parameters of safety were not evaluated.

CF-039-0002 (2002-2003) Comparison of SYMBICORT Turbuhaler 200/6 µg at fixed doses versus SYMBICORT Turbuhaler 200/6µg at doses adjusted to asthma control for 16 weeks of treatment in general practice

Please note that only the study synopsis has provided in English (in accordance with the request by the EMA) and is discussed here.

Objective(s): to compare the efficacy and safety of two SYMBICORT maintenance strategies over a period of 16 weeks.

Study design: this was a multi-centre (1442 centres in France), randomized, open-label, parallel-group, 16 week, Phase IV study. The study comprised 2 treatment periods:
Period 1 (week 0-4): 2 inhalations of SYMBICORT Turbuhaler 200/6µg bid
Period 2 (week 5-16): patients controlled after period 1 were randomized either to the fixed dose group or the adjustable dose group.

Study population /Sample size: Based on the assumptions of an exacerbation rate of 11% in the fixed dose group and a maximum of 12 % in the adjusted dose group the number of patients necessary to conclude on equivalence (4% equivalence zone, one sided alpha risk: 2.5%, power: 90%) was 4752. As the rate of uninterpretable cases was estimated to be 20%, it was planned to include 6000 patients.
Main inclusion criteria were: asthma patients ≥ 12 years of age currently treated with either a combination of ICS+LABA and stabilized or insufficiently controlled on ICS and SABA.

Treatments (period 2):
SYMBICORT Turbuhaler 200/6 µg 2 inhalations bid
or
SYMBICORT Turbuhaler 200/6 µg 2 inhalations in one or two doses or 2 inhalations bid (adjustable dose group)

Outcomes/endpoints

Primary endpoint: severe asthma exacerbations

Statistical Methods
Non-inferiority of the adjusted dose strategy was assumed, if the upper limit of the bilateral 95% confidence interval of the difference between groups regarding the primary parameter was <4%.

Results
Recruitment/ Number analysed
2068 patients were randomized (77 adolescents), 1702 patients completed the study.18.4% of the patients in the fixed dose group compared to 17.0% of the patients in the adjustable dose group discontinued prematurely. Both groups were comparable with regard to demographic characteristics as well as characteristics of disease severity.

Efficacy results:
3.3% of the patients in the fixed dose group and 3.5% of the patients in the adjusted dose group experienced a severe asthma exacerbation. The difference between groups was -0.2% (95% confidence interval: (-1.9;1.6). Non-inferiority was concluded. The number of days without asthma symptoms was higher in the adjusted dose group (p=0.02, difference between treatments: 1.6%). The number of inhalations of SYMBICORT per day was lower in the adjusted dose group (2.14 versus 3.91, p=<0.001). No significant differences were detected with regard to the other secondary end-points.

Safety results:
22.6% of the patients in the fixed dose group and 23.2% of the patients in the adjusted dose group experienced at least one AE. The percentage of SAE and AEs leading to discontinuation were comparable between groups. There were 3 deaths in the fixed dose group and no deaths in the adjusted dose group.

Conclusion:
Efficacy and safety variables were comparable between both treatment groups.

Assessor's comment: Only rather sparse information is available on this study .No differences between treatments were detected. Non-inferiority was concluded. However it has to be mentioned that this study might as well have been insensitive due to its design.

CI-SYM-0001 (2001-2002) Control of Asthma by Symbicort Turbuhaler, Effectiveness and safety of a flexible individualised dosing regimen versus a standard twice daily regimen

Objective(s): The primary aim of the study was to evaluate the efficacy and safety of a maintenance regimen with Symbicort administered at fixed dose twice a day compared to a flexible dose regimen according to the Asthma Control Plan (PAC), with the Symbicort maintenance dose adjusted up or down on the basis of asthmatic symptoms course.

Study design: Multi-centre, randomized, open, parallel group, 3 months Phase III study conducted in 154 centres in Italy.

Study population /Sample size: Patients aged ≥ 6 years currently well managed with a combination therapy including an inhaled corticosteroid and a long acting bronchodilator, or patients currently managed with an inhaled corticosteroid and a short acting bronchodilator, the latter in presence of symptoms requiring further therapy were to be recruited.
A total of 980 randomised subjects with asthma, derived from an estimated 1100 recruited subjects, were required for each treatment group for 90% power of detecting a 5% difference between groups in % failure rate.

Treatments:
Group A (fixed twice daily dosing) received Symbicort 80/4.5µ g or 160/4.5µg, 2 inhalations bid.
Group B (Symbicort PAC, with planned dosing adjustments) received Symbicort 80/4.5 or 160/4.5 µg 2 inhalations twice daily for 1 month (run-in period), followed by 1-4 inhalations twice daily according to symptoms (or two inhalations nocte where appropriate) (maintenance period). The Symbicort strength was to be selected on the basis of the age and the current prescribed dose of inhaled corticosteroid.

Outcomes/endpoints

Primary endpoint: proportion of treatment failures, defined as an exacerbation of asthma prompting a serious adverse event report or requiring hospitalisation or emergency treatment, or requiring treatment with oral corticosteroids or study withdrawal, with modification of maintenance therapy.

Statistical Methods
The primary endpoint was analysed according to the Cochran Mantel-Haenszel test, stratified on the basis of the study stratification criterion (i.e. the Symbicort high/low dose), and described with the estimated common relative odds ratio together with 95% CI and p-value. Homogeneity of the odds ratios over strata was tested. The proportion of patients fulfilling each of the criteria for treatment failure was also separately analysed. Analyses were carried out in the "efficacy" population (main analysis, all patients randomised who completed the run-in period and started the maintenance period) and in the ITT population (confirmatory analysis).

Results
Recruitment/ Number analysed
2358 patients were randomised and analysed for efficacy (149 patients < 18 years of age). 1899 completed the trial. The percentage of discontinuations was similar between groups (18.6% fixed dose group, 20.3% adjustable dose group). Patients were comparable with regard to baseline data.

Efficacy results:
Failure rate was similar in the fixed and adjustable dose groups (4.6% and 4.8% of patients in the efficacy populations of the two groups, respectively). Frequency of failure reasons was evenly distributed among groups, except for asthma related SAEs, present only in the fixed dose group with 3 cases (0.3%), and of modified asthma maintenance therapy, slightly more frequent in the adjustable dose (2.3%) than in the fixed dose group (1.4%) (no significant differences from the Cochran Mantel- Haenszel test).
There was a significant reduction of number of Symbicort inhalations in the adjustable dose regimen (2.95 inhalations/day on the average) *vs* the fixed dose regimen (3.86 inhalations/day) ($p<0.0001$ at ANCOVA) as well as a significant reduction in total direct costs (-36.56 € per patient, $p<0.0001$), and total costs (-64.57 € per patient, $p<0.0001$).

Safety results:
The percentage of patients reporting at least one adverse event was similar in both groups (20.1% in the fixed dose and 19.8% in the adjustable dose group), with similar frequencies of treatment related adverse events (3.5% and 3.3% of patients in the two groups), serious adverse events (0.9% and 0.7% of patients in the two groups), and similar frequency of patients discontinuing treatment in view of adverse events (3.5% in the fixed dose and 3.1% in the adjustable dose group). Individual adverse events occurred in <5% of patients in both groups, and most frequently involved the upper and lower respiratory systems, except for tremor. The latter was reported with similar frequency in both groups (1.2% in the fixed dose and 1.4% in the adjustable dose group).

Conclusion:
Adjustable maintenance treatment with Symbicort showed similar efficacy and safety to fixed dosing regimen, at a significantly lower overall dose compared with fixed dosing. Adjustable maintenance treatment results in a significantly lower direct and total cost compared with fixed dosing.

Assessor's comment: Both treatments showed similar efficacy and safety. However the study is not designed to really establish non-inferiority. The highest dose used here (2x 4 inhalations) is

higher than the licensed dose for the paediatric population. It is not clear how many paediatric patients received this dose

DC-039-0001 (2001-2002) The effectiveness and safety of an individualised Symbicort® Turbuhaler® maintenance dosing regimen (Symbicort® Asthma Control Plan) versus Symbicort® Turbuhaler® given as regular twice daily therapy – SMART

Objective(s): The primary objective of the study was to evaluate the relative effectiveness of two different Symbicort® Turbuhaler® treatment regimens (fixed dose versus adjustable dose).

Study design: This was a randomised, open-label, parallel group, multicentre (95 centres in Canada), six months Phase III study.

Study population /Sample size: Male or female asthma patients aged ≥12 years of age using ICSs for at least six months prior to study start and with a post-bronchodilator FEV1 ≥ 70 % of predicted normal value were to be enrolled.
A total of 478 randomized patients per group with the diagnosis of asthma, derived from an estimated 597 enrolled patients, were required for detecting 9% difference in the proportion of treatment failures, with a probability of 90%. This assumed a 5% significance level and a two-sided alternative hypothesis.

Treatments:
Budesonide/formoterol (Symbicort® Turbuhaler®)) as either 80/4.5 µg per inhalation or 160/4.5 µg per inhalation was given as a fixed dose regular therapy: two inhalations bid, or as an adjustable dosing regimen: one or two inhalations morning and evening, with the option of stepping up to four inhalations morning and evening for 7 or 14 days in case of asthma worsening.

Outcomes/endpoints

Primary endpoint: The proportion of patients experiencing a treatment failure.
A treatment failure occurred when the patient experienced at least one of the following: Asthma related serious adverse event (SAE), treatment (e.g., bronchodilators) at emergency room due to worsening of asthma, need for other inhaled and/or oral glucocorticosteroid due to worsening of asthma, study withdrawal due to the need for added asthma maintenance therapy.

Statistical Methods
Efficacy was assessed by comparing the proportion of patients with treatment failures between the two groups using the Cochran Mantel-Haenszel (CMH) test, stratified by strength of Symbicort® Turbuhaler® (80/4.5 µg and 160/4.5µg). Time to first treatment failure was compared between treatments using a Kaplan-Meier curve. The average number of Symbicort® inhalations in each treatment group during the treatment period was compared using an analysis of variance (ANOVA).

Results

Recruitment/ Number analysed
995 (66 patients < 18 years of age) patients were randomised and analysed for efficacy and safety. 883 completed the study. The percentage of patients who discontinued was similar between groups (fixed dose group: 12%, adjusted dose group: 10.6%). Patients were comparable with regard to baseline characteristics.

Efficacy results : There was a significantly lower proportion of patients with at least one

treatment failure in the adjustable treatment group compared to the fixed treatment group (4.0% vs 8.9%; p=0.002).
Results from secondary efficacy variables indicated satisfactory asthma control in both treatment groups. The adjustable treatment group had significantly lower use of study medication (p<0.001), with a daily mean number of inhalations of 2.51 as compared to 3.92 in the fixed treatment group. Analyses of other secondary variables showed no differences between the two treatment groups. Health economic costs, total asthma medication costs, sum of health care costs, sum of direct costs and total costs were all lower in the Symbicort® adjustable treatment arm.

Safety results:
All treatments in both groups were well tolerated. No clinically important drug related safety findings were identified in this study. The percentage of patients with at least one AE (fixed dose: 72%, adjustable dose: 69.1%), SAE (fixed dose:1.4% ,adjustable dose:1%) and DAEs (fixed dose:2.6%, adjustable dose: 1.8%), were similar in both groups. The most commonly reported AE was respiratory infection.

Conclusion:
Symbicort® adjustable treatment reduced the incidence of treatment failures and maintained overall asthma control. The patients in the adjusted dose group used less asthma medication and had lesser total costs. No safety concerns were identified.

Assessor's comment: The study established superiority of the adjustable dosing regimen over the fixed dose regimen with regard to treatment failure. Stepping up-and down the dose is in agreement with the recommendations of current guidelines. Although the highest doses used here are not licensed for the adolescent population. It is not clear how many, if any, adolescents used this dose. Anyway, it will probably not be possible to draw final conclusions, because the number of adolescent enrolled in the study is low and the study did not evaluate standard parameters of safety like lab chemistry.

LD-039-001 (2001-2002) The effectiveness and safety of an individualised Symbicort® Turbuhaler® maintenance dosing regimen (Symbicort Asthma Control Plan) versus Symbicort Turbuhaler given as standard regular twice daily therapy

Objective(s): to evaluate the relative efficacy and safety of Symbicort Turbuhaler given either as a fixed or an adjustable maintenance regimen.

Study design: Multi-centre (94 centres in Sweden), randomized, open, parallel group, active controlled, 6 months study.

Study population /Sample size: Male and female patients aged ≥12 years of age currently well managed with a combination therapy including an inhaled corticosteroid and a long acting bronchodilator, or patients currently sub-optimally controlled with an inhaled corticosteroid and a short acting bronchodilatator.
A total of 956 subjects were required to detect a 9% difference in the proportion of treatment failures with a probability of 90% (5% significance level, two-sided alternative hypothesis).

Treatments:
Fixed dose group: Symbicort 80/4.5µ g or 160/4.5µg, 2 inhalations bid.
Adjusted dose group: Symbicort 80/4.5 or 160/4.5 µg 2 x 1-4 inhalations bid during the active study period according to symptoms.

Outcomes/endpoints

Primary endpoint: Primary variable: proportion of treatment failures, defined as a serious asthma related adverse event or treatment at a medical care unit due to worsening asthma or requiring treatment with oral corticosteroids due to worsening asthma or study withdrawal, due to modification of maintenance therapy.

Statistical Methods
The full analysis set was considered as the main analysis population. The primary analysis was the Cochran Mantel-Haenszel-Test, stratified by SYMBICORT dose. From this analysis the common relative odds ratio was reported.

Results

Recruitment/ Number analysed
1034 patients (75 adolescents) were randomised and analysed for efficacy and safety . 977 completed the trial. The percentage of discontinuations was similar between groups (5% fixed dose group, 6% adjustable dose group). Patients were comparable with regard to baseline data.

Efficacy results:
9.48% of the patients in the fixed dose group and 6.19% of the patients in the adjusted dose group experienced at least one treatment failure. Failure rate was significantly lower in the adjustable dose groups (p=0.0492). The adjusted dose group used significantly less study medication (p<0.001). The use of bronchodilatator for symptom relief was significantly higher in the adjusted dose group (p=0.0011). Night-time awakening occurred significantly more often in the adjusted dose group (1.7% versus 1.3%, p= 0.011). Asthma medication costs and total costs were significantly lower in the adjusted dose group (p<0.001).

Safety results:
The percentage of patients with serious AEs was low and comparable between groups (1.9% fixed dose group, 2.9% adjusted dose group). The number of discontinuations due to an AE was 14 in both groups. (Only SAEs and DAEs were collected).

Conclusion:
SYMBICORT given as adjustable maintenance therapy showed less treatment failures compared to the fixed dose regimen. No safety concerns were detected.

Assessor's comment: This study also fails to evaluate standard parameters of safety. Only AEs and DAEs were collected.

MA-SYM-001 (2001-2003)The effectiveness and safety of an individualised Symbicort Turbuhaler maintenance dosing regimen (Symbicort Asthma Control Plan) versus Symbicort Turbuhaler given as standard regular twice daily therapy THE SYMBICORT ADJUSTABLE MAINTENANCE STUDY (SAM)

Objective(s): The objective of the study was to evaluate the relative effectiveness and safety of Symbicort given either as a fixed dose treatment regimen or an adjustable dose regimen adjusted to asthma symptoms. The aim of the Symbicort Asthma Control Plan was to maintain effective asthma control on lower overall doses of both corticosteroid and long-acting bronchodilator.

Study design: This was a multi-centre (56 centres in 17 countries in North and South America, Africa and Europe), randomised, open, 12 weeks (active treatment) study with a parallel group design.

Study population /Sample size:
This study was planned to include patients ≥12 years of age who at time of inclusion were well managed with both inhaled corticosteroids and long-acting bronchodilator or patients who at time of inclusion were not well-controlled on inhaled corticosteroid and short-acting bronchodilatator.
A total of 420 randomised and evaluable patients were required to detect a 10% difference in the proportion of treatment failures, 21% in the fixed and 11% in the adjustable treatment group, with a probability of 80%. This assumed a 5% significance level and a two-sided alternative hypothesis. Allowing of a 20% drop-out rate during the run-in period a minimum of 508 patients were to be enrolled into the study.

Treatments:
Group A - Fixed twice daily dosing*:* Symbicort 80/4.5 µg or Symbicort 160/4.5 µg, 2 inhalations bid

Group B – Symbicort adjustable dose group:
Symbicort 80/4.5 µg or 160/4.5µg, 2 inhalations twice daily, followed by 1, 2 or 4 inhalations once or twice daily according to symptoms.

Outcomes/endpoints

Primary endpoint: The proportion of treatment failures occurring from randomisation to the end of the study and treatment success as defined by the movement of a patient from one classification of severity to a less severe classification of asthma severity score at the end of the study period.

Statistical Methods
The proportion of treatment failures was compared between the treatment groups by using the Cochran Mantel-Haenszel test, stratified by the dose of SYMBICORT. Odds ratios and 95% confidence intervals are presented both as a total and for each of the two doses of Symbicort separately. The proportion of patients in each asthma severity category was compared between the treatment groups by using the Cochran Mantel-Haenszel test (for ordinal responses), stratified by dose of Symbicort and the initial asthma severity.

Results

Recruitment/ Number analysed
537 patients (33 adolescents) were randomised and analysed for safety. 523 patients were analysed for efficacy. 503 completed the trial. The percentage of discontinuations was similar between groups (3% fixed dose group, 4% adjustable dose group). Patients were comparable with regard to baseline data.

Efficacy results:
The proportion of patients with at least one treatment failure was lower in the adjustable treatment group, (4.6%), compared to the fixed treatment group (7.0%), which was not statistically significant (p= 0.233). The same tendency was also seen in the two Symbicort dose groups. In total 145 (57.5%) patients in the fixed and 144 (56.9%) in the adjustable treatment group changed to a milder asthma severity category. The corresponding

proportions for the low Symbicort dose group were 60.3% versus 53.0% and for the high Symbicort dose group 55.0% versus 60.1%. There was no difference between the two treatment groups, either in total or in any of the two Symbicort dose groups, as concerns the treatment success. Patients in the adjusted dose group took significantly less inhalations per day compared to the fixed dose group.

Safety results:
The percentage of patients with at least one AE was similar between groups (fixed dose group: 13.6%, adjusted dose group 14.3%). The most commonly reported AE was asthma aggravated (fixed dose group: 3.8%, adjusted dose group 2.9%). 1 patients in the fixed dose group and 2 patients in the adjusted dose group discontinued due to an AE. 4 SAEs (2 in each group) occurred during the randomise period.

Conclusion:
Symbicort adjustable treatment had a lower but not significantly different proportion of treatment failures as compared to fixed dose treatment. Both treatments were well tolerated and no safety concerns were identified.

Assessor's comment: The study did not show differences between treatments in efficacy. Safety evaluation again is incomplete.

Overall comment on Symbicort Turbuhaler adjustable maintenance studies:
The applicant submitted 8 studies. The studies included 8665 patients, among them 470 patients < 18 years (approx. 5%). This kind of therapy is in accordance with current guidelines. This is also reflected in the SPC which indicates that patients should receive the lowest dose sufficient to keep their asthma controlled. However, the highest doses used here exceed the doses licensed in the paediatric population. The number of patients (if any) who received these high doses is not given. However this number will definitely be too low to allow for meaningful conclusions. This is also true for the population 6-<12 years of each. Only one dose is recommended here, which makes stepping up and down more difficult. However only study CI-SYM-0001 enrolled patients from 6 years of age and the number of subjects in the age range 6-12 years will definitely be not be sufficient for new recommendations. Therefore the applicant's statement, that "no firm conclusion" can be drawn is supported.

Symbicort pMDI studies:

D5896C00005 (2003-2005) A two-stage randomized, open-label, parallel group, phase III, multicenter, 7-month study to assess the efficacy and safety of SYMBICORT® pMDI administered either as fixed or as an adjustable regimen versus a fixed regimen of Advair™ in subjects 12 years of age and older with asthma

Objective(s):
Primary: The primary objective of the study was to compare the efficacy of SYMBICORT pMDI given as an adjustable regimen with that of a fixed regimen of Advair Diskus® in subjects 12 years of age and older with asthma. In addition, the efficacy of SYMBICORT® pMDI given as a fixed regimen was compared with that of a fixed regimen of Advair. The primary variable in this study was asthma control as assessed by exacerbations.

Study design: This was a 7-months, multi-center (145 centres in the US), randomized, open-label, Phase III study.

The study had 3 phases: Screening/Run-in (10-14 days), Treatment Period 1 (1 month), and Treatment Period 2 (6 months). At Screening/Run-in, eligible subjects remained on their current asthma therapy for a period of 10-14 days. If eligible at the end of run-in, subjects entered Treatment Period 1 and received either fixed-dose SYMBICORT pMDI or Advair in a 2:1 randomization scheme. After subjects had completed Treatment Period 1, subjects on SYMBICORT pMDI were randomized again (Randomization 2) to either fixed- or adjustable-dose SYMBICORT pMDI in a 1:1 randomization scheme. Subjects randomized to Advair during Treatment Period 1 remained on Advair throughout the course of the study. At the beginning of Treatment Period 2, subjects randomized to adjustable-dose SYMBICORT pMDI whose asthma was controlled had their SYMBICORT dose "stepped down" from 2 actuations twice daily (bid) to 2 actuations once daily (qd). Those subjects in the adjustable-dose group not meeting step-down criteria were to remain at 2 actuations bid for the first 3 months of Treatment Period 2, after which time, those who met step-down criteria were to have their SYMBICORT dose adjusted from 2 actuations bid to 2 actuations qd. Subjects still not meeting step-down criteria were to remain on 2 actuations bid for the duration of the study. During times of asthma deterioration, all subjects in the adjustable-dose SYMBICORT pMDI group were to use 4 actuations bid for 7-14 days and then return to their previous regimen.

Study population /Sample size:
The target subject population included male and female asthma patients ≥12 years of age, who were in stable condition. Subjects should have received maintenance asthma treatment with ICS or ICS/LABA combination therapy for ≥12 weeks prior to the screening visit. Subjects were also required to have an FEV1 ≥50% of predicted normal. For the time to first exacerbation, a sample size of 400 subjects per treatment group would provide at least 90% power for a hazard ratio of at least 1.4 and at least 80% power for a hazard ratio of 1.3. This sample size would also provide about 90% power to detect a 0.15 L difference in FEV1.

Treatments:
Fixed-dose SYMBICORT pMDI 160/4.5 µg: 2 actuations bid
or
Adjustable-dose SYMBICORT pMDI 160/4.5 µg: 2 actuations qd, 2 actuations bid, or 4 actuations bid
or
Fixed-dose Advair 250/50 µg (fluticasone/salmeterol): 1 inhalation bid.

Outcomes/endpoints

Primary endpoint: The primary efficacy endpoint was asthma control as measured by asthma exacerbations.

Statistical Methods
The primary variable was asthma exacerbations, measured by time to first exacerbation, the number and percentage of subjects with at least 1 asthma exacerbation, and the total number of exacerbations. Time (in days) from the first dose of randomized treatment to the first exacerbation was presented as the primary derivation of this variable, because it was used to power the study. It was analyzed using a log-rank test and also described using a Kaplan-Meier plot. Additionally, a Cox proportional hazards model was used to estimate hazard ratios. The number and percentage of subjects with at least 1 asthma exacerbation during randomized treatment was analyzed using a chi-square test. The number of exacerbations was expressed as the number per subject-treatment year and analyzed using a Poisson regression model adjusting for subject exposure. Exacerbation data were additionally analyzed using the per-protocol analysis set.

Results

Recruitment/ Number analysed
1225 patients were randomized to enter Treatment Period 1 (817 fixed-dose SYMBICORT pMDI; 408 Advair). At Visit 3, the 778 subjects remaining in the fixed-dose SYMBICORT pMDI group were randomized into Treatment Period 2: 389 subjects in each of the adjustable-dose SYMBICORT pMDI and fixed-dose SYMBICORT pMDI groups. The safety analysis set consisted of 1222 patients including 173 12-< 18 years of age. Demographic and baseline characteristics were generally well balanced across treatment groups. The discontinuation rate during Treatment Period 1 was similar for the fixed-dose SYMBICORT pMDI and Advair groups (14.6% and 13.2%, respectively). During Treatment Period 2, 11.2% of the adjustable-dose SYMBICORT pMDI group, and 9.5% of each of the fixed-dose SYMBICORT pMDI and Advair groups discontinued. The most common reasons for discontinuation among randomized subjects were loss to follow-up and unwillingness to continue the study.

Efficacy results:
Primary variable: There were no statistically significant differences between treatment groups for any measure of asthma exacerbation, including time to first asthma exacerbation, the number and percentage of subjects who had at least 1 asthma exacerbation, and the total number of asthma exacerbations per subject-treatment year during the overall randomized treatment period.

Safety results:
Overall, fixed-dose and adjustable-dose SYMBICORT pMDI and Advair were well tolerated
No new safety concerns were identified. The percentage of subjects with AEs during the overall randomized treatment period was similar across treatment groups (SYMBICORT fixed dose: 61.6%, SYMBICORT adjustable dose:57.8%, Advair: 58.6%).
The percentage of subjects with SAEs was low and similar across treatment groups (SYMBICORT fixed dose group: 2.1%, Symbicort adjusted dose 1.8%, Advair 2.2%). The percentage of subjects with DAEs was low overall and slightly higher in the fixed-dose SYMBICORT pMDI group compared with the adjustable-dose SYMBICORT pMDI group and Advair groups (4.2%, 2.1%, 2.0%, respectively). There were 3 DAEs of asthma: 2 (0.5%) in the Advair group and 1 (0.2%) in the fixed-dose SYMBICORT pMDI group.

Conclusion:
There were no differences in efficacy among the 3 treatment groups for the primary endpoint, asthma exacerbation. No new safety concerns were identified.

Assessor's comment: This study evaluates Symbicort pMDI. It was negative as no differences in efficacy were seen between treatments. The safety evaluation is incomplete. No conclusion regarding Symbicort TBH can be drawn

Symbicort maintenance and reliever therapy
Symbicort Turbuhaler studies:

D5890C00002 (2005-2006) Efficacy and safety of Symbicort® Turbuhaler® 160/4.5 µg/inhalation,two inhalations twice daily plus as-needed, compared with Seretide™ Diskus™ 50/500 µg/inhalation, one inhalation twice daily plus terbutaline Turbuhaler 0.4 mg/inhalation as-needed - a 6-month, randomised,double-blind, parallel-group, active-controlled, multi-national phase IIIB study in adult and adolescent patients with persistent asthma (AHEAD)

Objective(s):
Primary: The primary objective of this study was to compare the efficacy of 2 inhalations of Symbicort Turbuhaler 160/4.5 µg/inhalation twice daily plus Symbicort Turbuhaler 160/4.5 µg/inhalation as-needed with 1 inhalation of Seretide Diskus 50/500 µg/inhalation twice daily plus terbutaline Turbuhaler 0.4 mg/inhalation as-needed in patients with persistent asthma.

Study design: This was a 6-month, randomised, double-blind, parallel-group, active-controlled, multi-national (184 centres in Europe, Africa, Asia, American and Australia) study.

Study population /Sample size:
Males and females, at least 12 years old, with persistent asthma, and a pre-bronchodilatory FEV1 >50% of predicted normal value with at least 12% reversibility were enrolled. Patients were to require frequent use of as-needed reliever medication (ie, 5 out of the last 7 days of run-in), despite daily use of inhaled ICS and should have experienced at least 1 clinically important asthma exacerbation within 1 to 12 months before enrolment in the study.
Assuming that 11% of patients would experience a severe asthma exacerbation in the Symbicort group and 16% of patients would experience a severe asthma exacerbation in the Seretide group, 985 randomised and evaluable patients per group would be required to detect this difference with 90% probability using a log-rank test with a two-sided alternative hypothesis and a significance level of 5%. In order to compensate for withdrawals, the sample size was set to 1050 patients per group.

Treatments:
Symbicort (budesonide/formoterol) Turbuhaler 160/4.5 µg/inhalation 2 inhaltions bid as maintenance treatment plus Symbicort Turbuhaler 160/4.5 µg/inhalation as-needed
or
Seretide (salmeterol/fluticasone) Diskus 50/500 µg/inhalation one inhalation bid as maintenance treatment plus terbutaline Turbuhaler 0.4 mg/inhalation as-needed.

Outcomes/endpoints

Primary endpoint: time to first severe asthma exacerbation

Statistical Methods
Time to first severe asthma exacerbation was described using Kaplan-Meier curves, and the treatment groups were compared using a Cox proportional hazards model, stratified by country and with treatment as factor. Mean number of severe asthma exacerbations per patient was compared between the treatments using a Poisson regression model with treatment and country as factor and total time in study as an offset variable.

Results

Recruitment/ Number analysed
2309 patients were randomized. 324 patients were in the age range 12-17 years of age. 2304 patients were analysed for efficacy and safety. 2097 patients completed the study. The percentage of patients who discontinued was comparable between groups (SYMBICORT group 8%, Seretide group 10%).

Efficacy results:
There were fewer severe asthma exacerbations and fewer patients that experienced severe asthma exacerbations in the Symbicort group (137 events among 108 patients) than in the Seretide group (173 events among 130 patients). There was not a statistically significant

difference in the primary outcome variable, time to first severe asthma exacerbation (Symbicort versus Seretide hazard ratio 0.82; P=0.12). There was a statistically significant advantage for Symbicort in the number of severe exacerbations per patient per 6 months (Symbicort 0.12 versus Seretide 0.16; risk ratio: 0.79, P=0.039).
Additional analysis performed on the individual criteria for severe exacerbations showed statistically significant differences in favour of Symbicort SMART for the time to first asthma hospitalisation/ER treatment (Symbicort SMART versus Seretide hazard ratio 0.64; P=0.031) and the number of asthma hospitalisations/ER treatments per patient per 6 months (Symbicort SMART 0.05 versus Seretide 0.07; risk ratio 0.69; P=0.046). For all other secondary variables, no statistically significant differences were detected between the Symbicort and Seretide treatments.
The Symbicort group used on average 0.95 as-needed inhalations of Symbicort per day, while the Seretide group used on average 1.01 as-needed inhalations of terbutaline per day. Patients in the Symbicort group thus received a mean budesonide dose of 792 µg, compared to the fixed 1000-µg fluticasone dose in the Seretide group.

Safety results:
The percentage of patients who experienced at least one AE was 39% in the SYMBICORT and 40% in the Seretide group. One death occurred during the study (treatment group: Symbicort; cause of death: typhoid fever). The number of patients reporting SAEs was similar (3%) in both treatment groups. Discontinuations were 1% (n=11) in the SYMBICORT and 2% (n=20) in the Seretide group. The most commonly reported AEs were upper respiratory tract infection and nasopharyngitis.

Conclusion:
For the primary outcome variable, time to first severe asthma exacerbation, the study did not demonstrate any difference between Symbicort maintenance and reliever therapy and Seretide at its highest approved dose. Overall, both treatments raised no new safety concerns.

Assessor's comment: This study was negative as regards the primary variable. Safety evalaution again is incomplete.

SD-039-0667 (2001-2002) Efficacy and safety of SYMBICORT Turbuhaler as Single therapy in patients with mild to moderate asthma-STEAM

Objective(s): the primary objective was to compare the efficacy of SYMBICORT Turbuhaler 2x80/4.5 µg OD plus SYMBICORT Turbuhaler as needed with that of Pulmicort 2x160 µg OD plus Bricanyl Turbuhaler 0.4 mg as needed.

Study design:
This was a 6 month, randomised, double-blind, active controlled, parallel-group, multicentre (77 centres in Argentina, Brazil, China, Denmark, Indonesia, Norway, The Philippines, Spain and Sweden) study.

Study population /Sample size:
Male or female asthma patients, aged between 12 and 80 years, treated with 200-500µg ICS with a FEV1 of 60-100% predicted normal.
A total of 250 evaluable patients was required per treatment group to detect a true difference in mPEF of 13 l/min with 90% power.

Treatments:
SYMBICORT Turbuhaler 2x 80/4.5 µg OD plus SYMBICORT Turbuhaler 80/4.5 µg as needed

Or
Pulmicort 2x160 µg (delivered dose) OD plus Bricanyl Turbuhaler 0.4 mg as needed.

During the 2 week run-in patients received Pulmicort Turbuhaler 100 µg (metered dose) bid plus Bricanyl Turbuhaler 0.5 mg as needed.

Outcomes/endpoints

Primary endpoint: change in average mPEF from run-in to the treatment period.

Statistical Methods
The full analysis set was used in all efficacy and safety analyses. The primary variable was analysed using an analysis of variance model with treatment and country as fixed factors and the run-in average as covariate.

Results

Recruitment/ Number analysed
697 patients (109 < 18 years of age) were randomised, 638 completed the study. 696 patients were analysed for safety and efficacy. The number of patients who discontinued the study was 27 for the SYMBICORT group and 31 for the Pulmicort group. Treatment groups were balanced at baseline.

Efficacy results:
There was a significant improvement of mPEF in the SYMBICORT group compared to the Pulmicort group (difference 25 L/min, p<0.001). Patients in the SYMBICORT group also showed significant improvements compared to the Pulmicort groups for most secondary parameters. Evaluation of the time to the first severe exacerbation as well as the number of severe exacerbations showed significantly better results in the SYMBICORT group. Use of as-needed medication was lower in the Symbicort group. The mean budesonide dose was 240 µg in the Symbicort group and 320µg in the Pulmicort group.

Safety results:
The percentage of patients who had at least one AE was similar between groups (SYMBICORT 38%, Pulmicort 41%). 6 SEAs occurred in each group. 3 patients in the SYMBICORT group and 8 patients in the Pulmicort group discontinued due to an AE. The most commonly reported AE was respiratory infection. No clinically important differences were seen with regard to laboratory evaluations, ECGs or vital signs.

Conclusion: SYMBICORT used as maintenance and reliever therapy improved lung function as well as asthma control compared to conventional ICS+ SABA therapy. No relevant safety signal was detected.

Assessor's comment: Although the budesonide maintenance dose is higher in the Pulmicort group, it is hard to say, if the effect seen here should be attributed to the addition of a LABA component or to the use of Symbicort as as-needed medication. It would have been easier to draw conclusions, if both groups had used Symbicort as maintenance treatment.

SD-039-0668 (2001-2003) Efficacy and safety of SYMBICORT Turbuhaler as single therapy in subjects with moderate-severe asthma.Comparison with conventional asthma therapy, Pulmicort Turbuhaler as regular treatment complemented with Bricanyl Turbuhaler

Objective(s):
The primary objective of the study was to compare the regular use of SYMBICORT Turbuhaler 160/4.5 µg 2 inhalations OD, complemented with SYMBICORT Turbuhaler 160/4.5 µg as needed with Pulmicort Turbuhaler 2x 160 µg bid, complemented with Bricanyl Turbuhaler 0.4 mg as needed.

Study design:
This was a 12 month, randomised, double-blind, double-dummy, active controlled, parallel-group, multicentre (211 centres world-wide) study.

Study population /Sample size:
Male or female asthma patients, aged between 12 and 80 years, treated with 400-1600µg ICS with a FEV1 of 50-90% predicted normal.
Assuming that the incidence of severe exacerbations was 25% in one group, 800 randomised patients per group were required to give a 80% probability to detect a reduction to 19.2% in the other group.

Treatments:
SYMBICORT Turbuhaler 2x 160/4.5 µg OD plus SYMBICORT Turbuhaler 160/4.5 µg as needed
Or
Pulmicort 2x160 µg bid plus Bricanyl Turbuhaler 0.4 mg as needed.

- **Outcomes/endpoints**

Primary endpoint: severe asthma exacerbations.

- **Statistical Methods**

The full analysis set was used in all efficacy and safety analyses. The time to first asthma exacerbation was analysed using a log-rank test. Additional descriptions were made using a Cox proportional hazards model with treatment as factor. The total number of severe asthma exacerbations was compared using a Poisson regression model with treatment as factor and the time in study as an offset variable. The confidence limits and p value were adjusted for overdispersion.

Results

Recruitment/ Number analysed
1890 patients (121 < 18 years of age) were randomised and analysed for efficacy and safety, 1573 completed the study. The number of patients who discontinued the study was 144 for the SYMBICORT group and 173 for the Pulmicort group.
Treatment groups were well balanced with regard to most parameters.

Efficacy results:
Results with regard to the primary variable were significantly better in the SYMBICORT group ($p< 0.001$). The SYMBICORT group was also shown to be significantly better compared to the Pulmicort group with regards to the mean number of severe asthma exacerbations per subject (0.3 and 0.51, respectively). The Symbicort group had the lower as-needed use. The mean budesonide dose was 424 µg/d in the Symbicort group and 640µg/d in the Pulmicort group.

Safety results:

The percentage of patients who had at least one AE was similar between groups (SYMBICORT 56%, Pulmicort 57%). The percentage of patients who reported at least one non-fatal SAE was 5% in each group. 1 patient in the SYMBICORT group and 2 patients in the Pulmicort group died during the study (carcinoma, myocardial infarction, hypertrophic cardiomyopathy) .24 patients in the SYMBICORT group and 38 patients in the Pulmicort group discontinued due to an AE. The most commonly reported AE was respiratory infection. No clinically important differences were seen with regard to laboratory evaluations (including evaluation of the HPA axis), ECGs or vital signs.

Conclusion: SYMBICORT given as maintenance as well as as-needed regimen improved asthma control compared to a regular ICS+SABA regimen. No new safety concern was detected.

Assessor's comment: This study also faces the problem of different maintenance therapies.. Therefore it is hard to decide if the effect can really be attributed to the different "as-needed" regimen.

SD-039-0673 (2001-2003) Efficacy and safety of Symbicort Turbuhaler as single therapy in patients with mild-moderate asthma. Comparison with SYMBICORT Turbuhaler and Pulmicort Turbuhaler as maintenance therapy, both complemented with Bricanyl Turbuhaler (STAY)

Objective(s): the primary objective was to compare the efficacy of the regular use of SYMBICORT 80/4.5 µg bid, complemented by the as-needed use of the same product with the same dosage of SYMBICORT complemented with Bricanyl Turbuhaler 0.4 mg as-needed.

Study design:
This was a 12 months, randomised, double-blind, active controlled, parallel-group, multicentre (246 centres world-wide) study.

Study population /Sample size:
Male or female asthma patients, aged between 4 and 80 years, treated with 400-1000µg (200-500 µg for patients 4-11 years of age) ICS with a FEV1 of 60-90% predicted normal. Assuming that the incidence of severe exacerbations was 25% in one group, 800 randomised patients per group were required to give a 80% probability to detect a reduction to 19.2% in the other group.

Treatments:
SYMBICORT SiT group: SYMBICORT Turbuhaler 1x 80/4.5 µg bid plus SYMBICORT Turbuhaler 80/4.5 µg as needed
Or
SYMBICORT group: SYMBICORT Turbuhaler 1x 80/4.5 µg bid plus Bricanyl Turbuhaler 0.4 mg as needed
Or
Pulmicort group: Pulmicort 1x 320 µg bid plus Bricanyl Turbuhaler 0.4 mg as needed.

Subjects 4-11 years of age received half the regular dose (once daily regimen in the evening).

- **Outcomes/endpoints**

Primary endpoint: severe asthma exacerbations.

Statistical Methods
The full analysis set was used in all efficacy and safety analyses. The time to first asthma exacerbation was analysed using a log-rank test. Additional descriptions were made using a Cox proportional hazards model with treatment as factor. The total number of severe asthma exacerbations was compared using a Poisson regression model with treatment as factor and the time in study as an offset variable. The confidence limits and p value were adjusted for overdispersion.

Results

Recruitment/ Number analysed
2760 patients (341 patients ≤11 years of age, 316 patients 12-17 years of age) were randomised, 2341 completed the study. 2753 patients were analysed for efficacy and safety. The number of patients who discontinued the study was 122 in the SYMBICORT SiT group, 148 in the SYMBICORT group and 142 for the Pulmicort group. Treatment groups were balanced at baseline.

Efficacy result :
Results with regard to the primary variable were significantly better in the SYMBICORT SiT group ($p< 0.001$) compared to the SYMBICORT and the Pulmicort group . The SYMBICORT SiT group was also shown to be significantly better compared to the SYMBICORT group as well as the Pulmicort group with regards to the mean number of severe asthma exacerbations per subject (0.29, 0.54 and 0.54, respectively). In the sub-group analyses of the patients 4-11 years of age SYMBICORT SiT was shown to be significantly better compared to the SYMBICORT group as well as the Pulmicort group with regard to the primary parameter “time to first severe asthma exacerbation”. With regard to the number of severe asthma exacerbations per subject SYMBICORT SiT was significantly better compared to SYMBICORT. It was numerically but not significantly superior to the Pulmicort group (0.41 versus 0.48 events per subject; $p= 0.59$). the Symbicort group had the lowest as needed use.

Safety results:
The percentage of patients who had at least one AE was similar between groups (SYMBICORT SiT 54%, SYMBICORT 52%, Pulmicort 57%). The percentage of patients who reported at least one non-fatal SAE was 5% in the SYMBICORT SIT and the Pulmicort group and 7% in the SYMBICORT group. 2 patients in the SYMBICORT group (sudden death, asthma exacerbation) and 1 patient in the Pulmicort group (coma+cyanosis) died during the study. 14 patients in the SYMBICORT SiT group, 29 patients in the SYMBICORT group and 24 patients in the Pulmicort group discontinued due to an AE. The most commonly reported AE was respiratory infection for all subjects and pharyngitis for subjects 4-11 years of age. The nature of the AEs was rather similar between groups. However in the subgroup 4-11 years of age, a higher incidence of asthma aggravated was seen in the Pulmicort and the SYMBICORT group. Effects on the HPA axis were more pronounced in the Pulmicort group (higher budesonide dose). Apart from this, no clinically important differences were seen with regard to laboratory evaluations (including evaluation of the HPA axis), ECGs or vital signs.

Conclusion:
SYMBICORT SiT regimen improved asthma controlled compared to SYMBICORT and Pulmicort complemented by SABA therapy. No new safety concerns were idenitified.

Assessor’s comment:The study compared Symbicort maintenance therapy at a low dose combined either with conventional SABA as needed therapy or with Symbicort as needed and Pulmicort at a higher dose combined with conventional SABA as needed therapy. Due to the

fact that the maintenance dose was rather low it is questionable if the results are transferable to real life. During the run-in the patients used their own inhaled ICS plus Bricanyl as need. Part of the effect might be attributable to the addition of a LABA.

SD-039-0734 (2003-2004) Efficacy of Symbicort® Turbuhaler® 160/4.5 µg as needed versus Oxis® 4.5 µg as needed and Bricanyl® 0.4 mg as needed in adults and adolescents with asthma receiving Symbicort® Turbuhaler® 160/4.5 µg twice daily as maintenance treatment. A 12-month, randomised, double-blind, parallel-group, active-controlled, phase IIIB, multi-centre study.

Objective(s): The primary objective was to compare the efficacy of Symbicort® Turbuhaler® 160/4.5 µg/inhalation as needed with that of Oxis® Turbuhaler 4.5 µg/inhalation as needed in asthmatic patients using Symbicort Turbuhaler maintenance therapy.

Study design: This was a 12-month double-blind, randomised, active-controlled, parallel-group, multi-centre (289 centres in Afrika, Asia and Europe) study.

Study population /Sample size:
Adults and adolescents with moderate to severe asthma and with documented symptoms despite use of ICSs.
Under the assumption that 25% of the patients have experienced a severe asthma exacerbation in one treatment group and 19% of the patients have experienced a severe asthma exacerbation in the other group, a log-rank test (with a two-sided alternative hypothesis and a significance level of 5%) can detect this difference with 90% probability, given that the study includes 1000 patients per group.

Treatments:
During the treatment period all patients received Symbicort Turbuhaler 160/4.5 µg/inhalation, one inhalation bid as maintenance treatment.

In addition, patients were randomised to one of the following as-needed medications:

Symbicort Turbuhaler 160/4.5 µg/inhalation (SIT group)
or
Formoterol Turbuhaler 4.5 µg /inhalation (referred to as Oxis) (SYMBICORT +Oxis group)
or
Terbutaline Turbuhaler 0.4 mg /inhalation (referred to as Bricanyl). (SYMBICORT+ Bricanyl group).

Outcomes/endpoints

Primary endpoint: time to first severe asthma exacerbation

Statistical Methods
All efficacy analyses were based on the full analysis set.
Time to first severe asthma exacerbation was compared between treatments using a log-rank test. In addition, treatment differences were described using a Cox Proportional Hazards model. The mean number of severe asthma exacerbations per patient was compared between treatments using Poisson regression.

Results

Recruitment/ Number analysed

3349 patients (354 adolescents) were randomised. 3382 were analysed for efficacy and safety. 2989 patients completed the study. The number of patients who discontinued the study was 116 in the SYMBICORT SIT group, 129 for the SYMBICORT+Oxis group and 148 in the SYMBICORT+ Bricanyl group. Treatment groups were balanced at baseline.

Efficacy results :
Symbicort SIT statistically significantly prolonged the time to first severe exacerbation compared to both Symbicort + Oxis as needed (hazard ratio 0.73, p=0.0038) and Symbicort + Bricanyl as needed (hazard ratio 0.55, p<0.001). The instantaneous risk of having a severe asthma exacerbation for patients treated with Symbicort SIT was reduced by 27% versus Symbicort + Oxis as needed and by 45% versus Symbicort + Bricanyl as needed. Fewer patient experienced exacerbations in the Symbicort SIT group (13%) than in the Symbicort + Oxis as needed group (17%) and Symbicort+ Bricanyl as needed group (22%). In addition, there were statistically significantly fewer severe exacerbations per patient-year in the Symbicort SIT group (0.19) versus the Symbicort + Oxis as needed group (0.29) and the Symbicort + Bricanyl as needed group (0.37) (p<0.001 for both comparisons).
Results from the secondary variables supported those of the primary variable. Symbicort SIT was superior to both comparators with statistically significant decreases in as-needed use; increases in as-needed-free days; increases in morning and evening PEF, FEV1, and FVC; decreases in asthma symptoms; fewer mild exacerbation days; and improvements in ACQ score. For symptom-free days and for asthma-control days, there was no clear difference between the 3 treatments. The gains in asthma control seen with Symbicort SIT were achieved with a mean daily Symbicort dose of 483/13.6 µg. The average daily as-needed use and the frequency of high as-needed use were lower for Symbicort SIT compared with both comparators.

Safety results:
The percentage of patients with at least one AE was similar between groups (50% SYMBICORT SIT and SYMBICORT+Bricanyl, 48% SYMBICORT+Oxis).On a preferred term level, nasopharyngitis, upper respiratory tract infection and pharyngitis were the most frequently reported AEs, as summarised over all treatment groups.
Four deaths were reported in the study, one in the Symbicort SIT group (death, reason can not be defined) and Symbicort + Oxis as needed group (brain tumor) respectively, and two in the Symbicort + Bricanyl (hepatic carcinoma, cardiac arrest) as needed group. In total, 251 non-fatal serious adverse events (SAEs) were reported, 97 in the Symbicort SIT group, 71 in the Symbicort + Oxis as needed group and 83 in the Symbicort + Bricanyl as needed group. The most frequently reported non-fatal SAE by preferred term was asthma, and the number of patients reporting was slightly lower in the Symbicort SIT group than in the comparator groups. The number of discontinuations due to adverse events (DAEs) was low overall. The most frequently reported DAE was asthma.

Conclusion: Symbicort SIT provided better asthma control, as evidenced by a prolongation of time to first severe exacerbation, than the same Symbicort maintenance treatment plus additional inhalations of either Oxis or Bricanyl as needed.
All treatments were well tolerated and no new or unexpected safety concerns were identified.

Assessor's comment: This is a rather large study which showed that Symbicort SiT prolonged the time to frist severe asthma exacerbation compared to conventional regimens. Naturally the ICS doses were higher in the Symbicort group. Despite of that the applicant did not evaluate effects on the HPA axis or growth which are important to the paediatric population.

SD-039-0735 (2003-2005) Comparison of the efficacy and safety of one inhalation of Symbicort® Turbuhaler® 160/4.5 µg bid plus as-needed with two inhalations of SeretideTM EvohalerTM 25/125 µg bid plus Terbutaline Turbuhaler® 0.4 mg as-needed, and one inhalation of Symbicort® Turbuhaler® 320/9 µg bid plus Terbutaline Turbuhaler® 0.4 mg as-needed. A 6-month, randomised, double-blind, double-dummy, parallel-group, active-controlled, multicentre, phase IIIB study in adult and adolescent asthmatic patients.

Objective(s): to compare the efficacy of Symbicort® Turbuhaler® 160/4.5 µg/inhalation bid plus as-needed with two inhalations of SeretideTM EvohalerTM 25/125 µg/inhalation bid plus Terbutaline Turbuhaler 0.4 mg/inhalation as-needed.

Study design: This was a 6-months, randomised, double-blind, double-dummy, parallel-group, active-controlled, multi-centre (235 centres worl-wide), study.

Study population /Sample size: Adults and adolescents with persistent asthma, FEV1 ≥50% of predicted normal, and with documented symptoms despite use of inhaled ICSs were enrolled. Under the assumption that 20% of the patients have experienced a severe asthma exacerbation in 1 treatment group and 14.5% of the patients have experienced a severe asthma exacerbation in the other group, a log-rank test (with a two-sided alternative hypothesis and a significance level of 5%) can detect this difference with 90% probability, given that the study includes 1000 patients per group.

Treatments:
During the run-in period patients were using their regular dose and brand of inhaled steroids plus Bricanyl Turbuhaler as-needed (0.5 mg/dose).
Patients were randomised to one of the following treatment arms
• Symbicort Turbuhaler (budesonide/formoterol) 160/4.5 µg/inhalation, one inhalation twice daily as maintenance treatment plus Symbicort Turbuhaler 160/4.5 µg/inhalation as-needed.
or
• Seretide Evohaler (salmeterol/fluticasone), 25/125 µg/inhalation, two inhalations twice daily as maintenance treatment plus Terbutaline Turbuhaler 0.4 mg/inhalation as-needed.
or
• Symbicort Turbuhaler (budesonide/formoterol) 320/9 µg/inhalation, one inhalation twice daily as maintenance treatment plus Terbutaline Turbuhaler 0.4 mg/inhalation as-needed

The treatment arm with Symbicort as both maintenance and as-needed treatment will be referred to as Symbicort Single Inhaler Therapy (SIT), the treatment arm with Symbicort as maintenance and terbutaline as-needed will be referred to as Symbicort + Bricanyl a.n., and the treatment arm with Seretide as maintenance and terbutaline as needed will be referred to as Seretide + Bricanyl a.n.

Outcomes/endpoints

Primary endpoint: time to first severe asthma exacerbation

Statistical Methods
All efficacy analyses were based on the full analysis set. Time to first severe asthma exacerbation was compared between treatments using a log-rank test. In addition, treatment differences were described using Cox Proportional Hazards models. The mean number of severe asthma exacerbations per patient was compared between treatments using Poisson regression. In addition, an extended Cox model was used to compare time to all severe asthma exacerbations.

Results

Recruitment/ Number analysed

3335 patients (623 adolescents) were randomised. 3321 were analysed for efficacy and safety. 3172 patients completed the study. The number of patients who discontinued the study was 51 in the SYMBICORT SIT group, 53 in the SYMBICORT+Bricanyl a.n. group and 45 in the Seretide+Bricanyl a.n. group.
Treatment groups were balanced at baseline.

Efficacy results :

Symbicort SIT versus Seretide plus Bricanyl as-needed

Symbicort SIT prolonged the time to first severe asthma exacerbation compared with Seretide + Bricanyl as-needed, with a hazard ratio of 0.67 (p=0.003), corresponding to a 33% reduction in instantaneous risk of having a first severe asthma exacerbation. Fewer patients experienced exacerbations in the Symbicort SIT group (9%) than in the Seretide + Bricanyl as-needed group (12%), and there were fewer severe exacerbations per patient per 6 months in the Symbicort SIT group (0.12) than the Seretide + Bricanyl group (0.19) (rate ratio 0.61; p<0.001).

Symbicort SIT versus Symbicort plus Bricanyl as-needed

Symbicort SIT prolonged the time to first severe asthma exacerbation compared with Symbicort at a higher fixed maintenance dose + Bricanyl as-needed, with a hazard ratio of 0.74 (p=0.026), corresponding to a 26% reduction in instantaneous risk of having a first severe asthma exacerbation. Fewer patients experienced exacerbations in the Symbicort SIT group (9%) than in the Symbicort + Bricanyl as-needed group (11%), and there were fewer severe exacerbations per patient per 6 months in the Symbicort SIT group (0.12) than the Symbicort + Bricanyl as-needed group (0.16) (rate ratio 0.72; p=0.0048).

Symbicort plus Bricanyl as-needed versus Seretide plus Bricanyl as-needed

No statistically significant difference was detected between Symbicort + Bricanyl as-needed and Seretide + Bricanyl as-needed regarding time to first severe asthma exacerbation or number of severe asthma exacerbations, or time to first hospitalisation/ER treatment.
The mean daily ICS dose calculated by maintenance dose plus the average mean of as-needed medication was 483/13.6 µg in the Symbicort SIT group, which may be compared with the prescribed fixed dose of 640/18 µg/day in the Symbicort +Bricanyl as-needed group. In the Symbicort SIT group, 65% used 480/13.5 µg/day or less, on average, and 83% of the patients used 640/18 µg/day, on average, or less.

Safety results: 41% of the patients in the SYMBICORT SIT group, 40% of the patients in the SYMBICORT + Bricanyl a.n. group and 38% of the patients in the Seretide + Bricanyl a.n. group experienced at least one AE. On a preferred term level, upper respiratory infection, pharyngitis, and nasopharyngitis were the most frequently reported AEs, as summarized over all treatment groups. Two deaths were reported in the study, 1 in the Symbicort SIT group (respiratory failure) and 1 in the Seretide + Bricanyl as-needed group (cardiac failure). One additional death was reported in the Symbicort SIT treatment group 16 weeks post study (severe acute respiratory syndrome). In total, 128 non-fatal SAEs were reported, 37 in the Symbicort SIT group, 49 in the Symbicort + Bricanyl as-needed group, and 42 in the Seretide + Bricanyl as-needed group. The most frequently reported non-fatal SAE by preferred term was asthma, and the number of patients reporting such AE was similar in all treatment groups. Four non-fatal SAEs were considered by the investigator to be possibly caused by the investigational product: 3 of the SAEs were reported by patients in the Symbicort SIT group (pneumonia, gastritis, asthma), and 1 in the Seretide + Bricanyl as-needed group (asthma).

The number of discontinuations of treatment with investigational treatment due to AE (DAEs) was low overall, 1% for each treatment group. The most frequently reported reason for discontinuation due to an adverse event was asthma, as summarized over all treatments. No other adverse events (OAEs) were identified in the study.

Conclusion:
Symbicort SIT was superior to Seretide + Bricanyl as-needed and Symbicort (at a higher fixed dose)+ Bricanyl as needed regarding effect on severe exacerbations. Superior efficacy was achieved with a lower total mean daily dose in the Symbicort SIT group. No new safety concerns were identified.

Assessor's comment: this study evaluates the effect of Symbicort SIT compared to a conventional regimen of Seretide and Bricanyl and Symbicort at a higher dose plus Bricanyl. Again, safety evaluation is incomplete.

SD-039-0691 (2002-2004) A comparison of the effectiveness of treatment with Symbicort® Turbuhaler® (budesonide/formoterol; 160/4.5 µg) Single Inhaler Therapy and Seretide™ Diskus™ (salmeterol/fluticasone; 50/100, 50/250 or 50/500 µg) plus Ventoline™ (salbutamol) as needed in steroid-treated adult and adolescent asthmatic subjects. A randomised, open, parallel-group, phase IIIB, multicentre, 12-month study.

Objective(s): The primary objective of the study was to compare the effectiveness of treatment with Symbicort Turbuhaler Single Inhaler Therapy and Seretide Diskus plus Ventoline Diskus (or equivalent) as needed. The secondary objective was to study safety by evaluation of the incidence and type of adverse events (AEs).

Study design: This was a randomised, open, parallel-group, phase IIIB, multicentre (246 centres), 12-month study.

Study population /Sample size:
Male or female adults and adolescents with asthma, currently treated with inhaled glucocorticosteroids (GCSs), with at least one severe asthma exacerbation during the past year, and with a documented use of medication for relief of asthma symptoms.
Using a log-rank test, a sample size of 1000 patients per treatment group was required for 90% power to detect a decrease from 15% to approximately 10% between the groups in the percentage of patients with severe asthma exacerbations.

Treatments:
Budesonide/formoterol (Symbicort Turbuhaler) 160/4.5 µg.
• First 4 weeks: 2 inhalations bid plus more as needed
• Doses that could be prescribed during the 11-month dose adjustment period:
2 inhalations bid plus more as needed or
1 inhalation bid daily plus more as needed or
2 inhalations OD plus more as needed
or
Salmeterol/fluticasone (Seretide Diskus) 50/100, 50/250, 50/500 µg.
• First 4 weeks: 50/250 µg, 1 inhalation bid plus Ventoline Diskus (salbutamol) (or equivalent) as needed
• Doses that could be prescribed during the 11-month dose adjustment period:
50/100 µg, 1 inhalation bid plus Ventoline Diskus or equivalent as needed
or
50/250 µg, 1 inhalation bid plus Ventoline Diskus or equivalent as needed

or
50/500 µg, 1 inhalation bid plus Ventoline Diskus or equivalent as needed

Outcomes/endpoints

Primary endpoint: time to first severe asthma exacerbation

Statistical Methods
All analyses were based on the full analysis set. The time to first severe asthma exacerbation was compared between the treatment groups using a log-rank test. Additional descriptions were made using Cox proportional hazards models. The total number of severe asthma exacerbations was analysed using Poisson regression.

Results

Recruitment/ Number analysed
2143 patients (76 adolescents) were randomised. 2135 were analysed for efficacy and safety. 1866 patients completed the study. The number of patients who discontinued the study was 119 in the SYMBICORT SIT group and 150 in the Seretide group. Treatment groups were balanced with regard to baseline.
Efficacy results:
Symbicort SIT was more effective than Seretide plus Ventoline as measured by the primary variable. The risk reduction for the time to the first exacerbation was 25% (hazard ratio 0.75; 95% confidence interval 0.61 to 0.93, p=0.0076).
There were 255 exacerbations (0.24 per patient) in the Symbicort group and 329 (0.31 per patient) in the Seretide group, corresponding to a 22% reduction in the total number of exacerbations with Symbicort (hazard ratio 0.78; 95% confidence interval 0.66 to 0.91, p=0.0025).
Pre- and post-bronchodilator FEV1 increased in both treatment groups and the increases were numerically greater in the Symbicort group. The mean difference between treatment groups was statistically significant for the post-bronchodilator value (0.025 L; p=0.045), but not for the pre-bronchodilator value (0.026 L; p=0.066).
The average total dose of inhaled corticosteroid was 653 µg for budesonide vs 583 µg for fluticasone.
Similar improvements in patient reported outcomes were seen for both treatment groups, and no differences were detected between the treatment groups. Health care resource utilisation was generally numerically lower in the Symbicort group.

Safety results:
The percentage of patients who reported at least one AE was 58% in the SYMBICORT SIT und 59% in the Seretide group. 6% of the patients in boths group reported non-fatal SAEs. 2 patients in the Seretdie group died (intracerebral bleeding, car accident). 3% of the patients in each group discontinued the study due to an AE. Nasopharyngitis, bronchitis and upper respiratory tract infection were the most common AEs.

Conclusion:
Symbicort SIT was more effective in increasing the time to first asthma exacerbation than adjustable therapy with Seretide. There was no important difference between the treatments in the safety profile.

Assessor's comment: This study evaluates two different regimens: Symbicort as single inhaler therapy or Seretide given in an adjustable regimen combined with Ventolin Diskus as needed.

Symbicort SIT was shown to be statistically superior. The study had an open design and enrolled 3.5% adolescents. Therefore no firm conclusion can be drawn here.

LD-039-0003 (2003-2004) An open, randomized, parallel-group, multicentre, phase IIIB study to evaluate the efficacy of Symbicort® Turbuhaler® Single Inhaler Therapy(SiT), given as a low maintenance dose once or twice daily plus as needed, compared to a higher maintenance dose of Symbicort Turbuhaler given twice daily plus Oxis® Turbuhaler® as needed during 24 weeks in asthmatic patients

Objective(s): The primary objective of this study was to evaluate the efficacy of 2 Symbicort Single inhaler Therapy (SiT) regimens, with Symbicort given as a low maintenance dose either once or twice daily plus as needed, compared to a higher maintenance dose of Symbicort plus Oxis Turbuhaler as needed.

Study design: This was an open, randomized, parallel-group, multicentre (53 centres in Sweden) phase IIIB study.

Study population /Sample size: The study included male and female asthma patients from the age of 6 years either not well controlled on inhaled ICS alone or well controlled on inhaled ICS plus LABA.
The sample size calculation was based on both the Asthma Control Questionnaire (ACQ) variable and the morning peak expiratory flow (mPEF) variable. The variable that determines the sample size is the ACQ. A total of 139 randomized and completed patients with asthma, derived from an estimated 155 randomized patients, were required per treatment group to detect a 0.5 unit difference between groups in change from baseline in ACQ score with a power of 80%. This assumed a 5% significance level and a 2-sided alternative hypothesis. Similarly, a total of 139 randomized and completed patients with asthma, derived from an estimated 155 randomized patients, were required per treatment group to detect a 15 L/min difference between groups in change from baseline in mPEF with a power of 80%. This also assumed a 5% significance level and a 2-sided alternative hypothesis.

Treatments:
Symbicort Turbuhaler 160/4.5 µg one inhalation bid plus
Symbicort Turbuhaler160/4.5 µg as needed for patients 12 years or older

Symbicort Turbuhaler 80/4.5 µg one inhalation bid plus
Symbicort Turbuhaler 80/4.5 µg as needed for patients 6 to 11 years of age

or
Symbicort Turbuhaler 160/4.5 µg one inhalation od plus
Symbicort Turbuhaler 160/4.5 µg as needed for patients 12 years or older

Symbicort Turbuhaler 80/4.5 µg one inhalation od plus
Symbicort Turbuhaler 80/4.5 µg as needed for patients 6 to 11 years of age

or
Symbicort Turbuhaler 160/4.5 µg 2 inhalations bid plus
Oxis (formoterol) Turbuhaler 4.5 µg as needed, for patients 12 years or older

Symbicort Turbuhaler 80/4.5 µg 2 inhalations bid plus
Oxis (formoterol) Turbuhaler 4.5 µg as needed, for patients 6 to 11 years of age

Symbicort SiT treatment with 1 inhalation bid as maintenance plus as needed will be referred to as SiT 1x2 and the Symbicort SiT treatment with 1 inhalation od as maintenance plus as needed will be referred to as SiT 1x1. The fixed Symbicort treatment with the 2 inhalations bid as maintenance plus Oxis as needed will be referred to as Symb 2x2+Oxis prn

Outcomes/endpoints

Primary endpoints: Change in ACQ score from baseline to Visit 4

- Change in mPEF from baseline to all treatment period data.

Statistical Methods

The full analysis set was used in all efficacy analyses. The change in ACQ score from Visit 2 to Visit 4 was compared between treatments using an analysis of variance model with treatment and centre as factors and the Visit 2 value as a covariate. Mean treatment differences, 95% confidence intervals, and p-values for pair-wise treatment differences were calculated from the model. For morning PEF, period averages were calculated for each patient using all values during the run-in and the treatment period, respectively. The change in period average from the run-in to the treatment period was analysed using an analysis of variance model with treatment and centre as factors and the runin period average as a covariate. Mean treatment differences, 95% confidence intervals and p-values for pair-wise treatment differences were calculated from the model.

Results

Recruitment/ Number analysed

491 patients (58 patients 6-11 years of age and, 51 patients 12-17 years of age) were randomised. 489 were analysed for efficacy and safety. 430 patients completed the study. The number of patients who discontinued the study was 13 in the 2x2 Oxis group, 8 in the SiT 1x2 group and 16 in the SiT 1x1 group.
Treatment groups were balanced at baseline.

Efficacy results :

There were no statistically significant differences between the 3 treatment groups in change in ACQ score from baseline to Visit 4. There were statistically significant differences in mean change in mPEF from baseline to the treatment period, favouring the Symb 2x2+Oxis prn group versus both the SiT 1x1 group (+12.2 L/min, $p<0.001$) and the SiT 1x2 group (+8.6 L/min, $p=0.006$).

Safety results:

6 (3.7%) of the patients in the Symb 2x2+Oxis prn treatment group, 7 (4.3%) patients in the SiT 1x2 group, and 4 (2.5%) in the SiT 1x1 group had one or more SAE. In addition, 2 SAEs were reported post-study: one in the Symb 2x2+Oxis group (stillbirth), and one in the SiT 1x1 group (pneumonia in a newborn).
There were 14 patients reporting DAEs during randomized treatment: 3 (1.8%) in the Symb 2x2+Oxis prn treatment group, 6 (3.7%) in the SiT 1x2 group, and 5 (3.1%) in the SiT 1x1 group.

Conclusion:

This open study showed that asthma control as measured by ACQ did not significantly differ between Symbicort SiT with a 1 inhalation od or bid regimend compared to Symbicort plus Oxis 2 inhalations bid. However a reduction in lung function as measured by morning PEF was detected with both SiT regimens. No new safety signal was detected.

Assessor's comment: this study has to be considered negative with regard to the SiT regimens. Safety evaluation once again is incomplete.

D5890L00004 (2004-2005) A comparison of Symbicort® SMART (Symbicort® 200 Turbuhaler® 1 inhalation b.i.d. plus as-needed) and conventional best practice for the treatment of persistent asthma in adolescents and adults – a 26-week, randomised, open label, parallel group, multicentre study

Objective(s): The primary objective of the study was to compare the effectiveness of Symbicort® Maintenance and Reliever Therapy (Symbicort® SMART) in asthma with treatment according to conventional best practice.

Study design: This was a 26 weeks randomized, open-label, phase IIIB, multicentre (91 centres in Canada) study with a parallel-group design.

Study population /Sample size:
Male and female, adolescent (> 12 years of age) and adult subjects with persistent asthma,currently treated with inhaled glucocorticosteroids (ICSs) or ICS and long-acting β2-agonist (LABA).
Using a log-rank test, a sample size of 650 subjects per treatment group (a total of 1300 randomized subjects) was required in order to detect a difference between the two treatment groups with 80% probability. It was under the assumption that, at the end of the study, 13% of the patients would have experienced a severe exacerbation in one treatment group and 8.2% of the patients would have experienced a severe exacerbation on the other treatment group. In order to compensate for an estimated 15% dropout rate during the run-in period, a total of 1530 subjects were to be enrolled in this study.

Treatments:
Symbicort® Turbuhaler® 160/4.5 µg/ inhalation 1 inhalation b.i.d. as maintenance dosing plus as-needed, in response to symptoms (SMART).
Or
Conventional best practice medications according to the investigator's judgement, following the Canadian Asthma Consensus Report1,2 (CBP).

Outcomes/endpoints

Primary endpoint:: Time to first severe asthma exacerbation

Statistical Methods
All efficacy analyses were based on the full analysis set.
Time to first severe asthma exacerbation was described using Kaplan-Meier curves and compared between treatments using a log-rank test and Cox proportional hazards (Cox PH) model with treatment as a factor. The mean number of severe asthma exacerbations per patient was compared between treatments using a Poisson regression model.

Results

Recruitment/ Number analysed
1538 (91 adolescents) patients were randomised and analysed for effficacy and safety. 1400 completed the study. 91 patients in the SMART group and 47 patients in the CBP group discontinued the study. The treatment groups were well-balanced as regards demography and other baseline characteristics.

Efficacy results :
The time to first severe asthma exacerbation was not significantly different between the Symbicort® SMART arm and Conventional Best Practice arm, with a hazard ratio of 0.989 (p=0.952).
The number of severe exacerbations for Symbicort® SMART and CBP was 19 versus 21 events/year/100 patients, p=0.634. Mean as-needed use was significantly lower with Symbicort® SMART versus the CBP group (0.94 inh./day versus 1.09 inh./day, p=0.0036). The mean daily dose of inhaled steroid use was significantly lower in the Symbicort® SMART arm versus the CBP arm (478 versus 585 µg/day, p<0.0001). The mean daily dose of inhaled steroid use expressed as BDP equivalent was also significantly lower in the Symbicort® SMART arm versus the CBP arm (748 versus 1015 µg/day, p<0.0001). A total of 82 % of the subjects in the CBP arm were prescribed a combination treatment of an inhaled glucocorticosteroid and long acting Beta-2 agonist (in combination therapy or as mono products). Both groups showed similar improvement in asthma symptoms as measured by improvement in ACQ score.
Total out-of-pocket expenses were less in the Symbicort® SMART arm ($810 versus $974 in CBP arm). The number of days lost by subject was 311 in the Symbicort® SMART arm versus 205 in the CBP arm. The asthma medication and the total costs per patient per year were 28% and 23% lower, respectively with Symbicort® SMART versus CBP. The difference between the Symbicort® SMART group and CBP arm regarding asthma medication cost was $ 353.60 and the difference regarding total yearly societal cost was $ 315.55.

Safety results:
The number of subjects who had an adverse event that started in the treatment phase was similar for both treatment groups (SMART: 474; CBP: 491). Similarily, the number of subjects with serious adverse events that started in the treatment phase was similar for both treatment groups (SMART: 17; CBP:15). The number of subjects that discontinued the study due to an adverse event was higher in the Symbicort® SMART arm (n= 27) when compared to the CBP arm (n=6). 1 patient in the SMART arm (accident) and 2 patients in the CBP arm (myocarial infarction, myocarditis) died during the study. The most common AEs were nasopharyngitis, upper respiratory tract infection and sinusitis.

Conclusion:
Regarding time to first severe asthma exacerbation and rate of severe asthma Exacerbations both treatments were not significantly different. The numer of patienst who discontinued the study due to an AE was higher in the SMART group. Otherwise no concerns regarding safety were identified.

Assessor's comment: This study compares Symbicort SMART to CBP therpay which results in a controll group with no standardized medication. The study was inconclusive as regards the primary parameter. The distincly higher number of DAES in the Symbicort SMART group is of concern.

Assessor's overall comment on Symbicort maintenance and reliever studies: *The applicant submitted 9 studies which evaluated the effect of Symbicort Turbuhaler as maintenance and reliever therapy. At least the majority of these studies had been submitted for previous procedures, which did not result in a paediatric license for the single inhaler therapy. As described above problems exist with regard to the design of some of these studies. In other studies the proportion of paediatric patients is rather low and no sub-group analyses are given. In addition, the safety evaluation does not seem to be sufficient to warrant a license in the paediatric population. Therefore the applicant's statement that no changes to the SPC are necessary is supported*

Symbicort Turbuhaler as single dose for the relief of acute brochoconstriction:

SD-039-0693 (2002-2003) A randomised, double- blind, double-dummy, parallel –group, multi-centre, pahse III study to investigate the effect of Symbicort Trubuhaler 1280/36 µg total delivered dose in the treatment of acute asthma compared with Oxis Turbuhaler 36 µg total delivered dose in adolescent and adult patients not responding adequately to ß2-agonists

Objective(s): The primary objective of this study was to evaluate the efficacy of Symbicort Turbuhaler with that of Oxis Turbuhaler

Study design: This was a 3 hour, randomized, duble-blind, double-dummy, parallel-group, multicentre (8 centres in Argentina, Mexico and South Africa) phase III study.

Study population /Sample size: The study included male and female asthma patients from the age of 12 years with a FEV1 ≥30 and ≤ 55 % , reversibility in FEV1 ≤ 8%.
50 patients per group were needed to have a 80% chance to detect a true, difference of 12 % in FEV1 assuming a 5% significance level in a two-sided test.

Treatments:
Symbicort Turbuhaler 320/9 µg two inhalations at -5 min and 2 inhalations at 0 min, total dose 1280/36 µg (budesonide/formoterol)
or
Oxis Turbuhaler 9 µg two inhalations at -5 min and 2 inhalations at 0 min, total dose 36 µg formoterol

Outcomes/endpoints

Primary endpoint: Average FEV1 from intake to 90 min measurement

Statistical Methods
The full analysis set was used in all efficacy analyses. The primary endpoint was calculated as area under the curve divided by the observation time. Treatments were compared by a multiplicative analysis of variance model with fixed factors treatment and country and using baseline FEV1 as a covariate.

Results

Recruitment/ Number analysed:
115 patients (5 patients < 18 years of age) were randomised and analysed for efficacy and safety. 114 patients completed the study. One patient in the Oxis group discontinued the study due to an AE.
Except for ICS dose at study entry which was higher in the Oxis group, treatment groups were balanced at baseline.

Efficacy results:
After inhalation of study drugs, FEV1 increased in both groups. There were no statistically significant differences between the treatment groups regarding the primary endpoint.

Safety results:
16% of the patients in each group reported an AE. 1 SAE was reported in each group. 1 patient in the Oxis group discontinued due to an AE. Most frequently reported AEs were tremor and headache. Patients in the Symbicort group had a statistically significant lower maximum value

for heart rate. No significant differences were detected with regard to serum potassium, other vital signs, ECG and oxygen saturation (average, minimum and maximum).

Conclusion:
No difference between groups was detected with regard to change of FEV1 over time.No safety signal was detected either.

Assessor's comment: this is a rather short study which does not allow to really conclude on non-inferiority. The number of adolescents enrolled is low.

SD-039-702 (2001-2002) Efficacy of Symbicort® Turbuhaler® (budesonide/formoterol) 1280/36 µg total delivered dose compared to salbutamol pMDI with spacer 1600 µg total metered dose in the management of acute asthma in adolescents and adults. A double-blind, double-dummy, randomised, parallel-group, phase-III, multicentre study.

Objective(s): The primary objective was to compare the efficacy of inhaled Symbicort Turbuhaler with that of salbutamol pressurised metered dose inhaler (pMDI) with VolumaticTM spacer.

Study design: The study was designed as a 3-hour, randomised, double-blind, double-dummy, parallel-group, multicentre (10 centres in East Asia) trial.

Study population /Sample size: Male and female subjects with acute asthma ≥ 12 years of age seeking medical attention with FEV1≥ 30% and ≤ 60% of predicted normal values.
A total of 50 randomised subjects were required per treatment group for an 80% chance of detecting a true difference of 12% between treatments assuming a 5% significance level in the two-sided t-test.

Treatments:
Symbicort Turbuhaler 320/9 µg/inhalation, two inhalations at -5 minutes and two inhalations at zero minutes, giving a total dose of 1280 µg budesonide and 36 µg formoterol
or
Salbutamol pMDI 100 µg/dose with VolumaticTM spacer, eight doses at -5 minutes and eight doses at zero minutes, giving a total dose of 1600 µg salbutamol,

Outcomes/endpoints

Primary endpoint:: Primary endpoint: average FEV1 from first intake of investigational product to the 90-minute measurement.

Statistical Methods
The full analysis set was used. For FEV1 variables, a multiplicative ANOVA was used with treatment and country as fixed factors and the baseline measurement as covariate.

Results

Recruitment/ Number analysed
103 patients (55 Symbicort, 48 Salbutamol) were randomised, received active treatment and were analysed for efficacy and safety. Adolescents were only enrolled in the Salbutamol group (n= 3). One patient in the Salbutamol group discontinued the study (eligibility criteria not fulfilled).

Efficacy results:
Regarding the primary endpoint average FEV1 from first intake of investigational product to the 90-minute measurement, no difference between the Symbicort and salbutamol treatment groups could be detected in this study.

Safety results:
In all, 8 adverse events occurred during treatment, 5 in the Symbicort group and 3 in the salbutamol group. The majority were related to well-known class-effects of β2-agonists, and all reports were of mild intensity. Regarding serum potassium, vital signs, ECG, and oxygen saturation, there were small changes over time. The number of individual changes was similar between treatments. Both treatments were safe and well tolerated in subjects with acute bronchoconstriction, with Symbicort showing similar systemic activity compared with salbutamol.

Conclusion:
No difference in FEV1 over time was dected between the two groups. No new safety signal was detected either.

Assessor's comment: No adolescent patient received Symbicort in this trial. Therefore it is not relevant to this assessment.

Symbicort Turbuhaler used as needed only

AF-039-0001 (2003-2004)A randomised, double blind, parallel-group, multicentre, phase III study to evaluate the efficacy of Symbicort Turbuhaler (budesonide/formoterol; 160/4.5 µg) given as needed compared to Oxis Turbuhaler (formoterol 4.5 µg) given as needed during 6 months in adults with mild intermittent asthma – SOMA.

Objective(s):
Primary: The primary objective of this study was to evaluate the efficacy of Symbicort Turbuhaler given as needed compared to Oxis Turbuhaler given as needed in patients with mild intermittent asthma.

Study design:
This was a 6 month randomised, double-blind, parallel-group, multicentre (5 centres in Finland and Sweden) study.

Study population /Sample size:
Male or female patients, aged between 6 and 65 years, with mild intermittent asthma and a documented need of short-acting ß2-agonist for relief of asthma symptoms.
The change in level of fractional exhaled nitric oxide (FENO) was used to calculate the sample size. With a two-sided alternative hypothesis, a 5% significance level and a power of 90%, a total of 79 evaluable patients that completed the study to visit 5, were required to detect a change in FENO level of 1.5 ppb.

Treatments:
Symbicort Turbuhaler 160/4.5 µg, 1 inhalation for relief of asthma symptoms or prophylactic purposes
or
Oxis Turbuhaler 4.5 µg, 1 inhalation for relief of asthma symptoms or prophylactic purposes,

Outcomes/endpoints

Primary endpoint: The primary variable of efficacy was the change in level of FENO

Statistical Methods
The full analysis set was used in all efficacy analyses. The change from visit 1-2, visit 2 (baseline) to visit 3-5 (all treatment data) was analysed using an analysis of covariance with treatment as factor and the mean level at visit 1-2 as a covariate.

Results

Recruitment/ Number analysed
There were 92 patients (2 patients < 18 years of age) in the full analysis set and the treatment groups were well balanced in terms of demographic characteristics and baseline characteristics. There were only three patients in total below the age of 18.

Efficacy results:
There was a statistically significantly higher decrease in level of exhaled FENO in the Symbicort treatment group compared to the Oxis treatment group (Symbicort: -8.3ppb, Oxis: -2.8ppb, p<0.001).
Analyses of secondary efficacy variables showed a statistically significant difference in favour of the Symbicort treatment group for FEV1 measured at clinic visits. No statistically significant differences between the groups were observed for patient reported outcomes, i.e., morning and evening PEF, asthma symptoms, asthma free days and use of as needed medication. The number of patients and number of days with use of as needed medication of 5 or more doses per day were lower in the Symbicort group than in the Oxis group.

Safety results:
The study collected data on serious Adverse Events and Discontinuations due to Adverse Events. Only 3 patients, all in the SYMBICORT reported SAEs. No DAE occurred during the active treatment phase.

Conclusion:
Treatment with Symbicort Turbuhaler as needed was found statistically significantly superior to Oxis Turbuhaler as needed in reducing airway inflammation as measured by the level of exhaled nitric oxide (NO) and in improving lung function. No safety issues were identified.

Assessor's comment: This study enrolled only three patients < 18 years of age. No relevant conclusions can be drawn here.

Clinical pharmacology study
Symbicort pMDI:

D5896C00013 (2004) An open, randomized, two-way crossover study evaluating the pharmacokinetics of budesonide and formoterol from Symbicort® pMDI versus Oxis® Turbuhaler® plus Pulmicort® Turbuhaler® when given to children with asthma aged 6 to 11 years

Objective(s):
Primary: To compare the systemic availability of budesonide after inhalation from Symbicort® pMDI (pressurized metered dose inhaler) and Pulmicort® Turbuhaler® in asthmatic children 6 to 11 years of age.

Study design:

This was an open-label, randomized, single-center (US) study to evaluate the pharmacokinetics, safety, and tolerability of Symbicort pMDI and Oxis Turbuhaler plus Pulmicort Turbuhaler when given as single doses in a crossover fashion.

Study population /Sample size:
Outpatients with asthma of either sex, aged 6 to 11 years, using a constant daily dose of ICS were enrolled.
Twenty-four (24) patients were to be randomized in order to obtain 20 evaluable patients. To ensure an equal distribution of ages, at least 10 patients were to be 6 to 8 years of age and 10 patients were to be 9 to 11 years of age.

Treatments:
A. Symbicort pMDI 160/4.5 µg per actuation, 4 actuations given as a single dose of 640/18 µg.

B. Oxis Turbuhaler 4.5 µg per inhalation, 4 inhalations given as a single dose of 18 µg plus Pulmicort Turbuhaler 200 µg per inhalation, 4 inhalations given as a single dose of 800 µg, corresponding to a delivered dose of 640 µg.

Outcomes/endpoints

Primary endpoint: $AUC_{0-\infty}$ for budesonide was the primary outcome variable

Statistical Methods
The study was descriptive. There were no predefined statistical hypotheses and no predetermined tests or decision rules. All analyses were based on the full analysis set, comprising all randomized patients with data. The AUC for budesonide was compared between treatments using a multiplicative (ie, log-transformation) analysis of variance (ANOVA) model with treatment, period, and patient as fixed factors. Mean treatment ratios were estimated and 90% confidence limits were calculated from the model.

Results

Recruitment/ Number analysed
24 patients were randomized and analysed for PK and safety. All patients except one (Caucasian) were Black. All randomized patients completed the study.

PK results:
Budesonide
The mean plasma concentration of budesonide was lower after a single-dose treatment withSymbicort pMDI compared with a single-dose treatment with Pulmicort Turbuhaler plus Oxis Turbuhaler. The mean AUC ratio was 73% (90% confidence limits: 52% to 103%) and the mean Cmax ratio was 59% (90% confidence limits: 38% to 92%). The result for AUC0-t was similar to the result for AUC. Data variability was large.
Formoterol
The mean fraction of formoterol excreted unchanged into the urine over 24 hours was similar after a single-dose treatment with Symbicort pMDI and a single-dose treatment with Pulmicort Turbuhaler plus Oxis Turbuhaler. The mean fe0-24h ratio was 113% (90% confidence limits: 80% to 158%). On average 3.5% of the formoterol dose was excreted unchanged in urine after inhalation of a single dose of Symbicort pMDI, compared with 3.1% after inhalation of a single dose of Pulmicort Turbuhaler plus Oxis Turbuhaler. The variability in data was large.

Safety results:

No AEs were reported in this study and no clinically relevant findings were identified in clinical laboratory results, vital signs, or physical examination.

Conclusion:
Both the systemic bioavailability (AUC) and Cmax of budesonide were numerically lower after inhalation from Symbicort pMDI than from Pulmicort Turbuhaler plus Oxis Turbuhaler.
The fraction of the dose excreted unchanged in urine during 24 h (fe0-24h) for formoterol was similar for Symbicort pMDI and Pulmicort Turbuhaler plus Oxis Turbuhaler.
No new safety findings were reported.

Assessor's comment: This study evaluates PK data after inhalation of Symbicort pMDI which is not licensed in the EU. The relevance for this procedure is limited.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Overall conclusion
The applicant submitted altogether 39 studies. These studies concerned Symbicort Turbuhaler as well as Symbicort pMDI, which is not licensed in the EU. Studies of **Symbicort pMDI** were submitted because this medicinal product contains the same active ingredients as Symbicort Turbuhaler, and the MAH felt that these studies might therefore be relevant to this procedure. Keeping in mind the difficulties in drawing conclusions from studies which have been performed with different devices, assessment of the Symbicort pMDI studies did not reveal compound specific new information.
Some of the studies submitted for **Symbicort Turbuhaler** had already been submitted and assessed for previous procedures.
Different posologies are investigated.
Symbicort **maintenance therapy** studies were conducted with a fixed regimen. Symbicort Turbuhaler is licensed from 6 years of age. Two studies enrolled younger children from 4 years of age. One of these had already been submitted for the initial licensing procedure in children. However the number of these children is not deemed sufficient to draw meaningful conclusions on the effect of Symbicort Turbuhaler in this age group. The remaining studies did not reveal important new information warranting changes to the SPC.
Symbicort **adjustable maintenance dosing** studies investigated a more flexible dosing regimen depending on the level of asthma control. This is also covered to some extent in the current license. However, the highest doses used here, exceed the ones licensed in the paediatric population. Again the number of subjects < 18 years of age is too low to draw meaningful conclusions.
The majority of the studies submitted for **Symbicort maintenance and reliever therapy** had been submitted and assessed before and did not result in a paediatric license. No sub-group analyses have been provided, some studies enrolled only a low proportion of adolescents and the safety evaluation is not sufficient to recommend changes to the SPC.
The applicant also submitted studies investigating Symbicort THB as a **single dose for the acute relief of acute bronchoconstriction** and **used as needed only**. These studies enrolled a very low proportion of patients < 18 years of age. No firm conclusions can be drawn.

Therefore apart from an update of the paediatric information in Section 5.1 of the SPC and the inclusion of a note that children should administer Symbicort Turbuhaler under the supervision of an adult no further regulatory action is deemed necessary.

➢ Recommendation / List of Questions

1.) The paediatric information in Section 5.1 of the SPC should be updated. The applicant is asked to give a proposal.

This request was endorsed by UK, FR and SE.

2.) A note that children should administer Symbicort TBH under the supervision of an adult should be included in Section 4.2 of the SPC and Section 3 of the PIL.

This request was endorsed by UK and SE (as regards the PIL), but not completely supported by FR as many children learn to use their inhaler correctly. However it is the assessor's opinion that this note is important to ensure a correct inhalation technique at least for younger children and for those who have not used Symbicort Turbuhaler before.

VI. ASSESSMENT OF RESPONSE TO QUESTIONS

1.) The paediatric information in Section 5.1 of the SPC should be updated. The applicant is asked to give a proposal.
This request was endorsed by UK, FR and SE.

AstraZeneca's response:
AstraZeneca agrees to update the paediatric information in Section 5.1 of the SmPC.
Based on the Assessor's comments in the Day 89 Draft Assessment Report, AstraZeneca has identified one study, study SD-039-0688, that contains information relevant for an updated Section 5.1. As the study design is similar to the pediatric study SD-039-0353, which is already summarised in the currently approved SmPC, AstraZeneca proposes the following update, which combines the results from these 2 studies:

~~In a~~ Two 12-week paediatric studies~~y~~ have been performed in which 265 ~~85~~ children aged 6-11 years were treated with a maintenance dose of budesonide/formoterol (2 inhalations of 80 micrograms /4.5 micrograms/inhalation twice daily), and a short acting beta2 adrenoceptor agonist as needed. In both studies, ~~L~~lung function was improved and the treatment was well tolerated compared to the corresponding dose of budesonide alone. In one of the studies, the effect on lung function of budesonide/formoterol was shown to be equal to that of the free combination of budesonide and formoterol.

Assessor's comment: In general, the applicant's proposal seems to be acceptable. However the sentence "In one study, the effect on lung function……budesonide and formoterol" has to be deleted as the study was not designed to establish equivalence of the fixed and the free combination.

IV.4 Proposed update of paediatric information in Section 4.2 of the SmPC and Section 3 of the PIL

Assessor's comment:
2.) A note that children should administer Symbicort TBH under the supervision of an adult should be included in Section 4.2 of the SPC and Section 3 of the PIL.
This request was endorsed by UK and SE (as regards the PIL), but not completely supported by FR as many children learn to use their inhaler correctly. However it is the assessor's opinion that this note is important to ensure a correct inhalation technique at least for younger children and for those who have not used Symbicort Turbuhaler before.

AstraZeneca's response:
It is AstraZeneca's view that a note that children should administer Symbicort Turbuhaler under the supervision of an adult is not warranted in Section 4.2 of the SmPC or Section 3 of the PIL. For all patients using Symbicort Turbuhaler, regardless of age, a correct inhalation technique should be ensured as is clearly stated in Section 4.2 of the SmPC:
Note: It is important to instruct the patient

- to carefully read the instructions for use in the patient information leaflet which is packed together with each Symbicort Turbuhaler Inhaler.
- to breathe in forcefully and deeply through the mouthpiece to ensure that an optimal dose is delivered to the lungs.
- never to breathe out through the mouthpiece.
- to replace the cover of the Symbicort Turbuhaler Inhaler after use.
- to rinse their mouth out with water after inhaling the maintenance dose to minimise the risk of oropharyngeal thrush. If oropharyngeal thrush occurs, patients should also rinse their mouth with water after the as-needed inhalations.

The prescribing physician should ensure that the correct use is explained to the patient, and for younger children or children who have not used Symbicort Turbuhaler before thorough and careful instructions may be needed, but as pointed out by FR many children learn to use their inhaler correctly after which adult supervision of administration should not be necessary.

Assessor's comment: The caretakers play an important role in paediatric asthma therapy. It is acknowledged that instruction of all patients by the prescribing physician is important. However, in the special case of a paediatric patient, depending on the age, the caretakers will have to be instructed together with the patient. Subsequent supervision by the instructed caretaker can not be forgone, although need for this supervision might diminish with duration of therapy. Therefore the inclusion of the following sentence in the PIL is requested: "Young children and those not experienced in the use of Symbicort Turbuhaler should administer Symbicort Turbuhaler under the supervision of a competent adult."

VIa. Applicant's response to the final assessment report and Rapporteur's assessment

UPDATE OF THE PAEDIATRIC INFORMATION IN SECTION 5.1

AstraZeneca's response to the FAR:
AstraZeneca agrees that the sentence can be improved to more accurately reflect the study's design and limitations. The study in question, SD-039-0688, was designed to establish superiority of Symbicort Turbuhaler over Pulmicort Turbuhaler. Symbicort Turbuhaler was also compared with the free combination budesonide plus formoterol at the corresponding doses (ie, Pulmicort Turbuhaler plus Oxis Turbuhaler). There were no statistically significant differences between these 2 treatments in improvements in lung function, based on the primary outcome variable, FEV1, or secondary outcome variables forced vital capacity or morning or evening peak expiratory flow. AstraZeneca, therefore, suggests the following revision:
Two 12-week paediatric studies have been performed in which 265 children aged 6-11

years were treated with a maintenance dose of budesonide/formoterol (2 inhalations of 80 micrograms /4.5 micrograms/inhalation twice daily), and a short acting beta2-adrenoceptor agonist as needed. In both studies, lung function was improved and the treatment was well tolerated compared to the corresponding dose of budesonide alone. One of these studies also compared the budesonide/formoterol treatment with a combination of budesonide and formoterol administered via separate inhalers at corresponding doses. No difference between these treatments was detected in improvements in lung function.

Assessor's comment: It is acknowledged that no statistically significant differences were seen in the end-points listed above. However, the study was not designed to establish equivalence. Therefore the information in the last two sentences will not add any relevant information to this chapter. These sentences should be deleted.

PROPOSED UPDATE OF PAEDIATRIC INFORMATION IN SECTION 3 OF THE PIL/ Note that administration should be supervised by an adult

AstraZeneca's response:
AstraZeneca agrees to add a note but is concerned that the proposed text may imply to some readers that either 1) the Turbuhaler inhaler itself is difficult to use compared with other inhalation products (which do not have such a warning) or 2) that there is a substantial risk or danger associated with the administration of Symbicort Turbuhaler that requires adult supervision.
AstraZeneca considers the Turbuhaler inhaler to be relatively simple to use (simpler than many inhalers on the market that do not have a similar note) and that children can learn how to use the inhaler correctly. Furthermore, Symbicort Turbuhaler has a broad therapeutic range and the risk for overdose or misuse is rather low.

Based on these concerns, AstraZeneca proposes the following underlined text be added to Section 3 *How to use Symbicort Turbuhaler* of the PIL (paediatric text underlined):
How to take an inhalation
Every time you need to take an inhalation, follow the instructions below.
1. Unscrew the cover and lift it off. You may hear a rattling sound.
2. Hold your Turbuhaler upright with the red grip at the bottom.
3. Do not hold the mouthpiece when you load your Turbuhaler. To load your Turbuhaler with a dose, turn the red grip as far as it will go in one direction. Then turn it as far as it will go in the other direction (it does not matter which way you turn it first). You should hear a click sound. Your Turbuhaler is now loaded and ready to use. Only load your Turbuhaler when you need to use it.
4. Hold your Turbuhaler away from your mouth. Breathe out gently (as far as is comfortable). Do not breathe out through your Turbuhaler.
5. Place the mouthpiece gently between your teeth. Close your lips. Breathe in as deeply and as hard as you can through your mouth. Do not chew or bite on the mouthpiece.
6. Remove your Turbuhaler from your mouth. Then breathe out gently. The amount of medicine that is inhaled is very small. This means you may not be able to taste it after inhalation. If you have followed the instructions, you can still be confident that you have inhaled the dose and the medicine is now in your lungs.
7. If you are to take a second inhalation, repeat steps 2 to 6.
8. Replace the cover tightly after use.

9. Rinse your mouth with water after your daily morning and/or evening doses, and spit it out.
Do not try to remove or twist the mouthpiece. It is fixed to your Turbuhaler and must not be taken off. Do not use your Turbuhaler if it has been damaged or if the mouthpiece has come apart from your Turbuhaler.

As with all inhalers, caregivers should ensure that children prescribed Symbicort Turbuhaler use correct inhalation technique, as described above.

Assessors comment: The applicant's proposal is acceptable.

VII. FINAL RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Overall conclusion /Recommendation

Type IB variation concerning amendments to Section 5.1/SPC and Chapter 3/PIL as detailed below to be requested from the MAH within 60 days.

Additional wording in SECTION 3 OF THE PIL:
"*As with all inhalers, caregivers should ensure that children prescribed Symbicort Turbuhaler use correct inhalation technique, as described above."*

Update of paediatric information in Chapter 5.1 of the SPC:
"*Two 12-week paediatric studies have been performed in which 265 children aged 6-11 years were treated with a maintenance dose of budesonide/formoterol (2 inhalations of 80 micrograms /4.5 micrograms/inhalation twice daily), and a short acting beta2-adrenoceptor agonist as needed. In both studies, lung function was improved and the treatment was well tolerated compared to the corresponding dose of budesonide alone."*

VIII. LIST OF MEDICINCAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Name of the medicinal product: Symbicort® Turbohaler® (80/4.5 µg, 160/4.5 µg, 320/9 µg)
Active substance(s): Budesonide + Formoterol
MAH: Astra Zeneca