10.1.3.2.2 Efficacy

10.1.3.2.2.1 Primary Variables

Two co-primary efficacy variables were used, each intended to demonstrate the contribution of an individual component to the efficacy of Symbicort. Baseline was defined as the pre-dose FEV_1 measured on the day of randomization (Visit 2). Baseline-adjusted average 12-hour FEV_1 at Week 2 (LOCF) was used to demonstrate the bronchodilatory effect largely contributed by the formoterol component. Pre-dose FEV_1 was used to demonstrate the stabilizing, anti-inflammatory effect largely contributed by the budesonide component. The ANCOVA analyses included factors for center, ICS dose strata, and treatment, with a covariate of baseline FEV_1.

Baseline-adjusted average 12-hour FEV_1 is an often-used and well-accepted variable for evaluation of a bronchodilator drug. As such, it is an acceptable variable for this comparison. The endpoint of Week 2 is acceptable and not affected by withdrawals, although other time points throughout the study are of interest.

Pre-dose FEV_1 is an often-used and well-accepted variable for evaluation of a controller drug. As such, it is an acceptable variable for this comparison, even though it was elevated from a secondary to a primary variable during the course of the study. Averaging pre-dose FEV_1 over the course of the study is acceptable, although the effect of withdrawals on this endpoint must be taken into consideration as the study progresses.

10.1.3.2.2.1.1 Baseline-adjusted average 12-hour FEV_1

Baseline-adjusted average 12-hour FEV_1 at Week 2 (EAS) was the primary variable/endpoint/population for evaluation of the contribution of the formoterol component to the combination drug product (Symbicort minus budesonide comparison). Results for this variable are shown in the tables and figures below. Treatment means at **Week 2 (primary endpoint)**, and at the secondary endpoints of End of Treatment (12 weeks LOCF) and Week 12 are shown in Table 81 and Table 82, respectively. Treatment comparisons at Week 2 (primary endpoint) and End of Treatment (12 weeks LOCF, secondary endpoint) are shown in Table 83. The primary comparison of Symbicort to budesonide at Week 2 was significant ($p<0.001$), and is shown **bolded**. Of note, the three comparisons between Symbicort to placebo and each mono-component product to placebo were significant, providing study assay sensitivity. Secondary analyses of interest including 12-hour FEV_1 at the end of treatment (Week 12, LOCF) were quite similar to the primary results, implying that the combination maintained efficacy throughout the study treatment period. Also of note, the results for Symbicort and the individual monoproducts taken together were similar, providing some clinical support for the lack of any substantial pharmaceutical differences between MDI and DPI products.

Since the ANCOVA analysis included factors for center, ICS dose strata, and treatment, with a covariate of baseline FEV_1, the sponsor evaluated the effect of these factors on this endpoint. Treatment was highly significant in the model; baseline FEV_1, ICS dose strata, and center were not, but were retained to follow the planned analysis. Sensitivity analyses included: an estimate of the population standard deviation (0.31 L, smaller than the 0.50 L value used in the sample size calculation), assessment of the impact of mis-stratifications on the primary analysis (no impact on results from: 5 randomized to mod-dose stratum but were below minimum ICS

requirements, 13 randomized to mod-dose instead of high-dose stratum, 10 randomized to high-dose instead of mod-dose stratum), ICS dose stratum entry-by-treatment interaction term, an assessment of outliers (primary model judged to be insensitive to outliers), consistency across centers (center-by-treatment effect p=0. 454 with pooling of centers with 5 or fewer patients, p=0.097 with pooling of centers with 12 or fewer patients, but results consistent with primary analysis), and consistency across different levels of baseline (at all levels of baseline [by quartile] FEV_1 the Symbicort minus budesonide comparison was statistically significant. [p226-33]

The applicant states that the amount of missing data was small, but provided various sensitivity analyses to evaluate various extrapolation methods to replace missing values in the 12-hour FEV_1 profiles. Results were consistent with the primary analysis. Results across age, sex, and race were explored in separate analyses and were similar to the primary analysis. There were too few patients less than 12 years of age and too few patients outside of Caucasians to make any conclusion regarding consistency of results for these parameters. There was no evidence of a differential in results across sex. [p229-30]

The FDA statistician, Dr. Guo, was able to duplicate the applicant's results. Of note, because of the multiple data sets from which the variables needed to be obtained for analysis, Dr. Guo's analyses yielded slight variations in numbers of patients at various timepoints and for various variables, thus yielding minor variations in the results but not affecting the overall results or their interpretation. Please see Dr. Guo's review for details.

The LS mean FEV_1 values at the primary endpoint of Week 2 LOCF are shown in Figure 24. The mean percent change from baseline in FEV_1 with the first treatment on the day of randomization, at Week 2 LOCF, and at End of Treatment LOCF are shown in Figure 25, Figure 26, and Figure 27, respectively. The percent change from baseline figures compensate for changes in baseline due to the corticosteroid component, and allow comparison of the time curves for the bronchodilator component at each time point and over the course of the study. Comparison of the 12-hour FEV_1 time curves between Symbicort and the two mono-components used together also allows a rough comparison of the pharmaceutic differences between Symbicort MDI and the Oxis Turbuhaler when budesonide is added to the Oxis. Comparison of the 12-hour FEV_1 time curves between Symbicort MDI and the Oxis Turbuhaler provides a visual estimation of the PD effects of the formoterol component in the two products with the first dose, thus allowing a rough comparison of the pharmaceutic differences between the two. The time curves are substantially similar, with a small amount of visual separation in the 6-to-12 hour time period. However, over the course of the study, the addition of budesonide seems to prevent the tachyphylaxis that occurs with formoterol alone.

Table 81. SD-039-0717, Baseline-adjusted average 12-hour FEV_1 (L), Treatment Means Week 2 (EAS)

Treatment	N	Baseline FEV_1 (L)	Baseline-adjusted average 12-hour FEV_1 (L) Week 2 LOCF*		
			Observed value	From ANCOVA	
		Mean (SD)	Mean (SD)	LS Mean (SEM)	95% CI
Symbicort	**124**	**2.24** (0.72)	**0.34** (0.33)	**0.32** (0.03)	**(0.26, 0.38)**
Budesonide	**109**	**2.30** (0.63)	**0.15** (0.26)	**0.13** (0.03)	**(0.06, 0.19)**
Formoterol	123	2.18 (0.60)	0.19 (0.28)	0.17 (0.03)	(0.11, 0.23)
Budesonide + Formoterol	115	2.24 (0.61)	0.32 (0.29)	0.31 (0.03)	(0.24, 0.37)
Placebo	125	2.28 (0.68)	-0.03 (0.34)	-0.05 (0.03)	(-0.11, 0.02)
*Treatment means at Week 2 LOCF using the WV Pre-CF imputation method (EAS). Primary comparison is **bolded**.					
Source: T28, p149 and T11.2.1.4.1, p 2898; SD-039-0717					

Table 82. SD-039-0717, Baseline-adjusted average 12-hour FEV_1 (L), Treatment Means at End of Treatment and at Week 12 (EAS)

Treatment	End of Treatment (Week 12, LOCF)				Week 12			
	N	Baseline	Observed	ANCOVA	N	Baseline	Observed	ANCOVA
		Mean	Mean	LS Mean (95% CI)		Mean	Mean	LS Mean (95% CI)
Symbicort	124	2.24	0.37	0.34 (0.27, 0.40)	98	2.25	0.37	0.35 (0.28, 0.43)
Budesonide	109	2.30	0.15	0.11 (0.04, 0.18)	79	2.33	0.19	0.15 (0.07, 0.23)
Formoterol	123	2.18	0.17	0.14 (0.08, 0.21)	65	2.23	0.21	0.19 (0.10, 0.28)
Budesonide + Formoterol	115	2.24	0.35	0.33 (0.26, 0.40)	88	2.24	0.35	0.33 (0.25, 0.41)
Placebo	125	2.28	-0.03	-0.07 (-0.13, 0.00)	51	2.29	0.06	0.03 (-0.07, 0.13)
*Treatment means at EOT (Week 12 LOCF) and at Week 12 using the WV Pre-CF imputation method (EAS)								
Source: 11.2.1.4.1, p2898; SD-039-0717								

Table 83. SD-039-0717, Baseline-adjusted average 12-hour FEV_1 (L), Treatment Comparisons (EAS)

Treatment Comparisons*	Week 2			End of Treatment		
	LS Mean (SEM)	95% CI	p-value	LS Mean (SEM)	95% CI	p-value
Symbicort minus Placebo	0.37 (0.04)	(0.29, 0.45)	<0.001	0.40 (0.04)	(0.32, 0.48)	<0.001
Symbicort minus Budesonide	**0.20** (0.04)	**(0.11, 0.28)**	**<0.001**	0.23 (0.04)	(0.14, 0.31)	<0.001
Symbicort minus Formoterol	0.15 (0.04)	(0.07, 0.23)	<0.001	0.19 (0.04)	(0.11, 0.28)	<0.001
Symbicort minus Bud + Form	0.01 (0.04)	(-0.07, 0.09)	0.739	0.01 (0.04)	(-0.08, 0.09)	0.871
Budesonide minus Placebo	0.17 (0.04)	(0.09, 0.25)	<0.001	0.18 (0.04)	(0.09, 0.26)	<0.001
Formoterol minus Placebo	0.22 (0.04)	(0.14, 0.30)	<0.001	0.21 (0.04)	(0.13, 0.29)	<0.001
*Treatment comparisons at **Week 2 LOCF (primary endpoint)** and at End of Treatment (Week 12 LOCF) using the WV Pre-CF imputation method (EAS ≥12 yr). Primary comparison is **bolded**.						
Source: T29, T31, p149-50; SD-039-0717						

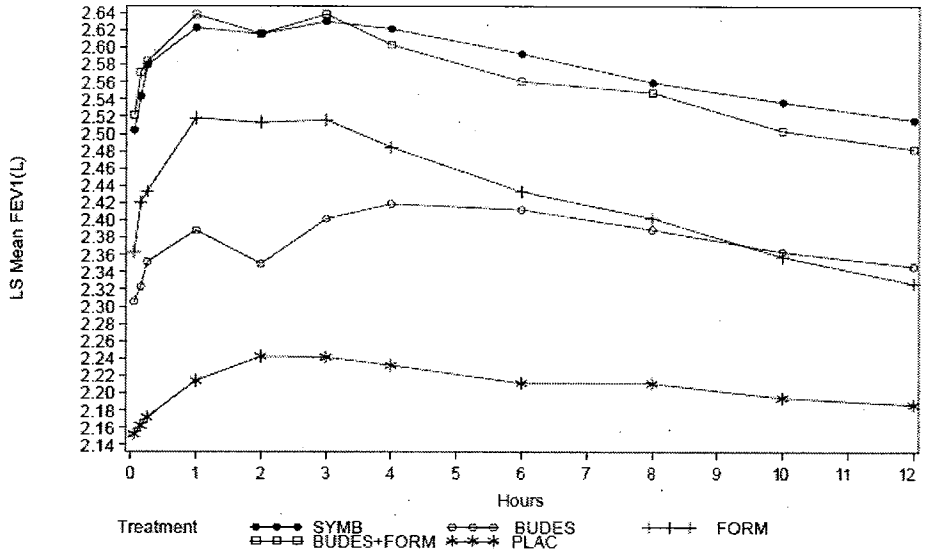

Figure 24. SD-039-0717, LS mean FEV_1 values at Week 2 LOCF (EAS)

Source: F4, p152; SD-039-0717

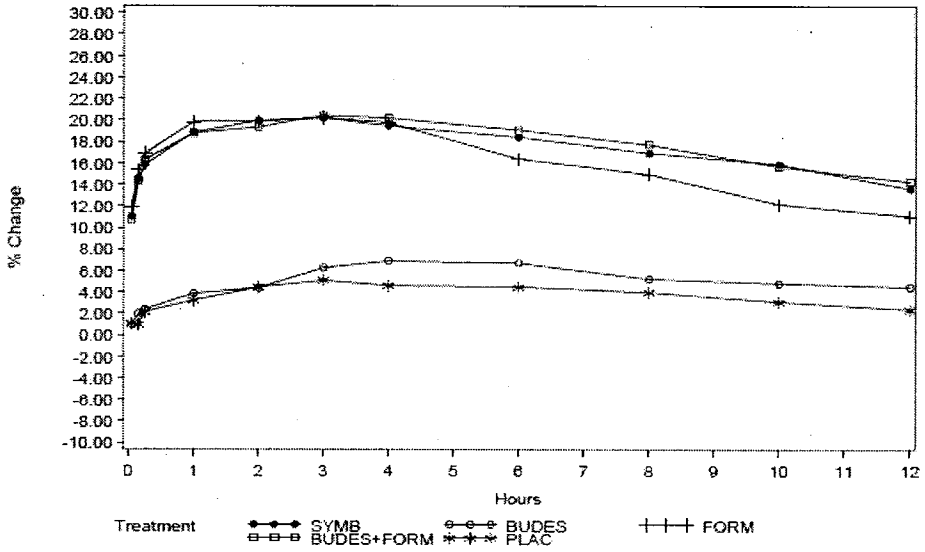

Figure 25. SD-039-0717, Mean percent change from baseline in FEV_1 on Day of Randomization (EAS)

Source: F5, p153; SD-039-0717

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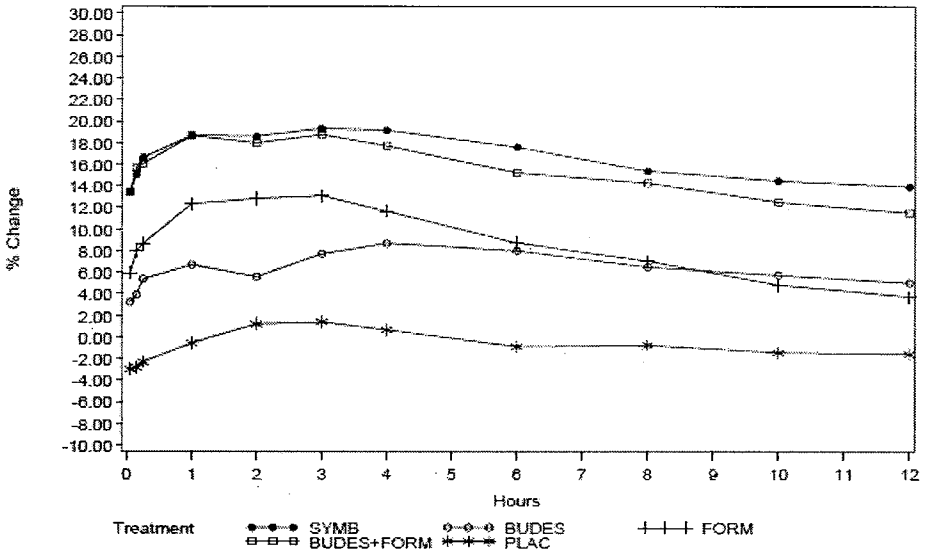


Figure 26. SD-039-0717, Mean percent change from baseline in FEV_1 at Week 2 LOCF (EAS)

Source: F6, p154; SD-039-0717

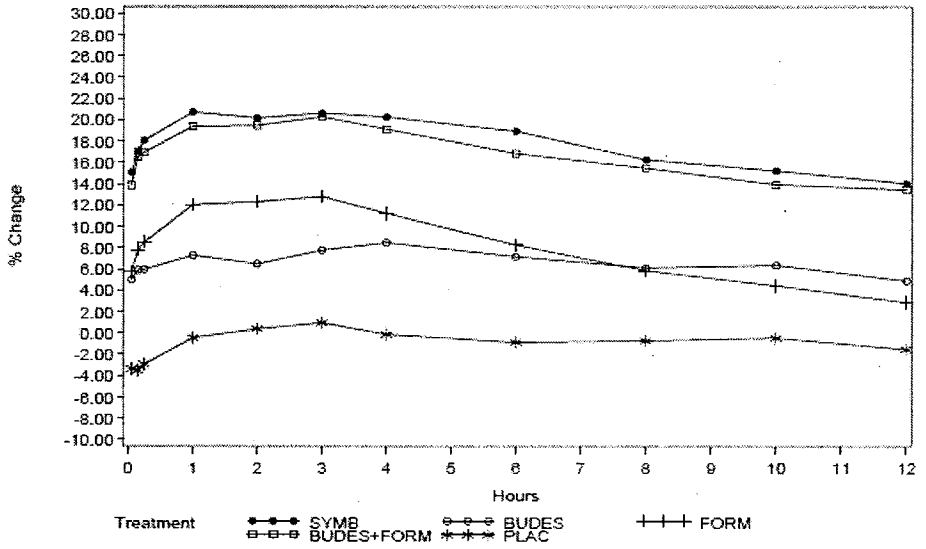


Figure 27. SD-039-0717, Mean percent change from baseline in FEV_1 at End of treatment LOCF (EAS)

Source: F7, p155; SD-039-0717

10.1.3.2.2.1.2 Pre-dose FEV_1

Change from baseline in average pre-dose FEV_1 averaged over the treatment period (EAS) was the primary variable/endpoint/population for evaluation of the contribution of the budesonide component to the combination drug product (Symbicort minus formoterol comparison). Results for this variable are shown in the tables and figures below. Treatment means and treatment comparisons from ANCOVA are summarized in Table 84 and Table 85, respectively. The primary comparison of Symbicort to formoterol was significant ($p<0.001$), and is shown **bolded**.

The three comparisons between Symbicort to placebo and each mono- component product to placebo were significant, providing study assay sensitivity.

Of note, results for Symbicort and the individual monoproducts taken together were similar, providing some clinical support for the lack of any substantial pharmaceutical differences between MDI and DPI products.

Secondary analyses included change from baseline in pre-dose FEV_1 at each visit, shown graphically in Figure 28. The Symbicort minus formoterol comparison was significant at all time points, including at Week 2 ($p<0.001$), Week 6 ($p<0.001$), Week 12 ($p=0.001$), and at the End of Treatment (defined as last available visit after receiving randomized treatment, i.e. Week 12 LOCF; S-F comparison: $p<0.001$). [T11.2.2.4.2, p3985; SD-039-0717.pdf] The results in this study did not match those of study 716, where pre-dose FEV_1 improved markedly in the three active treatment groups over the first two weeks of treatment, then stabilized and remained relatively constant between weeks 6 and 12. In this study, pre-dose FEV_1 improved over the first two weeks only for both combination arms containing Symbicort or both mono-components taken together. At two weeks, pre-dose FEV_1 increased just slightly for the budesonide, and decreased for both the formoterol and placebo arms. Over the course of the study, there was a small separation between the Symbicort and the budesonide + formoterol arms: the budesonide + formoterol arm drifted down slightly compared to the Symbicort arm, which remained about the same. The budesonide, formoterol, and placebo arms gradually drifted higher after the two-week time point. Treatment comparisons at various time points over the course of the study are shown in Table 86. The difference between Week 12 and End of Treatment may be due to the effect of withdrawals, as there were clear differences between various imputation methodologies [LOCF vs whomever was still in the study] as the study progressed.

Since the ANCOVA analysis included factors for center, ICS dose strata, and treatment, with a covariate of baseline FEV_1, the sponsor evaluated the effect of these factors on this endpoint. Treatment, baseline FEV_1, and ICS dose strata at entry were highly significant in the model; center was not, but was retained to follow the planned analysis. Sensitivity analyses included: an estimate of the population standard deviation (0.32 L, smaller than the 0.50 L value used in the sample size calculation), assessment of the impact of mis-stratifications on the primary analysis (no impact on results), ICS dose stratum entry-by-treatment interaction term, an assessment of outliers (primary model judged to be insensitive to outliers), consistency across centers (center-by-treatment effect $p=0.043$ with pooling of centers with 5 or fewer patients, $p=0.116$ with pooling of centers with 12 or fewer patients, but results consistent with primary analysis), and consistency across different levels of baseline (at all levels of baseline [by quartile] FEV_1 the Symbicort minus budesonide comparison was statistically significant. [p226-33]

Results across age, sex, and race were explored in separate analyses and were similar to the primary analysis. There were too few patients outside of Caucasians to make any conclusion regarding consistency of results for these parameters. There was no evidence of a differential in results across sex. [p230]

The FDA statistician, Dr. Guo, was able to duplicate the applicant's results. Of note, because of the multiple data sets from which the variables needed to be obtained for analysis, Dr. Guo's analyses yielded slight variations in numbers of patients at various timepoints and for various

variables, thus yielding minor variations in the results but not affecting the overall results or their interpretation. Please see Dr. Guo's review for details.

Since there were such a large number of withdrawals during the study (Table 78), particularly in the placebo and formoterol treatment groups, we examined both the overall effect of all withdrawals as well as the specific effect of withdrawals due to asthma exacerbations. We considered the effects of withdrawal on both primary variables and endpoints. However, because the timing of the two primary endpoints were different, we presumed that there would be minimal or no effect on the endpoint of baseline-adjusted average 12-hour FEV_1, which was at Week 2, but more chance of an effect on the endpoint of pre-dose FEV_1, which was averaged over the entire study period.

It is very difficult to assess the effect of withdrawals due to the pre-specified criteria for asthma exacerbations on the pre-dose FEV_1 variable. With Amendment 3, withdrawals due to asthma exacerbation was demoted from a co-primary to a secondary efficacy variable (subsequently renamed withdrawals due to pre-defined asthma events) to assess the contribution of the budesonide component to the combination product (Symbicort minus formoterol comparison). At the same time, Amendment 3 raised pre-dose FEV_1 to a co-primary variable for this comparison. While some patients were withdrawn and no further data collected, other patients who met the pre-specified withdrawal criteria and qualified for discontinuation were not discontinued because investigators judged them to be clinically stable. With the institution of pre-dose FEV_1 as a primary efficacy variable, keeping patients in the study allowed collection of more complete FEV_1 data. However, the subset of patients who were withdrawn no longer contributed to endpoints measured thereafter, thereby potentially creating an uneven effect on the results. Since this discontinuation criterion remained throughout the study even after the Amendment, discontinuations for having met withdrawal criteria apply to the entire study, not just to those patients enrolled prior to Amendment 3. As previously shown in Table 78, the numbers of patients involved varied by treatment group, with the majority of patients being in the placebo and formoterol treatment groups. In this study, the numbers of patients withdrawn was due to an asthma exacerbation was substantial, 36% of formoterol patients and 49% of placebo patients. Fewer patients were involved when considering the primary comparison between Symbicort minus formoterol than when considering secondary comparisons between any active and placebo.

We assessed the overall impact of withdrawals by examining the corresponding drift in baseline FEV_1 from Week 2 to Week 12, shown in Table 87. For convenience, the numbers of patients enrolled at ITT, Week 2, Week 6, and Week 12, and the number of study completers are shown. In addition, the observed pre-dose FEV_1 for patients still enrolled and who completed spirometric maneuvers at Week 12 is also shown. By Week 12, there were far more withdrawals in the placebo and formoterol groups than the other three (budesonide-containing) treatment groups. Unlike in study 716, where both the placebo and formoterol groups showed a gradual increase in baseline FEV_1 throughout the treatment period, in this study baseline did not shift over time except for the formoterol group, which started slightly lower than the rest and drifted up slightly. By Week 12, the baseline mean for the remaining patients was similar across all treatment groups (Symbicort 2.25 L, budesonide 2.33 L, formoterol 2.26 L, bud + form 2.24 L, placebo 2.28 L). While in study716 the implication was that the predominance of withdrawals in the placebo group were in patients who had poorer asthma control and lower baseline mean

FEV_1 values, this was not the case in this study. As a result, the withdrawal pattern did not appear to affect the treatment group differences at various timepoints throughout the study, as shown in Table 86, which shows the treatment comparisons at Week 2, Week 12 and End of Treatment.

Table 84. SD-039-0717, Pre-dose FEV_1 (L), Treatment Means (EAS)

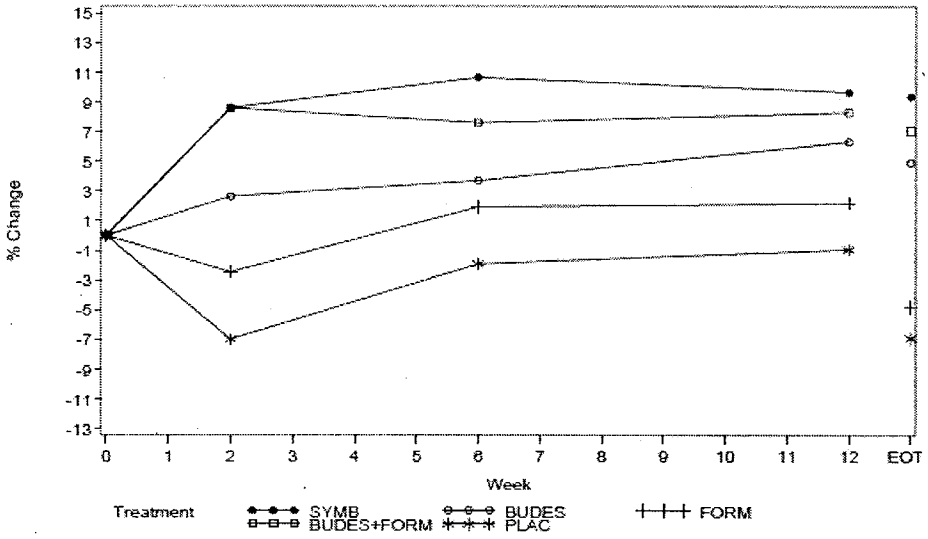
Treatment	N	Baseline FEV_1(L)	FEV_1 (L) over Treatment period*			
			Observed value	Change from baseline	From ANCOVA	
		Mean (SD)	Mean (SD)	Mean (SD)	LS Mean (SEM)	95% CI
Symbicort	**117**	**2.23** (0.72)	**2.41** (0.77)	**0.18** (0.28)	**0.17** (0.03)	**(0.10, 0.23)**
Budesonide	108	2.30 (0.64)	2.37 (0.69)	0.07 (0.33)	0.05 (0.03)	(-0.02, 0.12)
Formoterol	**114**	**2.19** (0.59)	**2.12** (0.65)	**-0.07** (0.31)	**-0.09** (0.03)	**(-0.16, -0.03)**
Bud + Form	111	2.23 (0.62)	2.39 (0.66)	0.15 (0.26)	0.13 (0.03)	(0.07, 0.20)
Placebo	116	2.29 (0.69)	2.11 (0.69)	-0.18 (0.39)	-0.20 (0.03)	(-0.26, -0.13)
*Mean of all pre-dose FEV_1 values obtained during the double-blind treatment period (EAS)						
Source: T32, p158; SD-039-0717						

Table 85. SD-039-0717, Pre-dose FEV_1 (L), Treatment Comparisons, Average over Double-blind Period (EAS)

Comparison*	ANCOVA		
	LS Mean (SEM)	95% CI	p-value
Symbicort minus Placebo	0.37 (0.04)	(0.28, 0.45)	<0.001
Symbicort minus Budesonide	0.12 (0.04)	(0.04, 0.21)	0.006
Symbicort minus Formoterol	**0.26** (0.04)	**(0.17, 0.35)**	**<0.001**
Symbicort minus Bud + Form	0.04 (0.04)	(-0.05, 0.12)	0.399
Budesonide minus Placebo	0.25 (0.04)	(0.16, 0.33)	<0.001
Formoterol minus Placebo	0.11 (0.04)	(0.02, 0.19)	0.012
*Treatment comparisons for change from baseline to the entire double-blind treatment period (EAS)			
Source: T33, p158; SD-039-0717			

Table 86. SD-039-0717, Pre-dose FEV_1 Treatment Comparisons at Various Study Timepoints (EAS)

Treatment Comparisons*	Week 2		Week 12		End of Treatment*	
	LS Mean	95% CI	LS Mean	95% CI	LS Mean	95% CI
Symbicort minus Placebo	0.35	(0.26, 0.44)	0.23	(0.11, 0.34)	0.37	(0.27, 0.47)
Symbicort minus Budesonide	0.12	(0.03, 0.21)	0.07	(0.04, 0.17)	0.10	(0.00, 0.21)
Symbicort minus Formoterol	0.22	(0.14, 0.31)	0.18	(0.07, 0.29)	0.31	(0.20, 0.41)
Symbicort minus Bud + Form	0.00	(-0.09, 0.09)	0.04	(-0.06, 0.14)	0.05	(-0.05, 0.15)
Budesonide minus Placebo	0.23	(0.14, 0.32)	0.16	(0.04, 0.28)	0.27	(0.16, 0.37)
Formoterol minus Placebo	0.13	(0.04, 0.21)	0.05	(-0.08, 0.17)	0.06	(-0.04, 0.17)
*End of Treatment was defined as Week 12, LOCF						
Source: T11.2.2.4.2, p3985; SD-039-0717						



	Week 2 N	Week 6 N	Week 12 N	EOT N
SYMB	117	107	100	117
Budes	108	90	79	108
Form	114	83	68	114
Budes+Form	111	102	92	111
Plac	116	70	56	116

Figure 28. SD-039-0717, Mean percent change from baseline in pre-dose FEV_1 by visit (EAS)

Source: F8, p163; SD-039-0717

Table 87. SD-039-0717, Shift in Baseline Pre-dose FEV_1 (L) over the Study (EAS[1])

Treatment	ITT	Week 2		Week 6		Week 12[1]			Comp[2]
		N	Baseline Mean (SD)	N	Baseline Mean (SD)	N	Baseline Mean (SD)	Observed Mean (SD)	N
Symbicort	124	117	2.23 (0.72)	107	2.23 (0.74)	100	2.25 (0.75)	2.45 (0.83)	97
Budesonide	109	108	2.30 (0.64)	90	2.36 (0.64)	79	2.33 (0.62)	2.47 (0.69)	78
Formoterol	123	114	2.19 (0.59)	83	2.25 (0.61)	68	2.26 (0.61)	2.28 (0.64)	60
Bud + Form	115	111	2.23 (0.62)	102	2.25 (0.62)	92	2.24 (0.63)	2.41 (0.69)	86
Placebo	125	116	2.29 (0.69)	70	2.29 (0.68)	56	2.28 (0.67)	2.25 (0.72)	50

[1] The numbers of patients who were enrolled and performed spirometric maneuvers at various time points differ slightly from the results obtained by the FDA statistician. This is likely due to the multiple datasets used to create the various composite tables.

[2] The numbers of patients who were enrolled and who performed spirometric maneuvers at Week 12 differs slightly from the numbers of patients who completed the study (see Table 78).

Source: T11.2.2.4.1, p3984; F2, p123; SD-039-0717

10.1.3.2.2.2 Secondary Variables

Multiple secondary efficacy variables were declared, including: pre-defined asthma events, other spirometry-related variables (2-hour post-dose FEV_1, maximum FEV_1, onset of effect [15% improvement in FEV_1], time to onset of effect), electronic Diary variables (morning and evening PEF, nighttime and daytime asthma symptom scores, nighttime awakenings, rescue medication use), and various global and PRO assessments, including AQLQ. However, the applicant considered 3 variables to be key secondary variables: pre-defined asthma events, percentage of

symptom free days, and AQLQ(S) overall score. AstraZeneca wishes to place information on certain of these variables in the labeling, including AM and PM PEF, symptom-free days, withdrawals due to pre-defined asthma events, reduction in asthma symptoms, use of rescue medications. As noted previously, one of the secondary variables (withdrawals due to pre-defined asthma events) was originally a co-primary variable. Because of this I have chosen to show more details regarding secondary variables rather than would otherwise be shown, although a brief summary follows:

For secondary variables, the study report considered the comparison of Symbicort to placebo to be the pre-specified primary comparison. However, this focus deemphasizes other comparisons, which are of more interest than the comparison of Symbicort to placebo. These comparisons include examination of the relative benefits of Symbicort, budesonide and formoterol to each other as well as placebo. Relevant comparisons are discussed throughout this section.

Secondary variables generally favored Symbicort and each mono-component in comparison to placebo; the results thereby provided support for the internal validity of the study findings. Secondary variables also generally favored Symbicort in comparison to each mono-component, depending upon the endpoint (as discussed below); the results thereby provided support for the primary efficacy outcome analyses. Any potential added or negative benefit of the combination was considered. In addition to the expected corticosteroid controller results, the addition of budesonide to formoterol appeared to prevent [or delay for the period of the study] the phenomenon of tachyphylaxis to continuous beta-agonist use. In addition to the expected LABA bronchodilator benefits, the addition of formoterol to budesonide appeared to decrease the frequency of events that might lead to or be associated with exacerbations, increase the time to first event, decrease asthma symptom scores and rescue medication use, and improve AQLQ beyond that of either monoproduct.

It should be noted that the Symbicort results were closely replicated by the free combination product arms, but differ from the results found in study **716** in more mild asthmatics, where little gain from addition of formoterol was noted but the prevention [or delay] of tachyphylaxis was still present.

10.1.3.2.2.2.1 CRF pre-defined asthma events and Withdrawals due to pre-defined asthma events

It is of note that the study report does not actually discuss the impact of withdrawals due to asthma exacerbations (see discussion under pre-dose FEV_1) in any depth. Having demoted the endpoint of withdrawals due to pre-defined asthma events, the withdrawal endpoint is relegated to a relatively minor prominence in the study report. Instead, the study report refers to "CRF pre-defined asthma events" that were listed as an asthma exacerbation (ASTEXAC) in the CRF. The report states that criteria for these events were identical to the criteria for discontinuation due to such an event (i.e. withdrawals due to pre-defined asthma event). As such, the CRF approach theoretically should have captured both subsets of patients who met the pre-defined criteria, including those withdrawn and those not. In general, I agree with this interpretation. While data for withdrawals due to pre-defined asthma event and CRF pre-defined asthma events are both presented, the "CRF pre-defined asthma event" approach is correctly presented in far greater detail. The report also discusses the pros and cons for other mechanisms for capturing information, including that from dairy and spirometry data. Theoretically, the electronic diary or

spirometry data should have been transposed to the CRF. But if they were not, using additional means to capture data would yield more complete information on patients who qualified for a predefined asthma event. This more inclusive collection methodology was called "CDS pre-defined asthma events." Although listings are given in the appendix for the CDS approach [*Note: all 3 approaches are in the listings*], the study report opts to present the CRF approach, stating that both the CRF and CDS capturing approaches yielded nearly identical results.

However, the reader should take note of several important issues in this section. While it was placed at the beginning of the secondary variables section, the applicant tried to de-emphasize the importance of these events as a secondary variable by suggesting that for all secondary variables the comparison of Symbicort to placebo would be the pre-specified primary comparison. However, as a former primary variable and having been declared while the study was ongoing but still blinded, the comparison to formoterol is of most interest. In addition, the introduction to this section of the study report states that "the consistency of the results for these 2 variables [i.e. CRF and withdrawal methods for evaluation of this endpoint] obviates the need to assess the impact of protocol Amendment 3 on the variable of withdrawals due to pre-defined asthma events." [p205] I definitely disagree with this statement. Regardless of how one performs the methodology to assess the variable, as a demoted primary variable the evaluation of all events [regardless of methodology] that qualified a patient for withdrawal due a pre-defined asthma event needs to be evaluated as if this were still a primary variable, and the results should be considered for inclusion in the labeling.

CRF pre-defined asthma events

The number and percentage of patients with a CRF pre-defined asthma event are shown in Table 88 for all patient population strata, with a partial breakdown by dosage strata. Treatment group comparisons for the EAS population are shown in Table 89. In the EAS population, the percentage of patients with at least 1 pre-defined asthma event was lower in the Symbicort (29.8%) and budesonide + formoterol (20.9%) groups than in the budesonide (44.0%), formoterol (55.3%) and placebo (67.2%) groups. The most commonly met criterion was nighttime awakenings due to asthma followed by decrease in FEV_1; however, all criteria contributed to the treatment difference. An odds ratio was used for evaluation of the statistical significance of these events. Treatment group comparisons show that the proportion of patients with at least 1 pre-defined asthma event was significantly lower for Symbicort vs formoterol ($p<0.001$) as well as for Symbicort vs placebo ($p<0.001$). Kaplan-Meier curves for time (days) to first event (EAS) are shown in Figure 29. The time to the first pre-defined asthma event was longest for budesonide + formoterol followed by Symbicort, budesonide, formoterol, and placebo. [p165-7]

In both studies 716 and 717, formoterol treatment alone appeared to fare only a little better than placebo, implying that when used alone it has no benefit in prevention of exacerbations. Whereas in study 716 the frequency of qualifying asthma events were similar in the Symbicort and budesonide treatment arms, in this study both Symbicort and the free combination arms experienced less frequent pre-defined events. The implication is that in a population of less severe asthmatics (study 716) the addition of formoterol to budesonide adds little for control of a series of asthma indices that are often indicative of exacerbations, in a more severe population (study 717) there may be some benefit from the addition of formoterol to budesonide over either used alone. This is borne out by the results of both the Symbicort and free combination arms.

Table 88. SD-039-0717, Number and percentage of patients with a CRF pre-defined asthma event (EAS)

Criteria	Treatment group, n (%)					
	Symbicort	Bud	Form	Bud + Form	Placebo	Total
EAS population (All)	124	109	123	115	115	596
Pre-defined asthma event	37 (29.8)	48 (44.0)	68 (55.3)	24 (20.9)	84 (67.2)	261 (43.8)
Time to event (Mean days)	33.6	22.2	29.2	30.5	18.6	25.2
Criterion 1: Decrease in FEV_1	4 (3.2)	7 (6.4)	15 (12.2)	8 (7.0)	14 (11.2)	48 (8.1)
Criterion 2: Rescue medication	2 (1.6)	3 (2.8)	3 (2.4)	0	7 (5.6)	15 (2.5)
Criterion 3: Decrease in AM PEF	2 (1.6)	5 (4.6)	17 (13.8)	5 (4.3)	15 (12.0)	44 (7.4)
Criterion 4: Nighttime awakening	24 (19.4)	29 (26.6)	32 (26.0)	11 (9.6)	49 (39.2)	145 (24.3)
Criterion 5: Clinical exacerbation:	7 (5.6)	5 (4.6)	17 (13.8)	6 (5.2)	16 (12.8)	51 (8.6)
ER treatment	3 (2.4)	1 (0.9)	1 (0.8)	0	0	5 (0.8)
Hospitalization	2 (1.6)	0	0	0	0	2 (0.3)
Disallowed asthma medication:	7 (5.6)	4 (3.7)	16 (13.0)	6 (5.2)	16 (12.8)	49 (8.2)
• Nebulized bronchodilator	4 (3.2)	1 (0.9)	5 (4.1)	2 (1.7)	7 (5.6)	19 (3.2)
• Steroid	5 (4.0)	4 (3.7)	12 (9.8)	4 (3.5)	12 (9.6)	37 (6.2)
• Leukotriene modifier	1 (0.8)	0	4 (3.3)	0	1 (0.8)	6 (1.0)
• Other	1 (0.8)	1 (0.9)	5 (4.1)	2 (1.7)	5 (4.0)	14 (2.3)
EAS population (Moderate dose)	91	81	86	82	87	427
Pre-defined asthma event	24 (26.4)	38 (46.9)	43 (50.0)	17 (20.7)	55 (63.2)	177 (41.5)
Time to event (Mean days)	35.5	24.1	30.4	34.0	20.9	27.1
EAS population (High dose)	33	28	37	33	38	169
Pre-defined asthma event	13 (39.4)	10 (35.7)	25 (67.6)	7 (21.2)	29 (76.3)	84 (49.7)
Time to event (Mean days)	30.0	15.1	27.1	22.1	14.1	21.2
Data derived from ASTEXAC in CRF						
Source: T38, p165; T11.2.3.1.1, p4008-16; SD-039-0717						

Table 89. SD-039-0717, Treatment comparisons for percentage of patients with at least 1 CRF pre-defined asthma event (EAS)

Comparison*	Odds ratio	95% CI	P-value
Symbicort vs Placebo	**0.21**	**(0.12, 0.35)**	**<0.001**
Symbicort vs Budesonide	0.54	(0.32, 0.93)	0.025
Symbicort vs Formoterol	**0.34**	**(0.20, 0.58)**	**<0.001**
Symbicort vs Budesonide + Formoterol	1.62	(0.90, 2.94)	0.107
Budesonide vs Placebo	0.39	(0.23, 0.66)	<0.001
Formoterol vs Placebo	0.60	(0.36, 1.01)	0.053
*The applicant states that as a secondary variable, the comparison of Symbicort to placebo is the pre-specified primary comparison. However, as a former primary variable, the comparison to formoterol is of most interest. Both are **bolded**.			
Source: T39, p166; SD-039-0717			

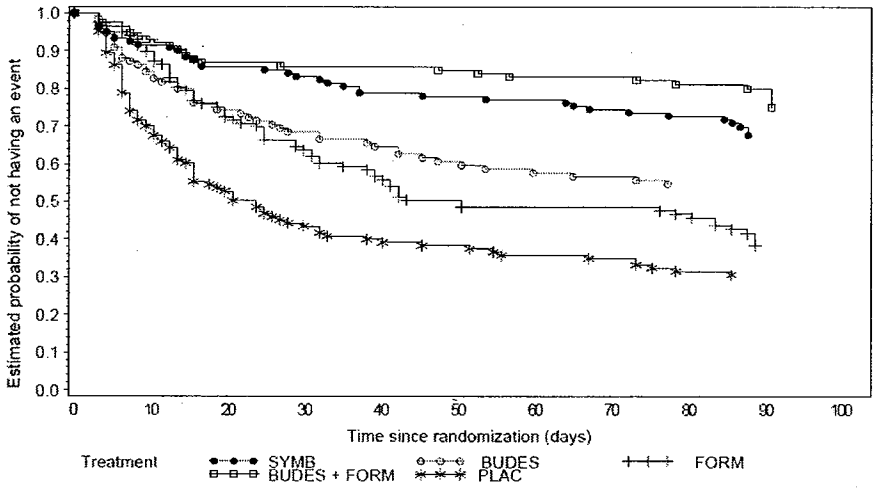


Figure 29. SD-039-0717, Kaplan-Meier curves of time (days) to first CRF pre-defined asthma event (EAS), All dose strata

Source: F11.2.3.21.6, p4087; SD-039-0717

Withdrawals due to pre-defined asthma events

The number and percentage of patients withdrawn due to a pre-defined asthma event are shown in Table 90 for all patient population strata, with a partial breakdown by dosage strata. Analysis of this variable (withdrawal due to pre-defined asthma events) was based on those patients who were identified on the termination CRF as having been withdrawn due to "development of study-specific discontinuation criteria." Some patients met the criteria but were not withdrawn from the study; these were identified as protocol deviations. The results are comparable to those of the CRF pre-defined asthma events discussed above.

Table 90. SD-039-0717, Withdrawals due to pre-defined asthma event (EAS)

Criteria	Treatment group, n (%)					
	Symbicort	Bud	Form	Bud + Form	Placebo	Total
EAS All	124	109	123	115	125	596
Pre-defined asthma event	13 (10.5)	22 (20.2)	44 (35.8)	13 (11.3)	62 (49.6)	154 (25.8)
Time to Event (Mean days)	26.8	25.2	30.8	36.5	20.7	26.0
Criterion 1: Decrease in FEV_1	3 (2.4)	7 (6.4)	15 (12.2)	7 (6.1)	21 (16.8)	53 (8.9)
Criterion 2: Rescue medication	2 (1.6)	4 (3.7)	5 (4.1)	0	7 (5.6)	18 (3.0)
Criterion 3: Decrease in AM PEF	2 (1.6)	5 (4.6)	17 (13.8)	4 (3.5)	14 (11.2)	40 (6.7)
Criterion 4: Nighttime awakening	5 (4.0)	5 (4.6)	8 (6.5)	2 (1.7)	20 (16.0)	40 (6.7)
Criterion 5: Clinical exacerbation:	3 (2.4)	4 (3.7)	14 (11.4)	6 (5.2)	14 (11.2)	41 (6.9)
ER treatment	0	1 (0.9)	1 (0.8)	0	0	2 (0.3)
Hospitalization	0	0	0	0	0	0
Disallowed asthma medication	3 (2.4)	3 (2.8)	13 (10.6)	6 (5.2)	14 (11.2)	39 (6.5)
EAS (Moderate dose)	91	81	86	82	87	427
Pre-defined asthma event	9 (9.9)	17 (21.0)	25 (29.1)	6 (7.3)	39 (44.8)	96 (22.5)
Time to Event (Mean days)	33.7	25.6	30.8	47.3	23.2	28.1
EAS (High dose)	33	28	37	33	38	169
Pre-defined asthma event	4 (12.1)	5 (17.9)	19 (51.4)	7 (21.2)	23 (60.5)	58 (34.3)
Time to Event (Mean days)	11.3	23.8	30.7	27.1	16.3	22.6

Source: T11.2.3.3.1, p4168-76; SD-039-0717

10.1.3.2.2.2.2 Improvements of 15% in FEV_1

Onset of effect was evaluated over the first 60 minutes after the first dose on the day of randomization. Specifically, the first post-dose time point was determined at which patients achieved a 15% improvement in FEV_1 relative to their pre-dose FEV_1. Comparison of the onset of action between Symbicort MDI and the Oxis Turbuhaler provides the additional benefit of a visual estimation of the PD effects of the formoterol component with the first dose, thus allowing a rough comparison of the pharmaceutic differences between the two.

Figure 30 presents a Kaplan-Meier plot for estimated time to 15% improvement in FEV_1 during the first 60 minutes after dosing. The number and percentage of subjects who had an estimated time to the first 15% improvement in FEV_1 within 3, 9, 15 (the pre-specified time point of comparison), and 60 minutes post-dose, or after 60 minutes, or not at all are shown in Table 91. As expected, neither budesonide nor placebo showed much bronchodilatory effect. Although there was a slight visual advantage for the Oxis TBH in the figure, the percent of patients in the Symbicort MDI, Oxis TBH, and budesonide MDI + formoterol TBH (Oxis TBH) groups who achieved a 15% improvement in FEV_1 within 15 minutes (Symbicort 57%, Oxis 57%, budesonide + Oxis 52%) and within 60 minutes (Symbicort 63%, Oxis 70%, budesonide + Oxis 65%) were substantially similar.

On the last day of treatment, 32% of the Oxis compared to 59% of the Symbicort and 56% of the budesonide + formoterol patients achieved a 15% improvement in FEV_1 within 15 minutes, and 42% of the Oxis compared to 66% of the Symbicort and 64% of the budesonide + formoterol patients achieved a 15% improvement in FEV_1 within 60 minutes. The results reflect a formoterol tachyphylaxis-sparing effect of the budesonide component in Symbicort and in the two drugs given concurrently.

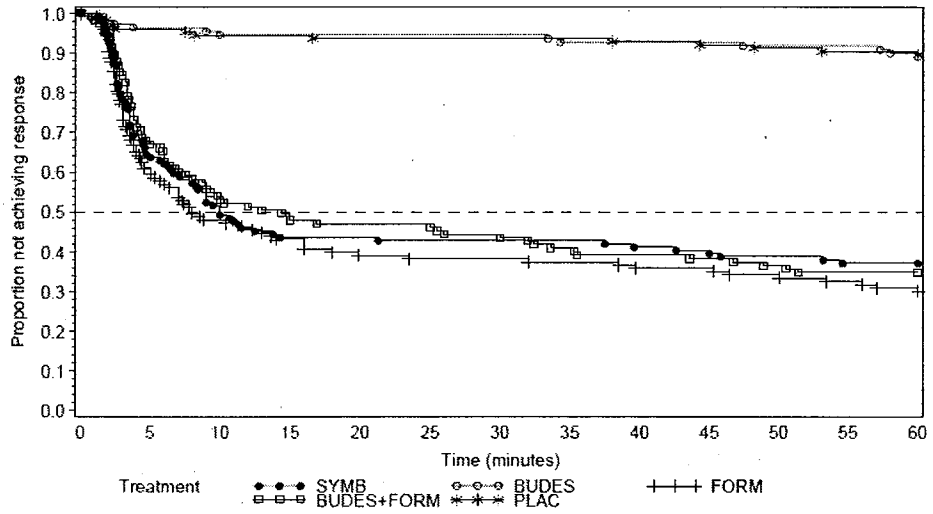


Figure 30. SD-039-0717, Kaplan-Meier plot of time to 15% improvement in FEV_1 during the first 60 minutes after first dose, Day 1 (EAS)

Source: F10 p170; SD-039-0717

Table 91. SD-039-0717, Number (%) of patients achieving 15% improvement in FEV_1 (EAS)

Estimated time to 15% Imp.	Symbicort n=124	Budesonide n=109	Formoterol n=123	BUD + Form n=115	Placebo n=125
Within 3 minutes	27 (21.8)	3 (2.8)	33 (26.8)	18 (15.7)	5 (4.0)
Within 9 minutes	59 (47.6)	5 (4.6)	64 (52.0)	51 (44.3)	7 (5.6)
Within 15 minutes*	**70 (56.5)**	**6 (5.5)**	**70 (56.9)**	**60 (52.2)**	**7 (5.6)**
Within 60 minutes	78 (62.9)	12 (11.0)	86 (69.9)	75 (65.2)	13 (10.4)
Longer than 60 minutes	16 (12.9)	20 (18.3)	10 (8.1)	10 (8.7)	23 (18.4)
Less than 15% improvement	30 (24.2)	77 (70.60)	27 (22.0)	30 (26.1)	89 (71.2)
*The 15-minute time point was pre specified as the primary time point for comparison.					
Source: T40 p171; SD-039-0717					

10.1.3.2.2.2.3 Morning and Evening PEF

Table 92 summarizes the morning and evening PEF parameters. Over the course of the study PEFR measurements declined slightly in placebo patients, remained stable in formoterol patients, increased slightly in budesonide patients, and increased in both the Symbicort and budesonide + formoterol patients. These results are comparable to the pre-dose FEV_1 results, in which patients on Symbicort of the free combination had higher pre-dose FEV_1s than patients on budesonide or formoterol alone, and support the additive effect of the combination in more severe asthmatics..

Table 92. SD-039-0717, Mean Morning and Evening PEF (EAS)

PEFs	N	Baseline	Observed value	Change from baseline
Morning PEF (L/min)				
Symbicort	121	341.3	376.4	35.1
Budesonide	109	342.3	350.3	8.0
Formoterol	118	339.4	341.4	2.0
Budesonide + Formoterol	113	337.6	365.5	27.9
Placebo	124	354.9	341.7	-13.3
Evening PEF (L/min)				
Symbicort	121	351.1	384.6	33.5
Budesonide	109	357.0	362.8	5.7
Formoterol	119	353.6	354.2	0.6
Budesonide + Formoterol	112	347.6	373.9	26.4
Placebo	123	369.4	355.6	-13.8
Source: T53, p192; SD-039-0717				

10.1.3.2.2.2.4 Asthma symptoms

Table 93 summarizes the average daily symptom score (i.e., the average of the daytime and nighttime scores measured on the same day), daytime symptom score, nighttime symptom score, percentage of symptom-free days, and percentage of awakening-free nights. Symbicort and budesonide + formoterol showed a comparable and greater reduction from baseline compared with the individual monoproducts or placebo for all parameters. The study report notes that improvement with Symbicort treatment relative to placebo was seen within 1 day of the first dose. [p197] Budesonide and formoterol had comparable but intermediate results. The results differ from study 716 in milder asthmatics, in which Symbicort and budesonide gave comparable results. These results support the additive effect of the combination in more severe asthmatics.

Table 93. SD-039-0717, Asthma symptom scores (EAS)

Asthma symptom score	N	Baseline	Observed value	Change from baseline
Average daily symptom score (0-3)				
Symbicort	121	0.99	0.71	-0.28
Budesonide	109	1.04	0.91	-0.13
Formoterol	119	1.04	0.92	-0.12
Budesonide + Formoterol	113	1.03	0.74	-0.28
Placebo	124	1.08	1.15	0.07
Daytime symptom score (0-3)				
Symbicort	121	1.04	0.73	-0.31
Budesonide	109	1.13	0.96	-0.17
Formoterol	119	1.10	0.99	-0.12
Budesonide + Formoterol	112	1.11	0.79	-0.32
Placebo	123	1.14	1.19	0.05
Nighttime symptom score (0-3)				
Symbicort	121	0.92	0.68	-0.24
Budesonide	109	0.95	0.85	-0.10
Formoterol	118	0.96	0.86	-0.10
Budesonide + Formoterol	113	0.93	0.70	-0.24
Placebo	124	1.03	1.12	0.09
Symptom free days (% of days)				
Symbicort	121	10.7	30.3	19.6
Budesonide	109	10.3	18.5	8.2
Formoterol	119	10.8	15.7	4.9
Budesonide + Formoterol	113	7.9	26.8	18.9
Placebo	124	6.8	7.9	1.1
Awakening free nights (% of nights)				
Symbicort	121	74.9	87.6	12.6
Budesonide	109	74.5	90.1	15.6
Formoterol	119	76.7	87.5	10.8
Budesonide + Formoterol	113	76.6	90.5	13.8
Placebo	124	71.7	80.3	8.6
Source: T55, p195; SD-039-0717				

10.1.3.2.2.2.5 Rescue medicine use

Table 94 summarizes the parameters of rescue medication use for the different treatment arms. As with asthma symptom scores, both Symbicort and budesonide + formoterol showed a comparable and greater reduction from baseline compared with the individual monoproducts or placebo for all parameters. Budesonide and formoterol had comparable but intermediate results. These results support the additive effect of the combination in more severe asthmatics.

Table 94. SD-039-0717, Rescue medication use (EAS)

Rescue medication use	N	Baseline	Observed value	Change from baseline
Total number of daily inhalations				
Symbicort	121	2.10	1.09	-1.01
Budesonide	109	2.74	2.19	-0.55
Formoterol	119	2.50	1.85	-0.65

Rescue medication use	N	Baseline	Observed value	Change from baseline
Budesonide + Formoterol	113	2.25	0.88	-1.37
Placebo	124	2.44	3.13	0.69
Daytime number of inhalations				
Symbicort	121	1.27	0.66	-0.61
Budesonide	109	1.69	1.38	-0.31
Formoterol	119	1.58	1.18	-0.40
Budesonide + Formoterol	112	1.48	0.61	-0.88
Placebo	123	1.52	1.91	0.40
Nighttime number of inhalations				
Symbicort	121	0.96	0.50	-0.45
Budesonide	109	1.24	0.92	-0.31
Formoterol	118	1.08	0.75	-0.33
Budesonide + Formoterol	113	0.91	0.32	-0.59
Placebo	124	1.10	1.40	0.30
Rescue med-free days (% of days)				
Symbicort	121	38.3	67.9	29.6
Budesonide	109	33.7	44.4	10.6
Formoterol	119	32.7	49.9	17.2
Budesonide + Formoterol	113	33.2	67.8	34.7
Placebo	124	35.5	32.7	-2.8
Source: T57, p199; SD-039-0717				

10.1.3.2.2.2.6 Patient-Reported Outcomes (PROs)

PROs included the standardized Asthma Quality of Life Questionnaire (AQLQ[S]) for patients ≥18 years of age, PAQLQ(S) for patients less than 18 years of age, the MOS Sleep Scale, and the Patient Satisfaction with Asthma (PSAM) Questionnaire. Overall, the results for PROs were similar to those for other secondary endpoints, with comparable results for Symbicort and budesonide + formoterol, a step-down to the monoproducts, and little change for placebo.

AstraZeneca is seeking to place information from the AQLQ[S] in the labeling. AQLQ was performed on the day of randomization, at 2, 6, and 12 weeks, and at the end of treatment. The change in score from baseline to the end of treatment was analyzed for each of the 4 individual domains, scored separately, and the overall score. The AQLQ has previously been clinically validated and correlated to clinically meaningful differences for patients, referred to as "minimally important differences" or MID, and defined as a change in score of ≥0.5 points either within or between treatment groups. AQLQ(S) results are shown in Table 95. Consistent with the withdrawal pattern, patients on placebo and formoterol worsened slightly. The overall score for budesonide was not clinically relevant, nor was the overall score for Symbicort. This differs from study 716, where the overall Symbicort score was both clinically relevant and the 95% confidence intervals excluded the MID of 0.5. Results were similar for individual scores.

AQLQ[S] treatment comparisons for the overall score at the end of treatment are shown in Table 96. The overall score for the comparison of Symbicort to placebo was clinically relevant (0.70) and statistically significant (p-value <0.001), with 95% confidence intervals (0.47, 0.93) did not quite exclude the MID of 0.5. This comparison was made clinically relevant because of the drop in the placebo group in this study, whereas in study 716 the placebo group did not drop and the

comparison was still relevant and significant. In this study neither mono-product comparison to placebo was both clinically relevant and statistically significant.

Table 95. SD-039-0717, AQLQ(S) for patients ≥18 years of age

AQLQ	N	Baseline	End of Treatment			
			Observed value	Change from baseline	From ANCOVA	
					LS mean	95% CI
AQLQ (S) Overall score						
Symbicort	110	5.30	5.71	0.41	0.43	0.25, 0.61
Budesonide	101	5.13	5.35	0.23	0.14	-0.05, 0.32
Formoterol	101	5.18	5.08	-0.10	-0.17	-0.35, 0.02
Budesonide + Formoterol	107	5.24	5.80	0.56	0.53	0.35, 0.71
Placebo	106	5.20	4.98	-0.22	-0.27	-0.45, 0.08
Symptoms						
Symbicort	110	5.13	5.63	0.51	0.50	0.30, 0.70
Budesonide	101	5.00	5.35	0.35	0.24	0.04, 0.44
Formoterol	101	5.03	4.97	-0.06	-0.16	-0.37, 0.04
Budesonide + Formoterol	107	5.13	5.75	0.62	0.61	0.41, 0.81
Placebo	106	5.06	4.92	-0.24	-0.31	-0.51, 0.11
Activity limitation						
Symbicort	110	5.66	5.91	0.25	0.28	0.10, 0.46
Budesonide	101	5.42	5.55	0.12	0.02	0.16, 0.21
Formoterol	102	5.55	5.34	-0.21	-0.25	-0.43, -0.07
Budesonide + Formoterol	107	5.56	6.00	0.44	0.40	0.23, 0.58
Placebo	106	5.53	5.28	-0.25	-0.30	-0.48, 0.12
Emotional function						
Symbicort	110	5.18	5.58	0.40	0.47	0.23, 0.71
Budesonide	101	5.02	5.23	0.21	0.19	-0.06, 0.43
Formoterol	101	4.98	4.85	-0.13	-0.15	-0.40, 0.09
Budesonide + Formoterol	107	5.03	5.66	0.63	0.62	0.38, 0.86
Placebo	106	4.95	4.70	-0.24	-0.29	-0.53, -0.05
Environmental exposure						
Symbicort	110	5.01	5.62	0.61	0.65	0.43, 0.87
Budesonide	101	4.82	5.00	0.18	0.09	-0.13, 0.32
Formoterol	101	4.84	4.95	0.11	0.03	-0.19, 0.26
Budesonide + Formoterol	107	4.96	5.59	0.64	0.60	0.38, 0.82
Placebo	106	5.02	5.00	-0.02	-0.02	-0.24, 0.21
Source: T65, p209; SD-039-0717						

Table 96. SD-039-0717, AQLQ[S] treatment comparisons, overall scores, end of treatment

Comparison	LS mean	95% CI	p-value
AQLQ (S) Overall score			
Symbicort minus Placebo	0.70	0.47, 0.93	<0.001
Budesonide minus Placebo	0.41	0.17, 0.64	<0.001
Formoterol minus Placebo	0.10	0.14, 0.34	0.402
Symbicort minus Budesonide	0.29	0.06, 0.53	0.015
Symbicort minus Formoterol	0.60	0.36, 0.83	<0.001
Symbicort minus Budesonide + Formoterol	-0.10	-0.33, 0.13	0.392
Source: T66, p210; SD-039-0717			

10.1.3.2.3 Pharmacokinetics

Consenting patients underwent plasma sampling over 6 hours post-dosing at Week 2.

Budesonide

Results of adjusted means for budesonide PK parameters for the PK analysis set are shown in Table 97, and plasma-time concentration curves are shown in Figure 31. Results were comparable for the three treatment groups.

At the beginning of the PK section, the study report states that patients who were randomized to budesonide were not tested for formoterol and visa versa, although through a logistical error in the analytical lab some placebo and formoterol samples were tested for budesonide. As a result, 5 patients who received either placebo or formoterol alone had measurable budesonide concentrations for at least one time point. However, the study report notes that "measurable concentrations were very low (<0.10 nmol/L) and often close to the limits of detection." Typically only 1 value was noted; therefore AZ asserts that the concentration pattern was not suggestive of having inhaled budesonide. The actual PK values from these patients are not presented in the study report. [p215]

Table 97. SD-039-0717, Adjusted means for budesonide PK parameters (PK analysis set)

	Symbicort		Budesonide		Budesonide + Formoterol	
	n	LS mean	n	LS mean	n	LS mean
AUC 0-4 (nmol*h/L)	21	3.482	26	3.645	31	3.873
Cmax (nmol/L)	21	1.311	26	1.301	31	1.369
Source: T69, p220; SD-039-0717						

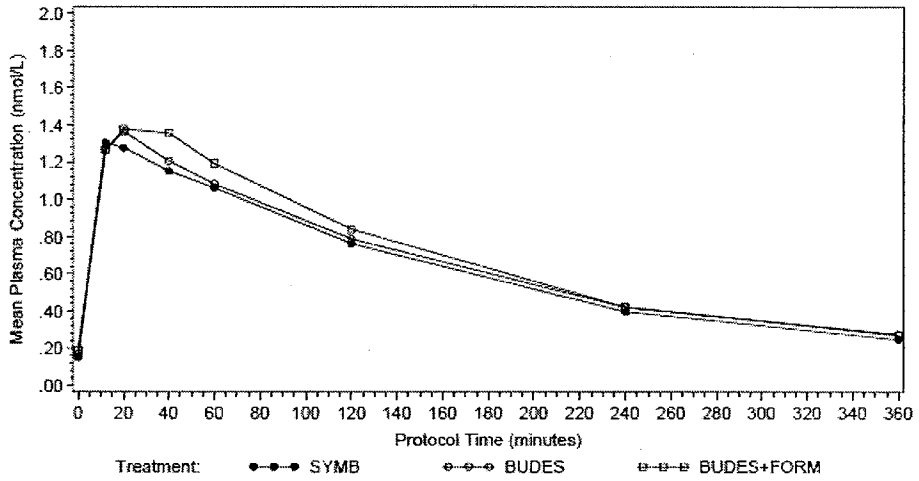


Figure 31. SD-039-0717, Mean budesonide plasma concentrations (PK analysis set)

Two actuations BID: Symbicort 160/4.5, Budesonide HFA MDI 160, Budesonide HFA MDI 160 + Formoterol (Oxis) TBH 4.5

Source: F19, p219; SD-039-0717

Formoterol

Results of adjusted means for formoterol PK parameters for the PK analysis set are shown in Table 98. The report notes that many patients "had plasma concentrations that were low and

relatively unchanged across the sampling interval, which is an unexpected pattern for formoterol plasma concentration-time curves, based on previous results in healthy subjects, where the typical plasma concentration-time profile demonstrates a peak plasma concentration at the first time point postdose followed by a rapid decline in concentration over the first hour postdose." [p221]

Mean plasma concentration-time profiles are shown in Figure 32. The results for Symbicort are generally similar to but flatter than those for the other two groups, lacking the peak in the 20-40 minute post-dose time period shown by both formoterol (Oxis TBH) and formoterol (Oxis TBH) + budesonide. The study report notes that, although it is more apparent in the Symbicort group, the concentration-time profiles are flatter for all three treatment groups than is seen when similar measurements are performed in healthy volunteers. The reason was not able to be explained by the applicant, and is unclear. [p236]

At the beginning of the PK section, the study report states that patients who were randomized to formoterol were not tested for budesonide and visa versa, although through a logistical error in the analytical lab some samples were tested for alternative drug. [p215] Interestingly the study report goes on to state that "formoterol was not detected in the plasma of any subject who received either placebo or budesonide alone." The statement stands alone, and appears to imply that all samples were tested in this manner, whereas the study report made it clear up front that this was not the case. [p221]

Table 98. SD-039-0717, Adjusted means for formoterol PK parameters (PK analysis set)

PK parameter	Symbicort		Formoterol		Budesonide + Formoterol	
	n	LS mean	n	LS mean	n	LS mean
AUC 0-4 (nmol*h/L)	20	76.564	22	77.217	30	80.919
Cmax (nmol/L)	20	19.642	22	21.255	30	24.681
Source: T71, p225; SD-039-0717						

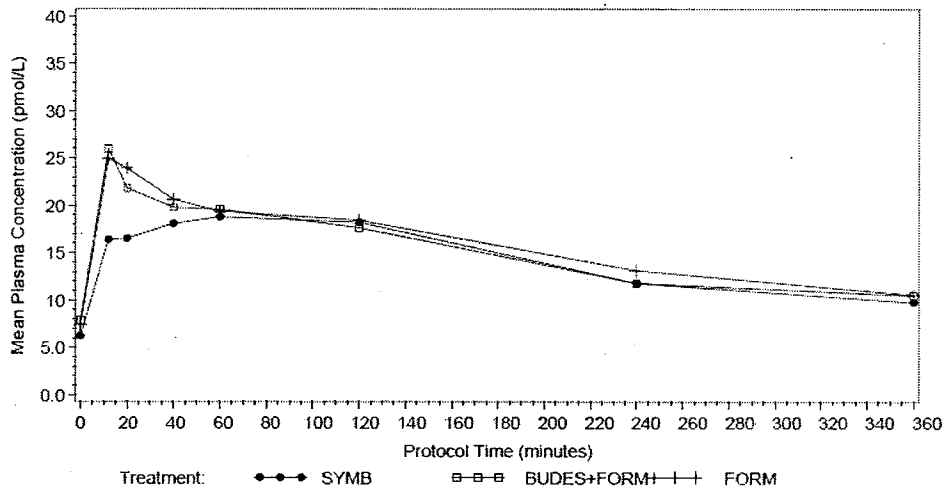


Figure 32. SD-039-0717, Mean formoterol plasma concentrations (PK analysis set)

Two actuations BID: Symbicort 160/4.5, Formoterol TBH 4.5, Budesonide HFA MDI 160 + Formoterol (Oxis) TBH 4.5

Source: F23, p224; F11.2.17.10, p5895; SD-039-0717.pdf

10.1.3.2.4 Safety

Overall, no unexpected or unusual safety trends were revealed during the review of this study.

10.1.3.2.4.1 Exposure

Results for the extent of exposure (Table 99) among treatment groups in this study parallel the results for study discontinuations (Table 78) and withdrawals due to pre-defined asthma events (Table 90) *[Reviewer's Note: The numbers in the tables referred to above do not match up exactly. This is due to the tables being derived from different datasets.]* There were more withdrawals in the placebo and formoterol groups, hence less exposure in these two groups. While the exposure to Symbicort and budesonide dropped off in the last 2 weeks of the study, the exposure to formoterol dropped throughout the study, potentially affecting the outcome measure of pre-dose FEV_1, which was used to evaluate the budesonide component (Symbicort minus formoterol comparison).

Table 99. SD-039-0717, Exposure ITT/SAS

	Symbicort n=124	Budesonide n=109	Formoterol n=123	Bud + Form n=115	Placebo n=125
Run-in (Mean days, SD)	13.0 (4.3)	13.1 (4.7)	12.4 (4.1)	13.0 (4.7)	13.2 (4.9)
Treatment period (Mean days, SD)	73.8 (26.4)	71.4 (27.1)	57.9 (31.6)	74.5 (23.9)	49.4 (33.7)
Treatment Period (n, %)					
At least 2 weeks	116 (93.5)	105 (96.3)	112 (91.1)	110 (95.7)	105 (84.0)
At least 4 weeks	108 (87.1)	93 (85.3)	91 (74.0)	102 (88.7)	74 (59.2)
At least 6 weeks	106 (85.5)	90 (82.6)	77 (62.6)	101 (87.8)	67 (53.6)
At least 8 weeks	102 (82.3)	85 (78.0)	68 (55.3)	98 (85.2)	58 (46.4)
At least 10 weeks	102 (82.3)	83 (76.1)	68 (55.3)	92 (80.0)	56 (44.8)
At least 12 weeks	83 (66.9)	70 (64.2)	57 (46.3)	74 (64.3)	44 (35.2)

Source: T75, p244; and T11.3.1.1.1.1, T11.3.1.2.1.1; SD-039-717.pdf

10.1.3.2.4.2 Adverse events

An overall summary of AEs in this study is shown in Table 100. The overall percentage of patients with at least one adverse event was similar in all active treatment groups, and lower in the placebo group. This pattern was relatively consistent with the duration of exposure for each treatment group except formoterol, which experienced more AEs per day of exposure than the other groups. This imbalance appeared to be driven by more frequent AEs in the high-dose ICS formoterol sub-group (26 out of 37 patients). What is surprising in this group is the fact that only two patients in this sub-group discontinued due to an AE.

There were no deaths and no pregnancies; 9 patients experienced a serious adverse event (SAE) during the treatment period (none in the run-in or post-treatment period): 4 in the Symbicort (2 asthma [E7010010][E7079012]: both met pre-defined asthma event criteria for D/C; 1 URI [E7025006]; 1 ECG T wave inversion [E7037015]), 2 in the formoterol (muscle rupture [E7044012]; angina pectoris [E7115016]), and 3 in the budesonide + formoterol (small intestinal obstruction [E7040002]; abdominal injury [E7061042]; pneumonia [E7116008]) treatment groups. All 4 Symbicort patient and 2 budesonide + formoterol (small intestine obstruction; pneumonia) patients with SAEs were discontinued from treatment. One SAE in the Symbicort

group (ECG T wave inversion one day after starting treatment) was considered by the investigators to be study drug-related.

A total of 30 patients had AEs leading to discontinuation (DAE) during the treatment period; one patient had and AE leading to discontinuation prior to treatment. AEs leading to discontinuation were slightly more frequent in the Symbicort and budesonide + formoterol than in the other treatment groups. None were in patients over 65 years of age.

Table 101 provides a listing of all patients in the safety analysis set who experienced an SAE or were discontinued due to an AE, listed by treatment group. The listing includes the nature and timing of the AE or SAE and some demographic information. Two patients on Symbicort, one on budesonide, three on budesonide + formoterol, and one on placebo were withdrawn due to a cardiac AE. More patients in the formoterol group (4) than the other treatment groups (3 Symbicort, 1 budesonide, 4 formoterol, 1 budesonide + formoterol, 1 placebo) were withdrawn due to worsening asthma.

Adverse events reported during the treatment period, listed by system organ class and sorted by decreasing order of frequency across all treatment groups, are shown in Table 102. No significant trends were identified.

Adverse events reported by ≥3% of patients in any treatment group during the treatment period are shown in Table 103. No significant safety trends were identified, with AEs generally similar across treatment groups except that a higher percentage of patients in the three budesonide-containing groups reported pharyngolaryngeal pain. Four patients in the Symbicort group and three patients in the budesonide + formoterol groups had oral candidiasis. Hoarseness was reported for 3 Symbicort (E7052031, E7105001, E7106002), and 1 formoterol (E7024013), and 2 budesonide + formoterol patients (E7042011, E7044004).

In the individual listings, there were 16 cardiac or cardiac-related AEs: 3 Symbicort (palpitations, E7018009; atrial fibrillation, E7050006; electrocardiogram T wave inversion, E7037015), 2 budesonide (ventricular tachycardia, E7003015; heart rate increased, E7016001), 4 formoterol (palpitations, E7019019; angina pectoris, E7115016; heart rate increased, E7032037; carotid pulse abnormal, E7059006), 5 budesonide + formoterol (ventricular tachycardia, E7014021; bradycardia, E7036018; supra-ventricular tachycardia, E7016008; electrocardiogram T wave inversion, E7106004; ECG signs of myocardial ischemia, E7010004), and 2 placebo patients (ventricular tachycardia, E7003009 [treatment assignment was unblinded for this subject at the time of discontinuation]; cardiac flutter, E7010021). Nine AEs resulted from ECG or Holter findings, with 8 of these patients reporting no concurrent signs or symptoms. The majority of cardiac and cardiac-related AEs occurred during the first 4 weeks of treatment, including 7 of the 9 ECG or Holter monitor AEs. [p249-50]

The overall incidence of AEs was similar for males and females in Symbicort and placebo groups, whereas the incidence was slightly higher for females than males in the budesonide, formoterol, and budesonide + formoterol groups. The incidence of 3 AEs was higher in females than in males: cardiac (females 2.2%, males 0.9%), stomach discomfort (females 4.3%, males 1.3%), and pharyngolaryngeal pain (females 7.1%, males 4.4%). [p252]

The overall incidence of AEs was lower in Black than Caucasian patients both in the Symbicort (50.0% versus 64.3%, respectively) and placebo (35.0% versus 45.5%, respectively) groups, whereas the incidence of AEs was higher in Black than Caucasian subjects in the budesonide

(70.6% versus 54.8%, respectively), formoterol (66.7% versus 63.7%, respectively), and budesonide + formoterol (65.0% versus 62.9%, respectively) groups. There was only 1 SAE reported among black patients (angina pectoris, E7115016). The incidence of asthma AEs was similar between Black and Caucasian subjects.

In patients ≥65, there were 3 cardiac or cardiac-related AEs reported (1 budesonide [heart rate increased, E7016001]; 1 formoterol [angina pectoris, E7115016]; and 1 placebo [cardiac flutter, E7010021]), and 1 SAE (formoterol, E7115016). In patients ≥12 to <16 years of age, there was 1 SAE (budesonide + formoterol, E7116008) which led to discontinuation and 1 DAE (formoterol, E7038002).

Table 100. SD-039-0717, Adverse event overview (ITT/SAS)

AEs (n, %)	Symbicort	Budesonide	Formoterol	Bud + Form	Placebo
All (n)	124	109	123	115	125
Mean duration of exposure (days)	73.8	71.4	57.8	74.5	49.4
Any AE*, n (%)	76 (61.3)	64 (58.7)	77 (62.6)	73 (63.5)	54 (43.2)
SAE	4 (3.2)	0	2 (1.6)	3 (2.6)	0
SAE leading to death	0	0	0	0	0
SAE leading to discontinuation	4 (3.2)	0	0	2 (1.7)	0
Discontinuations due to an AE	8 (6.5)	4 (3.1)	5 (4.1)	9 (7.8)	4 (3.2)
Total number of AEs					
Any AE, n (%)	231	182	226	185	144
SAE	4	0	2	3	0
Other significant AEs	0	0	0	0	0
Mod dose group (n)	91	81	86	82	87
Mean duration of exposure (days)	75.8	70.9	61.7	75.1	53.3
Any AE*, n (%)	56 (61.5)	49 (60.5)	51 (59.3)	52 (63.4)	43 (49.4)
SAE	2 (2.2)	0	1 (1.2)	2 (2.4)	0
SAE leading to death	0	0	0	0	0
SAE leading to discontinuation	2 (2.2)	0	0	1 (1.2)	0
Discontinuations due to an AE	5 (5.5)	3 (3.7)	3 (3.5)	8 (9.8)	3 (3.4)
High dose group (n)	33	28	37	33	38
Mean duration of exposure (days)	68.2	72.9	49.1	73.1	40.3
Any AE*, n (%)	20 (60.6)	15 (53.6)	26 (70.3)	21 (63.6)	11 (28.9)
SAE	2 (6.1)	0	1 (2.7)	1 (3.0)	0
SAE leading to death	0	0	0	0	0
SAE leading to discontinuation	2 (6.1)	0	0	1 (3.0)	0
Discontinuations due to an AE	3 (9.1)	1 (3.6)	2 (5.4)	1 (3.0)	1 (2.6)

Source: T76, p246; and T11.3.2.1.4 p5996-8; SD-039-717.pdf

Table 101. SD-039-0717, Listing of SAEs and DAEs during all study phases* (SAS)

Identifier	DAE	Age	Sex	Race	AE Onset	SAE	DAE
Symbicort							
E7010010	Asthma exacerbation	33	F	C	74	Yes	Yes
E7012010	Asthma exacerbation	47	M	B	6		Yes
E7025006	Upper respiratory infection	18	M	C	79	Yes	Yes
E7026022	Bronchitis	35	F	C	66		Yes
E7037015	New T-wave inversion, v5, v6	50	M	C	1	Yes	Yes
E705006	Atrial fibrillation	41	F	C	43		Yes
E7052031	Left ankle throbbing	54	F	C	15		Yes

Identifier	DAE	Age	Sex	Race	AE Onset	SAE	DAE
	Right knee pain						
	Hoarseness				16		
E7079012	Asthma exacerbation	53	F	C	23	Yes	Yes
Budesonide							
E7003015	Ventricular tachycardia (8-beat run)	62	F	C	14		Yes
E7030018	Increased SAR symptoms	40	M	B	12		Yes
E7041023	Asthma exacerbation	40	M	B	3		Yes
E7060008	Abdominal bloating Increased appetite	38	M	C	36		Yes
Formoterol							
E7028003	Asthma exacerbation	39	F	B	12		Yes
E7038002	Asthma exacerbation	12	M	C	28		Yes
E7040004	Asthma exacerbation	51	M	Other	17		Yes
E7050010	Bilateral wheeze	36	M	O	84		Yes
E7060004	Sinusitis	49	F	C	6		Yes
E7073005	Asthma exacerbation	49	F	C	Prior		Yes
Budesonide + Formoterol							
E7003014	Pharyngitis	28	M	Other	38		Yes
E7010004	Ischemia on ECG	59	F	C	15		Yes
E7016008	Supraventricular tachycardia	43	F	C	15		Yes
E7019021	Bilateral arm, hand joint pain	40	F	Other	28		Yes
E7040002	Small bowel obstruction	60	F	C	21	Yes	Yes
	Insomnia				23		
	Heartburn				24		
E7088005	Dry cough	37	M	B	3		Yes
E7106004	Worsening T-wave inversion	60	F	C	43		Yes
E7114003	Eczema exacerbation	42	F	C	5		Yes
E7116008	Pneumonia	15	F	C	55	Yes	Yes
Placebo							
E7003009	Ventricular tachycardia (5-beat run)	20	F	C	13		Yes
E7011001	Upper respiratory infection	52	F	C	13		Yes
	Bronchitis				20		
E7036026	Sinusitis	57	M	C	80		Yes
E7037019	Asthma exacerbation	35	M	C	6		Yes

* There were no events in the run-in or post-treatment periods. Onset day is not the same as day of withdrawal.
C = Caucasian, B = Black, O = Oriental, Other = Other
Source: T11.3.5.2.1, p 7866-97; SD-039-0717.pdf

Table 102. SD-039-0717, Summary of system organ class (SOC) categories with at least 1 AE reported during the treatment period, sorted by decreasing order of frequency across all treatment groups (ITT/SAS)

AEs by SOC	Symbicort n=124	Budesonide n=109	Formoterol n=123	Bud + Form n=115	Placebo n=125
Mean duration of exposure (days)	73.8	71.4	57.9	74.5	49.4
Number of patients with any AE	76 (61.3)	64 (58.7)	77 (62.6)	73 (63.5)	54 (43.2)
Infections and infestations	44 (35.5)	28 (25.7)	33 (26.8)	39 (33.9)	30 (24.0)
Respiratory, thoracic and mediastinal	26 (21.0)	20 (18.3)	28 (22.8)	20 (17.4)	19 (15.2)
Nervous system	19 (15.3)	19 (17.4)	18 (14.6)	15 (13.0)	13 (10.4)
Gastrointestinal	21 (16.1)	14 (12.8)	15 (12.2)	14 (12.2)	13 (10.4)
Musculoskeletal and connective	8 (6.5)	8 (7.3)	9 (7.3)	9 (7.8)	6 (4.8)

AEs by SOC	Symbicort n=124	Budesonide n=109	Formoterol n=123	Bud + Form n=115	Placebo n=125
tissue					
General disorders & administration site conditions	10 (8.1)	7 (6.4)	10 (8.1)	6 (5.2)	5 (4.0)
Injury, poisoning & procedural complications	6 (4.8)	5 (4.6)	7 (5.7)	5 (4.3)	3 (2.4)
Skin and subcutaneous tissue	2 (1.8)	5 (4.6)	4 (3.3)	3 (2.6)	1 (0.8)
Psychiatric	4 (3.2)	0	5 (4.1)	3 (2.6)	0
Cardiac	2 (1.8)	1 (0.9)	2 (1.6)	3 (2.6)	2 (1.6)
Eye	0	4 (3.7)	3 (2.4)	1 (0.9)	1 (0.8)
Investigations	1 (0.9)	1 (0.9)	3 (2.4)	2 (1.8)	1 (0.8)
Ear and labyrinth	1 (0.9)	1 (0.9)	0	3 (2.6)	2 (1.6)
Reproductive system and breast	1 (0.9)	1 (0.9)	2 (1.6)	2 (1.8)	0
Immune system	0	2 (1.8)	1 (0.8)	1 (0.9)	1 (0.8
Metabolism and nutrition	0	2 (1.8)	2 (1.6)	0	0
Vascular	1 (0.9)	1 (0.9)	0	1 (0.9)	0
Blood and lymphatic system	1 (0.9)	0	0	1 (0.9)	0
Neoplasms benign, malignant & unspecified (incl. cysts & polyps)	0	1 (0.9)	0	1 (0.9)	0
Surgical and medical procedures	0	0	0	1 (0.9)	0

Source: T77, p248; SD-039-0717.pdf

Table 103. SD-039-0717, Adverse events reported by at least 3% of patients in any treatment group during the treatment period (ITT/SAS)

AEs by Preferred Term	Symbicort n=123	Budesonide n=109	Formoterol n=123	Bud + Form n=115	Placebo n=125
Mean duration of exposure (days)	73.8	71.4	57.9	74.5	49.4
Number of patients with any AE	76 (61.3)	64 (58.7)	77 (62.6)	73 (63.5)	54 (43.2)
Headache	14 (11.3)	14 (12.8)	13 (10.6)	11 (9.6)	10 (8.0)
Upper respiratory tract infection	13 (10.5)	10 (9.2)	10 (8.1)	10 (8.7)	14 (11.2)
Nasopharyngitis	12 (9.7)	12 (11.0)	8 (6.5)	9 (7.8)	9 (7.2)
Pharyngolaryngeal pain	11 (8.8)	8 (7.3)	4 (3.3)	10 (8.7)	3 (2.4)
Sinusitis	6 (4.8)	3 (2.8)	9 (7.3)	6 (5.2)	5 (4.0)
Cough	3 (2.4)	3 (2.8)	8 (6.5)	8 (7.0)	4 (3.2)
Stomach discomfort	8 (6.5)	5 (4.6)	3 (2.4)	1 (0.9)	2 (1.5)
Asthma	3 (2.4)	3 (2.8)	4 (3.3)	0	4 (3.2)
Vomiting	4 (3.2)	3 (2.8)	3 (2.4)	1 (0.9)	3 (2.4)
Diarrhea	3 (2.4)	3 (2.8)	4 (3.3)	1 (0.9)	2 (1.5)
Pyrexia	3 (2.4)	2 (1.8)	1 (0.8)	4 (3.5)	3 (2.4)
Back pain	2 (1.6)	6 (5.5)	2 (1.6)	1 (0.9)	0
Chest discomfort	1 (0.8)	2 (1.8)	5 (4.1)	1 (0.9)	1 (0.8)
Influenza	3 (2.4)	1 (0.9)	4 (3.3)	2 (1.7)	0
Nasal congestion	4 (3.2)	4 (3.7)	1 (0.8)	1 (0.9)	0
Nausea	3 (2.4)	1 (0.9)	5 (4.1)	0	1 (0.8)
Oral candidiasis	4 (3.2)	0	0	3 (2.6)	0

Source: T78, p251; SD-039-0717.pdf

10.1.3.2.4.3 Clinical labs

Clinical lab results reviewed included those for hematology, clinical chemistry, glucose, and potassium. Within each set of laboratory parameters, results were considered by change in mean values over time, changes by individual patient (shift tables), and individual clinically important abnormalities.

For clinical laboratory values, other than expected changes based on pharmacologic effects of ICS and beta-agonists, there were no significant or clinically meaningful findings. Two patients from the Symbicort treatment group (E7106002 and E7090011) had [AE reports of] anemia with the lowest hemoglobin level of 111 and 85 g/L, respectively. An additional two patients from the Symbicort treatment group (E7005018 and E7026003) had anemia not reported as an AE, with a decrease from baseline of 116 to 81g/L and 109 to 95 g/L, respectively.

There were small increases from baseline in mean serum glucose, but patients were not fasting for sampling so the results are difficult to interpret. Results were similar among treatment groups. One patient from the formoterol treatment group had an AE of insulin-dependent diabetes, but no serum glucose levels above 9.0 g/L were reported.

There were small decreases from baseline in mean serum potassium in all but the placebo treatment group. While the study report notes that there were no cardiac or potassium-related AE reported for any patients with high or low potassium values and no Holter findings related to low or high potassium values during treatment, it also notes that one patient (E7113002) on budesonide had [an AE report of] asymptomatic hypokalemia at Week 2 (3.1 mmol/L) [concurrent ECG findings not reported], and one patient (E7018007) on Symbicort had increased inferior T wave abnormalities on ECG at Week 2 associated with a potassium level of 3.2 mmol/L. [p267]

10.1.3.2.4.4 ECG, Holter monitor, vital signs, physical findings

Safety evaluations included ECG (pre-dose Visit 1 as baseline and 1 to 2 hours post-dose at treatment visits, and read by an independent central cardiologist), 24-hour Holter monitor (in a subset of 213 patients at run in and at 2 weeks), vital signs (including systolic and diastolic blood pressures, pulse rate, height, and weight), and physical examinations. Just as for laboratory parameters, results were considered by change in mean values over time, changes by individual patient (shift tables), and individual clinically important abnormalities.

Results for HR, QT (uncorrected), QTcB (Bazett), QTcF (Fridericia) showed minimal differences between treatments, and no clinically relevant differences between treatment groups. A total of 36 patients had a QT, QTcB, or QTcF of ≥450 msec or a change from baseline of ≥60msec at least once during the study: 8 Symbicort, 9 budesonide, 4 formoterol, 9 budesonide + formoterol, and 6 placebo. No patients had values ≥500 msec. Overall ECG evaluations (characterized as normal, borderline, or abnormal) did not necessarily correlate with QT or QTc findings. In the Symbicort group, 3 patients had a QT/QTc of ≥450 msec, of whom 1 had a QT/QTc change of ≥60 msec (E7026022), but not on the same ECG. In the budesonide group, 6 patients had a QT/QTc of ≥450 msec, of whom 2 (E7014041 and E7098009) had a QT/QTc change of ≥60 msec. In the formoterol group, no patients had a QT/QTc of ≥450 msec. In the budesonide + formoterol group, 3 patients had a QT/QTc of ≥450 msec, none of whom had a QT/QTc change of ≥ 60msec. In the placebo group, 1 patient had a QT/QTc of ≥450 msec, but

did not have a QT/QTc change of ≥60 msec. The remaining 19 patients had a change in QT/QTc ≥60 msec but no QT/QTc value ≥450 msec (5 Symbicort, 3 budesonide, 4 formoterol, 6 budesonide + formoterol, 5 placebo). [p279, T93, p 281-4]

Results of Holter examinations were available from 213 patients, of whom 177 had an on-treatment reading of at least 16 hours duration. Evaluations included average heart rate, minimum heart rate, sinus pause, ventricular ectopic beats, ventricular runs (≥3 ectopic beats), supraventricular ectopic beats, and overall assessments. The results did not reveal any significant or unusual safety trends. Eight patients had heart rate abnormalities on Holter: 1 Symbicort, 3 formoterol, and 1 placebo patient had a shift in average heart rate from normal to high (>100 bpm), and 1 budesonide plus 2 placebo patients had high baseline heart rates that remained high. Nine patients developed ≥50 ventricular ectopic beats: 2 Symbicort, 2 budesonide, 2 formoterol, 2 budesonide + formoterol, 1 placebo. Ten developed ≥50 supraventricular ectopic beats: 1 Symbicort, 1 budesonide, 1 formoterol, 5 budesonide + formoterol, 2 placebo. The study report states that 4 patients were withdrawn due to having met protocol-specific Holter withdrawal criteria (2 budesonide, 1 budesonide + formoterol, and 1 placebo), although only 3 were reported as DAEs and 1 (budesonide, E7039012) was identified after the study was unblinded. One patient remained in the study following cardiologist evaluation despite having met Holter withdrawal criteria (1 budesonide + formoterol, E7014021). Six patients did not meet withdrawal criteria but had clinically notable findings (1 budesonide, 2 formoterol, 2 budesonide + formoterol, 1 placebo). [p295-9]

There were no unusual findings for vital signs, including systolic and diastolic blood pressure, pulse rate, height, or weight. Not surprisingly, a higher percentage of patients in the formoterol (33 [26.8%]) and placebo groups (36 [28.8%]) had lung abnormalities reported on physical examination at the end of treatment compared to Symbicort (11 [8.9%]), budesonide + formoterol (13 [11.3%]), and budesonide (14 [12.8%]). [T11.3.10.1.1, p10232-3]

10.1.3.3 Summary and Conclusions

Study SD-039-0717 was a randomized, double-blind, double-dummy, placebo-controlled 12-week study comparing the efficacy and safety of Symbicort MDI (160/4.5 mcg dosage strength) with its pharmacologic monoproducts, budesonide MDI (160 mcg) and formoterol (Oxis) Turbuhaler, the free combination of monoproducts, and placebo, each administered as 2 inhalations BID, in 596 adolescents and adults ≥12 years of age with moderate-to-severe asthma (FEV_1 on moderate to high dose ICS therapy 45% to 80% predicted). Randomization was stratified by previous ICS treatment. The study comprised a screening visit, a 14 (±7) day single-blind budesonide (80 mcg, 2 inhalations BID) run-in period, and a 12-week double-blind treatment period. The study population was approximately 78% Caucasian, 16% Black, 38% male, and 62% female. The mean age was 41 years (range 12 to 87 years), with 37 patients ≥65 years of age and 37 below 16 years of age. The average length of asthma history was 23 years. At screening, 427 (71.6%) were on moderate doses of ICS and 169 (28.4%) were on high doses; the mean pre-dose FEV_1 was 2.2 L, and mean percent reversibility was 22.2% (range -0.4% to 97.7%). At baseline, the mean percent predicted FEV_1 for most patients was in the moderate range (68.1 % predicted) while being treated with an average ICS dose of 590 mcg daily (range 160 to 1600 mcg a day). Based on the ICS dose strata, 71.6% of patients (427) were considered to have moderate asthma and 28.4% of patients (169) were considered to have severe asthma.

Safety assessments included the incidence of adverse events (AEs), serious adverse events (SAEs), discontinuations due to adverse events, and results of laboratory testing, 12-lead electrocardiograms (ECG), 24-hour Holter monitoring, physical examinations, and vital signs. The study included a set of pre-defined criteria for withdrawal of patients due to an asthma event. Events that mandated withdrawal included: a decrease in morning pre-dose FEV_1 of ≥20% from the pre-dose FEV_1 at randomization, or a decrease to <40% predicted; use of ≥12 actuations of albuterol/day on 3 or more days within 7 consecutive days; a decrease in morning PEF of ≥20% from baseline (mean of 7 days prior to randomization) on 3 or more days within 7 consecutive days; a clinical exacerbation requiring emergency treatment, hospitalization, or use of asthma medication not allowed by the protocol. The following event allowed an investigator to determine whether the patients should remain in the trial: 2 or more nights with awakening due to asthma, which required rescue medication use within 7 consecutive days. Events meeting any of these criteria were to be recorded on the asthma exacerbation (ASTEXAC) CRF.

Because Symbicort contains two asthma medications, co-primary efficacy variables were used to demonstrate the contribution of each of the individual components, budesonide or formoterol, to the efficacy of the combination drug product. The co-primary efficacy variables were: baseline-adjusted average 12-hour FEV_1 and pre-dose FEV_1. **Baseline-adjusted average 12-hour FEV_1 averaged over the study** was used to demonstrate the bronchodilator effect of the long-acting beta-agonist (formoterol) component (comparison: Symbicort minus budesonide). **Pre-dose FEV_1 at 2 weeks** was used to demonstrate the stabilizing, anti-inflammatory effect of the corticosteroid (budesonide) component (comparison: Symbicort minus formoterol). Secondary efficacy variables included: pre-defined asthma events and withdrawals due to pre-defined asthma events; other spirometry-related variables (2-hour post-dose FEV_1, maximum FEV_1, onset of effect [15% improvement in FEV_1 from baseline on Visit 2], time to onset of effect; diary variables (morning and evening PEF, nighttime and daytime asthma symptom scores, nighttime awakenings, rescue medication use; and patient reported outcomes including AQLQ and an Onset of Effect Questionnaire.

Originally, the study had declared **withdrawals due to a pre-defined asthma event** as a co-primary variable for evaluation of the corticosteroid component. During the course of the study, this variable was demoted to a secondary efficacy variable and pre-dose FEV_1 elevated, because investigators were confused about whether patients who met withdrawal criteria due to the pre-defined asthma events were required to be withdrawn from the study or whether they could continue at the investigator's discretion; some patients who met withdrawal criteria were not discontinued because investigators judged them clinically stable. This was a major review issue.

The study population was relatively balanced across treatment groups at baseline. Baseline mean percent predicted FEV_1 was 68.1%. The safety evaluation revealed no unexpected or unusual safety trends.

Symbicort showed statistical superiority over its monoproducts for each of the co-primary efficacy endpoints, FEV_1 0-12 hours for the formoterol component and pre-dose FEV_1 for the corticosteroid component. Symbicort and each of the mono-component products showed statistical superiority over placebo, providing internal validity to the studies and supporting the primary comparisons of Symbicort to its respective mono-components.

Secondary variables generally favored Symbicort and each mono-component in comparison to placebo; the results thereby provided support for the internal validity of the study findings.

Secondary variables also generally favored Symbicort in comparison to each mono-component, depending upon the endpoint (as discussed below); the results thereby provided support for the primary efficacy outcome analyses. For this study in moderate to severe asthmatics, the expected corticosteroid effects of budesonide, namely as an anti-inflammatory controller medication, were seen. These were expressed in endpoints such as the key secondary endpoint of pre-specified asthma events [regardless of methodology], which combined many clinically meaningful endpoints such as drops in FEV_1 and PEF, asthma exacerbations, etc., as well as in most diary and PRO endpoints, including asthma symptom scores, rescue medication use, and PROs. Likewise, the expected beta-agonist effects of formoterol, namely as a bronchodilator that exerts effects for about 12 hours, were also seen. This was noted in spirometric endpoints, including onset of action, maximal FEV_1 etc.

In addition, any potential added or negative benefit of the combination was considered. In addition to the expected corticosteroid controller results, the addition of budesonide to formoterol appeared to prevent [or delay for the period of the study] the phenomenon of tachyphylaxis with continuous beta-agonist use. In addition to the expected LABA bronchodilator benefits, in this population the addition of formoterol to budesonide did appear to have an effect beyond either of the two monoproduct arms with regard to multiple secondary endpoints including key factors in asthma control such as frequency and severity of exacerbations, time to exacerbations, rescue medication use, etc.

It should be noted that the Symbicort results in this study differ from the results found in study **716** in mild to moderate asthmatics. Except for AM and PM PEFR and the prevention [or delay] of tachyphylaxis, in the milder study population there was little if any additive effect for the combination in comparison to the monoproducts for their respective expected endpoint results.

In summary, this study supports the efficacy of Symbicort. It also lends support to the rationale of the addition of a LABA to ICS in a moderate to severe asthmatic population.

10.1.4 Study SD-039-0726. A 12-week, safety and efficacy study evaluating Symbicort (80/4.5 mcg) 2 puffs once daily as maintenance therapy in asthmatics ≥16 years of age previously stable on Symbicort 80/4.5 mcg, 2 actuations BID

this secondary study was reviewed because it provides some evidence of dose replication for the Symbicort 80/4.5 dosage strength BID program.

Protocol #:	SD-039-0726
Title:	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
Study Dates:	April 4, 2003 to June 22, 2004
Sites:	151 centers in the US. A subset of 56 study centers performed serial spirometry.
Ethics and	Performed in accordance with the ethical principles outlined in the

IRBs: Declaration of Helsinki and consistent with ICH/Good Clinical Practices. IRBs were local to study centers.

Source: M5, SD-039-0726.pdf

10.1.4.1 Protocol

This was a 12-week, multicenter, randomized, double-blind, double-dummy, placebo and active-controlled, Phase 3 study to investigate the efficacy, health-related quality of life, and safety of Symbicort once daily as maintenance therapy in asthmatics ≥16 years of age previously stable on Symbicort 80/4.5 mcg, 2 actuations BID. \ one of the secondary objectives was to demonstrate the efficacy of Symbicort 80/4.5 mcg, 2 actuations BID, compared to placebo. At screening, patients had to have an FEV_1 between 60-90% of predicted off short-acting beta agonists for at least 6 hours and reversibility of ≥12% and ≥0.20L from baseline within 15-30 minutes after beta-agonist treatment.

The studies employed a study design of randomization following a 4- to 5-week single-blind run-in period with Symbicort 80/4.5 mcg, 2 actuations BID, to assure clinical stability. Those patients who had stable asthma symptoms during the run-in period and who met the other inclusion/exclusion criteria were then randomized to 12 weeks of double-blind treatment with 1 of the following treatments: (1) Symbicort 160/4.5 mcg, 2 actuations QD, (2) Symbicort 80/4.5 mcg, 2 actuations QD (3) **Symbicort 80/4.5 mcg, 2 actuations BID** [Batches: P65401A during run-in, and P6503 during study], (4) budesonide pMDI 160 mcg, 2 actuations QD or (5) **Placebo pMDI**. Patients were then followed to see if they maintained, improved, or lost stability. Albuterol MDI was used as a rescue medication prn.

The primary variable was evening PEF from a daily electronic diary , with the primary comparison between Symbicort 160/4.5 mcg, 2 actuations QD, sequentially compared to placebo and to budesonide 160 mcg, 2 actuations QD. Secondary variables included morning and evening pre-dose FEV_1 and several other spirometry measures including FEV_1 0-12h in a subset of patients, other electronic diary variables (AM PEF, nighttime awakenings due to asthma, rescue medication use), predefined asthma events and withdrawals due to predefined asthma events, global assessments, and PROs. Safety was monitored by adverse events, laboratory results, 12-lead ECG, 24-hour Holder, 24-hour urinary cortisol, vital signs, and physical examinations.

10.1.4.2 Results

10.1.4.2.1 Disposition, Demographics, Analysis Sets, and Baseline Characteristics

The study entered 1200 patients into the run-in period, and randomized 752 patients at 141 centers (45 centers performing spirometry), 490 (65.2%) women, 261 (34.8%) men, 603 (80.3%) Caucasian, 74 (9.9%) Black, 13 (1.7%) Oriental, 61 (8.1%) Other, with a mean age of 38 years (range 16-79, 14 (1.9%) ≥65 years), and a history of asthma for approximately 20 years. The mean FEV_1 was 75.3% predicted at screening (with 20.4 % reversibility) and 85.5% predicted at randomization (i.e. post-run-in). Treatment groups were relatively similar in baseline

characteristics, including FEV_1, other pulmonary function measurements, and symptom scores. [p110-3, 123-4]

In this study, the overall criteria for withdrawal due to predefined asthma events were substantially similar to those declared in the two pivotal studies (716 and 717), but differed slightly in application. During the randomized treatment period, patients who met any of the following 6 criteria were to be withdrawn: [p71]

- Decrease in pre-dose FEV_1 to <50% of predicted normal value.
- Decrease in morning PEF >35% from baseline (defined as the mean of all morning PEF values from the 10 day period immediately prior to randomization) on 3 or more days within any period of 7 consecutive days.
- The use of ≥12 actuations of albuterol per day on 3 or more days within any period of 7 consecutive days
- Five or more nights with an awakening due to asthma which required the use of rescue medication within any period of 7 consecutive days
- Symptom score (combined daytime and nighttime scores) of greater than 15 summed over any period of 3 consecutive days
- Clinical exacerbation requiring emergency treatment, hospitalization or asthma medication not allowed by the protocol.

Of those randomized, 589 patients (78.3%) completed the study. Discontinuations included 163 patients: 14 did not fulfill entry criteria, 94 met study-specific discontinuation criteria (i.e. withdrawals due to predefined asthma events, defined above), 21 had an adverse event, 19 were not willing to continue, 5 lost to follow-up, 10 other reasons. Of the discontinuations, only the discontinuation criterion of predefined asthma events was imbalanced among treatment groups, with 4 (2.6%), 10 (6.8%), 7 (4.6%), 18 (12.4%), and 55 (35.9%) patients withdrawing from the Symbicort 80 BID, 160 QD, 80 QD, budesonide 160 QD, and placebo BID arms, respectively.

Most protocol deviations were minor, and were judged not to affect the outcome of the study (I concur). The safety analysis set included 751 patients (1 patient who was randomized did not receive treatment, and was excluded from all analyses). The efficacy analysis set (n=745) excluded 6 patients who had "insufficient efficacy data." The per-protocol analysis set (n=699) excluded 46 patients from the efficacy subset who did not meet FEV_1 criteria (3), had medication unacceptable % FEV_1 reversibility (1), were not treated with consistent ICS at entry (27), were not treated with ICS at entry (2), used a disallowed medication during run-in (7), did not meet pre-dose FEV_1 criteria at randomization (9), or had the blind broken during the study (1). The serial spirometry set included 189 patients, 40, 38, 41, 39, 31 in the Symbicort 80 BID, 160 QD, 80 QD, budesonide 160 QD, and placebo BID arms, respectively. [p119-20]

Compliance with study medication was similar among treatment groups. [p125-7]

10.1.4.2.2 Efficacy

Treatment means for primary variable of evening PEF at the primary endpoint and the secondary variables at endpoint for evening PEF, evening FEV_1, and morning FEV_1 are shown in Table 104. For the primary variable of evening PEF, the comparison of Symbicort 80/4.5, 2 actuations BID to placebo was significant at $p < 0.001$. Although not an entirely fair comparison, the same

was true for comparisons of BID dosing to any of the daily Symbicort or budesonide dosing regimens. For the secondary variables of evening and morning FEV_1, the comparison of Symbicort 80/4.5, 2 actuations BID to placebo were significant at $p < 0.001$.

All patients randomized to Symbicort 80/4.5, 2 actuations BID had been on the same medication and dose during the single-blind run-in period. As expected, these patients maintained the gain in pulmonary function parameters seen during the run-in period, whereas patients on placebo or daily treatment regimens began to lose stability. Loss of stability appeared to dose-order, as shown most clearly in Figure 33, which shows the mean change from baseline in evening PEF by study day (EAS, LOCF). This dose-ordering was found across all primary and secondary variables, and is seen in Table 105, which shows the number and percentage of patients with a CRF predefined asthma event.

The mean percent change from baseline in serial FEV_1 over 0-12 hours at Week 2 is shown in Figure 34. Again, serial FEV_1 appeared to dose-order, with secondary dose-ordering for patients not on formoterol.

Table 104. SD-039-0726, Treatment Means, Evening & Morning PEF, Evening & Morning FEV_1 (EAS)

	N	Baseline	Observed value	Change from baseline
Evening PEF (L/min)				
Symbicort 80/4.5, BID	152	442	443	1
Symbicort 160/4.5, QD	147	422	408	-14
Symbicort 80/4.5, QD	152	413	399	-14
Budesonide 160, QD	144	415	383	-34
Placebo	150	414	375	-39
Morning PEF (L/min)				
Symbicort 80/4.5, BID	152	436	437	1
Symbicort 160/4.5, QD	147	415	411	-4
Symbicort 80/4.5, QD	152	408	402	-6
Budesonide 160, QD	144	406	376	-30
Placebo	150	409	365	-43
Evening pre-dose FEV_1 (L)				
Symbicort 80/4.5, BID	138	3.05	3.05	0
Symbicort 160/4.5, QD	133	2.91	2.82	-0.09
Symbicort 80/4.5, QD	143	2.81	2.70	-0.11
Budesonide 160, QD	130	2.91	2.77	-0.15
Placebo	116	2.97	2.68	-0.28
Morning pre-dose FEV_1 (L)				
Symbicort 80/4.5, BID	143	3.03	2.98	-0.04
Symbicort 160/4.5, QD	141	2.89	2.82	-0.07
Symbicort 80/4.5, QD	143	2.79	2.73	-0.06
Budesonide 160, QD	137	2.88	2.68	-0.20
Placebo	131	2.91	2.60	-0.31
Source: T24, p137; T28, p142; T34, p147; T40, p155; SD-039-0726				

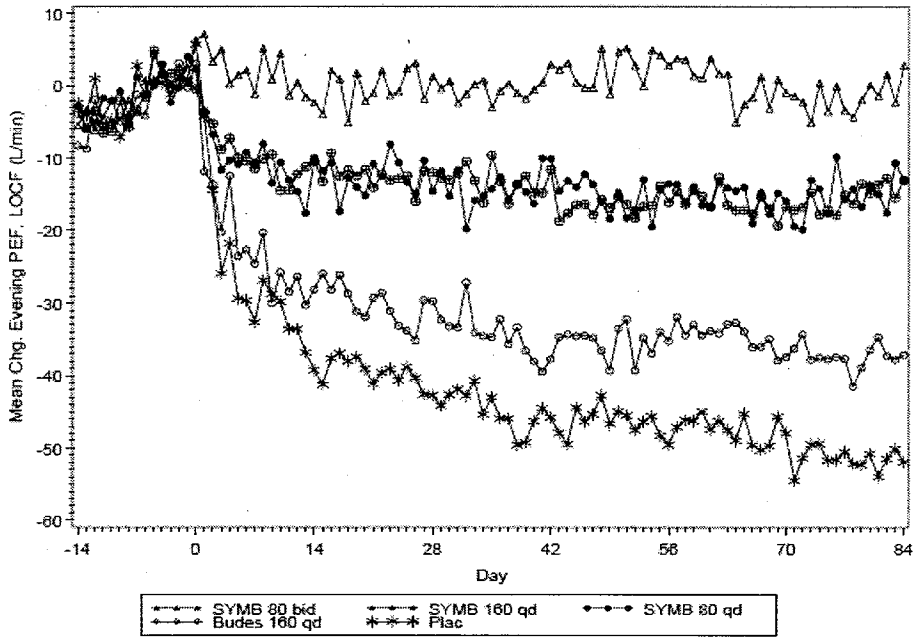


Figure 33. SD-039-0726, Evening PEF, Mean change from baseline by study day (EAS, LOCF)

Source: F4, p139; SD-039-0726

Table 105. SD-039-0726, Number and percentage of patients with a CRF pre-defined asthma event (EAS)

Criteria	Treatment group, n (%)					
	Symb 80 BID	Symb 160 QD	Symb 80 QD	Bud 160 QD	Placebo	Total
EAS population (All)	152	147	152	144	150	745
Pre-defined asthma event	5 (3.3)	10 (6.8)	8 (5.3)	18 (12.5)	55 (36.7)	96 (12.9)
Time to event (Mean days)	47.8	51.1	30.4	38.8	33.3	36.7
Criterion 1: Decrease in FEV_1	1 (0.7)	0	1 (0.7)	1 (0.7)	6 (4.0)	9 (1.2)
Criterion 2: Decrease in AM PEF	2 (1.3)		2 (1.3)	8 (5.6)	15 (10.0)	33 (4.4)
Criterion 3: Rescue medication	0	2 (1.4)	0	0	6 (4.0)	8 (1.1)
Criterion 4: Nighttime awakening	1 (0.7)	0	0	6 (4.2)	19 (12.7)	26 (3.5)
Criterion 5: Symptom score	0	0	0	1 (0.7)	2 (1.3)	3 (0.4)
Criterion 5: Clinical exacerbation:	1 (0.7)	2 (1.4)	5 (3.3)	2 (1.4)	12 (8.0)	22 (3.0)
ER treatment	0	0	0	0	2 (1.3)	2 (0.3)
Hospitalization	0	0	0	0	0	0
Disallowed asthma medication:	1 (0.7)	2 (1.4)	5 (3.3)	2 (1.4)	12 (8.0)	22 (3.0)
• Nebulized bronchodilator	1 (0.7)	1 (0.7)	1 (0.7)	0	8 (5.3)	11 (1.5)
• Steroid	1 (0.7)	1 (0.7)	4 (2.6)	2 (1.4)	9 (6.0)	17 (2.3)
• Other	0	1 (0.7)	2 (1.3)		4 (2.7)	7 (0.9)
Data derived from ASTEXAC in CRF						
Source: T48, p170; T11.2.3.1.1, p1663-4; SD-039-0726						

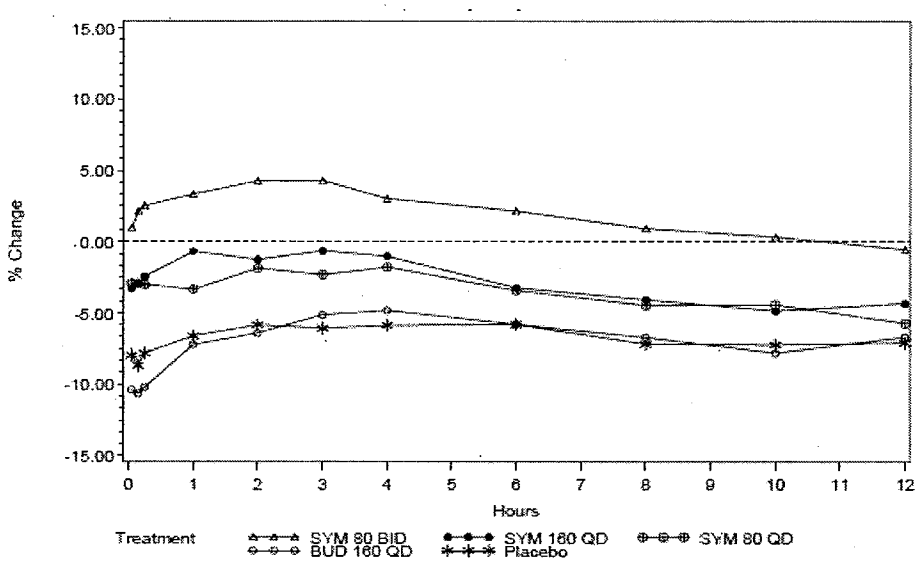


Figure 34. SD-039-0726, Mean % change from baseline in FEV_1 0-12 hours at Week 2

Source: F5, p152; SD-039-0726

10.1.4.2.3 Safety

There were no specific safety concerns raised by this study.

There were no deaths. There were 3 pregnancies. Sixteen patients experienced an SAE, of whom 5 were during the run-in period and 5 were during the double-blind treatment period. None of the SAEs were due to a severe asthma exacerbation, and none appear to have been related to study drug treatment. Examination of AEs and AEs leading to discontinuation did not lead to identification of any safety trends.

Other than expected glucose potassium changes, there were no clinically important changes in laboratory parameters, ECG, or physical examinations. While HPA axis was evaluated in this study by means of 24-hour urinary cortisol levels, the results were not reviewed in depth. The applicant reported substantial variability in all treatment groups, similar mean results for all treatment groups, and no disproportionate number of outliers in any one treatment group.

10.1.4.3 Conclusions

This study did not provide an evaluation of the individual mono-components dosed on a BID basis. However, it did provide a limited opportunity to evaluate maintenance of lung function with various doses of Symbicort, [redacted]. The main limitation is that Symbicort 80/4.5 mcg was used in the run-in period, thereby presuming effectiveness of Symbicort prior to demonstrating it. Nevertheless, some limited measure of improvement can be taken from the improvement in FEV_1 from screening to baseline during the run-in period. Despite the limitation, in this maintenance of lung function setting, the Symbicort 80/4.5 mcg dosage strength administered as 2 actuations BID showed a clear separation from placebo, and from QD dosing using various dosage strengths and doses of Symbicort and one dose of budesonide alone. *[Note: budesonide in a different form, as Pulmicort Turbuhaler, is approved as maintenance treatment for some patients who are stable on a BID dosing schedule.]*

It is evident that even in this setting, daily dosing does not maintain pulmonary function to the same extent as BID dosing.

10.1.5 Study SD-039-0681

This study was performed to support the Symbicort HFA MDI 160/4.5 mcg BID dosing program in patients ≥12 years of age. It is a secondary study because the comparators were Pulmicort (budesonide CFC 200 mcg) MDI and Symbicort Turbuhaler 160/4.5 mcg, did not use placebo, and the primary efficacy variable was AM PEF. The study evaluated superiority comparison to Pulmicort CFC MDI and equivalence comparison to Symbicort Turbuhaler.

10.1.5.1 Study Design

This was a 12-week, multinational (non-US), multicenter, randomized, double-blind, active-controlled, Phase 3 study to investigate the efficacy and safety of Symbicort HFA MDI 160/4.5 mcg [batches P6041/A; P6353; P6254; P6359], Pulmicort® CFC MDI (budesonide 200 mcg), and Symbicort Turbuhaler® (budesonide/formoterol 160/4.5 mcg) administered as 2 actuations BID in 680 asthmatics ≥12 years of age. At screening, patients had to have a pre-bronchodilator FEV_1 between 50-90% of predicted and reversibility of ≥12% from baseline at 15 minutes after beta-agonist treatment, and had to be on daily ICS for at least 3 months within a dose range of 500-1600 mcg/day. Randomization followed a 2-week single-blind run-in period during which patients continued on their regular ICS (500-1600 mcg/day). Those patients who had an FEV_1 ≤90 % predicted, had asthma symptom scores of at least 1 on 4 of the previous 7 days, and met the other inclusion/exclusion criteria were then randomized to 12 weeks of double-blind treatment. Albuterol MDI was used as a rescue medication prn.

The primary variable was the change from baseline (mean of the 10 last days of the run-in period) to the treatment period (mean of the 12-week treatment period) in morning mPEF. The primary comparison was Symbicort HFA MDI to Pulmicort. Secondary variables included evening PEF, asthma symptom scores, nighttime awakenings due to asthma, rescue medication use, symptom free days, asthma control days, FEV_1 and FVC (change from spirometry at randomization visit to spirometry on last day of treatment), and AQLQ. Safety was monitored by adverse events, laboratory results, vital signs, and physical examinations.

10.1.5.2 Results

The study randomized 680 patients at 62 centers in 8 countries (Brazil, Bulgaria, Canada, Hungary, Mexico, the Philippines, Thailand, and the UK), 429 women, 251 men, 440 Caucasian, 10 Black, 140 Oriental, 90 Other, with a mean age of 40 years (range 11-79, 10 ≥65 years), and a history of asthma for approximately 9 years. Most (535, 79%) were non-smokers. The mean FEV_1 was 2.06 L and 70% predicted. Treatment groups were relatively similar in baseline characteristics, including FEV_1, other pulmonary function measurements, and symptom scores. This study included an overall criterion of deterioration of asthma necessitating a change in therapy as one of the withdrawal criteria, but did not include specific criteria for withdrawal due to predefined asthma events. Of those randomized, 600 patients completed the study.

Discontinuations included 79 patients: 21did not fulfill entry criteria, 30 had an adverse event, 3 lost to follow-up, 25 other reasons. One patient had no data on treatment. Of the discontinuations, the number of AEs was slightly imbalanced: Pulmicort (15), followed by Symbicort MDI (11), and Symbicort Turbuhaler (4). Most protocol deviations were minor, and were judged not to affect the outcome of the study. Compliance with study medication was similar among treatment groups.

10.1.5.2.1 Efficacy

Treatment means for primary variable of AM PEF at the primary endpoint and key secondary variables are shown in Table 104. For the primary variable of AM mPEF, Symbicort HFA pMDI 160/4.5 mcg 2 actuations BID was shown to be superior to Pulmicort CFC pMDI 200 µg 2 actuations BID in increasing mPEF. The mean value of mPEF was 29 L/min higher in the Symbicort pMDI group than in the Pulmicort pMDI group ($p < 0.001$). Results are shown graphically in Figure 35. The results for secondary variables supported those for the primary variable with statistically significant improvements in favor of Symbicort pMDI over Pulmicort pMDI for ePEF, daytime and night-time asthma-symptom scores, symptom-free days, night-time awakenings due to asthma symptoms, use of rescue medication (day and night), asthma-control days, FEV1, FVC, and AQLQ(S) overall score. For the primary variable of AM PEF, the secondary comparison of Symbicort TBH 160/4.5 to Pulmicort CFC MDI 200 was also significant ($p < 0.001$).

Table 106. SD-039-0681, Treatment Means

	N	Baseline	Observed value	Change from baseline
Morning PEF (L/min)				
Symbicort MDI	229	326	356	29.3
Pulmicort MDI	216	318	319	0.6
Symbicort TBH	223	321	353	32.0
Evening PEF (L/min)				
Symbicort MDI	229	335	359	24.3
Pulmicort MDI	216	324	324	-0.6
Symbicort TBH	223	329	354	25.1
Total Asthma Symptom Score				
Symbicort MDI	229	1.93	1.26	-0.70
Pulmicort MDI	216	2.07	1.61	-0.44
Symbicort TBH	223	1.98	1.15	-0.84
Rescue Medication Use				
Symbicort MDI	229	2.08	1.07	-0.94
Pulmicort MDI	216	1.97	1.59	-0.35
Symbicort TBH	223	1.79	0.92	-0.92
FEV_1 (L)				
Symbicort MDI	229	2.15	2.47	0.32
Pulmicort MDI	213	2.11	2.22	0.12
Symbicort TBH	222	2.20	2.50	0.29
Source: T17, p81; T21, p 86; SD-039-0681				

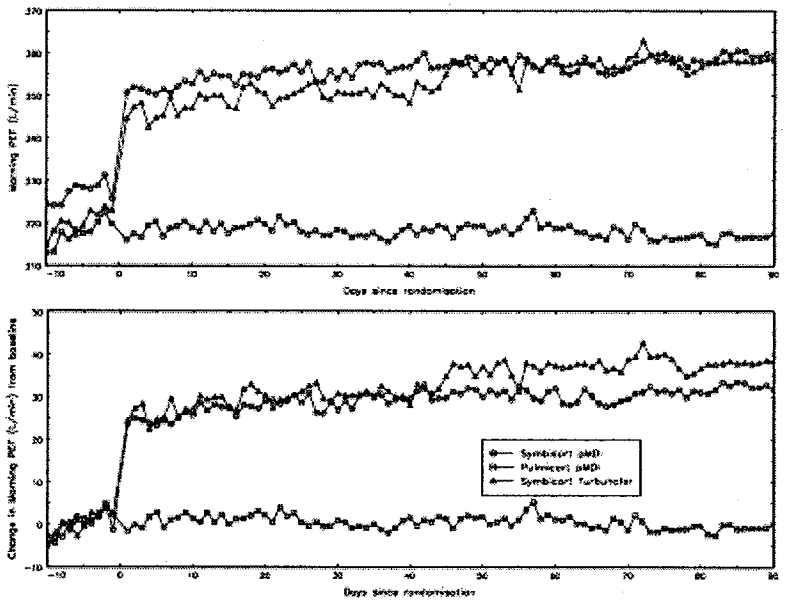


Figure 35. SD-039-0681, Daily mean PEF, Top: Absolute values; Bottom: Change from mean

Source: F4, p80; SD-039-0681

10.1.5.2.2 Safety

No specific safety trends were identified during the review. There were no deaths. Four patients experienced an SAE during treatment, 2 on Symbicort MDI (1 increased liver enzymes, 1 excessive menstruation) and 2 on Pulmicort MDI (1 severe asthma exacerbation, 1 fracture). There were no unexpected trends in AEs by preferred term. There were 5 cases of hoarseness (3 Symbicort MDI, 2 Pulmicort), 4 case of dysphonia (1 Symbicort MDI, 1 Pulmicort, 2 Symbicort TBH), 10 cases of oral candidiasis (2 Symbicort MDI, 3 Pulmicort, 5 Symbicort TBH), 2 cases of muscle cramps (2 Symbicort TBH), 7 cases of palpitations (1 Symbicort MDI, 6 Symbicort TBH), 1 case of tachycardia (1 Symbicort MDI), and 3 cases of tremor (1 Pulmicort, 2 Symbicort TBH).

10.1.5.3 Conclusions

While this study evaluated the Symbicort HFA MDI 160/4.5 mcg formulation/device administered BID, the study did not provide an evaluation of the individual mono-components with the same formulation/device, placebo, or FEV_1 as a primary outcome measure. The study did provide some evaluation of efficacy against a CFC MDI formulation of budesonide. The primary measure of AM PEF and secondary measures generally match with the results of the pivotal studies. No specific safety trends were identified.

10.1.6 Study SD-039-0682

This study was performed to support the Symbicort HFA MDI 80/4.5 mcg BID dosing program in patients 6 to 11 years of age. It is a secondary study because the comparators were Pulmicort (budesonide CFC 100 mcg) MDI and Symbicort Turbuhaler 80/4.5 mcg, did not use placebo, and the primary efficacy variable was AM PEF. The study evaluated superiority comparison to Pulmicort CFC MDI and equivalence comparison to Symbicort Turbuhaler.

10.1.6.1 Study Design

This was a 12-week, multinational (non-US), multicenter, randomized, double-blind, double-dummy, active-controlled, Phase 3 study to investigate the efficacy and safety of Symbicort HFA MDI 80/4.5 mcg [batches P6038; P6501/A; P6186; P6254; P6349], Pulmicort® CFC MDI (budesonide 100 mcg), and Symbicort Turbuhaler® (budesonide/formoterol 80/4.5 mcg) administered as 2 actuations BID in 622 asthmatics 6-11 years of age. At screening, patients had to have a clinically important history of exercise-induced bronchoconstriction, daily use of 375-1000 mcg of ICS, and a pre-bronchodilator PEF ≥50% of predicted. Randomization followed a 2-week single-blind run-in period during which patients continued on their regular ICS. Those patients who had an mPEF of 50-85 % predicted, had asthma symptom scores of at least 1 on 4 of the previous 7 days, and met the other inclusion/exclusion criteria were then randomized to 12 weeks of double-blind treatment. Bricanyl (terbutaline sulfate) Turbuhaler 0.5 mg/dose was used as a rescue medication prn.

The primary variable was the change from baseline (mean of the 10 last days of the run-in period) to the treatment period (mean of the 12-week treatment period) in morning mPEF. The primary comparison was Symbicort MDI vs Pulmicort. Secondary variables included evening PEF, asthma symptom scores, nighttime awakenings due to asthma, rescue medication use, symptom free days, asthma control days, FEV_1 and FVC (change from spirometry at randomization visit to spirometry on last day of treatment), and AQLQ. Despite the fact that this was a pediatrics study, evaluation of percent predicted FEV_1 (which adjusts for age) was not assessed. Safety was monitored by adverse events, laboratory results, vital signs, and physical examinations.

10.1.6.2 Results

The study randomized 622 patients at 53 centers in 8 countries (Argentina, Brazil, Denmark, Hong Kong, Mexico, Slovakia, Thailand, and Poland), 212 females, 410 males, 373 Caucasian, 17 Black, 47 Oriental, 185 Other, with a mean age of 9 years (range 6-11), and a history of asthma for approximately 3 years. All except 1 patient were on ICS at study entry (mean 468 mcg, range 250-1000 mcg). The mean FEV_1 was 1.67 L and 88.5% predicted, with a mean PEF 223.4 L/min. Treatment groups were relatively similar in baseline characteristics, including FEV_1, other pulmonary function measurements, concomitant medication, and symptom scores. This study included an overall criterion of deterioration of asthma necessitating a change in therapy as one of the withdrawal criteria, but did not include specific criteria for withdrawal due to predefined asthma events. Of those randomized, 583 patients completed the study.

Discontinuations included 39 patients: 24 did not fulfill entry criteria, 11 had an adverse event, 4 other reasons. Of the discontinuations, the number of AEs was slightly imbalanced: Pulmicort (7), followed by Symbicort MDI (3), and Symbicort Turbuhaler (1). Most protocol deviations were minor, and were judged not to affect the outcome of the study. Compliance with study medication was similar among treatment groups.

10.1.6.2.1 Efficacy

Treatment means for primary variable of AM PEF at the primary endpoint and key secondary variables are shown in Table 107. For the primary variable of AM mPEF, Symbicort HFA pMDI 80/4.5 mcg 2 actuations BID was shown to be superior to Pulmicort CFC pMDI 100 µg 2 actuations BID in increasing mPEF. The mean value of mPEF was 9.5 L/min higher in the Symbicort pMDI group than in the Pulmicort pMDI group ($p < 0.001$). Results are shown graphically in Figure 36. The results for secondary variables of PM PEF and FEV_1 supported those for the primary variable. The results for other secondary variables of daytime and night-time asthma-symptom scores, symptom-free days, night-time awakenings due to asthma symptoms, use of rescue medication (day and night), asthma-control days, and AQLQ(S) overall score numerically trended in favor of Symbicort. For the primary variable of AM PEF, the secondary comparison of Symbicort TBH 80/4.5 to Pulmicort CFC MDI 100 was also significant ($p < 0.001$).

Table 107. SD-039-0682, Treatment Means

	N	Baseline	Observed value	Change from baseline
Morning PEF (L/min)				
Symbicort MDI	203	220	245	29.5
Pulmicort MDI	206	221	237	19.9
Symbicort TBH	212	217	244	30.2
Evening PEF (L/min)				
Symbicort MDI	203	227	248	24.0
Pulmicort MDI	205	229	242	17.6
Symbicort TBH	212	224	247	26.3
Total Asthma Symptom Score				
Symbicort MDI	203	1.59	0.89	-0.68
Pulmicort MDI	206	1.71	0.95	-0.69
Symbicort TBH	212	1.53	0.78	-0.77
Rescue Medication Use				
Symbicort MDI	202	0.92	0.43	-0.50
Pulmicort MDI	204	1.12	0.58	-0.42
Symbicort TBH	211	0.90	0.39	-0.54
FEV_1 (L)				
Symbicort MDI	201	1.70	1.82	0.146
Pulmicort MDI	205	1.67	1.72	0.075
Symbicort TBH	209	1.66	1.81	0.182
Source: T18, p86-7; T22, p 92; SD-039-0682				

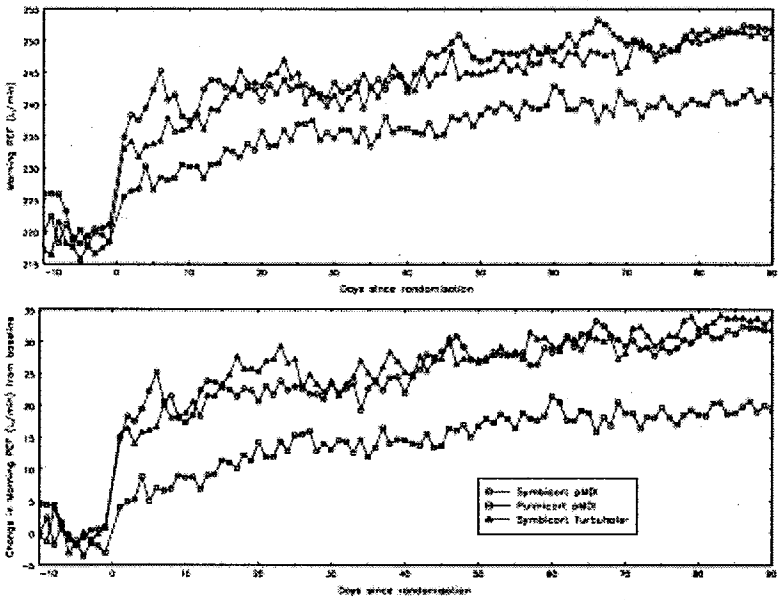


Figure 36. SD-039-0682, Daily mean PEF, Top: Absolute values; Bottom: Change from mean

Source: F4, p85; SD-039-0682

10.1.6.2.2 Safety

No specific safety trends were identified during the review. There were no deaths. Five patients experienced an SAE during treatment, 3 on Pulmicort MDI (2 asthma exacerbation, 1 nervousness) and 2 on Symbicort TBH (1 sinusitis, 1 migraine). The numbers of AEs were too small to interpret any differences. However, more patients on Pulmicort had an aggravation of asthma (7 [3%], 13 [6%], 7 [3%]) or fever (4 [2%], 10 [5%], 4[2%]), but less had rhinitis symptoms (6 [3%], 1 [0.5%], 8 [4%]) for the Symb MDI, Pulm MDI, and Symb TBH treatment groups, respectively. There were 4 cases of hoarseness (1 Pulmicort, 3 Symbicort TBH), 1 case of palpitations (Symbicort MDI), and 1 case of tremor (Symbicort TBH), but no cases of tachycardia, dysphonia or oral candidiasis.

10.1.6.3 Conclusions

While this study evaluated the Symbicort HFA MDI 80/4.5 mcg formulation/device administered BID, the study did not provide an evaluation of the individual mono-components with the same formulation/device, placebo, or FEV_1 as a primary outcome measure. FEV_1 percent predicted, the evaluation of choice in this population, was not evaluated. The primary measure of AM PEF and secondary measure of FEV_1 generally match with the results found in the pivotal studies. No specific safety trends were identified.

10.1.7 Study SD-039-0715. One-year safety study with Symbicort MDI 160/4.5 in asthmatics ≥12 years of age

This long-term safety study provides open-label, uncontrolled (the study had an active control, but the active control was a different formulation of Symbicort, i.e. Symbicort TBH) safety data for the Symbicort MDI 160/4.5 drug product in adults.

Protocol #:	SD-039-0715
Title:	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
Study Dates:	March 18, 2002 to November 8, 2004
Sites:	60 centers: 14 Australia, 17 France, 1 the Philippines, 18 Slovakia, 9 South Africa, 1 Thailand
Ethics and IRBs:	Performed in accordance with the ethical principles outlined in the Declaration of Helsinki and consistent with ICH/Good Clinical Practices. IRBs were local to study centers.

Source: M5, SD-039-0715.pdf

10.1.7.1 Protocol

This was a 52-week, multicenter, multinational, open-label, randomized, active-controlled, Phase 3 study to investigate the safety of Symbicort HFA pMDI 160/4.5 mcg and Symbicort TBH 160/4.5 mcg, each administered as 2 actuations BID, in 673 asthmatics ≥12 years of age. Randomization was 2:1 to Symbicort MDI 160/4.5 mcg [Batches: P6039; P6039B; P6040; P6041; P6041A; P6502A; P6675] or Symbicort Turbuhaler® (M3) 160/4.5 mcg [Batches: P6386; P6499]. The primary objective was to compare the long-term safety profile of Symbicort MDI with that of Symbicort TBH by means of safety assessments, as assessed by: Adverse Events (AEs), physical examinations, laboratory parameters (hematology, clinical chemistry, urinalysis, 24-hour urinary-cortisol [in a subgroup of 25 patients in France and Slovakia], P-cortisol [8-9 AM plasma measurement in all patients]), vital signs (pulse, blood pressure), and electrocardiograms (12-lead ECG post-dose). The secondary objective was to compare the efficacy of the two Symbicort drug products, as assessed by change from the baseline visit to the average of the 52-week treatment period for FEV_1, FVC, and time to first severe asthma exacerbation.

Inclusion criteria included asthma patients ≥12 years of age with a pre-bronchodilator FEV_1 ≥50% predicted, reversibility of ≥12% after inhalation of 1 mg of Bricanyl Turbuhaler (terbutaline sulfate), daily use of ICS (400-1200 mcg/day) with need for additional therapy with inhaled SABA or LABA for ≥3 months, and the ability to use an MDI and/or Turbuhaler. Exclusion criteria were typical for an asthma study, including pregnancy, breastfeeding, or planned pregnancy, need for contraception for fertile women; use of oral, parenteral, intranasal, or rectal corticosteroids within 30 days; history of respiratory infection within 30 days;

significant diseases or disorders which might place the patient at risk; known hypersensitivity to any of the active drugs or excipients/propellants; history of smoking ≥10 pack-years; beta-blocker use; planned donation of blood or hospitalization; alcohol or drug abuse; previous participation in this study; and participation in any study within 30 days.

There were 6 study visits over the 52-week treatment period, the first occurring on the day of randomization/study entry (Visit 1), followed by visits at 2, 12, 26, 38, and 52 (Visit 6) weeks. Withdrawal criteria included withdrawal of informed consent, incorrect randomization, pregnancy, development of an exclusion criterion related to safety, other safety reasons, or 3rd treatment of a severe asthma exacerbation within 3 months or in total 5 treatments during the study. Bricanyl Turbuhaler (terbutaline sulfate) was used as a rescue medication prn. Treatment compliance was evaluated by completion of a daily study diary, which was returned at each study visit. The study plan for each visit is shown below.

Reviewer's Note: It is important to note that all study evaluations (e.g. ECGs and spirometry) performed as part of study visits after Visit 1 were performed at an undefined time point post-dose, and were not performed not pre-dose. Since the timing of sampling (including spirometry) within a visit and in relation to study medication was not stated in the study report, the Division sent an Information Request to better understand the study conduct. AstraZeneca responded [Submission 5/15/2006A] that patients were instructed to take their morning medication prior to each scheduled visit after Visit 1. Therefore, ECGs and spirometry were performed at study visits at an undefined time point post-dose. The impact is that study evaluations would have been performed at a post-dose time approximating the maximal pharmacodynamic effects of formoterol. While this is appropriate for ECGs, the effect for the spirometry endpoint is to inappropriately use visit post-dose values as an efficacy endpoint. Post-dose values will capture the beta-adrenergic effects of the LABA, but will not be of benefit to capture the anti-inflammatory effects of the corticosteroid component. In addition, in this study the timing of baseline FEV_1 is not defined. It is unclear whether baseline was a pre- or a post-dose value, although the study report states that an effort was made to have spirometry performed at about the same time at each visit. If baseline was a pre-dose value, it would explain the large and consistent improvement in FEV_1 seen at Visits 2-6 compared to Visit 1. This information should be taken into consideration when reading the Efficacy Section below.

Table 108. SD-039-0715, Study Plan

Week	< 0	0	2	12	26	38	52
Visit	Information	1	2	3	4	5	6
Informed consent (E-code)[1]	X	X					
Reversibility test [2]		X					
Allocation of randomisation code		X					
Medical and surgical history		X					
Physical examination		X			X		X
Pulse		X	X	X	X		X
Blood pressure		X	X	X	X		X
Haematology[3]		X	X	X	X		X
Clinical chemistry[3]		X	X	X	X		X
Urinalysis (excl. cortisol)		X	X	X	X		X
ECG[3]		X	X	X	X		X
24-hour U-cortisol (subgroups in France and Slovakia)		X			X		X
P-cortisol		X			X		X
Dispense/return of study medication		d	d/r	d/r	d/r	d/r	r
Lungfunction - FEV_1, FVC		X	X	X	X	X	X
Dispense/return of notebook		d	d/r	d/r	d/r	d/r	r
Compliance/AEs in notebook		I——	——	——	——	——	——I
AEs		X	X	X	X	X	X

1. Informed consent could be obtained either at an information visit prior to Visit 1, or at Visit 1 according to local practice.
2. If not previously performed and documented within 6 months.
3. Study drug was administered when rising in the morning, and assessments made between 8 and 9 am.

Source: T2, p33; SD-039-0715

There were 4 amendments to the protocol. Review showed that all were minor would not have interfered with the ability of the study to detect a safety signal.

10.1.7.2 Results

10.1.7.2.1 Disposition, Demographics, Analysis Sets, and Baseline Characteristics

The study enrolled 817 patients at 60 centers, of whom 673 were randomized: 405 (60.2%) women, 268 (39.8%) men, 554 (82.3%) Caucasian, 14 (2.1%) Black, 92 (13.7%) Oriental, 13 (1.9%) Other, with a mean age of 40 years (range 12-85, 54 (8.0%) ≥65 years), and a history of asthma for approximately 11 years. All but one were on ICS, with an average dose of 689 mcg (range 200-1600 mcg) per day. The mean FEV_1 was 2.49 L, 80.2% predicted, with 24% reversibility. Treatment groups were relatively similar in baseline and demographic characteristics, including FEV_1, other pulmonary function measurements.

The Symbicort MDI group comprised 446 patients: 273 (61.2%) women, 173 (38.8%) men, 370 (83.0%) Caucasian, 8 (1.8%) Black, 61 (13.7%) Oriental, 7 (1.6%) Other, with a mean age of 40 years (range 12-85, 58 12-17 and 36 (8.1%) ≥65 years), and a history of asthma for approximately 10 years. The average ICS dose was 686 mcg (range 200-1600 mcg) per day. The mean FEV_1 was 2.47 L, 80.3% predicted, with 24% reversibility. [p70]

Reviewer's Note: It is of significance that only 14 Black patients were randomized, of whom 8 were in the Symbicort MDI group. Please refer to the Summary of Safety for a discussion of how well safety information from one racial group may be extrapolated to another.

Of those randomized, 598 patients (88.9%) completed the study. Discontinuations included 75 patients: 22 did not fulfill entry criteria, 1 met study-specific discontinuation criteria, 14 had an adverse event, 105 lost to follow-up, 28 other reasons. Of the discontinuations, only the discontinuation criterion of adverse events was imbalanced among treatment groups, with 12 (3.6%) and 2 (0.9%) patients withdrawing from the Symbicort MDI and TBH arms, respectively.

No patients were excluded due to a protocol deviation. Based on the daily dairy, compliance with study medication was similar among treatment groups, and reported s 97.5% for AM study treatment use and 97.0% for PM use. [p71]

10.1.7.2.2 Efficacy

Efficacy was evaluated by FEV_1, FVC, and time to first severe asthma exacerbation. Since time to first severe exacerbation is also a safety issue, these data are reviewed within the safety section.

10.1.7.2.2.1 Spirometry measures

Treatment means and ranges for spirometry variables are shown in tabular format in Table 109 and graphically for FEV_1 in Figure 37. The effect size seen is similar to that found in other studies. FEV_1 by subgroup for the Symbicort MDI treatment group are shown in Table 110. Sample sizes for other than Caucasians 18-64 years of age are too small to interpret meaningfully.

Reviewer's Note: Please see my Reviewer's Note at the beginning of this study review. Spirometry at Visits 2-6 were performed at an undetermined time post-dose; the timing of the baseline value was not defined.

Table 109. SD-039-0715, Treatment Means and Ranges, FEV_1 and FVC

	N	Visit 1	Visits 2-6	Adjusted diff*
FEV_1 (L)				
Symbicort MDI	440	2.48 (0.80-6.57)	2.79 (0.81-6.24)	0.268
Symbicort TBH	225	2.52 (1.05-7.38)	2.85 (0.95-5.93)	0.286
FVC (L)				
Symbicort MDI	440	3.28 (1.25-8.37)	3.52 (1.35-7.64)	0.185
Symbicort TBH	225	3.30 (1.45-7.46)	3.59 (1.34-6.25)	0.224
*ANOVA adjusted for country and baseline				
Source: T23, p79; SD-039-0715				

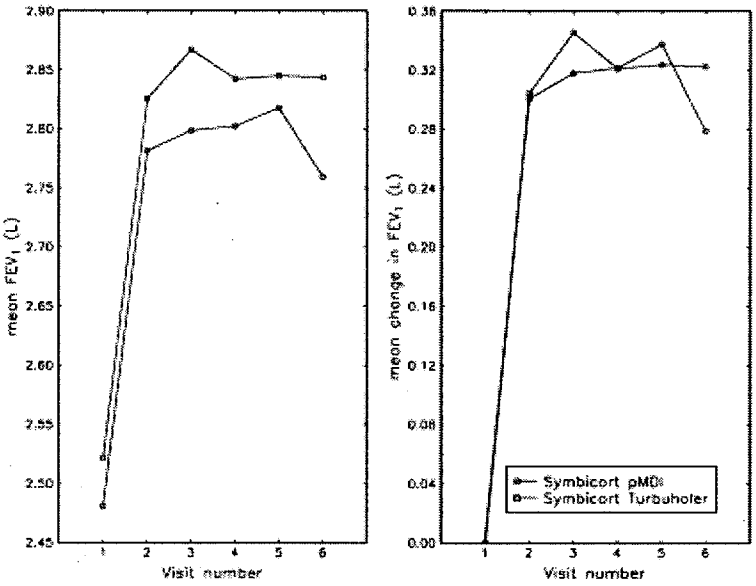


Figure 37. SD-039-0715, Mean FEV_1; Absolute values (left) and change from baseline (right)

Source: F3, p78; SD-039-0715

Table 110. SD-039-0715, FEV_1 by subgroup, Symbicort MDI treatment group

	N	Visit 1	Visits 2-6	Adjusted diff*
Sex				
Male	171	2.83	3.14	0.34
Female	269	2.26	2.57	0.29
Race				
Caucasian	365	2.57	2.90	0.34
Black	8	2.35	2.84	0.48
Oriental	60	1.89	2.04	0.08
Other	7	2.76	3.30	0.56
Age (years)				
12-17	58	2.66	3.07	0.43
18-64	347	2.53	2.84	0.31
≥65	35	1.69	1.89	0.13
*ANOVA adjusted for country and baseline				
Source: T25, p80-1; SD-039-0715				

10.1.7.2.3 Safety

This long-term (52 week) safety study provides open-label, uncontrolled (the study had an active control, but the active control was a different formulation of Symbicort, i.e. Symbicort TBH) safety data for the Symbicort MDI 160/4.5 drug product in adults. Review of the study did not pick up on any new and unexpected safety concerns. Review was complicated by the fact that the issues of potential concern, occurrence of severe or life-threatening asthma events and/or cardiac events would be expected to be, and were, infrequent. Without a placebo control, the study report was geared to a comparison of the two Symbicort drug products, and not to an overall evaluation of the safety risks of the drugs. Lack of a placebo control made the review of safety from this study difficult to perform and the occurrence of these infrequent adverse events

difficult to place of into context. Nevertheless, the study was specifically reviewed for the occurrence of severe or life-threatening asthma events, known corticosteroid toxicities, and systemic beta-agonist effects.

Mean exposure was 336.7 and 344.2 days for the Symbicort MDI and TBH treatment groups, respectively.

10.1.7.2.3.1 AEs

The most commonly reported AEs are summarized in Table 111. No clear pattern is present except for cough, which was far more frequent in the Symbicort pMDI group than in the Symbicort Turbuhaler group.

Table 111. SD-039-0715, AEs by preferred term

AEs (preferred term)	Symbicort MDI n=446	Symbicort TBH N=227
URTI	72 (16%)	33 (15%)
Headache	62 (14%)	28 (12%)
Pharyngitis	41 (9%)	27 (12%)
Nasopharyngitis	37 (8%)	25 (11%)
Influenza	36 (8%)	23 (10%)
Rhinitis nos	29 (7%)	18 (8%)
Sinusitis nos	31 (7%)	10 (4%)
Asthma aggravated	26 (6%)	15 (7%)
Rhinitis allergic nos	27 (6%)	12 (5%)
Bronchitis nos	21 (5%)	14 (6%)
Palpitations	21 (5%)	6 (3%)
Oral candidiasis	19 (4%)	4 (2%)
LRTI	18 (4%)	12 (5%)
Cough	16 (4%)	0
Back pain	15 (3%)	8 (4%)
Hoarseness	15 (3%)	5 (2%)
Tracheitis	11 (2%)	5 (2%)
Source: T34, p95; SD-039-0715.pdf		

10.1.7.2.3.2 Severe asthma exacerbations

Severe asthma exacerbations by patient are shown graphically in Figure 38. Table 112 summarizes the incidence of severe asthma exacerbations, in total and divided by sub criteria. The term "Multiple reason" indicates that a patient was treated with oral GCS and hospitalized/received emergency room treatment. A Kaplan-Meier plot showing the proportion of patients not experiencing a severe exacerbation is shown in Figure 39.

Without a placebo or other control, it is very difficult to place the frequency of severe asthma exacerbations seen in this study into context to other studies. That said, it is not surprising in a long-term study to see asthma exacerbations as was noted in this study.

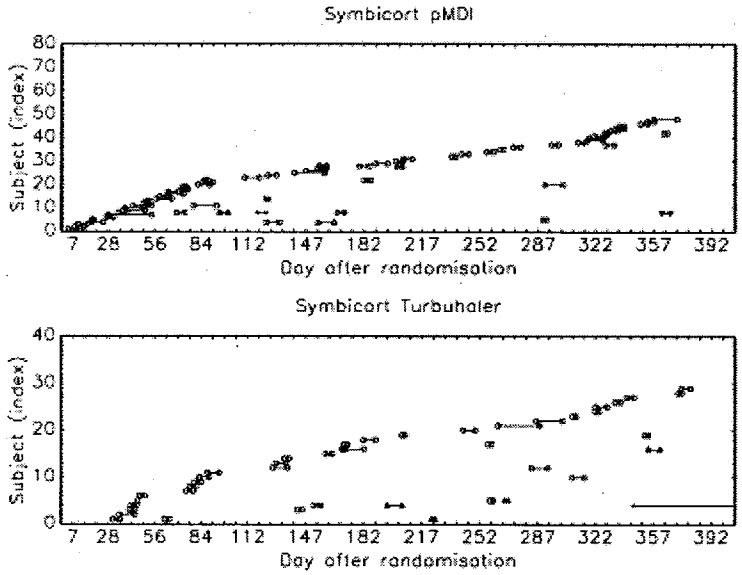


Figure 38. SD-039-0715, Severe asthma exacerbations by patient

Note: Each point on the y axis represents one patient, x-axis is time. Solid lines represent the start and end date for a particular exacerbation, and the symbols on the lines identify the number of the asthma exacerbation (the first asthma exacerbation is denoted by a circle, the second by a square, the third by a triangle, the fourth by a plus, the fifth by a diamond, and the sixth by an inverse triangle).

Source: F5, p83; SD-039-0715

Table 112. SD-039-0715, Number of patients with severe asthma exacerbations, total and by sub-criterion

	Symbicort MDI	Symbicort TBH
Severe asthma exacerbation		
No. of subjects	48 (11%)	29 (13%)
No. of events	64	43
No. with 1 event	38	20
No. with 2 events	7	5
No. with 3 events	2	3
No. with >3 events	1	1
Max events/subject	6	4
Oral CS		
No. of subjects	37 (8%)	20 (9%)
No. of events	49	26
No. with 1 event	31	16
No. with 2 events	3	2
No. with 3 events	2	2
No. with >3 events	1	0
Max events/subject	6	3
Hospitalizations / ER visits		
No. of subjects	4 (1%)	4 (2%)
No. of events	4	4
No. with 1 event	4	4
No. with 2 events	0	0
No. with 3 events	0	0
No. with >3 events	0	0

	Symbicort MDI	Symbicort TBH
Max events/subject	1	1
Multiple reasons		
No. of subjects	11 (2%)	9 (4%)
No. of events	11	13
No. with 1 event	11	6
No. with 2 events	0	2
No. with 3 events	0	1
No. with >3 events	0	0
Max events/subject	1	3
Source: T27, p84; SD-039-0715		

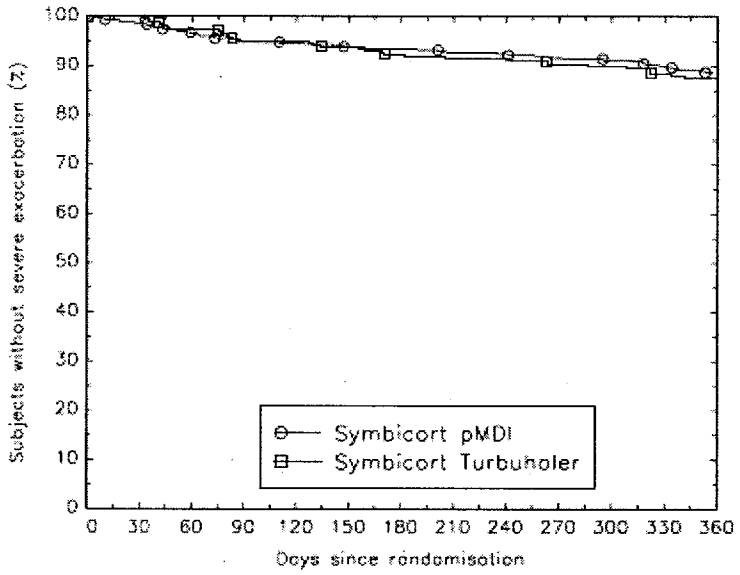


Figure 39. SD-039-0715, Kaplan-Meier plot of time to first severe asthma exacerbation

Source: F6, p85; SD-039-0715

10.1.7.2.3.3 Deaths, Serious Adverse Events, Discontinuations due to Adverse Events

One death occurred 7 weeks post study in the Symbicort MDI treatment arm due to a fatal asthma attack (Subj # 798). This was a 16 year old patient who completed the study on August 7, 2003. Her past medical history included dental caries. The study report states that "the patient was prescribed with asthma medication (flunizolide and SABA), but she was reported not to have taken the medication, which led to an attack . The patient developed severe breathlessness with circumoral cyanosis. The symptoms prompted an emergency consultation, however, the patient became unresponsive and was pronounced dead on arrival at the emergency room." [p227] This patient had experienced elevated liver functions at Visit 6 (ASAT 10.12, ALAT 16.49) [p269-70]

There were 53 SAE reports (comprising 72 symptoms or diagnoses) in 47 patients during the treatment period. The incidence of SAEs was similar (7%) across the two treatment groups. A tabular listing of SAEs follows (Table 113). In some instances the SAEs are grouped by

disorder, in other instances they are listed individually by preferred term. However, no attempt was otherwise made to group the events. While several cardiac events occurred, this is not unexpected in a study of this size and length. Without a placebo group, it is difficult to place events such as the four cardiac events into perspective, although it is conceivable that one or more were related to the formoterol component. All events of respiratory failure and acute asthma exacerbation were explored in more depth. The applicants listing of SAEs and DAEs by subject and narratives of events did not reveal any new information, and is therefore not presented here.

Two events were considered life-threatening: 1 event of ventricular tachycardia (Subject #5, Symbicort MDI) and 1 event of asthma aggravated (Subject #812, F/31, Symbicort TBH), summarized below.

> Subject 812 was a 31 year old female on Symbicort TBH. 37 weeks into treatment she was admitted to the ICU due to an asthma exacerbation. She was intubated for 3 days. CXR showed bilateral lower lobe changes, blood culture negative. Concomitant meds: terbutaline, paracetamol, panadeine, and seretide. Concomitant diagnoses: headaches, oral thrush, depression, eczema. [p253-4]
>
> Subject 5 was a 61 year old female on Symbicort MDI. 2.5 weeks into treatment she had sudden onset of chest tightness, heaviness, SOB, dizziness, and diaphoresis. ECG revealed supraventricular tachycardia. Symbicort was stopped. She underwent defibrillation and was treated with amiodarone and lidocaine drip. She recovered. [p249-50]

Fourteen patients were discontinued (Table 114), 12 (3%) in the Symbicort pMDI group and 2 (1%) in the Symbicort Turbuhaler group. Only one patient was discontinued due the study-specific criterion of asthma deterioration. The most commonly reported AE leading to discontinuation was hoarseness (3 in the Symbicort pMDI group).

There were 3 pregnancies during the treatment period, 1 of which was reported as an SAE (spontaneous abortion).

Table 113. SD-039-0715, SAEs

SAEs (SOC and preferred term)	Symbicort MDI n=446	Symbicort TBH N=227
Cardiac		
Supraventricular tachycardia	1	0
Tachycardia nos	0	1
Ventricular bigeminy	0	1
Ventricular tachycardia	1	0
Ear and labyrinth		
Otosclerosis	1	
Vertigo	1	1
Gastrointestinal		
Abdominal pain	1	0
Appendicitis	1	0
Constipation	0	1
Dyspepsia	1	0
Gastritis nos	0	1

SAEs (SOC and preferred term)	Symbicort MDI n=446	Symbicort TBH N=227
Gastroenteritis nos	0	1
Malocclusion nos	1	0
Nausea	0	1
Pancreatic disorder nos	1	0
Pancreatitis acute	1	0
Subileus	0	1
Vomiting nos	0	1
Hepatobiliary		
Hepatitis nos	1	0
Infections and infestations		
Arthritis infective nos	1	0
Bronchiectasis nos	0	1
Bronchitis acute nos	0	1
Bronchopneumonia nos	1	0
Cellulitis	1	0
Erysipelas	1	0
Lobar pneumonia nos	0	1
Otitis media nos	1	0
Pneumonia nos	2	1
Scrub typhus	0	1
Tracheitis nos	1	0
Respiratory		
Acute respiratory failure		1
Asthma exacerbated	8	6
Bronchitis	1	0
Fractures, tendon and ligamental injuries	5	1
Musculoskeletal, connective tissue	0	2
Neoplasms (GI adenoma)	0	1
Nervous system (Loss of consciousness, Nerve root lesion)	1, 1	0, 0
Renal (Nephrolithiasis, renal colic)	2, 0	1, 1
Reproductive		
Menorrhagia, metrorrhagia	1, 1	0
Ovarian cyst, mass	1, 1	0
Spontaneous abortion [post-study]	1	0
Skin (contusion, dermatitis)	1, 1	0, 0
Vascular (deep vein thrombosis)	1	0
Source: T35, p98-100; SD-039-0715.pdf		

Table 114. SD-039-0715, DAEs

DAEs (preferred term)	Symbicort MDI n=446	Symbicort TBH N=227
Hoarseness	3	0
Headache	2	0
Cough	2	0
Asthma aggravated	2	0

DAEs (preferred term)	Symbicort MDI n=446	Symbicort TBH N=227
Ventricular bigeminy	0	1
Ventricular tachycardia	1	0
Supraventricular tachycardia	1	0
Tremor	1	0
Pancreatitis acute	1	0
Hypotrichosis	0	1
Diarrhea nos	1	0
Alopecia	0	1
Abdominal pain nos	1	0
Source: T36, p101; SD-039-0715.pdf		

10.1.7.2.3.4 Laboratory parameters

Clinical lab results reviewed included those for hematology, clinical chemistry, glucose, potassium, plasma (spot AM) cortisol, and 24-hour urine cortisol. Within each set of laboratory parameters, results were considered by change in mean values over time, changes by individual patient (shift tables), and individual clinically important abnormalities.

For clinical laboratory values, other than expected changes (e.g. glucose and potassium) based on pharmacologic effects of ICS and beta-agonists, there were no significant or clinically meaningful findings.

Changes in mean plasma AM and 24-hour urine cortisol are shown in Table 115. Changes in mean plasma AM cortisol decreased slightly in both treatment groups, whereas changes in mean 24-hour urine results trended up for the MDI and down for the TBH treatment groups. For both sets of results, the range of results was quite large; the variability of results exceeded any mean differences, making interpretation difficult. Subgroup analyses for 24-hour urine cortisol included too few patients in any subgroup for meaningful interpretation. The study report provided a shift table for plasma AM cortisol and other laboratory parameters, but not for urine cortisol (provided in the Clinical Summary). The AM cortisol shift table (Table 116) showed a trend from normal to levels considered "abnormal" (below 150 mmol/L) at the end of treatment: 42 (10%) and 24 (11%) of the MDI and TBH patients, respectively. Mean values for urine cortisol are shown in Figure 40. There was a trend to decreased levels by Visit 4 (26 weeks), which abated by Visit 6 (52 weeks) at the end of study treatment. For urinary cortisol, among patients with a normal urinary cortisol at baseline, 16.3% (n=8) of Symbicort MDI and 13.6% (n=3) of Symbicort TBH patients shifted to less than the 5th percentile of baseline at end of treatment. Listings of individual values were reviewed. In general, patients who were low at baseline tended to remain low or drift upward, whereas only few patients were found whose values drifted downward. Lack of support for effect on HPA axis is likely due to the type of patients enrolled into the study, patients with a history of prior treatment with ICS who may already have had some effect of their ICS on HPA axis function.

Table 115. SD-039-0715, Mean cortisol results (Mean, range)

	N	Baseline (Visit 1)	Visit 6	Adjusted Visit 6*
Plasma spot AM cortisol (nmol/L)				
Symbicort MDI	424	276.9 (10-1280)	268.2 (10-2970)	246.1
Symbicort TBH	217	256.3 (10-1390)	235.6 (10-1410)	223.4
24-hour Urine cortisol (nmol)				
Symbicort MDI	59	46.1 (7-407)	48.3 (9-546)	51.9
Symbicort TBH	26	58.6 (5-441)	49.3 (9-263)	47.2
*Obtained from multiplicative ANOVA adjusted for country and baseline				
Source: T38, p107; T41, p110; SD-039-0715.pdf				

Table 116. SD-039-0715, Shift table for Plasma spot AM cortisol

Treatment	n	Baseline	End of Treatment	
			Observed value, n (%)	
			Normal	Abnormal*
Symbicort MDI	424	Normal	336 (79%)	42 (10%)
		Abnormal	30 (7%)	16 (4%)
Symbicort TBH	217	Normal	165 (76%)	24 (11%)
		Abnormal	15 (7%)	13 (6%)
*Abnormal values were any values below 150 mmol/L				
Source: T40, p108; SD-039-0715.pdf				

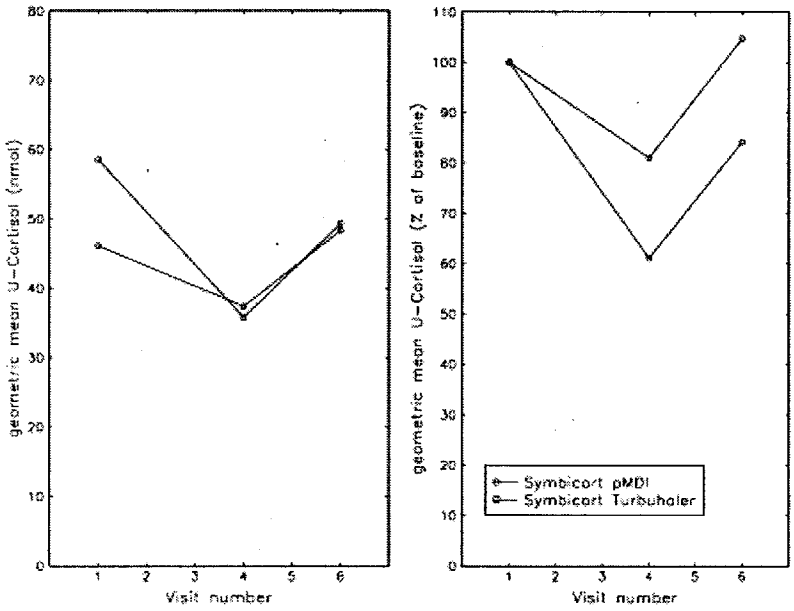


Figure 40. SD-039-0715, Mean 24-hour cortisol results

Source: F14, p109; SD-039-0715.pdf

10.1.7.2.3.5 Vital signs, ECGs, Physical examinations

Results were reviewed for vital signs, ECG, physical findings, and other safety observations. Within each set of parameters, results were considered by change in mean values over time, changes by individual patient (shift tables), and individual clinically important abnormalities. The overwhelming majority of the patients had normal values for pulse, blood pressure, and

ECG at baseline and normal values at end of treatment. No unusual findings were noted for these parameters.

A shift graph (Figure 41) and tables (Table 117, Table 118, and Table 119) for QT effects are shown below. No effect was seen on mean changes in heart rate, QT, QTcB or QTcF. Similar percents of patients in each treatment group experienced a QT, QTcB, or QTcF of ≥450 msec and/or increase by ≥30 msec during treatment. One patient in the Symbicort MDI treatment group experienced a QTcB of ≥500 msec, and 3 patients in the Symbicort MDI treatment group experienced an increase in QTcB of ≥60 msec during treatment.

Table 117. SD-039-0715, ECG findings

	N	Baseline	Observed	Change	ANCOVA LS mean (95% CI)
Heart Rate (BPM)					
Symbicort MDI	427	70.1	70.2	0.1 (9.2)	0.2 (-0.6, 0.9)
Pulmicort TBH	222	69.5	69.2	-0.3 (9.5)	-0.5 (-1.5, 0.6)
QT (msec)					
Symbicort MDI	427	393.2	394.0	0.8 (27.3)	0.2 (-2.1, 2.4)
Pulmicort TBH	222	397.5	396.2	-1.3 (28.5)	0.1 (-3.0, 3.2)
QTcB (msec)					
Symbicort MDI	427	421.7	423.5	1.8 (20.7)	1.3 (-0.4, 3.0)
Pulmicort TBH	222	424.3	422.3	-2.0 (19.2)	-1.1 (-3.4, 1.2)
QTcF (msec)					
Symbicort MDI	427	411.8	413.3	1.5 (19.2)	0.9 (-0.7, 2.5)
Pulmicort TBH	222	414.9	413.2	-1.7 (19.3)	-0.6 (-2.8, 1.6)
Source: Submission of 5/10/2006 T1, p5					

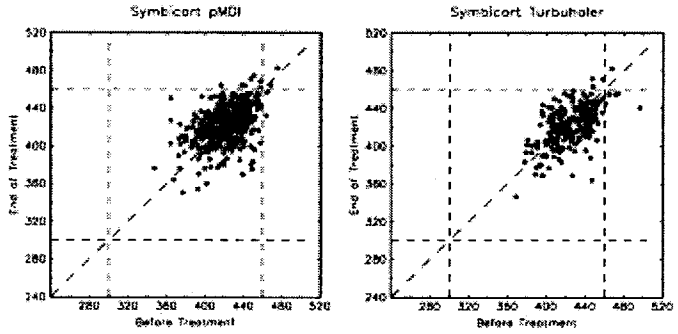


Figure 41. SD-039-0715, Shift graph for QTcB (msec)

Source: F6, p85; SD-039-0715

Appears This Way
On Original

Table 118. SD-039-0715, Shift table for QT, QTcB, and QTcF, Visit 1 to highest on-treatment result (msec)

Treatment	n	Baseline	End of Treatment		
			Observed value, n (%)		
			Normal	≥450	≥500
QT (msec)					
Symbicort MDI	432	Normal	381 (88%)	28 (6%)	1 (0.2%)
		≥450	5 (1%)	13 (3%)	2 (0.5%)
		≥500	0	2 (0.5%)	0
Symbicort TBH	222	Normal	187 (84%)	23 (10%)	1 (0.4%)
		≥450	3 (1%)	8 (4%)	0
		≥500	0	0	0
QTcB					
Symbicort MDI	432	Normal	339 (78%)	64 (15%)	0
		≥450	13 (3%)	15 (3%)	1 (0.2%)
		≥500	0	0	0
Symbicort TBH	222	Normal	161 (73%)	42 (19%)	0
		≥450	5 (2%)	14 (6%)	0
		≥500	0	0	0
QTcF					
Symbicort MDI	432	Normal	405 (95%)	18 (4%)	0
		≥450	5 (1%)	3 (1%)	1 (0.2%)
		≥500	0	0	0
Symbicort TBH	222	Normal	202 (91%)	12 (5%)	0
		≥450	2 (1%)	6 (3%)	0
		≥500	0	0	0

Source: T57, p127; T60, p130; T63, p133; SD-039-0715.pdf

Table 119. SD-039-0715, Summary of QT, QTcB, and QTcF positive and negative changes (msec)

Treatment	n	≥450	≥500	Negative Change		Positive Change	
				- ≥30	- ≥60	+ ≥30	+ ≥60
QT (msec)							
Symbicort MDI	446	46 (10%)	3 (1%)	159 (36%)	27 (6%)	147 (33%)	18 (4%)
Symbicort TBH	227	32 (14%)	1 (<0.5%)	88 (39%)	18 (8%)	68 (30%)	10(4%)
QTcB (msec)							
Symbicort MDI	446	80 (18%)	1 (<0.5%)	63 (14%)	8 (2%)	73 (16%)	3 (1%)
Symbicort TBH	227	56 (25%)	0	38 (17%)	3 (1%)	31 (14%)	0
QTcF (msec)							
Symbicort MDI	446	22 (5%)	1 (<0.5%)	68 (15%)	6 (1%)	61 (14%)	3 (1%)
Symbicort TBH	227	18 (8%)	0	33 (15%)	2 (1%)	22 (10%)	0

Source: T44, p113; T45, p114; SD-039-0715.pdf

10.1.7.3 Conclusions

Study SD-039-0715 was the pivotal long-term safety study for this application. This 52-week safety study provides open-label, non-placebo-controlled (the study had an active control, but the active control was a different formulation of Symbicort, i.e. Symbicort TBH) safety data for the Symbicort MDI 160/4.5 drug product in 673 adults, of whom 446 were randomized to Symbicort MDI and 392 completed one year of treatment with Symbicort MDI. The Symbicort MDI group comprised 446 patients: 273 (61.2%) women, 173 (38.8%) men, 370 (83.0%) Caucasian, 8

(1.8%) Black, 61 (13.7%) Oriental, 7 (1.6%) Other, with a mean age of 40 years (range 12-85, 58 12-17 and 36 (8.1%) ≥65 years), and a history of asthma for approximately 10 years. The average ICS dose was 686 mcg (range 200-1600 mcg) per day. The mean FEV_1 was 2.47 L, 80.3% predicted, with 24% reversibility.

Because spirometry was performed post-dose, efficacy assessments are of little value in this study.

Review of the study did not pick up on any new and unexpected safety concerns. However, review of this study was complicated by the lack of a balanced representation of all racial groups in the study. The applicability of the safety findings, and the ability to extrapolate safety from one racial group to another, is discussed further in the Summary of Safety section of this review.

Review was also complicated by the fact that the issues of potential concern, occurrence of severe or life-threatening asthma events and/or cardiac events would be expected to be, and were, infrequent. Lack of a placebo control made the occurrence of these infrequent adverse events difficult to place of into context. That said, several events occurred that were of concern. One patient on treatment experienced an SAE of supraventricular tachycardia, one patient on treatment experienced an SAE of severe asthma exacerbation requiring intubation, and one patient died of severe asthma approximately 7 weeks after completing the study. Changes in mean plasma AM cortisol decreased slightly in both treatment groups, whereas changes in mean 24-hour urine results trended up for the MDI and down for the TBH treatment groups. For both sets of results, the range of results was quite large; the variability of results exceeded any mean differences, making interpretation difficult. Lack of support for effect on HPA axis is likely due to the type of patients enrolled into the study, patients with a history of prior treatment with ICS who may already have had some effect of their ICS on HPA axis function.

10.1.8 Study SD-039-0719. Six-month safety study with Symbicort MDI 160/4.5 in asthmatic children 6 to 11 years of age

This long term safety study provides open-label safety data for the Symbicort MDI 160/4.5 drug product in children.

Protocol #:	SD-039-0719
Title:	A six-month, randomized, open-label safety study of Symbicort® (160/4.5 µg) compared to Pulmicort Turbuhaler® in asthmatic children 6 to 11 years.
Study Dates:	July 22, 2002 to October 6, 2003
Sites:	29 centers in the US
Ethics and IRBs:	Performed in accordance with the ethical principles outlined in the Declaration of Helsinki and consistent with ICH/Good Clinical Practices. IRBs were local to study centers.

Source: M5, SD-039-0719.pdf

10.1.8.1 Protocol

This was a 26-week, multicenter, open-label, randomized, active-controlled, safety study to investigate the safety of Symbicort HFA pMDI 160/4.5 mcg compared to Pulmicort TBH 200 mcg, each administered as 2 actuations BID, in 187 asthmatic children 6 to <12 years of age. After a 1-week baseline period, randomization was 2:1 to Symbicort HFA MDI 160/4.5 mcg [Batches: P6040; P6502A] or Pulmicort Turbuhaler® 200 mcg [Batches: P6478; P6583; X1447; DE1682]. On-treatment study visits were at 2, 12, and 26 weeks. Although there were no specific efficacy objectives, measures of efficacy included pre-dose FEV_1, FVC, FEF_{25-75}, PEFR, and physician and caregiver global assessments of asthma control. The primary objective was to compare the long-term safety profile of Symbicort MDI with that of Pulmicort TBH by means of safety assessments, as assessed by: Adverse Events (AEs), physical examinations, vital signs (temperature, pulse, blood pressure), laboratory parameters (hematology, clinical chemistry, urinalysis, 24-hour urinary-cortisol [at baseline, 12, 26 weeks]), PK for consenting patients [budesonide and formoterol Tmax, Cmax, and AUC_{0-6} at 2 weeks: 5 specimens drawn pre-dose and at 10, 40, 120 and 360 minutes]), and electrocardiograms (12-lead ECG 30 minutes post-dosing). The secondary objective was to compare the measurements of health economics and HRQOL (using the Pediatric Asthma Quality of Life Questionnaire in patients ≥7 years) between the two treatment groups. Medical resource utilization included: ER visits (all-cause and due to asthma or breathing problems); hospital admissions (all-cause and due to asthma or breathing problems); and urgent care visits, unscheduled visits, and unscheduled telephone calls due to asthma or breathing problems. Indirect asthma resource utilization included: days the child was unable to participate in normal daily activities, days the caregiver's daily routine was interrupted, and days the caregiver missed work due to asthma or breathing problems.

Inclusion criteria included asthma patients 6 to <12 years of age with a prebronchodilator FEV_1 ≥50% predicted, documented history of peak flow or FEV_1 reversibility of ≥12% after inhalation of fast-acting beta-agonist, needed daily use of ICS for at least 4 weeks, stable on immunotherapy, and the ability to use a Turbuhaler and/or MDI without a spacer. While the study report states that patients were selected who demonstrated a need for additional therapy with inhaled SABA or LABA, this was not an inclusion criterion. Exclusion criteria were typical for an asthma study, including pregnancy, breastfeeding, or planned pregnancy; lack of adequate contraception for fertile women; malignancy; significant diseases or disorders which might place the patient at risk; known hypersensitivity to any of the active drugs or excipients/propellants; beta-blocker use; unable to complete a 24-hour urine collection, including due to enuresis or incontinence; use of systemic corticosteroids after the screening visit or certain disallowed asthma treatments within specified time periods [p36]; abnormal screening labs, or ECG with a QTc >500 msec; previous participation in this study; and participation in any study within 4 weeks.

Withdrawal criteria included withdrawal of informed consent or not willing to continue in study, eligibility criteria not fulfilled, adverse event, lost to follow-up, and other (to be specified). Asthma exacerbations were treated according to "standard office practice" including a burst of systemic corticosteroids. Treatment compliance was evaluated by means of weekly telephone calls by caregivers to an interactive voice response system.

There were 4 amendments to the protocol. Review showed that all were minor would not have interfered with the ability of the study to detect a safety signal. [p68-72]

10.1.8.2 Results

10.1.8.2.1 Disposition, Demographics, Analysis Sets, and Baseline Characteristics

The study screened 252 patients at 29 centers and randomized 187 patients at 28 centers: 119 (36%) females, 67 (64%) males, 167 (89.8%) Caucasians, 14 (7.5%) Blacks, 2 (1.1%) Orientals, 3 (1.6%) Others, with a mean age of 9.0 years (range 6-11 years), and a history of asthma for approximately 6.0 years. The average daily ICS use was 307 mcg (range 44-1000 mcg) per day. The mean screening FEV_1 was 1.75 L, 84.2% predicted; the mean baseline FEV_1 was 1.74 L, 83.6% predicted. Treatment groups were relatively similar in baseline and demographic characteristics, including FEV_1, use of ICS, and other pulmonary function measurements. The Symbicort MDI group comprised 123 patients: 44 females, 79 males, 109 Caucasians, 11 Blacks, 1 Oriental, 2 Others, with a mean age of 9.0 years (range 6-11 years), and a history of asthma for approximately 6 years. The average ICS dose was 306 mcg (range 50-1000 mcg) per day. The mean baseline FEV_1 was 1.75 L, 84.0% predicted. [p77]

Reviewer's Note: The study included only 14 Black patients, of whom 11 were in the Symbicort MDI group. Please refer to the Summary of Safety for a discussion of how well safety information from one racial group may be extrapolated to another.

Of those randomized, 164 patients (87.7%) completed the study. Discontinuations included 23 patients: 9 were not willing to continue in the study, 5 had an adverse event, 3 lost to follow-up, 6 other reasons. The discontinuation criterion of adverse events was balanced among treatment groups, with 3 (2.4%) and 2 (3.2%) of patients withdrawing from the Symbicort MDI and Pulmicort TBH arms, respectively.

Most protocol deviations were minor, and no patients were excluded due to a protocol deviation. One patient was excluded from the safety analysis set because the patient was randomized but never received study drug. The PK analysis set was quite small: 11 total patients, 6 Symbicort and 5 Pulmicort; the reason for exclusion of all other patients was that they did not consent for PK. Based on the weekly telephone reports by caregivers to an interactive voice response system, compliance with study medication was similar among treatment groups, and reported as 76% for Symbicort MDI and 69% for Pulmicort TBH. [p78]

10.1.8.2.2 Efficacy and Pharmacokinetics

Efficacy was evaluated by FEV_1, FVC, FEF_{25-75}, and PEFR. Time to first severe asthma exacerbation, which was used as an efficacy variable in the adult safety study (715), was not used in this study.

10.1.8.2.2.1 Spirometry, PAQLQ, and Health Resource Utilization measures

Treatment means, ranges, and treatment comparisons for FEV_1 over the treatment and at the end of treatment are shown in tabular format in Table 120 and graphically for FEV_1in Figure 42. Results favored Symbicort MDI over Pulmicort TBH. It is unclear why the results changed so dramatically between 12 and 26 weeks into the study. Global physician assessments and PAQLQ overall as well as individual scores also favored Symbicort (not shown). Differences between treatment groups in direct health resource utilization did not clearly favor one drug product, although the numbers of urgent care visits were less in the Symbicort treatment group.

Differences between treatment groups in indirect health resource utilization numerically trended in favor of the Symbicort treatment group.

Table 120. SD-039-0719, Pre-dose FEV_1 (Mean, SD)

	N	Baseline	Observed	Change	ANCOVA LS mean (95% CI)	LS mean Diff (95% CI) p-value
FEV_1 (L) during treatment period						
Symbicort MDI	119	1.84 (0.45)	1.88 (0.44)	0.14 (0.16)	0.15 (0.11, 0.19)	0.08 (0.02, 0.13)
Pulmicort TBH	63	1.73 (0.40)	1.81 (0.40)	0.08 (0.19)	0.07 (0.02, 0.13)	p=0.009
FEV_1 (L) at treatment end (LOCF)						
Symbicort MDI	119	1.74 (0.45)	1.95 (0.47)	0.21 (0.20)	0.20 (0.16, 0.25)	0.11 (0.05, 0.18)
Pulmicort TBH	63	1.73 (0.40)	1.85 (0.41)	0.13 (0.21)	0.09 (0.03, 0.15)	p<0.001
Source: T19, T20, p86; T21, T22, p87; SD-039-0719						

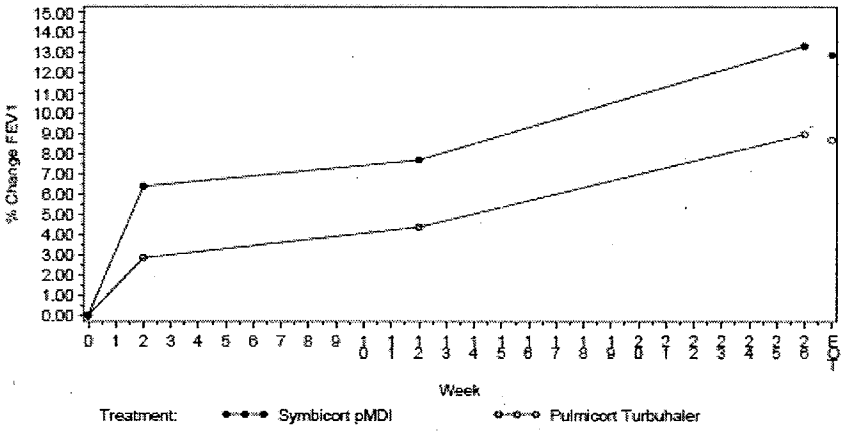


Figure 42. SD-039-0719, Mean percent change from baseline in pre-dose FEV_1

Source: F3, p88; SD-039-0719

10.1.8.2.2.2 Pharmacokinetics

The numbers of pediatric patients who agreed to PK evaluations were quite small (6), limiting usefulness of the results. There was considerable variability in budesonide levels, with no clear differences in results between the two drug products.

10.1.8.2.3 Safety

Review of this 6-month safety study in children 6-11 years of age did not pick up on any new safety concerns; however, issues regarding HPA axis findings and QT effects in this age group were elucidated. The study report was geared to a comparison of the Symbicort and Pulmicort drug products, and not to an overall evaluation of the safety risks of the drugs. This made review of safety from this study difficult to perform. Nevertheless, the study was specifically reviewed for the occurrence of severe or life-threatening asthma events, known corticosteroid toxicities, and systemic beta-agonist effects. That said, without a placebo control it is extremely difficult to place infrequent AEs into any perspective.

Both treatment groups exhibited a trend for decrease from baseline in mean 24-hour urinary cortisol over the course of the treatment period (numerically the decrease for Pulmicort was larger). This is different from the results of study 715 in adults, where changes in mean 24-hour urine results trended up for the Symbicort MDI and down for the Symbicort TBH treatment groups. Cortisol/creatinine ratios also showed similar trends for both treatment groups including a numerically larger decrease for the Pulmicort than the Symbicort group. Three patients in the Symbicort group had a QTcB of ≥450 msec and also had a change from baseline in QTcB of ≥60 msec. This is likely an effect of the formoterol component, and should be included in the labeling.

Mean exposure was 171.2 and 166.3 days for the Symbicort MDI and Pulmicort TBH treatment groups, respectively. This was consistent with the overall discontinuation rates.

10.1.8.2.3.1 Adverse Events

There were no deaths, and no pregnancies were reported. SAEs and DAEs are summarized in Table 122. There were 3 SAEs (2 Symbicort MDI [asthma, pneumonia], 1 Pulmicort TBH [sickle cell crisis]), all leading to temporary discontinuation of treatment but not permanent discontinuation. None were considered by the investigators to be drug related. One patient had an SAE of asthma during the screening period and was not randomized. One patient in the Symbicort group experienced an SAE of asthma in the post-treatment period. Four patients were discontinued due to an AE, 3 of which occurred during the first month of treatment. There were two asthma DAEs, one in each treatment group. One patient experienced Wolff-Parkinson-White syndrome prior to randomization and was discontinued shortly after starting treatment. One patient had an asthma exacerbation during the screening period and was not randomized, but was re-screened and randomized at a later date.

The numbers and percent of patients with AEs by SOC were similar between treatment groups, although the percent of patients with respiratory event was higher in the Symbicort MDI (41.5%) than in the Pulmicort TBH (34.9%) group. The most commonly reported AEs by MedDRA preferred term are summarized in Table 123. No clear pattern is present.

Table 121. SD-039-0719, Adverse event overview

Number (%) of patients with an AE	Symbicort MDI n=123	Pulmicort TBH n=63
Mean duration of exposure (days)	171.2	166.3
Any AE (during treatment)*	104 (84.6)	54 (85.7)
SAE	2 (1.6)	1 (1.6)
SAE leading to death	0	0
SAE leading to discontinuation	0	0
Discontinuations due to an AE	2 (1.6)	2 (3.2)
Other significant AEs	0	0
Total number of AEs		
Any AE	431	244
SAE	2	1
Source: T32, p113; T33 p116; SD-039-0719.pdf		

Table 122. SD-039-0719, Listing of SAEs and DAEs during all study phases (SAS)

Identifier	Term	Age	Sex	Race	AE Onset	SAE	DAE
Symbicort							
E9008004	Asthma	10	F	C	98	Yes	No
E9010012	Pneumonia	6	M	C	17	Yes	No
E9015007	Asthma	11	F	C	190 (7 days post study)	Yes	No
E9006011	Abdominal pain, upper	9	M	C	17	No	Yes
E9020011	Asthma	9	M	C	8	No	Yes
E9018008	Wolff-Parkinson-White syndrome		10M	O	Prior (-6)	No	Yes
E9010007 (E9010010)	Asthma	9	F	C	Prior (-45)	No	Yes
Pulmicort							
E9008011	Sickle cell crisis	8	F	B	45	Yes	No
E9005002	Asthma	6	M	C	21	No	Yes
E9026004	Disturbance in attention	8	M	C	34	No	Yes

Source: T36, p123; T37, p125; SD-039-0719.pdf

Table 123. SD-039-0719, AEs by preferred term

AEs (preferred term)	Symbicort MDI n=123	Pulmicort TBH N=63
Headache	26 (21%)	14 (22%)
URTI + viral URTI	26 (22%)	17 (27%)
Nasopharyngitis	20 (16%)	10 (16%)
Abdominal pain, upper	15 (12%)	8 (13%)
Asthma	16 (13%)	6 (10%)
Pharyngolaryngeal pain	15 (12%)	6 (10%)
Cough	15 (12%)	5 (8%)
Pyrexia	13 (11%)	4 (6%)
Dyspepsia	12 (10%)	3 (5%)
Nasal congestion	10 (8%)	3 (5%)
Sinusitis	8 (7%)	4 (6%)
Pharyngitis, streptococcal	8 (7%)	2 (3%)
Otitis media + Ear infection	7 (6%)	6 (10%)
Viral infection	5 (4%)	5 (8%)
Vomiting	6 (5%)	4 (6%)
Bronchitis	6 (5%)	3 (5%)
Influenza	6 (5%)	3 (5%)
Ear pain	5 (4%)	2 (3%)
Epistaxis	5 (4%)	1 (2%)
Gastroenteritis, viral	4 (3%)	2 (3%)
Diarrhea	3 (2%)	2 (3%)
Gastroenteritis	2 (2%)	3 (5%)
Myalgia	5 (4%)	0
Pain in extremity	4 (3%)	1 (2%)
Arthralgia	4 (3%)	0
Rhinorrhea	4 (3%)	0
Eye pruritis	1 (1%)	2 (3%)
Lymphadenopathy	1 (1%)	2 (3%)

AEs (preferred term)	Symbicort MDI n=123	Pulmicort TBH N=63
Conjunctivitis	0	2 (3%)
Constipation	0	2 (3%)
Urticaria	0	2 (3%)
Note: The table above combines several similar terms		
Source: T35, p119-20; SD-039-0719.pdf		

10.1.8.2.3.2 Laboratory parameters

Clinical lab results reviewed included those for hematology, clinical chemistry, glucose, potassium, and 24-hour urine cortisol. Within each set of laboratory parameters, results were considered by change in mean values over time, changes by individual patient (shift tables), and individual clinically important abnormalities. For clinical laboratory values, other than expected changes (e.g. glucose and potassium) based on pharmacologic effects of ICS and beta-agonists, there were no significant or clinically meaningful findings. Effects on HPA axis were noted, as measured by 24-hour urinary cortisol. The results are discussed below.

Changes in mean 24-hour urine cortisol levels over the course of the study are shown in Table 124. For both sets of results, the range of results was quite large; the variability of results exceeded any mean differences, making interpretation somewhat difficult. It should also be noted that the mean values remained well within the normal reference range. Nevertheless, both treatment groups exhibited a trend for a decrease from baseline in mean 24-hour urinary cortisol over the course of the treatment period (numerically the decrease for Pulmicort was larger). This trend is different from the results of study 715 in adults, where changes in mean 24-hour urine results trended up for the Symbicort MDI and down for the Symbicort TBH treatment groups. Cortisol/creatinine ratios also showed similar trends for both treatment groups including a numerically larger decrease for the Pulmicort than the Symbicort group. Results of urinary cortisol and creatinine-corrected cortisol were similar across genders. The study report provided a shift table for urine cortisol (Table 125) based on the low and high reference ranges for urine cortisol 1.4 to 18 mcg/24 hours [equivalent to 3.9 to 49.7 nmol/24 hours in SI units] for ages 6 to 7 years and 1.6 to 21 mcg/24 hours [equivalent to 4.4 to 57.9 nmol/24 hours in SI units] for ages 8 to 11 years. Six patients in each treatment group (4.9% of patients on Symbicort MDI, 9.5% of patients on Pulmicort TBH) shifted from normal or high at baseline to low at the end of treatment. The study report notes that no cortisol-related DAEs or SAEs were reported. In a brief review, I was not able to specifically identify any AEs due to the cortisol findings in the patients who experienced low levels on testing. A listing of patients who experienced a low urinary cortisol level at any time during treatment is shown in Table 126.

Table 124. SD-039-0719, Mean 24-hour cortisol results (nmol/24 hours)*

	N	Arithmetic mean (SD)	Geometric mean	Geometric mean %
Symbicort (TDD = 640/18 mcg/day)				
Baseline	122	29.3 (19.3)	23.5	
12 weeks	107	29.8 (28.6)	20.9	89.9%
26 weeks	106	24.6 (21.0)	17.7	75.7%
End of treatment	114	24.9 (20.5)	18.2	78.0%
Treatment average	114	27.6 (19.0)	21.7	93.4%

	N	Arithmetic mean (SD)	Geometric mean	Geometric mean %
Pulmicort (TDD = 800 mcg/day)				
Baseline	62	30.3 (17.0)	25.5	
12 weeks	56	24.6 (17.5)	18.3	68.3%
26 weeks	50	25.8 (29.7)	15.4	61.1%
End of treatment	57	24.9 (28.2)	15.4	59.5%
Treatment average	57	24.6 (17.6)	18.8	73.1%
*The reference range supplied by the testing laboratory for urinary cortisol (24h) was in different units of measurement (mcg/24hours) than the results presented in the study report. The reference range was: 1.4 to 18 mcg/24 hours [equivalent to 3.9 to 49.7 nmol/24 hours in SI units] for ages 6 to 7 years and 1.6 to 21 mcg/24 hours [equivalent to 4.4 to 57.9 nmol/24 hours in SI units] for ages 8 to 11 years.				
Source: T46, p134; SD-039-0719.pdf				

Table 125. SD-039-0719, Shift table for 24-hour urinary cortisol at end of treatment

Treatment	Baseline	End of Treatment				
		Observed value, n (%)				
		Low	Normal	High	Missing	Total
Symbicort MDI	Low	0	3 (2.4)	0	0	3 (2.4)
	Normal	5 (4.1)	90 (73.2)	5 (4.1)	7 (5.7)	107 (87.0)
	High	1 (0.8)	8 (6.5)	1 (0.8)	2 (1.6)	12 (9.8)
	Missing	0	0	1 (0.8)	0	1 (0.8)
	Total	6 (4.9)	101 (82.1)	7 (5.7)	9 (7.3)	123 (100)
Pulmicort TBH	Low	0	1 (1.6)	0	0	1 (1.6)
	Normal	5 (7.9)	45 (71.4)	3 (4.8)	6 (9.5)	59 (93.7)
	High	0	0	2 (3.2)	0	2 (3.2
	Missing	1 (1.6)	0	0	0	1 (1.6)
	Total	6 (9.5)	46 (73.0)	5 (7.9)	6 (9.5)	63 (100)
Source: T50, p138; SD-039-0719.pdf						

Table 126. SD-039-0719, Patients with clinically notable 24-hour urinary cortisol findings at any time during treatment

Identifier	Age	Sex	Race	Visit	Cortisol (nmol/24h)	Cortisol/Creatinine ratio (mcg/g)
Symbicort MDI						
E9002012	10	F	C	Screening	12.7	14.4
				Week 12	13.2	11.0
				Week 26	2.5	2.5
E9002015	9	M	C	Screening	12.7	9.7
				Week 12	1.4	1.0
				Week 26	6.6	4.7
E9006006	9	M	C	Screening	4.1	2.8
				Week 12	3.9	7.8
				Week 26	8.3	5.7
E9012001	8	M	C	Screening	16.3	8.3
				Week 12	4.7	2.9
				Week 26	3.0	1.8
E9015014	11	M	C	Screening	13.5	9.0
				Week 12	4.1	3.6
				Week 26	5.8	18.5
E9021012	11	M	C	Screening	22.9	9.1
				Week 12	39.7	11.9

Identifier	Age	Sex	Race	Visit	Cortisol (nmol/24h)	Cortisol/Creatinine ratio (mcg/g)
				Week 26	3.9	8.4
E9026007	10	M	C	Screening	4.4	8.0
				Week 12	1.4	0.6
				Week 26	3.6	1.1
E9026010	10	M	C	Screening	86.6	19.9
				Week 12	2.2	1.4
				Week 26	2.5	1.4
E9029001	11	F	C	Screening	20.4	15.2
				Week 12	33.4	20.6
				Week 26	3.6	4.7
Pulmicort TBH						
E9002013	7	F	C	Screening	13.5	11.3
				Week 12	3.0	2.2
				Week 26	3.9	3.5
E9005011	10	M	C	Screening	13.8	4.7
				Week 12	3.3	4.2
				Week 26	7.7	5.4
E9005013	9	F	C	Screening	Missing	Missing
				Week 12	Missing	Missing
				Week 26	2.2	1.9
E9006002	11	M	C	Screening	50.2	38.3
				Week 12	12.7	9.0
				Week 26	3.9	10.2
E9008011	8	F	B	Screening	48.3	39.0
				Week 12	3.9	5.9
				Week 26	7.2	8.4
E9013008	7	M	C	Screening	10.2	7.5
				Week 12	15.7	13.5
				Week 26	2.2	1.2
E9019005	11	M	C	Screening	41.7	14.8
				Week 12	40.6	10.1
				Week 26	3.0	0.6
E9021002	9	M	C	Screening	18.8	11.7
				Week 12	18.8	9.6
				Week 26	2.8	2.5
E9021009	11	F	C	Screening	26.5	10.8
				Week 12	49.9	27.3
				Week 26	3.3	1.5
E9026012	10	F	C	Screening	15.5	9.9
				Week 12	2.2	1.7
				Week 26	11.0	5.9
Source: T52, p140-1; SD-039-0719.pdf						

10.1.8.2.3.3 Vital signs, ECGs, Physical examinations

Results were reviewed for vital signs, ECG, physical findings, and other safety observations. Within each set of parameters, results were considered by change in mean values over time, changes by individual patient (shift tables), and individual clinically important abnormalities.

The overwhelming majority of the patients had normal values for pulse, blood pressure, and ECG at baseline and normal values at end of treatment. No unusual findings were noted for these parameters. Mean heart rate, uncorrected, and corrected QTc results are shown in Table 127. No patients on Pulmicort experienced a QT, QTcB, or QTcF of ≥450 msec. One Symbicort patient had an uncorrected QT ≥450 msec and 5 Symbicort patients had a QTcB ≥450 msec, but none of these experienced a QT, QTcB, or QTcF of ≥500 msec. In the Pulmicort group, 1 patient had a change from baseline of ≥60 msec in QTcB. In the Symbicort group, 2, 5, and 4 patients had a change from baseline of ≥60 msec in QT, QTcB, or QTcF, respectively. Ten patients met any of the above criteria, and their information was reviewed. In the Symbicort group, 3 patients had a QTcB of ≥450 msec and also had a change from baseline in QTcB of ≥60 msec (Table 128). [p144-56]

Table 127. SD-039-0719, ECG findings

	N	Baseline	Observed	Change	ANCOVA LS mean (95% CI)
Heart Rate (BPM)					
Symbicort MDI	123	75.9	76.4	-3.1 (10.9)	-3.5 (-5.9, -1.1)
Pulmicort TBH	63	78.0	75.4	-2.5 (12.4)	-3.0 (-6.4, 0.3)
QT (msec)					
Symbicort MDI	123	343.8	354.9	11.1 (24.4)	11.6 (6.2, 17.0)
Pulmicort TBH	63	347.8	355.9	7.6 (23.0)	7.5 (0.1, 15.0)
QTcB (msec)					
Symbicort MDI	123	393.4	396.8	3.5 (25.1)	2.9 (-2.0, 7.8)
Pulmicort TBH	63	393.9	395.1	12. (27.4)	0.4 (-6.4, 7.2)
QTcF (msec)					
Symbicort MDI	123	375.9	382.1	6.2 (21.7)	6.2 (1.8, 10.6)
Pulmicort TBH	63	377.7	381.1	3.5 (21.0)	3.3 (-2.8, 9.3)
Source: T53, p146; SD-039-0719					

Table 128. SD-039-0719, Patients with QTc ≥450 and QTcB change ≥60 msec (all on Symbicort)

Identifier	Age	Sex	Race	Visit	HR	QT	QTcB	QTcF	Δ≥60	Overall ECG assessment
E9006010	10	F	C	Baseline	107	265	354	321		Normal
				DOR	105	341	**451**	411	76/97B/90F	Normal
				Week 2	85	348	414	391	83/60B/70F	Normal
				Week 12	92	338	419	390	73/65B/69F	Normal
				Week 26	81	386	448	427	121/94B106F	Normal
E9013018	11	M	C	Baseline	58	381	375	377		Normal
				Week 2	100	340	439	403	64B	Normal
				Week 26	74	415	**461**	445	86B/68F	Normal
E9019006	11	F	C	Baseline	54	360	342	348		Normal
				DOR	78	362	413	395	71B	Normal
				Week 2	97	354	**450**	415	108B/67F	Normal
				Week 12	68	380	405	396	63B	Normal
E9019006	11	F	C	Baseline	54	360	342	348		Normal
				DOR	78	362	413	395	71B	Normal
				Week 2	97	354	**450**	415	108B/67F	Normal
				Week 12	68	380	405	396	63B	Normal
Source: T59, p154; SD-039-0719										

10.1.8.3 Conclusions

Review of this 6-month safety study in children 6-11 years of age did not pick up on any new or unexpected safety concerns. However, review of this study was complicated by the lack of a balanced representation of all racial groups in the study. The applicability of the safety findings, and the ability to extrapolate safety from one racial group to another, is discussed further in the Summary of Safety section of this review. Issues regarding HPA axis findings and QT effects in this age group were elucidated, although interpretation is hindered by lack of a placebo control. Both treatment groups exhibited a trend for decrease from baseline in mean 24-hour urinary cortisol over the course of the treatment period (numerically the decrease for Pulmicort was larger). This is different from the results of study 715 in adults, where changes in mean 24-hour urine results trended up for the Symbicort MDI and down for the Symbicort TBH treatment groups. Cortisol/creatinine ratios also showed similar trends for both treatment groups including a numerically larger decrease for the Pulmicort than the Symbicort group. Three patients in the Symbicort group had a QTcB of ≥450 msec and also had a change from baseline in QTcB of ≥60 msec. This is likely an effect of the formoterol component, and should be included in the labeling.

10.2 Line-by-Line Labeling Review

A line-by-line labeling review will be performed after this document has been finalized. However, many of the discussions and recommendations will be carried forward into the review of the labeling.

REFERENCES

Szefler S et al. Long-Term Effects Of Budesonide Or Nedocromil In Children With Asthma. New Engl. J. Med. (2000) 343 (15): 1054-1063

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Peter Starke
6/5/2006 08:56:35 AM
MEDICAL OFFICER

Badrul Chowdhury
6/5/2006 09:29:18 AM
MEDICAL OFFICER
I concur

11/10/05

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 21-929	**TRADE NAME:**	Symbicort® MDI
APPLICANT/SPONSOR:	AstraZeneca LP	**USAN NAME:**	Budesonide/formoterol
MEDICAL OFFICER:	J. Harry Gunkel, M.D.		
TEAM LEADER:	Peter Starke, M.D.	**CATEGORY:**	Asthma controller
FILING DATE:	November 22, 2005	**ROUTE:**	Oral inhalation

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
September 23, 2005	September 23, 2005	N-000	

RELATED APPLICATIONS

Document Date	Application Type	Comments
October 5, 2001	IND 63,394 Ser 000	The IND for this application
May 6, 2004	IND 63,394 Ser 247	Pre-NDA meeting briefing document

REVIEW SUMMARY: NDA 21-929 has been submitted by AstraZeneca for approval of its new product Symbicort® MDI. The application is fileable, and the primary review must be completed by May 23, 2006.

Symbicort is a fixed combination of the corticosteroid budesonide and the long-acting beta$_2$-agonist formoterol. Approval is sought for two dosage strengths of the product, 80 mcg budesonide/4.5 mcg formoterol per actuation and 160 mcg budesonide/4.5 mcg formoterol per actuation. Each would be administered as two actuations twice daily.

The proposed indication for Symbicort MDI is the long-term maintenance treatment of asthma in patients 12 years of age and older. The application includes a request for deferral for patients 6 to <12 years until 2007, pending resolution of some CMC issues with the pediatric dosage form product. There is also a request for partial waiver for patients 4 to <6 years. The Applicant's justification for both the deferral and partial waiver requests are valid and the Division will grant them.

The amount of clinical evidence offered in support of this application is huge because of other related products and the information that derives from them. There is a DPI form of Symbicort marketed internationally, and the two mono-product components of Symbicort are each marketed separately. The Applicant has identified core studies with those products which have been integrated and summarized for this NDA. The formoterol mono-product comparator presents a special challenge because it is a DPI formulation, unlike Symbicort MDI and the budesonide comparator. This raises pharmaceutics issues in evaluating the formoterol contribution to the product.

In addition, the program for Symbicort MDI itself encompassed 27 studies. The nine Phase 3 studies included adults and children, twice-daily [redacted] dosing regimens, and a total of five different comparator products. Although this comprises a large clinical database (almost 5000 patients), the program was constructed economically so that a significant review issue will be whether the program provides adequate evidence to satisfy the combination policy and also provides justification for the two proposed doses.

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS: X **FILEABLE** ____ **NOT FILEABLE**

Referential Notation: References to source material are provided in this review. Within text, the references are bracketed [ ] and follow a standard format: the module number within the NDA according to CTD format; the volume number; the section within the volume; and the page number(s) where the source material is located; for example, [M5, v 1.2, sec 5.3.5.1, p 499]. References to electronic material show the file name and letter date. References to hard copy material outside the submission (e.g., FDA reviews, correspondence, meeting minutes) are descriptive; for example, [NDA XX-XXX, Medical Officer's Review, December 12, 1998].

1. GENERAL INFORMATION

NDA 21-929 is a 505(b)(1) application for Symbicort® MDI, a new product from AstraZeneca LP (AZ). The stamp date for the application is September 23, 2005; the filing date is November 22, 2005; and the PDUFA date is July 23, 2006. The application is in CTD format and was filed electronically, but it is not an eCTD application.

Symbicort is a metered dose inhaler presentation using HFA 227 propellant. It is a fixed-dose combination product of budesonide and formoterol fumarate dihydrate. Throughout this review, references to dose forms of the product will be abbreviated by showing the nominal delivered doses of the two components, budesonide followed by formoterol; for example, 80 mcg budesonide + 4.5 mcg formoterol will be indicated by "80/4.5". Two dosage strengths are proposed for different asthma severities. Each is proposed for two actuations twice daily as shown in Table 1.

Table 1: Symbicort MDI Dosages

Dosage Strength	Dosage	Total Daily Dose
80 mcg budesonide + 4.5 mcg formoterol/actuation	2 actuations (160/9) BID	320/18
160 mcg budesonide + 4.5 mcg formoterol/actuation	2 actuations (320/9) BID	640/18
Source: summary/introsum.pdf, pp 2-3		

The proposed indication for Symbicort MDI is the ***"Long-term maintenance treatment of asthma in patients 12 years of age and older."***

The goals for this application have been curtailed in two significant ways since the pre-NDA meeting and discussion of June 28, 2004.

- The Applicant is not seeking an indication for children younger than 12 years.

2. REGULATORY BACKGROUND

IND 63,394 was filed in October, 2001, to study Symbicort in the U.S. The development program was ambitious from the beginning, involving as it did a combination product to be studied around the world, and intended for approval for adults and children in both twice daily and dosing regimens. Many clinical studies were planned and ultimately conducted, and much of the regulatory history of the product involved discussions between the Sponsor and the Division about clinical study design issues that arose. The several studies involved disparate populations, dosages, endpoints, and comparators. Early in development, it was questionable whether the program could satisfy the combination policy because the intended formoterol mono-product comparator was a dry powder inhaler (DPI) formulation, unlike Symbicort and the budesonide mono-product which are propellant-driven MDI presentations. The Division was concerned that it would be difficult to differentiate pharmacological effects from pharmaceutical effects in evaluating the contribution of formoterol to the product. Eventually, the Sponsor agreed to conduct a clinical study to sort out this issue. That study was performed and is included in the NDA.

At a CMC pre-NDA meeting of November, 2004, several substantive issues were identified by CMC reviewers and discussed with AZ.

. The Sponsor received the comments and followed up with work intended to correct the problems. A follow-up meeting occurred in June, 2005 *[Minutes of 6/22/05 meeting, DFS August 31, 2005].* At that meeting, AZ stated its belief that the problems had been addressed, but the Division indicated that full review of all data would be needed to make a determination. AZ believed its solutions had been adequate for the 80/4.5 and 160/4.5 presentations of the

NDA.

Other important milestones in the program included an End-of-Phase 2 meeting in April, 2002, and the clinical pre-NDA meeting in June, 2004.

2.1 FOREIGN MARKETING HISTORY

Symbicort MDI was approved in Switzerland in July, 2005. As of August 1, 2005, applications are pending in Australia, New Zealand, South Africa, UK, and Venezuela. Symbicort MDI has not been withdrawn from any market nor has regulatory approval been denied because of safety or effectiveness reasons. *[other\foreignm.pdf]*

A dry powder inhaler form of Symbicort known as Symbicort Turbuhaler is approved in 91 countries as of December, 2004. The mono-product components are each also available commercially in other countries. Budesonide is available in the US as Pulmicort® Turbuhaler® and Pulmicort Respules®, and is also available internationally.

The AZ formoterol product is available as OXIS® Turbuhaler in 82 countries, but is not approved nor the subject of an NDA in the US.

3. ITEMS REQUIRED FOR FILING

The Table below, copied from the NDA Table of Contents, indicates that all required elements are present in this NDA and shows their location.

Table 2: Contents of NDA 21-929

CTD Description	Paper Archive Copy Volume No.	Archive Copy Location Folder/File Name
Table of Contents	1	\ndatoc.pdf
1.2 Cover Letter	1	\cover.pdf
1.1.2 FDA Form 356h	1	\356h.pdf
1.3.5.1 Patent Information and Patent Certification	1	other\patinfo.pdf
1.3.3 Debarment Certification	1	other\debar.pdf
Establishment Description	N/A	N/A
1.3.2 Field Copy Certification	1	other\fieldcer.pdf
1.1.3 Copy of User Fee Cover Letter (FDA form 3397)	1	other\userfee.pdf
1.3.4 Financial Disclosure	1	other\finandis.pdf
1.4.1 Letter of Authorization	1	other\letrauth.pdf
1.9.2 Pediatric Deferral and Partial Waiver Requests	1	other\pedwaiv.pdf
1.3.5.3 Exclusivity Request	1	other\exclusivity.pdf
1.4.4 List of INDs, and NDAs	1	clinstat\indsndas.pdf
1.12.14 Environmental Assessment	1	cmc\environbudesonide.pdf
1.13.10 Foreign Marketing History	1	other\foreignm.pdf
1.16 Risk Management Program	1	other\riskman.pdf
1.14 Labeling		
1.14.1.5 Labeling History	N/A	N/A
1.14.1.3 Proposed Labeling Text		
Proposed PI (PDF Doc)	1	labeling\proposed_pi.pdf
Proposed PI (Word Doc)	1	labeling\proposed_pi.doc
Proposed PPI (PDF)	1	labeling\proposed_ppi.pdf
Proposed PPI (Word Document)	1	labeling\proposed_ppi.doc
Currently Used Labeling Text	N/A	N/A
Last Approved Labeling Text	N/A	N/A
Final Printed Package Insert	N/A	N/A

CTD Description	Paper Archive Copy Volume No.	Archive Copy Location Folder/File Name

1.14.1.1 Carton and Container Labels (Draft)		
Carton Label	1	labeling\carton\carton.pdf
Container Label	1	labeling\contain\container.pdf
1.14.3.2 Other Labels		
Summary of Information for Patients (PIL)	1	labeling\other\pil.pdf
dose card sample_draft_label	1	labeling\other\dose card sample_draft_label.pdf
dose card_draft_label	1	labeling\other\dose card_draft_label.pdf
1.14.1.2 Annotated Labeling Text	1	summary\annotated.pdf
References		
Advairdiskuspi: Advair diskus prescribing information, fluticasone propionate/salmeterol inhalation powder. September 2004 - RL-2128	1	labeling\references\advairdiskuspi.pdf
Pulmicort Respules Package Insert	1	labeling\references\pulmicortrespulespi.pdf
Module 2: Common Technical Document Summaries		summary\sumtoc.pdf
Module 3: Quality		cmc\cmctoc.pdf
Module 4: Nonclinical Study Reports		pharmtox\pharmtoc.pdf
Module 5: Clinical Study Reports		clinstat\clintoc.pdf

4. CLINICAL INFORMATION

4.1 Related Products

As noted in Section 2.1 above, there are several products that played key roles in the Symbicort MDI clinical development. They are listed and described in the Table below.

Table 3: NDA 21-929 Clinical Products

Product	Description
Symbicort pMDI	**The NDA drug**
Symbicort Turbuhaler (TBH)	DPI marketed for asthma and COPD outside US
Budesonide pMDI	***pMDI*** comparator mono-product – not a marketed product
Pulmicort Turbuhaler (budesonide)	DPI approved for asthma in US (NDA 20-441).
OXIS Turbuhaler (formoterol)	***DPI*** comparator mono-product. Marketed for asthma outside US

Three points are particularly notable about these products as they apply to this NDA.

1. Symbicort Turbuhaler is a DPI presentation of Symbicort marketed widely around the world, as noted in Section 2.1, but it has not been studied at all in the U.S. The Applicant's handling of data about this product as it relates to Symbicort MDI was discussed and agreed to with the Division at the pre-NDA meeting as follows.

More than 60 clinical studies with Symbicort TBH were grouped according to their designs and applicability to Symbicort MDI into the following categories:

1A. Placebo-controlled, parallel-group, blinded studies in patients with asthma
1B. Active-controlled, parallel-group, blinded studies in patients with asthma
1C. Active-controlled, parallel-group, open studies in patients with asthma
2. Uncontrolled, open, long-term studies in patients with asthma
3A. Controlled, cross-over, repetitive dose studies in patients with asthma
3B. Controlled, cross-over, single-dose studies in patients with asthma
4. Studies in healthy subjects
5. Studies in patients with acute asthma
6. Studies in patients with COPD
7A. Symbicort adjustable maintenance studies in patients with asthma
7B. Symbicort single inhaler studies in patients with asthma

Twenty-six studies fall into categories 1-5, and 12 of them were designated as "core" studies. As agreed with the Division, safety data from the core studies are presented in a separate Integrated Summary of Safety for Symbicort TBH *[clinstat\iss\symbicorttbhiss.pdf]*, and individual study reports are also included for those studies. For the other 14 studies that fall into categories 1-5, summaries of serious adverse events (SAE) and discontinuations due to adverse events (DAE) are provided. Studies that fell into categories 6-7B were not considered relevant and are not included in this application.

2. The formoterol mono-product comparator is marketed internationally as OXIS [redacted]. The same strategy was used to handle the OXIS studies as was used for the Symbicort TBH studies, but the categories were slightly different.

1A. Placebo-controlled, parallel-group, blinded studies in patients with asthma
1B. Active-controlled, parallel-group, blinded studies in patients with asthma
1C. Active-controlled, parallel-group, open studies in patients with asthma
2. Uncontrolled, open, long-term studies in patients with asthma
3A. Controlled, cross-over, repetitive dose studies in patients with asthma
3B. Controlled, cross-over, single-dose studies in patients with asthma
4. Studies in healthy subjects
5. Studies in patients with acute asthma
6. Studies in patients with COPD
7. Studies in patients with use on an as-needed basis
8. Studies with use in exercise-induced bronchospasm

For OXIS, 27 studies were considered to be core studies. They are included in an OXIS ISS *[clinstat\iss\oxisiss.pdf]*, and study reports are included in the application. Summaries of SAE and DAE are provided for another 66 studies, and studies from categories 6-8 are not included at all in the application.

OXIS has a critical role for this NDA. It is a DPI presentation, unlike Symbicort and the budesonide comparator which are MDI presentations, and this difference generates concern about distinguishing pharmaceutic from pharmacological effects in evaluating the contribution of the formoterol component to the combination product. After ongoing discussions on this issue with the Division, the Sponsor agreed to conduct a separate study to address it. That study was SD-039-0729. Its review will be pivotal in the determination of whether the application meets criteria for approvability.

3. Finally, the MDI budesonide mono-product comparator used in the program is not the same as the marketed Pulmicort DPI product. This is important because Pulmicort was also included in some studies as a comparator and the distinction will need to be maintained for review. Because Pulmicort is approved in the US, supportive information about its use is provided in the NDA by reference to the appropriate IND and NDAs, but is not included within this application.

Because of the multiple products and the ambition of the Symbicort MDI clinical program, review of the clinical sections of the NDA will need to account for these various points and distinctions about the products. How they increase the complexity of the clinical program is shown in more detail in the next section.

4.2 Symbicort MDI Clinical Program

Twenty-seven studies comprise the Symbicort MDI clinical program: 14 Phase 1, 4 Phase 2, and 9 Phase 3. The Applicant describes the broad objectives of the program's phases as follows. *[summary\clinover.pdf]*

- Phase 1 was intended generally to investigate the PK and bioavailability characteristics of Symbicort MDI, and specifically to evaluate the relative bioavailabilities of the Symbicort components and the mono-products and to determine dose proportionality PK characteristics among the Symbicort MDI doses.

- Phase 2 was intended to evaluate the bronchodilating properties of Symbicort MDI, but as already noted, the "pivotal" study in this evaluation was SD-039-0729 which addressed the pharmaceutic aspects of the pharmacodynamic behavior of formoterol.

- Phase 3 was originally intended to satisfy the combination policy; support adult indications; support dosage strengths; and support twice daily dosing

Reviewer's Comment: ***The Symbicort MDI clinical program does not appear to have included any sort of device reliability evaluation. A comment will be sent to the Applicant noting its absence.***

As agreed with the Division at the pre-NDA meeting, the Applicant pooled the Symbicort MDI studies, primarily for purposes of the safety evaluations and analyses. The pooling strategy was based on study designs, objectives, and exposures. The pools and numbers of subjects and patients are summarized in the next Table. The total number of persons

in the studies and the numbers who received Symbicort MDI are specified in the Table, but the breakdown by the various and several comparators is not shown.

Table 4: Number of Persons in Symbicort MDI Studies, by Pool

Study Pool	Number Treated	
	Symbicort MDI	Total
Pool 1: Phase 1 Studies	364	393
≥12 yrs	340	369
<12 yrs	24	24
Pool 2: Phase 2 Studies	289	310
≥12 yrs	289	310
<12 yrs	0	0
Pool 3: Placebo-controlled Studies with no Symbicort Run-in	254	1107
≥12 yrs	247	1076
<12 yrs	7	31
Pool 4: All placebo-controlled Phase 3 Studies	707	1858
≥12 yrs	700	1827
<12 yrs	7	31
Pool 5: Phase 3, active- or placebo-controlled Studies	2193	4951
≥12 yrs	1537	3504
<12 yrs	656	1447
Pool 6: All Symbicort exposure from all completed Phase 2/3 studies	3616	3616
≥12 yrs	2690	
<12 yrs	926	
All Exposures in all studies	3980	6321
≥12 yrs	3030	4694
<12 yrs	950	1627
Source: summary\clinsum.pdf, p 49		

The nine Phase 3 studies, which will provide the bulk of evidence for clinical effectiveness and safety, are shown in the next Table with some of their features. The Table illustrates the complexity of the program, with the several different doses and comparators. There is no within-study comparison of different doses in the entire program, so conclusions about dose responses will have to be inferred from the results of separate studies with similar enough designs.

Reviewer's Comment: ***Although there was not strict replication of dose-comparison results within this program, the Applicant has another NDA on file, #21-949, for the "M3" presentation of Pulmicort Turbuhaler. That application includes clinical data for metered doses of budesonide of 90 mcg and 180 mcg, the same metered doses of budesonide that are in Symbicort MDI. This body of evidence from the Pulmicort product may be considered supportive information for the Symbicort NDA.***

The Applicant does not designate any study as "pivotal," but only 716 and 717 encompass both mono-product comparators within a single study. They are also the two studies featured in the proposed package insert (see Section 5 below).

Table 5: Symbicort MDI Phase 3 Studies

Study/ Duration	Ages/N	Comparators	Symbicort MDI Daily Doses BID Program	Symbicort MDI Daily Doses QD Program	Primary Endpoints

			160/18	320/18	640/18	160/9	320/9	
716 12 wks	≥ 12 yrs/480 6-11 yrs/31	Bud, Form Placebo		X				Avg 12h FEV_1
717 12 wks	≥ 12 yrs/560	Bud, Form Bud+Form, Placebo			X			Avg 12h FEV_1
718 12 wks	6-15 yrs/411	Bud, Form	X					Morning PEF
681 12 wks	≥ 12 yrs/680	Bud Sym TBH			X			Morning PEF
682 12 wks	6-11 yrs/622	Bud Sym TBH		X				Morning PEF
719 26 wks	6-11 yrs/187	Pulm TBH			X			Safety
715 52 wks	≥ 12 yrs/673	Sym TBH			X			Safety
725 12 wks	6-15 yrs/540	Sym pMDI qd & bid Bud qd	X			X		Evening PEF
726 12 wks	≥ 16 yrs/750	Sym pMDI 2x160 qd Sym pMDI 2x80 qd & bid Bud qd Placebo		X		X	X	Evening PEF

Bud=budesonide MDI; Form=formoterol DPI (OXIS); Bud+Form=Bud administered concurrently with Form; Pulm TBH=Pulmicort TBH (budesonide DPI)

Source: summary\clinsum.pdf, p 2997

4.2.1 Ongoing studies

At the NDA cutoff date, there were four ongoing studies with Symbicort MDI. Three were for asthma [redacted]. Enrollment is completed in the asthma studies and safety results will be provided in the 4-month safety update to the NDA. The asthma studies are described in Table 6.

Table 6: Ongoing Symbicort MDI Asthma Studies

Study Description	Planned N	N at Cutoff Date
SD-039-0728: A 52-week, Phase 3 study comparing long-term safety of Symbicort pMDI 160/4.5 x 4 puffs BID to 2 puffs BID and budesonide 160 x 4 puffs BID in adults and adolescents	570	708

Study Description	Planned N	N at Cutoff Date
D5896C00001: 12-week study to compare efficacy and safety of Symbicort pMDI 160/4.5 x 2 puffs QD, Symbicort 80/4.5 x 2 puffs QD, Symbicort 80/4.5 x 2 puffs BID, budesonide 160 x 2 puffs QD in patients ≥ 12 years	600	620
D5896C00005: Two-stage, open-label, 7-month study to assess efficacy and safety of Symbicort pMDI either as a fixed-dose or adjustable-dose regimen vs. fixed regimen of Advair in patients ≥ 12 years	1200	1226
Source: summary\clinsum.pdf, p 1125		

5. PROPOSED LABELING

The application includes the requisite components of proposed labeling. The proposed package insert is modeled closely after that of Advair, the only analogous steroid/LABA combination product currently approved for asthma. Aspects of the proposed labeling that will be notable for review include the following. *[summary\annotated.pdf]*

- Much of the information about budesonide and formoterol is nearly verbatim from the Pulmicort and Foradil labels, respectively
- The Clinical Studies section presents results of the two studies 716 and 717. AE data from a third placebo-controlled study, 726, is included in the Adverse Events summary table. Two figures representing results of the primary efficacy endpoints from study 717 are proposed for the package insert to illustrate the effects of the drug. Those figures are reproduced below.

- Results of some secondary endpoints are also presented including some patient-reported outcomes. These will have to be carefully reviewed to determine whether their inclusion in the labeling can be justified.
- Although the indication specifies patients 12 years and older, there is no explicit statement otherwise that the drug is not approved for children <12 years and in fact the section on Pediatric Use might imply that the product may be used in those children.
- There is considerable attention paid in the Dosage and Administration section to the rapid onset of effect of Symbicort. Although the Warnings and Precautions sections caution against its use for acute relief, the information about rapid onset might represent a conflicting message. Whether to allow this information will need careful consideration.
- Information about the safety of LABAs that is currently being added to other products' labeling will also need to be included in the Symbicort labeling.

6. PEDIATRIC ISSUES

This application includes a request for deferral for children 6 to <12 years until 2007,

and the request for deferral will be granted until December 31, 2007.

The Applicant bases the partial waiver request for children 4 to <6 years on three points:

- A fixed dose combination product is not desirable for children in this young age range.
- Children <6 years may not be able to coordinate adequately for proper use of an MDI.

▪ Symbicort MDI does not represent a significant therapeutic benefit over existing therapies for this age group. Specifically Advair is approved for children down to 4.

The Division essentially concurs on these points. Although Advair is approved down to 4 years, the Diskus DPI device is probably easier to use than the MDI for those children and the Applicant's justification is valid.

7. FILING DECISION

The application is fileable.

8. TIMELINE FOR REVIEW

The important milestones for review of this application are shown in the Table below.

Table 7: NDA 21-929 Review Timeline

Milestone	Estimated Date of Completion
Stamp Date	August 23, 2005
Filing and Planning Meeting	November 9, 2005
Mid-Cycle Point	February 23, 2006
Complete Primary Review	***May 23, 2006***
Complete Secondary Review	June 11, 2006
Division Goal Date	July 9, 2006
PDUFA Date	**July 23, 2006**

9. DSI REVIEW AND AUDIT

A DSI review will be requested. Centers will be selected for audit according to several criteria: those from pivotal studies (e.g., 716 and 717) or studies otherwise critical to the program (e.g., study SD-039-0729); those that enrolled the most patients; those with a disproportionate number of protocol violations or dropouts or whose primary results were discrepant from overall results; or those with investigators with possible financial conflicts.

10. TRADE NAME REVIEW

The proposed trade name, Symbicort, was reviewed by the Division of Medication Errors and Technical Support (DMETS) in March, 2004. DMETS recommended against use of the name because of possible confusion with the product Synacort. The Division of Drug Marketing, Advertising and Communication (DDMAC) found the name acceptable from a promotional perspective. The Applicant rebutted the DMETS objection in December, 2004, by stating that Synacort was being withdrawn from the US market and was not marketed internationally. DMETS reconsidered the name in January, 2005, and reversed its objection. DMETS also noted that the name would have to be reviewed again approximately 90 days before an anticipated approval date.

11. SUMMARY AND DISCUSSION

NDA 21-929 has been submitted by AstraZeneca for approval of its new product Symbicort® MDI. The application is fileable, and the primary review must be completed by May 23, 2006.

Symbicort is a fixed combination of the corticosteroid budesonide and the long-acting beta2-agonist formoterol. Approval is sought for two dosage strengths of the product, 80 mcg budesonide/4.5 mcg formoterol per actuation and 160 mcg budesonide/4.5 mcg formoterol per actuation. Each would be administered as two actuations twice daily.

The proposed indication for Symbicort MDI is the long-term maintenance treatment of asthma in patients 12 years of age and older. The application includes a request for deferral for patients 6 to <12 years until 2007, [redacted]. There is also a request for partial waiver for patients 4 to <6 years. The Applicant's justifications for both the deferral and partial waiver requests are valid and the Division will grant them.

The amount of clinical evidence offered in support of this application is huge because of other related products and the information that derives from them. There is a DPI form of Symbicort marketed internationally, and the two mono-product components of Symbicort are each marketed separately. The Applicant has identified core studies with those products which have been integrated and summarized for this NDA. The formoterol mono-product comparator presents a special challenge because it is a DPI formulation, unlike Symbicort MDI and the budesonide comparator. This raises pharmaceutics issues in evaluating the formoterol contribution to the product.

In addition, the program for Symbicort MDI itself encompassed 27 studies. The nine Phase 3 studies included adults and children, twice-daily and once-daily dosing regimens, and a total of five different comparator products. Although this comprises a large clinical database (almost 5000 patients), the program was constructed economically so that a significant review issue will be whether the program provides adequate evidence to satisfy the combination policy and also provides justification for the two proposed doses.

12. COMMENT TO APPLICANT

We do not find any assessment of device reliability or satisfaction in your application. These evaluations are typically expected in the development of new metered dose inhaler products.

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/s/

John Gunkel
11/10/2005 10:03:24 AM
MEDICAL OFFICER

Peter Starke
11/10/2005 12:50:52 PM
MEDICAL OFFICER