Study 682 compared Symbicort MDI (80/4.5, 2 inhalations BID) and Symbicort TBH (80/4.5, 2 inhalations BID) at a total daily dose of 320/18 mcg/day with budesonide MDI CFC (80 mcg, 2 inhalations BID) 320 mcg/day total daily dose. There were no differences in mean AM plasma cortisol levels among treatment groups. Among patients with a normal AM plasma cortisol at baseline, 5.8% of Symbicort MDI, 2.4% of budesonide, and 6.4% of Symbicort TBH patients shifted to less than the 5th percentile of baseline at the end of treatment. Among patients with a normal urinary cortisol at baseline, 14.7% of Symbicort MDI, 8.6% of budesonide, and 17.1% of Symbicort TBH patients shifted to less than the 5th percentile of baseline at the end of treatment.

Study 715 was a 1-year adult safety study comparing Symbicort MDI (160/4.5) and Symbicort TBH (160/4.5), each administered as 2 inhalations BID for a total daily dose of 640/18 mcg/day. This study was the primary long-term safety for Symbicort MDI. The review may be found in the Appendix of this document. For convenience, the discussion of HPA axis results is reproduced below; the tables will be found within the study review.

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.

Study 719 was a 6-month pediatric safety study comparing Symbicort MDI (160/4.5) and budesonide TBH (160), each administered as 2 inhalations BID for a total daily dose of 640/18 or 640 mcg/day, respectively. Among patients with a normal urinary cortisol at baseline, 5.0% of Symbicort MDI and 9.4% of budesonide patients shifted from normal to low at the end of treatment.

Study 726 was a 12-week placebo-controlled safety and efficacy study performed [redacted]. However, it did have one study arm of Symbicort (80/4.5) administered as 2 inhalations BID for a total daily dose of 320/18 mcg/day. Among patients with a normal urinary cortisol at baseline, 1.8% of Symbicort MDI 320/18 (BID), 1.0% of Symbicort MDI 320/9 QD, 2.8% of budesonide QD, and none of the placebo of Symbicort 160/9 QD patients shifted from normal to low at the end of treatment.

Table 32. Mean 24-hour urinary cortisol results (nmol) (Mean, range)

Study	Treatment Total daily dose	N	Baseline	End of treatment	
			GM	Observed GM	ANCOVA GM
682	Symbicort MDI 320/18	41	18.0	21.7	23.1
	Budesonide 320	43	21.0	23.7	23.9
	Symbicort TBH 320/18	42	25.2	18.0	16.9
715*	Symbicort MDI 640/18	59	46.1	48.3	55.6
	Symbicort TBH 640/18	26	58.6	49.3	51.7
719	Symbicort MDI 640/18	113	22.9	17.8	19.8
	Budesonide 640	56	26.5	15.7	17.0
725	Symbicort MDI 160/9	132	25.4	24.6	26.3
	Symbicort MDI 160/18	150	25.4	26.6	29.5
	Budesonide 160	130	24.1	24.2	27.1
726	Symbicort MDI 160/9	126	45.2	44.9	45.6
	Symbicort MDI 320/9	116	40.9	37.2	38.3
	Symbicort MDI 320/18	129	52.4	47.0	44.4
	Budesonide 320	116	46.2	37.5	36.8
	Placebo	95	52.9	48.9	46.4
Source: T102, p3193; clinsum.pdf					

7.1.7.3.2 Analyses focused on measures of central tendency

Please see the discussion above and the individual study reviews in the Appendix.

7.1.7.3.3 Analyses focused on outliers or shifts from normal to abnormal

Please see the discussion above and the individual study reviews in the Appendix.

7.1.7.3.4 Marked outliers and dropouts for laboratory abnormalities

Please see the discussion above and the individual study reviews in the Appendix.

7.1.7.4 Additional analyses and explorations

No additional analyses were performed.

7.1.7.5 Special assessments

No special assessments were performed.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were preformed throughout the development program. Since the pharmacologic effects of both active drugs are well known and characterized, the review focused on elucidating any differences between the combination drug product and the individual monoproducts, as well as each to placebo when available. 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.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The review included analyses of the pivotal, some secondary, and the two long-term safety studies presented with the application. In addition, the applicant performed analyses including the various Pools of studies.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

In the placebo-controlled Phase 3 studies, mean changes from baseline for heart rate, systolic, and diastolic blood pressure showed no unusual or clinically meaningful trends. Please see the individual study reviews in the Appendix for further details.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

The percentages of patients with individual shifts in results from normal at baseline to abnormal were similar among treatment groups. Please see the individual study reviews in the Appendix for details.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Marked outliers for vital signs or dropouts due to changes in vital signs were not issues noted in the clinical studies.

7.1.8.4 Additional analyses and explorations

No additional analyses were performed.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECGs were preformed throughout the development program. ECGs were evaluated for heart rate, QT interval, and corrected QT by Bazett (QTcB) and Fridericia (QTcF) formulas. Since the pharmacologic effects of both active drugs are well known and characterized, the review focused on elucidating any differences between the combination drug product and the individual monoproducts, as well as each to placebo when available. 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.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The review included analyses of the pivotal, some secondary, and the two long-term safety studies presented with the application. In addition, the applicant performed analyses including the various Pools of studies. While all pools were reviewed, the review focused on Pool 5, the pool with by far the largest number of patients and ECG readings. Within Pool 5, the applicant

distinguished between patients with post-AM-dose assessments and all US studies and well as between US and non-US studies. In the post-AM-dose assessment sub-pool there were 562 patients on Symbicort assessed with 1997 ECGs during the treatment period. In the larger US Phase 3 study database, 1262 patients on Symbicort MDI were assessed with a total of 2819 ECGs, of which 562 patients were assessed with 1997 ECGs collected 30 minutes to 2 hours after the morning dose during the treatment period. In Study 715, the only non-US, Phase 3 study with ECG assessments, 433 patients on Symbicort MDI were assessed with 1653 ECGs, and 223 patients on Symbicort TBH were assessed with 850 ECGs during the treatment period.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

ECG findings for the Pool 5 patients who had AM assessments are shown in Table 33. For mean heart rate, all treatment groups experienced small changes from baseline to treatment maximum. Treatment means for Symbicort MDI were slightly higher compared to placebo and budesonide and slightly lower than formoterol; differences between Symbicort MDI and the other treatment groups were small and not clinically important. The percentage of patients that crossed the high threshold (>100 bpm) at any time was slightly higher for Symbicort MDI compared to placebo and budesonide, and slightly lower than formoterol (not shown). No important findings were noted for QRS and PR interval data (not shown). For mean QT, QTcB, and QTcF, all treatment groups experienced increases from baseline to treatment maximum. While differences between groups at treatment maximum were generally small with narrow 95% CIs, Symbicort MDI trended higher than the other treatment groups.

The ECGs interpretations performed by a cardiologist were tabulated (not shown). For the overall ECG interpretation, the percentage of subjects with shifts from normal to abnormal (most severe assessment) was slightly higher for Symbicort MDI compared to placebo or budesonide, but similar to formoterol. The most prevalent abnormality was ST-T wave changes, slightly higher in Symbicort MDI compared to the placebo, budesonide, and formoterol groups. This category included any change noted to the ST-T wave segment, without regard to clinical relevance. Other individual ECG abnormalities were similar among active treatment groups, with the lowest incidence noted in the placebo group.

Table 33. ECG findings, Pool 5 AM assessments

	N	Baseline	Observed	Change	ANCOVA LS mean (95% CI)
HR (bpm)					
Symbicort MDI	561	74.7	79.0	4.3	4.8 (4.0, 5.7)
Budesonide	441	73.9	76.9	3.0	3.2 (2.3, 4.1)
Formoterol	381	74.4	80.0	5.5	6.0 (4.9, 7.0)
Placebo	306	70.3	72.4	2.2	0.9 (-0.2, 2.0)
QT (msec)					
Symbicort MDI	561	358.2	378.8	20.7	19.8 (18.2, 21.3)
Budesonide	441	358.7	380.8	22.1	21.4 (19.6, 23.2)
Formoterol	381	360.4	378.0	17.6	17.4 (15.5, 19.3)
Placebo	306	368.1	385.8	17.7	19.8 (17.7, 22.0)

	N	Baseline	Observed	Change	ANCOVA LS mean (95% CI)
QTcB (msec)					
Symbicort MDI	561	396.1	411.4	15.3	15.3 (13.9, 16.7)
Budesonide	441	395.1	407.2	12.0	11.6 (10.0, 13.2)
Formoterol	381	398.0	412.7	14.7	15.7 (14.0, 17.5)
Placebo	306	395.3	405.6	10.2	9.8 (7.9, 11.8)
QTcF (msec)					
Symbicort MDI	561	382.7	397.9	15.2	14.8 (13.5, 16.0)
Budesonide	441	382.3	395.5	13.3	12.6 (11.3, 14.0)
Formoterol	381	384.7	398.5	13.8	14.3 (12.8, 15.8)
Placebo	306	385.8	396.7	10.9	11.9 (10.2, 13.5)
Source: T124, p3241; T126, p3242; clinsum.pdf					

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

A summary of changes in QT, QTcB, and QTcF for patients in Pool 5 with AM assessments is shown in Table 34. The table shows the number and percent of patients for each treatment group with an increase of ≥30 msec or a maximum treatment value ≥450 msec and ≥60 msec or a maximum treatment value ≥500 msec, subdivided by patients with increases of 30 or 60 msec and by patients with values ≥450 or ≥500 msec.

The percentage of patients with a QT, QTcB, or QTcF value that crossed the high threshold [450 msec] or a change from baseline ≥30 msec was similar across treatment groups, with the majority of patients having a change of ≥30 msec only. Of these, the percentage with QTcB or QTcF values crossing the 450 msec threshold was low, but slightly higher on Symbicort MDI compared to the other treatment groups; this was most evident for QTcB. Few patients experienced a change from baseline of ≥60 msec, making treatment group comparisons difficult.

Table 34. Summary of QT, QTcB, and QTcF changes (msec), Pool 5 AM assessments

Magnitude of change	Treatment	Number of patients, n (%)			
		n	Change ≥30 or ≥60	≥450 or ≥500	Either
QT (msec)					
Δ ≥30 or ≥450	Symbicort MDI	561	181 (32.3)	3 (0.5)	182 (32.4)
	Budesonide	441	140 (31.7)	4 (0.9)	142 (32.2)
	Formoterol	381	113 (29.7)	0	113 (29.7)
	Placebo	306	87 (28.4)	0	87 (28.4)
Δ ≥60 or ≥500	Symbicort MDI	561	16 (2.9)	0	16 (2.9)
	Budesonide	441	18 (4.1)	0	18 (4.1)
	Formoterol	381	7 (1.8)	0	7 (1.8)
	Placebo	306	7 (2.3)	0	7 (2.3)
QTcB (msec)					
Δ ≥30 or ≥450	Symbicort MDI	561	119 (21.2)	21 (3.7)	127 (22.6)
	Budesonide	441	91 (20.6)	5 (1.1)	94 (21.3)
	Formoterol	381	101 (26.5)	7 (1.8)	105 (27.6)
	Placebo	306	51 (16.7)	2 (0.7)	52 (17.0)
Δ ≥60 or ≥500	Symbicort MDI	561	14 (2.5)	0	14 (2.5)
	Budesonide	441	6 (1.4)	0	6 (1.4)
	Formoterol	381	5 (1.2)	0	5 (1.2)

Magnitude of change	Treatment	Number of patients, n (%)			
		n	Change ≥30 or ≥60	≥450 or ≥500	Either
	Placebo	306	2 (0.7)	0	2 (0.7)
QTcF (msec)					
Δ ≥30 or ≥450	Symbicort MDI	561	107 (19.1)	3 (0.5)	108 (19.3)
	Budesonide	441	65 (14.7)	1 (0.2)	66 (15.0)
	Formoterol	381	62 (16.3)	0	62 (16.3)
	Placebo	306	40 (13.1)	0	40 (13.1)
Δ ≥60 or ≥500	Symbicort MDI	561	7 (1.2)	0	7 (1.2)
	Budesonide	441	3 (0.7)	0	3 (0.7)
	Formoterol	381	3 (0.8)	0	3 (0.8)
	Placebo	306	0	0	0
Source: T128, p3246; clinsum.pdf					

Number of patients with QT, QTcB, or QTcF findings of note, Pool 5 AM assessments

	Treatment group, n (%)			
	Symbicort MDI n=561	Budesonide MDI N=441	Formoterol TBH n=381	Placebo n=306
Either QT, QTcB, or QTcF				
Total with findings of note	44 (7.8)	30 (6.8)	17 (4.5)	13 (4.2)
Baseline <450 to ≥450 msec	23 (4.1)	9 (2.0)	7 (1.8)	2 (0.7)
Increase from baseline of ≥60 msec	28 (5.0)	23 (5.2)	10 (2.6)	9 (2.9)
Baseline ≥450 to higher	4 (0.7)	1 (0.2)	1 (0.3)	2 (0.7)
QT				
Total with findings of note	20 (3.6)	21 (4.8)	7 (1.8)	7 (2.3)
Baseline <450 to ≥450 msec	3 (0.5)	4 (0.9)	0	0
Increase from baseline of ≥60 msec	16 (2.9)	18 (4.1)	7 (1.8)	7 (2.3)
Baseline ≥450 to higher	3 (0.5)	0	0	0
QTcB				
Total with findings of note	28 (5.0)	11 (2.5)	12 (3.1)	6 (2.0)
Baseline <450 to ≥450 msec	21 (3.7)	5 (1.1)	7 (1.8)	2 (0.7)
Increase from baseline of ≥60 msec	14 (2.5)	6 (1.4)	5 (1.3)	2 (0.7)
Baseline ≥450 to higher	0	1 (0.2)	1 (0.3)	2 (0.7)
QTcF				
Total with findings of note	10 (1.8)	3 (0.7)	3 (0.8)	0
Baseline <450 to ≥450 msec	3 (0.5)	1 (0.2)	0	0
Increase from baseline of ≥60 msec	7 (1.2)	3 (0.7)	3 (0.8)	0
Baseline ≥450 to higher	1 (0.2)	0	0	0
Source: T129, p3248; clinsum.pdf				

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

There were no marked outliers in any of the US Phase 3 studies; i.e. no patient had a QT, QTcB, or QTcF value exceeding 500 msec during treatment. However, in the 1-year ex-US study 715, 3 Symbicort MDI patients and 1 Symbicort TBH patient experienced a shift in QT or QTc to ≥500 msec while on treatment. The applicant states that differences in QT analysis methodology in study 715 compared to US studies rendered comparisons to US data difficult.

7.1.9.4 Additional analyses and explorations

Analyses of ECG findings (Pools 4 and 5) were carried out by age, race, sex, and baseline ICS dose. The analyses revealed no clear relationships between these factors and responses to Symbicort. The applicant states the following: "In some demographic subgroups compared to the overall population, including Black subjects and subjects <16 years of age, Symbicort MDI and formoterol were noted to have larger mean changes and/or higher incidences of potentially significant abnormalities in some ECG parameters relative to placebo or budesonide groups. The clinical relevance of these findings is unclear and given the relatively small number of subjects in some subgroups, should be interpreted with caution. In addition, these differences between Symbicort MDI and its monoproducts and placebo were generally small and were not reflected in an increase in AEs or considered to be of clinical concern." [p3203; clinsum.pdf]

Analyses of ECG findings were also carried out by Symbicort dose. The applicant states that there was a suggestion of some dose-ordered relationships for both budesonide and formoterol components of Symbicort MDI for heart rate, QT, QTcB, and QTcF, overall ECG interpretation, and ST-T wave changes. The same was true for BID vs QD regimen differences. The differences between Symbicort MDI treatment groups were small and not considered to be of clinical importance. Across studies, the relative effects of Symbicort MDI compared to placebo and the monoproducts on ECG variables were generally similar despite different doses. Therefore, the applicant considered that these effects might be due to pooling of results across different populations rather than due to differences in doses or treatment regimens.

7.1.10 Immunogenicity

As small molecules, immunogenicity of either of the two ingredients or the HFA propellant is not a clinical concern.

7.1.11 Human Carcinogenicity

An unusual frequency of cancer was not seen in the clinical studies, nor was this expected based on the safety profiles of the individual active drugs.

7.1.12 Special Safety Studies

No special safety studies requested or performed as part of this application.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The abuse potential of this drug product is expected to be low. If abused for the corticosteroid effects, the beta-adrenergic signs and symptoms would likely be dose-limiting.

While rebound or withdrawal was not studied, this is not expected to be more of a clinical issue than for any other corticosteroid or long-acting beta-agonist drug product.

7.1.14 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies with Symbicort or formoterol in pregnant women. Based on lack of human data and the preclinical findings, Symbicort will be labeled Pregnancy Category C.

Budesonide is classified as Pregnancy B. This is based on birth registry data submitted (and reviewed by myself) originally to the NDA (20-746, SLR-015) for Rhinocort Aqua, resulting in a change from Category C to B for all budesonide drug products.

There were 11 pregnancies reported during the Symbicort MDI clinical development program. Of these, 5 received Symbicort MD. Listings were reviewed. One patient on Symbicort MDI (study 715) had to undergo a D&C for a spontaneous abortion 6 weeks post-treatment. One patient on Symbicort MDI during the run-in period (study 726) received 48 days of treatment and had a spontaneous abortion. The other three pregnancies resulted in full-term, healthy infants.

7.1.15 Assessment of Effect on Growth

No formal growth studies were conducted with Symbicort. Growth data from the 6-month safety study (719) with Symbicort in children were inconclusive.

Based on the fact that systemic exposure with Symbicort is similar to or less than that with Pulmicort TBH, the applicant is seeking to add the results of study published in the literature (Szefler et al 2000) to the to the PRECAUTIONS, Pediatric Use subsection of the Symbicort label. This was a 5-year NIH-sponsored longitudinal study (CAMP study) of asthmatic children 5 to 12 years of age, evaluating Pulmicort TBH in doses of 200 mcg administered BID. AstraZeneca states that the results showed a 1.1 centimeter mean reduction in growth compared to those receiving placebo (n=418) at the end of 1 year. They state that the difference between these 2 treatment groups did not increase further during the study; by the end of the 5-year study period, children treated with budesonide and children treated with placebo had similar growth velocities and the projected final height was comparable in both groups. AstraZeneca states that it is their understanding that the NIH plans to make the datasets supporting these conclusions available to the public in the near future. However, these data were not submitted nor reviewed for this application. Since the data were not reviewed, it is not appropriate to include the results in the labeling at this time.

The inclusion of precautionary language about effects on growth is appropriate, based on the recommendations of the combined Pulmonary-Allergy Drugs Advisory Committee and Endocrinologic and Metabolic Drugs Advisory Committee meeting of July 30-31, 1998, at which the effect of orally inhaled and intranasal corticosteroids on growth in children was discussed.

7.1.16 Overdose Experience

There is no specific overdose experience with Symbicort, and no overdoses were reported during the clinical development program. However, there are data with each active ingredient, and the

potential for and risks of either acute or chronic overdose are considered small and manageable clinically.

Acute overdose with budesonide would not be expected to be a clinical issue. With chronic overexposure, signs and symptoms of glucocorticoid toxicity might be expected. Physicians should be well aware of this concern, and the labeling for glucocorticoids has warnings for the associated risks.

The applicant reports having studied the safety of formoterol at up to 90 mcg/day (Oxis TBH) over 3 hours in adults, and when administered at doses of 54 mcg/day (Oxis TBH) for 3 days. Symbicort TBH has also been studied at a dose of 1600/45 mcg over 1 hour on top of maintenance doses of budesonide (640 mcg) and formoterol (18 mcg), and well as when administered at a dose of 1280/36 mcg acutely for asthma, or as a high cumulative dose of 1920/54 mcg in a tolerability study. The sponsor reports that in all of the above settings there were no specific safety concerns. [p3295; clinsum.pdf] It is expected, however, that in acute or chronic overdose beta-adrenergic signs and symptoms might develop such as tremor, headache, palpitations, etc.

7.1.17 Postmarketing Experience

There is no postmarketing experience with Symbicort MDI. AstraZeneca submitted a summary of postmarketing reports for other products, including Symbicort TBH, Pulmicort TBH, etc.

Symbicort TBH. The database includes 1197 million treatment-days as of September 30, 2004. There were 4 deaths, none appearing to be causally related. There were 3 reports of hepatic enzyme elevations, including 1 report of AST and GGT increase; 1 report of GGT increase; and 1 report of hepatitis.

Pulmicort TBH. There were 5 postmarketing reports of liver function abnormalities: 1 report of increased ALT and GGT; 1 report of AST, ALT, and GGT increased; 2 nonspecific reports of hepatic enzyme increased or liver function test abnormal; 1 report of hyperbilirubinemia.

Other reports from either the published literature, clinical trials, or postmarketing events include: hypersensitivity reactions such as anaphylactic reaction and bronchospasm; symptoms of hypocorticism and hypercorticism; and psychiatric symptoms including aggressive reactions, agitation, behavioral disturbances, and psychosis. [p3298; clinsum.pdf]

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The primary data source for safety was from the clinical studies with the Symbicort MDI itself. However, the safety profile of Symbicort MDI is also based on the clinical experience with each of the monoproducts, which have been available in the US for some time. Symbicort is also available ex-US in a Turbuhaler presentation (see Section 7.2.2, Description of Secondary Data

Sources). Likewise, one the mono-ingredients is also available ex-US in a dry powder presentation as Oxis Turbuhaler (see Section 7.2.2, Description of Secondary Data Sources).

The application included safety data from 27 completed clinical studies: 14 Phase 1 and 13 Phase 2/3 studies. In addition, serious adverse event data from 4 ongoing Phase 2/3 Symbicort studies were included. These 4 studies were completed and included in the 4-month Safety Update (see Section 7.2.9 for details). The cutoff date for the application was not specifically stated, but appears to have been December 31, 2004.

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. Phase 1 and 2 studies were pooled separately. There were three pools used for Phase 3 studies in addition to a pool with Phase 2 and 3 studies and a final pool of all studies. Pool 4, for example, allowed evaluation of safety for pooled placebo-controlled studies and Pool 3 for just the two pivotal studies, whereas other pooling strategies allowed evaluation of safety from different perspectives. The pools and numbers of subjects and patients are summarized in Table 35. 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.

Since Phase 1 was primarily single-dose safety information, (while the information was reviewed) it was considered to provide data of less clinical import than longer-term Phase 2/3 studies. Therefore, the focus of this safety review was on pooled Phase 2/3 studies (Pool 6) for overall safety numbers; pooled completed Phase 3 studies (Pool 5) for breakdown of numbers by drug product, dose, and dosing frequency; and pooled pivotal placebo-controlled studies (Pool 3) for tables of adverse events for labeling purposes.

Table 35. Number of Subjects in Symbicort MDI Studies, by Pool

Study Pool	Number Treated		Studies*
	Total	Symbicort MDI	
Pool 1: Phase 1 Studies ≥12 yrs <12 yrs	393 369 24	364 340 24	626, 713, 720, 721, 722, 723, 724, 730, 749, D5896C00011, D5899C00006, D5896C00010, D5896C00011, D5896C00013, 738, D5899C00006
Pool 2: Phase 2 Studies ≥12 yrs <12 yrs	310 310 0	289 289 0	**729**, 732, 733, [736*]
Pool 3: Placebo-controlled Studies with no Symbicort Run-in ≥12 yrs <12 yrs	1107 1076 31	254 247 7	**716**, **717**
Pool 4: All placebo-controlled Phase 3 Studies ≥12 yrs <12 yrs	1858 1827 31	707 700 7	**716**, **717**, 726
Pool 5: Phase 3, active- or placebo-controlled Studies ≥12 yrs <12 yrs *Total, including safety update*	4951 3504 1447 *7499*	2193 1537 656	715, 681, 682, **716**, **717**, 718, 719, 725, 726 *728, D5896C00001,*

Study Pool	Number Treated		Studies*
	Total	Symbicort MDI	
			D5896C00005
Pool 6: All Symbicort exposure from all completed Phase 2/3 studies ≥12 yrs <12 yrs *Total, including safety update*	3616 *6070*	3616 2690 926	715, 681, 682, **716**, **717**, 718, 719, 725, 726, **729**, 732, 733, 736 *728, D5896C00001, D5896C00005*
All Exposures in all studies ≥12 yrs <12 yrs	6321 4694 1627	3980 3030 950	All studies (*plus 4 studies in 4-month safety update**)
* Study 736, a single-dose crossover study, was prematurely terminated. Pivotal studies are **bolded**. Safety data from *Italicized* studies were submitted with 4-month Safety Update (study reports not submitted to application). Note that the numbers in the table do not include the safety update studies.			
Source: T4, p2998; T11, p3017; clinsum.pdf and Safety Update of 1/19/2006, T4, p27; 4MSU.pdf			

7.2.1.1 Study type and design/patient enumeration

The Symbicort MDI clinical program was a stand-alone development program. Phase 1 included 14 studies, and Phases 2/3 included 13 completed and 4 ongoing studies (as of the cutoff date of December 31, 2004). Most (13/14) of the Phase 1 and three Phase 2 studies were single dose crossover studies. A total of 9 Phase 3 studies have been completed: 7 placebo- or active-controlled, 12-week efficacy studies; and 2 open-label, active-controlled, long-term safety studies (26 and 52 weeks of treatment, respectively). These studies are shown in Table 5.

As shown in Table 35, a total of 6321 subjects were evaluated as part of the Symbicort MDI clinical development program, of whom 3980 were exposed to Symbicort MDI, 4694 ≥12 years of age (3030 exposed to Symbicort MDI) and 1627 children 6 to <12 years of age (950 exposed to Symbicort MDI). A total of 4951 asthma patients received randomized treatment in Phase 3 studies, of whom 2193 received Symbicort MDI, 3504 ≥12 years of age (1537 received Symbicort MDI) and 1447 children 6 to <12 years of age (656 received Symbicort MDI). The program evaluated patients with a wide range severity of persistent asthma. Most patients were on a wide range of ICS, but the program did not specifically evaluate doses for conversion of patients who had been on oral corticosteroids. The 4-month Safety Update added a large number of patients exposed to Symbicort for long periods of time, significantly adding to the safety database. Please see the Safety Update section of this review for details. The additional numbers of patients are shown as separate line items in Table 35.

7.2.1.2 Demographics

The pivotal efficacy and safety studies **716** and **717** were balanced demographically and by other objective measures of asthma severity (Table 8), as were the pooled studies for evaluation of safety (Table 37). The safety database (Table 36) is typical of safety databases presented for new drug products, and was sufficient in size and scope to allow adequate assessment of all but infrequent (1:1000 or less events that might occur with long-term use). The major concern with the NDA safety database is the relative paucity of safety data for Black and Oriental patients. This is of some concern because of the known variations in beta-adrenergic receptors in different racial/ethnic populations. The additional data provided by the safety update make this of less

concern, as analyses including the additional population did not reveal any safety trends by race [*Note: Terminology follows that used by the Applicant*], sex, or age.

Table 36. Demographic characteristics, All Phase 2/3 studies (Pool 6)

Characteristic	Symbicort MDI n=3616	Characteristic	Symbicort MDI n=3616
Sex (n, %)		Age group (n, %)	
Male	1662 (46.0)	≥12 years	2690 (74.4)
Female	1954 (54.0)	6 to <12 years	926 (25.6)
Race (n, %) *		12 to <16 years	345 (9.5)
Caucasian	2754 (76.2)	16 to <65 years	2209 (61.1)
Black	380 (10.5)	≥65 years	136 (3.8)
Oriental	168 (4.6)	≥75 years	27 (0.7)
Hispanic	150 (4.1)	Baseline ICS (n, %)	
Other	164 (4.6)	None	2 (0.1)
Age (years)		Low	1113 (50.8)
Mean	29.8 (18.71)	Medium	877 (40.0)
Min, max	6, 85	High	201 (9.2)
Source: T26, p3041; clinsum.pdf and T1.3.6.1.1.1; p478; summary_appendices_2_7_4a.pdf			

Table 37. Demographic and Other characteristics, All Completed Phase 3 studies (Pool 5)

Characteristic	Treatment group, n (%)				
	Symbicort MDI n=2193	Budesonide MDI N=1182	Formoterol TBH n=384	Symbicort TBH n=668	Placebo n=409
Sex (n, %)					
Male	1049 (47.8)	597 (50.5)	179 (46.6)	325 (48.7)	166 (40.6)
Female	1144 (52.2)	585 (49.5)	205 (53.4)	343 (51.3)	243 (59.4)
Race (n, %)*					
Caucasian	1669 (76.1)	872 (73.8)	310 (80.7)	459 (68.7)	342 (83.6)
Black	183 (8.3)	105 (8.9)	54 (14.1)	17 (2.5)	41 (10.0)
Oriental	138 (6.3)	70 (5.9)	4 (1.0)	94 (14.1)	9 (2.2)
Other	203 (9.3)	135 (11.4)	16 (4.2)	98 (14.7)	17 (4.2)
Age (years)					
Mean	28.3 (19.02)	24.4 (18.70)	27.3 (18.55)	29.7 (20.32)	37.4 (14.94)
Min, max	6, 85	6, 80	6, 87	6, 79	6, 75
Age group (n, %)					
≥12 years	1537 (70.1)	703 (59.5)	294 (76.6)	455 (68.1)	400 (97.8)
6 to <12 years	656 (29.9)	479 (40.5)	90 (23.4)	213 (31.9)	9 (2.2)
12 to <16 years	248 (11.3)	154 (13.0)	84 (21.9)	47 (7.0)	17 (4.2)
16 to <65 years	1212 (55.3)	516 (43.7)	194 (50.5)	375 (56.1)	372 (91.0)
≥65 years	77 (3.5)	33 (2.8)	16 (4.2)	33 (4.9)	11 (2.7)
≥75 years	18 (0.8)	6 (0.5)	1 (0.3)	7 (1.0)	1 (0.2)
Baseline ICS (n, %)					
None	2 (0.1)	4 (0.3)	1 (0.3)	0	0
Low	1113 (50.8)	627 (53.0)	221 (57.6)	197 (29.5)	207 (50.6)
Medium	877 (40.0)	454 (38.4)	131 (34.1)	347 (51.9)	172 (42.1)
High	201 (9.2)	97 (8.2)	31 (8.1)	124 (18.6)	30 (7.3)
Screening % pred FEV_1 (mean, SD)	80.82 (14.1)	80.85 (14.1)	74.99 (12.9)	87.31 (14.7)	72.67 (9.9)
Baseline % pred FEV_1 (mean, SD)	82.03 (14.8)	80.92 (13.9)	74.85 (13.7)	80.59 (16.6)	75.65 (12.9)

Characteristic	Treatment group, n (%)				
	Symbicort MDI n=2193	Budesonide MDI N=1182	Formoterol TBH n=384	Symbicort TBH n=668	Placebo n=409
*Terminology follows that used by the Applicant.					
Source: T25, p3040; clinsum.pdf					

7.2.1.3 Extent of exposure (dose/duration)

The duration of exposure was adequate to allow assessment of safety risks from the studies and from the safety database.

Duration of exposure varied across studies and pooled datasets, as well as across total daily dose and regimen subgroups. Total Symbicort MDI exposure in all Phase 2/3 studies (Pool 6) is shown in Table 38, and duration of exposure in the completed Phase 3 studies (Pool 5) is shown in Table 39. The duration of exposure in completed Phase 3 studies (Pool 5) by dose of Symbicort MDI is shown in Table 40. Among the 2193 patients who received Symbicort MDI in the Phase 3 studies, 1981 (90%) were exposed for ≥8 weeks, 525 (24%) for at least 6 months (i.e. ≥ 24 weeks), and 392 (18%) for at least 1 year (i.e. >50 weeks).

Table 38. Duration of Symbicort MDI Exposure, All Phase 2/3 studies (Pool 6)

Duration of Treatment	Symbicort MDI n=3616
N (%) of subjects	
>0 to ≤4 weeks	592 (16.4)
>4 to ≤8 weeks	983 (27.2)
>8 to ≤14 weeks	792 (21.9)
>14 to ≤24 weeks	723 (20.0)
>24 to ≤50 weeks	134 (3.7)
>50 weeks	392 (10.8)
Source: T21, p3033; clinsum.pdf	

Table 39. Duration of Exposure, All Completed Phase 3 studies (Pool 5)

Duration of Exposure	Treatment group, n (%)				
	Symbicort MDI n=2193	Budesonide MDI N=1182	Formoterol TBH n=384	Symbicort TBH n=668	Placebo n=409
Duration of treatment, n (%) of patients					
>0 to ≤4 weeks	138 (6.3)	92 (7.8)	78 (20.3)	20 (3.0)	135 (33.0)
>4 to ≤8 weeks	76 (3.5)	69 (5.8)	45 (11.7)	12 (1.8)	48 (11.7)
>8 to ≤14 weeks	1435 (65.4)	958 (81.0)	259 (67.4)	412 (61.7)	225 (55.0)
>14 to ≤24 weeks	19 (0.9)	9 (0.8)	2 (0.5)	10 (1.5)	1 (0.2)
>24 to ≤50 weeks	133 (6.1)	54 (4.6)	0	11 (1.6)	0
>50 weeks	392 (17.9)	0	0	203 (30.4)	0
Cumulative Duration of treatment, n (%) of patients					
>4 weeks	2059 (93.9	1093 (92.5)	308 (80.2)	648 (97.0)	278 (68.0)
>8 weeks	1981 (90.3)	1024 (86.6)	261 (68.0)	637 (95.4)	227 (55.5)
>14 weeks	545 (24.9)	64 (5.4)	4 (1.0)	227 (34.0)	2 (0.5)
>24 weeks	525 (23.9)	54 (4.6)	0	214 (32.0)	0
>50 weeks	392 (17.9)	0	0	203 (30.4)	0
Source: T18, p3028; clinsum.pdf					

Table 40. Duration of Exposure to Symbicort MDI by total daily dose, All Completed Phase 3 studies (Pool 5)

Duration of Exposure by Dose	Symbicort MDI				
	QD dosing		BID dosing		
	160/9	320/9	160/18 80/9 BID	320/18 160/9 BID	640/18 320/9 BID
N	320	147	312	487	927
Mean days on treatment	77.2	77.3	75.9	78.7	214.1
Duration of treatment, n (%) of patients					
>0 to ≤4 weeks	20 (6.3)	9 (6.1)	25 (8.0)	27 (5.5)	57 (6.1)
>4 to ≤8 weeks	16 (5.05)	6 (4.1)	20 (6.47)	16 (3.3)	18 (1.9)
>8 to ≤14 weeks	282 (88.1)	131 (89.1)	266 (85.3)	441 (90.6)	315 (34.0)
>14 to ≤24 weeks	2 (0.6)	1 (0.7)	1 (0.3)	3 (0.6)	12 (1.3)
>24 to ≤50 weeks	0	0	0	0	133 (14.3)
>50 weeks	0	0	0	0	392 (42.3)
Source: T19, p3030; clinsum.pdf					

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Since each active ingredient is available in the United States, and the combination is available outside the US in a dry powder formulation, safety information from each of these products was submitted to, and in support of, the current application. Each of these is listed below, with a brief description of how the applicant handled the safety data from each of these products.

1. Symbicort Turbuhaler is a DPI presentation of Symbicort marketed widely around the world, as noted in Section 2.3, 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.

These studies provide background safety data for the combination of the two ingredients, but do not provide direct support for the safety of Symbicort MDI itself. In this review, they were considered as secondary sources to support the safety of both budesonide and formoterol when combined into one formulation.

2. The formoterol monoproduct comparator for this NDA is a DPI marketed internationally as Oxis Turbuhaler (TBH).

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.

Just as for the Symbicort TBH studies, other studies with the Oxis TBH provide background for safety of formoterol, but do not provide direct support for the safety of the Symbicort MDI drug product. In this review, they were considered as secondary sources to support of the safety of formoterol

3. 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. That information was not specifically reviewed as part of this application.

7.2.2.2 Postmarketing experience

Symbicort is not marketed in the United States; no postmarketing experience is available. Please see Section 7.2.17 of this review for a description of the postmarketing experience with other forms of Symbicort and the monoproducts.

7.2.2.3 Literature

Literature references were presented with the application. They were not reviewed.

7.2.3 Adequacy of Overall Clinical Experience

The clinical development program was judged adequate and of sufficient quality to make a reasonable assessment of safety for this application.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Other than the typical preclinical inhalational studies and the standard *in vitro* testing of inhalational drug products, no special animal testing or *in vitro* was required for this application.

7.2.5 Adequacy of Routine Clinical Testing

The clinical development program was judged adequate and of sufficient quality to make a reasonable assessment of safety for this application.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Since the metabolism and clearance of both active drugs are well characterized, no new studies were requested or performed for this application.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Since neither active drug is a new molecular entity, this section does not apply to this application. However, there are still clinical issues with the chronic use of long-acting beta agonists, including formoterol, in patients with asthma. Please see other sections of this review for details.

7.2.8 Assessment of Quality and Completeness of Data

The clinical development program was judged adequate and of sufficient quality to make a reasonable assessment of safety for this application.

7.2.9 Additional Submissions, Including 4-Month Safety Update

A 4-Month Safety Update (4MSU) was provided on January 19, 2006. The safety update contained data from 4 Phase 2/3clinical studies completed since the preparation of the original submission document.

[redacted]. The cutoff date for this submission was September 30, 2005.

Studies submitted with this safety update are briefly summarized below and in Table 41. There are several things to note about these studies. First, 3 of the studies were performed in the

patient population of asthmatics ≥12 years of age, evaluating doses, dosage strengths (80/4.5 and 160/4.5 mcg), dosing regimens (BID), and lengths of treatment (12 to 52 weeks) with Symbicort pertinent to the NDA application. Second, study **728** used doses at and higher than the dose being sought in the application, for a length of 1 year. Third, none [of the multiple-dose asthma studies] used a placebo control. While this makes them relevant to the NDA and allows them to add considerably to the overall safety database for Symbicort, it also means that none will add to the adverse event table in the PI. Fourth, it needs to be stated that the full study reports for these studies were not submitted, nor were they reviewed with this application [*The study report for study SD-039-0728 was submitted electronically to the Symbicort **IND** (IND 63,394) on May 15, 2006. Given the date that this study report was submitted, it was not reviewed.*]. Therefore, it would not be appropriate to place descriptions of these studies, particularly long-term safety study **728**, in the labeling [*Nor is this being requested*]. However, the labeling submitted with the 4MSU does seek to update the numbers of patients, such as geriatric patients, in the labeling and some other listings of adverse events after the AE table; this is appropriate. Finally, although the data was uncontrolled and the study reports not reviewed, the 4MSU adds to the numbers of non-Caucasians studied, contributing to the findings of safety in these populations.

The focus of the 4-month safety review was on the frequency and type of adverse events, laboratory, ECG, and HPA axis data, with the intent to elucidate any new information that would add to or modify the conclusions of the safety review. Except for more AEs with dosing at 1280/36 mcg/day (see discussion and tables below), no new safety trends were uncovered.

7.2.9.1 Studies with Safety Data Submitted to 4-Month Safety Update

SD-038-0728: This was a 52-week, randomized, double-blind, single-dummy, multicenter study comparing the long-term safety of Symbicort MDI 160/4.5 mcg x 4 actuations twice daily to Symbicort MDI 160/4.5 mcg x 2 actuations twice daily and budesonide HFA MDI 160 mcg x 4 actuations twice daily in 708 asthmatic patients ≥12 years of age.

D5896C00001: This was a randomized, double-blind, active-controlled, single dummy, multicenter, 12-week study to assess the efficacy and safety of Symbicort MDI 160/4.5 mcg x 2 actuations once-daily (QD) compared to Symbicort 80/4.5 mcg x 2 actuations QD, Symbicort MDI 80/4.5 mcg x 2 actuations twice-daily (BID) and to budesonide pMDI 160 mcg x 2 actuations QD in 618 asthmatic patients ≥12 years of age.

D5896C00005: This was a 2-stage, randomized, open-label, multicenter, 7-month study to assess the efficacy and safety of Symbicort MDI administered either as fixed or as an adjustable regimen versus a fixed regimen of Advair in 1222 asthmatic patients ≥12 years of age.

Table 41. Studies submitted with 4-Month Safety Update

Study Duration	Ages/N	Comparator	Symbicort Daily Doses and Formulation						
			BID Program				QD Program		AD[a]
			160/18	320/18	640/18	1280/36	160/9	320/9	
Asthma program									
SD-038-0728 52 wks	≥12 yrs/708	Bud MDI 160			160/4.5	160/4.5			
D5896C00001 12 wks	≥12 yrs/618	Bud MDI 160 2 QD		80/4.5			80/4.5	160/4.5	
D5896C00005 28 wks	≥12 yrs/1222	Advair Diskus 250/50 BID			160/4.5				See text[a]
[a] Adjustable dose Symbicort (160/4.5): 320/9 QD, 320/9 BID, or 640/18 BID based on criteria for asthma control and/or deterioration.									
[redacted]									
Source: T1, p23; T2, p25; 4MSU.pdf									

7.2.9.2 Methodology and Demographics of the 4-Month Safety Review

Methods for evaluation of safety data and pooling of data in the safety update were the same as those for the rest of the safety database. The number of patients added to the safety database and study Pools are shown in Table 35 as a line listing separate from each of the Pools submitted to the main application. Since there were no Phase 3 placebo-controlled asthma studies in the update, the update only added to Pools 2, 5, and 6. Updated demographic and cumulative duration of exposure information for Symbicort and budesonide is shown below.

Table 42. 4MSU, Updated demographic and other characteristics, Symbicort and Budesonide groups, All completed Phase 3 studies (Pool 5)

Characteristic	Symbicort MDI, n (%)			Budesonide, n(%)	
	NDA n=2193	4MSU N=1856	NDA+4MSU n=4094	NDA n=1182	4MSU N=286
Sex (n, %)					
Male	1049 (47.8)	725 (39.1)	1744 (43.8)	597 (50.5)	96 (33.6)
Female	1144 (52.2)	1131 (60.9)	2275 (56.2)	585 (49.5)	190 (66.4)
Race (n, %)*					
Caucasian	1669 (76.1)	1555 (83.8)	3224 (79.6)	872 (73.8)	240 (83.9)
Black	183 (8.3)	214 (11.5)	397 (9.8)	105 (8.9)	41 (14.3)
Oriental	138 (6.3)	23 (1.2)	161 (4.0)	70 (5.9)	1 (0.3)
Other	203 (9.3)	64 (3.4)	267 (6.6)	135 (11.4)	4 (1.4)
Age (years)					
Mean	28.3 (19.02)	38.5 (16.07)	33.0 (18.43)	24.4 (18.70)	37.9 (15.43)
Min, max	6, 85	12, 87	6, 87	6, 80	12, 76
Age group (n, %)					
≥12 years	1537 (70.1)	1856 (100.0)	3393 (83.8)	703 (59.5)	286 (100.0)
6 to <12 years	656 (29.9)	0	656 (16.2)	479 (40.5)	0
12 to <16 years	248 (11.3)	205 (11.0)	453 (11.2)	154 (13.0)	27 (9.4)
16 to <65 years	1212 (55.3)	1546 (83.3)	2758 (68.1)	516 (43.7)	247 (86.4)

Characteristic	Symbicort MDI, n (%)			Budesonide, n(%)	
	NDA n=2193	4MSU N=1856	NDA+4MSU n=4094	NDA n=1182	4MSU N=286
Sex (n, %)					
≥65 years	77 (3.5)	105 (5.7)	182 (4.5)	33 (2.8)	12 (4.2)
≥75 years	18 (0.8)	15 (0.8)	33 (0.8)	6 (0.5)	2 (0.7)
Baseline ICS (n, %)					
None	2 (0.1)	3 (0.2)	5 (0.1)	4 (0.3)	1 (0.3)
Low	1113 (50.8)	512 (27.6)	1625 (40.1)	627 (53.0)	130 (45.5)
Medium	877 (40.0)	1162 (62.6)	2039 (50.4)	454 (38.4)	135 (47.2)
High	201 (9.2)	179 (9.6)	380 (9.4)	97 (8.2)	20 (7.0)
Percent predicted FEV_1					
Screening (mean, SD)	80.82 (14.1)	76.15 (14.0)	78.52 (14.3)	80.85 (14.1)	74.24 (10.8)
Baseline (mean, SD)	82.03 (14.8)	79.43 (14.4)	80.84 (14.7)	80.92 (13.9)	79.67 (13.0)
*Terminology follows that used by the Applicant.					
Source: T15, p50; 4MSU.pdf					

Table 43. 4MSU, Cumulative duration of Symbicort MDI exposure, All Phase 2/3 studies (Pool 6)

Cumulative Duration of Treatment	NDA n=3616	4MSU N=2454	NDA+4MSU n=6070
N (%) of subjects			
>4 weeks	3089 (85.4)	2249 (91.6)	5338 (87.9)
>8 weeks	2046 (56.69)	1746 (71.1)	3792 (62.5)
>14 weeks	1252 (34.60)	1669 (68.0)	2921 (48.1)
>24 weeks	526 (14.5)	1214 (49.5)	1740 (28.7)
>50 weeks	392 (10.8)	473 (19.3)	865 (14.3)
Source: T14, p48; 4MSU.pdf			

7.2.9.3 Results of the 4-Month Safety Review

Overall, in the 4MSU the AE profile of Symbicort compared to budesonide was consistent with the NDA safety database (Table 44), with no new or unexpected safety trends and no new trends in SAEs (Table 45). There were 3 new cardiac SAEs in the 4MSU population: atrial fibrillation (Symbicort 1280/36 µg/day), coronary artery occlusion (adjustable dose regimen), angina pectoris (budesonide 640/18 µg/day). There were 8 DAEs due to asthma: 7 in the Symbicort and 1 in the budesonide treatment arms. As noted previously, as there were no placebo-controlled studies in the 4MSU, none of the studies contributed to changes in the proposed AE table. However, several new AE MedDRA PTs were identified, as discussed below. The 4-month Safety Update included safety information from study SD-039-0728 on a population of 443 patients treated with Symbicort at 1280/36 mcg/day for least 1 year (and compared to a similar budesonide dose in 133 patients and a dose of 640/18 of Symbicort in 132 patients). Not unexpectedly, the high-dose showed a dose-ordered relationship for AEs such as candidiasis, pharyngolaryngeal pain, muscle spasm, and tremor (Table 46).

When evaluated for events of interest (for Symbicort only) without respect to Symbicort dose, the incidence of local steroid effects, i.e. candida (NDA Symbicort 1.8%, 4MSU Symbicort 4.1%) and voice effects (NDA 1.4%, 4MSU 2.3%) were for Symbicort higher in this database than in the NDA database, likely because of the long-term exposure to higher doses in this database. However, systemic corticosteroid effects for Symbicort were minimally higher for

Symbicort in this database (NDA 1.2%, 4MSU 2.9%). For Symbicort, beta agonist effects, including tremor (NDA 0.4%, 4MSU 2.4%), muscle cramps (NDA 0.4%, 4MSU 1.9%), anxiety (NDA 0.4%, 4MSU Symbicort 1.7%), and glucose changes (NDA <0.1%, 4MSU 0.5%,) were higher than in the NDA database, but palpitations (NDA 1.2%, 4MSU 0.5%) were lower than in the NDA database. Total asthma-related events was slightly higher than in the NDA database for Symbicort (NDA 6.7%, 4MSU 8.1%), but asthma discontinuations (NDA 1.4%, 4MSU 0.7%), serious asthma events (NDA 0.6%, 4MSU 0.2%), and asthma events leading to discontinuation (NDA 1.0%, 4MSU 0.6%) were all less.

Results of ECG heart rate were also dose ordered but numerically small. There were no new findings for laboratory AE, vital signs, ECGs or other safety events.

Based on the additional data in the 4MSU, the following AEs (additional to those included in the draft prescribing information table) are proposed for the package insert. These AEs occurred with an incidence of ≥1% to <3% in patients ≥12 years of age who received doses of 80/9, 160/9, 320/9, or 640/18 mcg twice-daily in the Phase 3 clinical trial program (NDA plus 4MSU), regardless of the investigator's assessment of causality. These AEs, listed in decreasing order of incidence include: asthma, nausea, dysphonia, pyrexia, sinus headache, diarrhea, pharyngitis, tremor, lower respiratory tract infection, muscle spasms, urinary tract infection, rhinitis, arthralgia, myalgia, dyspepsia, gastroenteritis viral, abdominal pain upper, dizziness, sinus congestion, rhinitis allergic, pain in extremity, palpitations, bronchitis acute, tension headache, migraine, post procedural pain. AstraZeneca notes that, in addition to the above, the incidence of cough, bronchitis, and viral upper respiratory tract infection was ≥3% (but each <4%). However, they that they did not meet criteria for inclusion in the draft prescribing information table, as these data are not derived from placebo-controlled trials. I do not understand their reasoning, as the other events listed above are not from placebo-controlled datasets. [p79; 4MSU.pdf]

Table 44. 4MSU, Overview of adverse events during randomized treatment, All Phase 3 studies (Pool 5*)

4MSU, Overview of AEs, Pool 5	Treatment group, n (%)				
	Symbicort			Budesonide	
	NDA n=2193	4MSU N=1182	NDA+4MSU n=384	NDA n=668	4MSU n=409
Mean exposure (days)	135.2	203.0	166.3	80.9	192.9
Number of patients with an AE					
Any AE	1310 (59.7)	1218 (65.6)	241 (62.8)	617 (52.2)	202 (70.6)
SAEs	51 (2.3)	54 (2.9)	105 (2.6)	8 (0.7)	5 (1.7)
Deaths	0	0	0	0	0
Non-fatal SAEs	51 (2.3)	54 (2.9)	105 (2.6)	8 (0.7)	5 (1.7)
SAEs leading to discontinuation	15 (0.7)	134 (0.7)	281 (0.7)	4 (0.3)	1 (0.3)
DAEs	62 (2.8)	75 (4.0)	137 (3.4)	44 (3.7)	7 (2.4)
OAEs	1 (<0.01)	0	1 (<0.01)	0	0
Any study drug-related AE					
US	74 (5.6)	238 (12.8)	312 (9.9)	35 (4.6)	29 (10.1)
Non-US	3 (0.3)	NA	3 (0.3)	0	NA

*Pool 5 = All Phase 3 studies. See Table 35 for description of study pooling.
DAE = Adverse event leading to discontinuation; OAE = Other significant adverse event

Source: T17, p56; 4MSU.pdf

Table 45. 4MSU, SAEs, All Phase 3 studies (Pool 5*)

MedDRA SOC	Treatment group, n (%)				
	Symbicort			Budesonide	
	NDA n=2193	4MSU N=1182	NDA+4MSU n=384	NDA n=668	4MSU n=409
Mean exposure (days)	135.2	203.0	166.3	80.9	192.9
Patients with an SAE	51 (2.3)	54 (2.9)	105 (2.6)	8 (0.7)	5 (1.7)
Infections and infestations	14 (0.6)	11 (0.6)	25 (0.6)	0	2 (0.7)
Respiratory, thoracic & mediastinal	14 (0.6)	5 (0.3)	19 (0.3)	4 (0.3)	1 (0.3)
GI disorders	6 (0.3)	7 (0.4)	13 (0.3)	0	0
Injury, poisoning & procedural comp.	5 (0.2)	1 (0.1)	6 (0.1)	1 (0.1)	0
Neoplasms benign, malignant & unspecified	2 (0.1)	7 (0.4)	9 (0.2)	0	0
Reproductive system and breast	5 (0.2)	4 (0.2)	9 (0.2)	0	0
Cardiac	2 (0.1)	3 (0.2)	5 (0.1)	0	0
Musculoskeletal & connective tissue	1 (<0.1)	5 (0.3)	6 (0.1)	0	0
Nervous system	2 (0.1)	3 (0.2)	5 (0.1)	1 (0.1)	0
General disorders & admin site	0	4 (0.2)	4 (0.1)	0	1 (0.3)
Hepatobiliary	1 (<0.1)	4 (0.2)	5 (0.1)	0	0
Psychiatric	0	4 (0.2)	4 (0.1)	1 (0.1)	0
Ear and labyrinth	2 (0.1)	0	2 (0.1)	0	0
Pregnancy, puerperium & perinatal	0	2 (0.1)	2 (<0.1)	0	0
Renal and urinary	2 (0.1)	0	2 (<0.1)	0	0
Vascular disorders	1 (<0.1)	1 (0.1)	2 (<0.1)	0	1 (0.3)
Congenital, familial, and genetic	0	1 (0.1)	1 (<0.1)	1 (0.1)	0
Investigations	2 (0.1)	0	2 (<0.1)	0	0
Blood and lymphatic system	0	1 (0.1)	1 (<0.1)	0	0
Metabolism and nutrition	0	1 (0.1)	1 (<0.1)	0	0
Skin and subcutaneous tissue	1 (<0.1)	0	1 (<0.1)	0	0
*Pool 5 = All Phase 3 studies. See Table 35 for description of study pooling. Based on MedDRA Version 8					
Source: T30, p86; 4MSU.pdf					

Table 46. SD-039-0728, Most commonly reported AEs by dose

Study 728, Most common AEs	Treatment group, n (%)		
	Symbicort MDI N=132	Symbicort MDI N=443	Budesonide N=133
Total daily dose (mcg)	**640/18**	**1280/36**	**1280**
Dosage	**160/4.5 2 BID**	**160/4.5 4 BID**	**160 4 BID**
Mean exposure (days)	**328.5**	**321.9**	**322.4**
Number of patients with any AE	**111 (84.1)**	**394 (88.9)**	**118 (88.7)**
Adverse Event			
Nasopharyngitis	28 (21.2)	95 (21.4)	32 (24.1)
URTI	29 (22.0)	80 (18.1)	21 (15.8)
Sinusitis	14 (10.6)	53 (12.0)	20 (15.0)
Pharyngolaryngeal pain	11 (8.3)	57 (**12.9**)	17 (12.8)
Oral candidiasis	13 (9.8)	53 (**12.0**)	12 (9.0)
Influenza	13 (9.8)	42 (9.5)	13 (9.8)
Viral URTI	9 (6.8)	33 (7.4)	14 (10.5)
Cough	7 (5.3)	34 (**7.7**)	9 (6.8)

Headache	11 (8.3)	28 (6.3)	10 (7.5)
Bronchitis	9 (6.8)	24 (5.4)	13 (9.8)
Sinus headache	10 (7.6)	23 (5.2)	10 (7.5)
Back pain	11 (8.3)	19 (4.3)	7 (5.3)
Muscle spasms	3 (2.3)	30 (**6.8**)	3 (2.3)
Myalgia	9 (6.8)	18 (4.1)	5 (3.8)
Nasal congestion	7 (5.3)	20 (4.5)	5 (3.8)
Diarrhea	8 (6.1)	14 (3.2)	9 (6.8)
Tremor	0	30 (**6.8**)	1 (0.8)
Nausea	7 (5.3)	22 (5.0)	1 (0.8)
Lower respiratory tract infection	3 (2.3)	15 (3.4)	8 (6.0)
Urinary tract infection	7 (5.3)	15 (3.4)	3 (2.3)
Vomiting	8 (6.1)	10 (2.3)	1 (0.8)
Source: T23, p68; 4MSU.pdf			

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Please see Section 7.1.1.1, Identifying Common and Drug-Related Adverse Events, for a discussion of adverse events of particular relevance to the two active drugs in Symbicort. The only limitation found during the safety review of this application is the limited number patients from racial groups other than Caucasians evaluated in the pivotal safety and efficacy studies. Since beta-agonist receptors have been found to vary among racial groups, the specific concern is that there may be differences between racial groups for the potential to have severe, life-threatening asthma adverse events. While no concerns were raised in this regard during the course of this review, it would take a very large study on the order of a SMART study to elucidate such events. This type of study is not only impractical but also unnecessary prior to approval, since both active drugs are already approved for use for the same indication.

The indicated population as a maintenance treatment for asthma in patients ≥12 years of age is an appropriate population for use of a MDI inhaler and for treatment with each of the active ingredients, budesonide and formoterol. The conclusion of this review is that Symbicort is safe for use in the proposed indicated population at the proposed doses.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Please see Section 7.2.1, Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety, for a description of the methodology for pooling of data sources. A table of how studies were pooled for evaluation of safety endpoints is shown in Table 35.

7.4.1.2 Combining data

Please see Section 7.2.1, Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety, for a description of the methodology for pooling of data sources. A table of how studies were pooled for evaluation of safety endpoints is shown in Table 35.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The applicant did perform analyses evaluating dose dependency of adverse events. Please see Section 7.1 for details.

7.4.2.2 Explorations for time dependency for adverse findings

No formal analysis was performed for time dependency of adverse events.

7.4.2.3 Explorations for drug-demographic interactions

The applicant did perform analyses evaluating drug-demographic interactions for adverse events. Please see Section 7.1 for details.

7.4.2.4 Explorations for drug-disease interactions

The applicant did perform analyses evaluating drug-disease interactions for adverse events. Specifically, study 717 stratified randomization of patients by asthma severity, based on consistent use of moderate vs high dose ICS use prior to screening. Please see Section 7.1 and the study review for details.

7.4.2.5 Explorations for drug-drug interactions

No specific drug-drug interaction evaluations were performed.

7.4.3 Causality Determination

Evaluation of causality was performed by investigators as part of the routine for documentation of adverse events throughout the clinical development program. As part of the review of the adverse events presented in this application, I reviewed the determinations of causality, and found no specific or unexpected trends.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Dose selection for the Symbicort development program was based on separate dose-ranging studies conducted with the US commercially available budesonide monoproduct (Pulmicort TBH) and ex-US formoterol monoproduct (Oxis TBH). The applicant had also performed extensive testing of Symbicort TBH, which commercially available outside the United States; these doses are similar to those chosen for the Symbicort MDI program.

Dosing recommendations proposed in the Dosing and Administration section are consistent both with asthma treatment guidelines (NAEPP 2003) as well as the design and outcome of the pivotal trials. The clinical studies support dosing of 160/9 to 320/9 mcg administered as 2 inhalations of the appropriate dosage formulation (80/4.5 or 160/4.5 mcg) BID. The maximum proposed daily dose is appropriate, at 640/18 mcg/day, administered as 160/4.5, 2 inhalations BID. The Dosing and Administration section also has a table for converting patients from other corticosteroids to Symbicort. This is based on tables (not shown in this review) in the clinical study reports showing how many patients were on specific doses of various inhaled corticosteroids prior to the studies. Whether this table will remain in the final labeling has not been determined as of the finalization of this review, although the current Advair label also carries this type of table. The Dosing and Administration [and Clinical Trials] section[s] also propose to contain information on onset of action. This also will be the subject of evaluation during the line-by line labeling review, which will be performed after this document is finalized.

Of note, the 4-month Safety Update included safety information from study SD-039-0**728** on a population of 443 patients treated with Symbicort at 1280/36 mcg/day for least 1 year (and compared to a similar budesonide dose in 133 patients and a dose of 640/18 of Symbicort in 132 patients). Not unexpectedly, the high-dose showed a dose-ordered relationship for AEs such as candidiasis, pharyngolaryngeal pain, muscle spasm, and tremor (Table 46).

8.2 Drug-Drug Interactions

A PK drug interaction study (722) was performed with budesonide MDI and Oxis TBH, which showed no interaction between the component drugs. No other drug-drug interaction studies were performed. This is acceptable, given previous clinical experience with each of the two individual active drugs and the lack of an expected drug-drug interaction between the two. The individual drugs have been studied in this regard, and are labeled appropriately for potential interactions, briefly summarized below. The applicant performed analyses of AE's by use of concomitant medications, and no clinically meaningful safety trends were noted.

Budesonide. Ketoconazole, a potent P450 CYP3A4 inhibitor, has been shown to increase levels of budesonide with concomitant administration. Cimetidine has also been shown to effect the PK of oral budesonide.

Formoterol. Beta-adrenergic blockers, including eye drops, have been shown to diminish the effect of formoterol. Hypokalemia may be potentiated by concomitant formoterol and xanthine

derivatives, corticosteroids, and diuretic drugs. There is a theoretical risk that concomitant administration with other drugs that increase QT may cause a pharmacodynamic interaction with resultant ventricular arrhythmias.

8.3 Special Populations

No special population studies were performed, and none requested, as part of this application. Based on current knowledge of the individual active ingredients, there was no specific concern for geriatric patients of patients with renal or hepatic dysfunction. The warnings and precautions for corticosteroid drug products are generally well known and accepted in the labeling.

The Phase 2 and 3 Symbicort studies (safety Pool 6) included 136 patients ≥65 years of age. The 4-month Safety Update added information on an additional 117 patients, of whom 105 were exposed to Symbicort at various doses. The applicant's analyses included evaluations for effects of gender, race, and age on the frequency on adverse events, and none were found.

8.4 Pediatrics

Under PREA, AstraZeneca is requesting a deferral of submission of pediatric studies in patients 6 to <12 years of age until some time in 2007, and a partial waiver of pediatric studies below 6 years of age. The Division responded to these requests in the NDA acknowledgement letter, granting each. Specific reasoning is given below.

The request for a deferral of pediatric studies for asthma patients 6 years through 11 years of age is acceptable. As noted in the introduction to this review, AstraZeneca has already evaluated Symbicort MDI in asthma populations down to 6 years of age.

and limiting the current application to patients ≥12 years of age. The pediatric studies included 1627 children 6 to <12 years of age, with 950 patients exposed to Symbicort MDI, and a 6-month safety study (719, reviewed as part of this document). The deferral date of some time (unspecified) in 2007 is acceptable. Submission of these studies will become a post-marketing commitment.

The request for a partial waiver of pediatric studies below 6 years of age is acceptable. PREA is triggered by applications with a new ingredient, indication, dosage form, dosing regimen, or route of administration. Under PREA, waivers may be granted for any of the following: the condition does not occur in the pediatric population, the necessary studies are impossible or highly impracticable, there is strong evidence that suggests the drug or biologic would be ineffective or unsafe, or drug or biologic does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients. However, Pulmicort Respules provides treatment for this age group and Symbicort is not likely to be used in a substantial number of patients in that age group since the therapeutic benefit over existing treatments is unknown. In addition, based on the disease and the mechanism of action of the drug, it is not clear that long-acting beta agonists are appropriate for use in successively younger populations of asthmatic children, although the age cutoff is open to interpretation.

Symbicort represents a convenience packaging of budesonide and formoterol. Both monoproducts are approved and available in the US. A pediatric age-appropriate (nebulizer) formulation of budesonide, Pulmicort Respules, is approved for maintenance treatment of asthma in age groups of 8 years down to 12 months. Formoterol is available as Foradil Aerolizer, and is approved for maintenance treatment of asthma in patients 5 years of age and older. While a similar combination product, Advair Diskus, is currently labeled down to 4 years of age, AstraZeneca argues that a formulation of Symbicort suitable for pediatric populations below 6 years of age would require titration of the formoterol dose. As such, this would require development of a new drug product. Given the significant challenges and complexities in the development of inhalation drug products, development of a new inhaled formulation that would be pediatric friendly would invoke an entirely new drug development program that may also need to be addressed in adults and/or older children prior to evaluation in younger children. We have therefore not asked companies to do/attempt this. For these reasons, the Division accepted AstraZeneca's argument, and granted a partial waiver of studies below 6 years of age.

8.5 Advisory Committee Meeting

An Advisory Committee meeting was neither requested nor carried out as part of the assessment of this application. An Advisory Committee met on July 13, 2005, to discuss the safety findings associated with use of long-acting beta-agonists (LABAs). A recommendation was made that both salmeterol and formoterol drug products contain a **boxed warning**. During the course of this review, a boxed warning was updated for all the salmeterol drug products, and is being negotiated for the formoterol drug products. Therefore, during labeling negotiations a boxed warning will be sought for this drug product.

8.6 Literature Review

A literature review was not performed during the review of this application.

8.7 Postmarketing Risk Management Plan

AstraZeneca does not propose a risk management plan for Symbicort MDI. Based the safety profile of Symbicort, I concur that a risk management plan is not needed.

8.8 Other Relevant Materials

No other relevant materials were reviewed.

9 OVERALL ASSESSMENT

9.1 Conclusions

The studies provided in this 505(b)(1)application for Symbicort® 80/4.5 and 160/4.5 inhalation aerosol, support the conclusion that Symbicort is safe and effective for the maintenance treatment of asthma in patients ≥12 years of age.

9.2 Recommendation on Regulatory Action

I recommend approval of this application.

9.3 Recommendation on Postmarketing Actions

No specific postmarketing actions are indicated.

9.3.1 Risk Management Activity

AstraZeneca does not propose a risk management plan for Symbicort MDI. Because of the safety issues with long-acting beta-agonists (LABA), it will be necessary to include a Boxed Warning in the label. In addition, the Division has previously determined that a Medication Guide will be necessary for all LABAs. As of the time of finalization of this review, a Medication Guide has not been submitted. This will be discussed with AstraZeneca during labeling negotiations.

9.3.2 Required Phase 4 Commitments

Under PREA, AstraZeneca is requesting a deferral of submission of pediatric studies in patients 6 to <12 years of age until some time in 2007, and a partial waiver of pediatric studies below 6 years of age.

The request for a deferral of pediatric studies for asthma patients 6 years through 11 years of age is acceptable and will become a post-marketing commitment. The request for a partial waiver of pediatric studies below 6 years of age is acceptable. The Division responded to these requests in the NDA acknowledgement letter, granting each. The reasoning is discussed fully in Section 8.4 of this review.

9.3.3 Other Phase 4 Requests

I have no recommendations for other Phase 4 requests.

9.4 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.

9.5 Comments to Applicant

The only comments to the applicant will be those directed at PREA and the waiver and/or deferral of pediatric studies, addressed elsewhere. The wording for those comments are standardized, and therefore do not appear here.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study SD-039-0729. A randomized, multicenter, open-label, active-controlled, single-dose, 7-treatment, crossover study to evaluate the relative bronchodilating effects of formoterol when administered via Symbicort MDI or Oxis·Turbuhaler to adults with stable asthma

The key study in the Phase 2 program was Study SD-039-0729. This study was designed to bridge the pharmaceutical differences between formoterol when administered via a DPI [monoproduct] (Oxis TBH) and via an MDI [combination product] (Symbicort). The study evaluated the pharmacodynamic relationship for the formoterol component in the two products in order to eliminate concerns that the pharmaceutical differences would confound the results of the Phase 3 program. The study used the Symbicort 80/4.5 dosage strength but did not include the 160/4.5 dosage strength.

Protocol #:	SD-039-0729
Title:	A randomized, multicenter, open-label, active-controlled, single-dose, 5-period, incomplete block, crossover study to evaluate the relative bronchodilating effects of formoterol when administered via SYMBICORT·pMDI or Oxis·Turbuhaler to adults with stable asthma
Study Dates:	October 4, 2002 to May 20, 2003
Sites:	17 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-039-0729.pdf

10.1.1.1 Protocol

This was a randomized, multicenter, open-label, active-controlled, 7-treatment (5-period, incomplete-block, 21 treatment sequence), single-dose, crossover PK/PD study in adults with stable asthma. The study population included men and women ≥18 years of age with stable asthma and FEV_1 values between 45-90% predicted, and reversibility of FEV_1 of at least 15% and 0.20 L from baseline. The study comprised a screening visit (Visit 1), a 7- to 14-day budesonide run-in period, and a randomized treatment period. The study comprised a screening visit (Visit 1), a 7- to 14-day budesonide run-in period, and a randomized treatment phase. The randomized treatment phase comprised 5 single-day single-dose crossover treatment periods separated by a 3- to 14-day washout, as shown in Table 47. There were 21 treatment sequences, which specified the order in which subjects received 5 of 7 possible treatments. Patients were

maintained on budesonide MDI such that all patients received budesonide 320 mcg BID. Patients were administered 0, 1, 2, or 4 inhalations of Symbicort MDI or Oxis TBH. After each treatment was administered, spirometry was performed over a 12-hour period and urine was collected for later analysis of unchanged formoterol.

The primary variable was the average 12-hour FEV_1. This was determined from serial spirometry maneuvers and calculated on the basis of area under the curve (AUC) divided by observation time. Secondary variables included maximum FEV_1, FEV_1 at 12 hours after dosing, and onset of effect. Safety was monitored by adverse events, withdrawals due to AEs, laboratory results, ECG, vital signs, and physical examinations.

Table 47. SD-039-0729, Possible crossover treatments

Treatment designation	Possible treatment components						Total dose of each component	
	Symbicort		Budesonide MDI		Oxis TBH		Formoterol	Budesonide
	Actuations	Dose	Actuations	Dose	Inhalations	Dose		
B	0		4	320	0		0	320
S1	1	80/4.5	3	240	NA		4.5	320
S2	2	160/9	2	160	NA		9	320
S4	4	320/18	0	0	NA		18	320
O1	NA		4	320	1	4.5	4.5	320
O2	NA		4	320	2	9	9	320
O4	NA		4	320	4	18	18	320

NA = Not applicable
Symbicort = Symbicort HFA MDI 80/4.5 mcg/actuation, Batch number AM-732
Formoterol = Oxis Turbuhaler (TBH) 4.5 mcg/inhalation, Batch number AM-734
Budesonide = Budesonide HFA MDI 80 mcg/actuation, Batch number AM-733

Source: TS1, p4; SD-039-0729

10.1.1.1.1 Amendments

There was one amendment to the study, dated April 3, 2004, to correct a typographical error on page 3 of the synopsis.

10.1.1.2 Results

10.1.1.2.1 Disposition, Demographics, Analysis Sets, and Baseline Characteristics

The study randomized 201 patients at 17 centers, 122 (61%) women and 79 (39%) men, with a mean age of 42 years (range 18-80), history of asthma for approximately 26 years, a mean FEV_1 of 66.4% predicted, and reversibility ≥15% in 91% of patients (mean 24.3%). At randomization, mean FEV_1 was 69.1% predicted.

Of those randomized, 168 patients (83.6%) completed the study. Discontinuations included 33 patients: 1 did not fulfill entry criteria, 15 met discontinuation criteria, 7 had an adverse event, 4 were not willing to continue, 1 lost to follow-up, 5 other reasons.

Most protocol deviations were minor, and were judged not to affect the outcome of the study (I concur). The safety analysis subset included all 201 randomized patients. The efficacy analysis subset (n=189) excluded 12 patients who had <2 periods of treatment. The PK analysis subset (n=184) excluded 17 patients who had either <2 periods of treatment (12), had formoterol data

from <2 periods (3), or had unevaluable samples (2). The per-protocol analysis subset (n=180) excluded 9 patients from the efficacy subset who had medication deviations (7), unacceptable % predicted FEV_1 (1), or had unacceptable FEV_1 reversibility (1).

Pre-dose FEV_1 and other pulmonary function measurements were relatively constant across treatments.

10.1.1.2.2 Efficacy

Treatment means for average 12-hour FEV_1 are shown in Table 48, the adjusted means for FEV_1-over-time are shown in Figure 11, and the mean percent changes in FEV_1 over time from pre-dose value are shown in Figure 12. As expected, all formoterol treatments resulted in significantly greater bronchodilation than with budesonide alone ($p<0.001$). For the same-dose of formoterol (S1 vs O1; S2 vs O2; and S4 vs O4) the differences between treatments were small with narrow 95% CIs. Within each treatment, each dose doubling (i.e., S1 vs S2, S2 vs S4, O1 vs O2, and O2 vs O4) resulted in a statistically significant increase in bronchodilation. Maximum FEV_1 and FEV_1 at 12 hours were also comparable by dose of formoterol.

Onset of effect over the first 60 minutes after dosing is shown in Figure 13. The number and percentage of patients with onset of effect (defined as the first occurrence of a 15% or greater increase in FEV1 from pre-dose value) within 3, 9, 15, and 60 minutes after drug administration is shown in Table 49. The median time to onset were similar between treatments at each formoterol dose, and decreased as formoterol dose increased. At the 9 mcg dose, median time to onset was faster with Symbicort (25 minutes), compared with Oxis TBH (50 minutes), though this effect was not evident in the figure.

Estimates of relative dose potency were performed using adjusted LS means for average 12-hour FEV_1 at each dose. Using a parallel straight-line approach, the relative potency of Symbicort to the Oxis TBH was estimated to be 0.97, with a 95% CI of 0.732 to 1.265. Estimated on the basis of the Symbicort dose-response without regard to the Oxis dose response, the nominal reference dose of 9 mcg of formoterol from Oxis (2 inhalations) corresponded to 8.53 mcg from Symbicort (2 inhalations) (95% CI 6.167 to 11.693), as shown in Figure 14.

Urinary excretion of unchanged formoterol is shown in Figure 15. Formoterol excretion increased proportionally with increasing formoterol dose and was similar between treatment modalities (Symbicort vs Oxis). The systemic exposure to formoterol administered via Symbicort was 35% higher (mean ratio: 1.35; 95% CI: 1.207 to 1.502) than that achieved with Oxis TBH, an effect that was consistent across the dose range studied (between 31% and 39%) but not consistent with the pharmacodynamic results.

Table 48. SD-039-0729, Treatment means for average 12-hour FEV_1 (ANCOVA results, LOCF)

Treatment	Formoterol dose	N	FEV_1 (L), Mean (SD)		Average 12-h FEV_1 (L)		
			Pre-dose	Average 12-h	LS mean	SE	95% CI
S1	4.5	127	2.35 (0.716)	2.67 (0.758)	2.69	0.012	2.667, 2.713
S2	9	130	2.40 (0.697)	2.77 (0.779)	2.74	0.011	2.720, 2.765
S4	18	133	2.41 (0.724)	2.86 (0.805)	2.81	0.011	2.785, 2.830
O1	4.5	132	2.35 (0.676)	2.69 (0.745)	2.71	0.011	2.685, 2.730
O2	9	148	2.34 (0.726)	2.68 (0.800)	2.74	0.012	2.719, 2.765
O4	18	126	2.38 (0.764)	2.80 (0.834)	2.78	0.012	2.760, 2.806

Treatment	Formoterol dose	N	FEV_1 (L), Mean (SD)		Average 12-h FEV_1 (L)		
			Pre-dose	Average 12-h	LS mean	SE	95% CI
B	0	125	2.42 (0.732)	2.54 (0.792)	2.51	0.012	2.482, 2.528
Source: T21, p79; SD-039-0729							

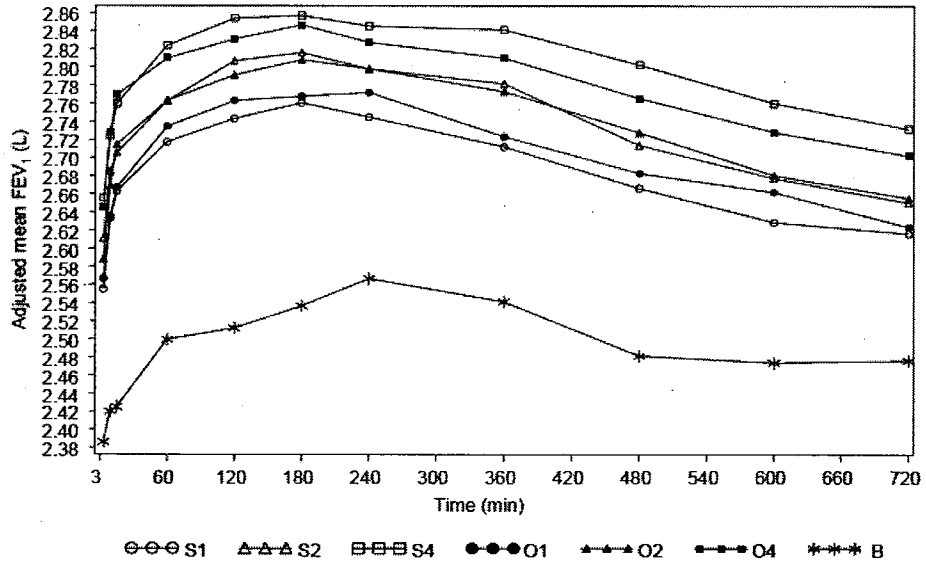

Figure 11. SD-039-0729, Adjusted mean FEV_1 over time, by treatment (LOCF)

Source: F6, p82; SD-039-0729

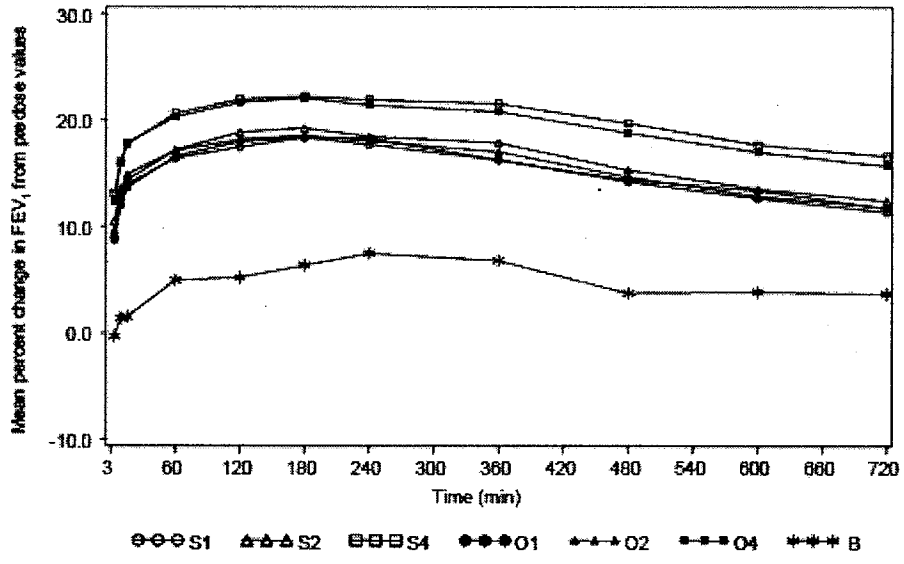

Figure 12. SD-039-0729, Mean percent change in FEV_1 over time from pre-dose value, by treatment (LOCF)

Source: F7, p83; SD-039-0729

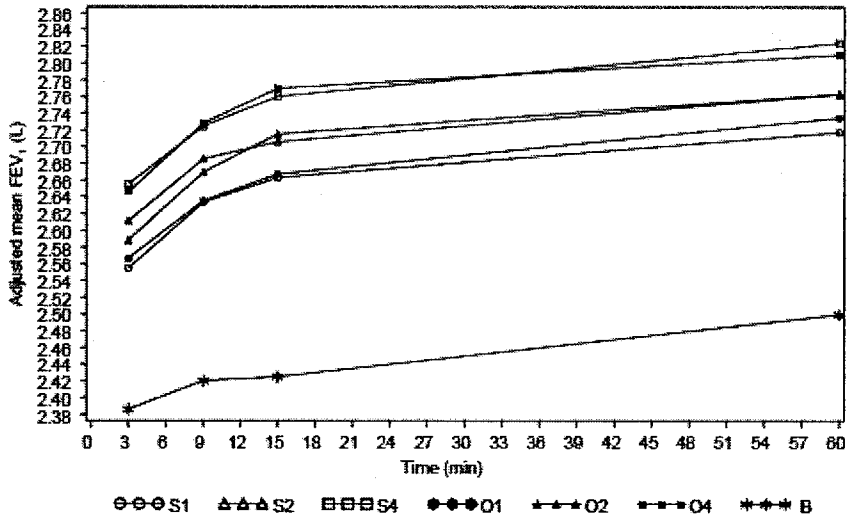

Figure 13. SD-039-0729, Adjusted mean FEV_1 over first 60 minutes after administration (LOCF)

Source: F8, p89; SD-039-0729

Table 49. SD-039-0729, Onset of treatment effect (≥15% increase in FEV_1), by treatment

Time	Treatment						
	S1 n=128	S2 n=130	S4 n=134	O1 n=133	O2 n=126	O4 n=126	B n=125
Patients with onset, n (%)							
Within 3 min	16 (12.5%)	27 (20.8%)	40 (29.9%)	15 (11.3%)	23 (18.0%)	30 (23.8%)	1 (0.8%)
Within 9 min	40 (31.3%)	55 (42.3%)	65 (48.5%)	38 (28.6%)	42 (32.8%)	62 (49.2%)	4 (3.2%)
Within 15 min	55 (43.0%)	62 (47.7%)	73 (54.5%)	53 (39.8%)	48 (37.5%)	69 (54.8%)	6 (4.8%)
Within 60 min	67 (52.3%)	73 (56.2%)	89 (66.4%)	65 (48.9%)	69 (53.9%)	79 (62.7%)	15 (12.0%)
After 60 min	61 (47.7%)	57 (43.8%)	45 (33.6%)	68 (51.1%)	59 (46.1%)	47 (37.3%)	110 (88.0%)
Time to onset, min							
Median	57.15	24.85	10.65	60.00	50.20	9.65	60.00
Min, Max	1.4, 60.0	1.5, 60.0	1.1, 60.0	0.8, 60.0	1.0, 60.0	0.9, 60.0	1.9, 60.0
Source: T27, p89, SD-039-0729.pdf							

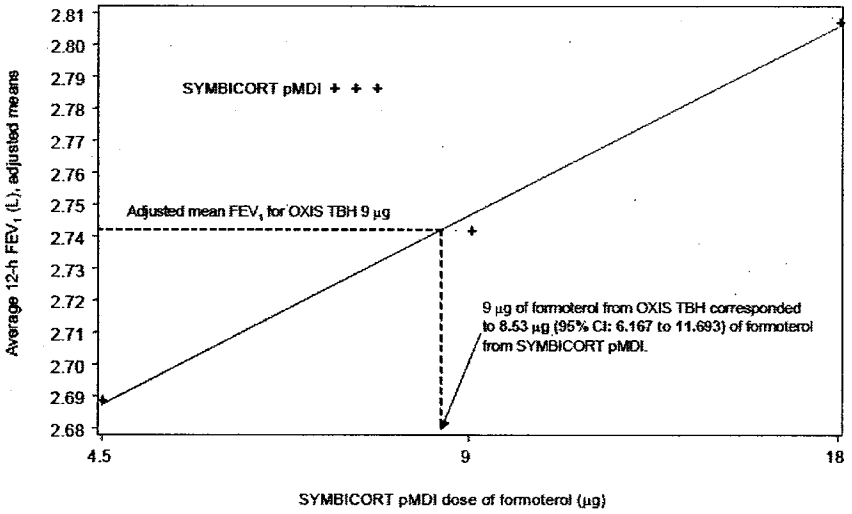

Figure 14. SD-039-0729, Straight-line approximation of Symbicort dose response and dose corresponding to 9 mcg of Oxis TBH based on average 12-hour FEV_1 (adjusted means; LOCF)

Source: F5, p82; SD-039-0729

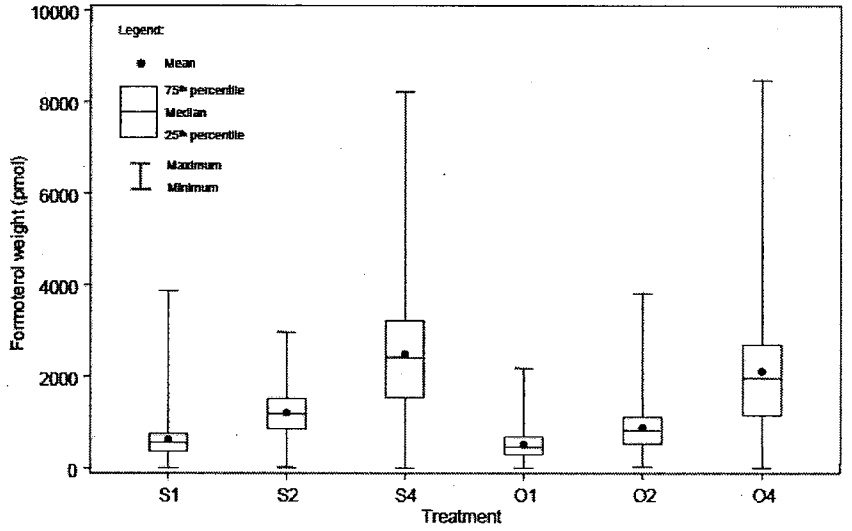

Figure 15. SD-039-0729, Twelve-hour excretion of unchanged formoterol by treatment and dose

Source: F9, p91; SD-039-0729

10.1.1.2.3 Safety

There were no specific safety concerns raised by this single-dose crossover study.

There were no SAEs or deaths. While 66 patients had 131 AEs most were mild to moderate; 11 had 16 AEs considered drug related by the investigator. The most common AEs (3.0% to 6.0% incidence) were headache, nasopharyngitis, upper respiratory tract infection, and nausea. Seven patients withdrew because of 9 AEs, 4 of which were severe in intensity; none of the 9 AEs were considered by the investigator to be causally related to study drug.

Mean dose-related increases in glucose concentration and decreases in potassium concentration were expected and not clinically important. Individual clinically important glucose or potassium abnormalities were infrequent (.8.4% per parameter per treatment). Mean differences in ECG parameters among treatments were small; very few patients had absolute values for heart rate, QT interval, or QTc that met the criteria for clinical importance or had changes from baseline that were considered severe. Symbicort and Oxis TBH produced similar small, clinically irrelevant dose-related increases in mean heart rate, while Symbicort but not Oxis TBH produced small, clinically irrelevant dose-related increases in mean QTc interval. There were no relevant abnormalities in vital signs with treatment. Other clinical chemistry results (i.e., excluding glucose or potassium results) and findings on physical examinations were generally unremarkable. [p97]

10.1.1.3 Conclusions

As measured by average 12-hour FEV_1, the bronchodilating effects of formoterol from Symbicort and Oxis TBH were comparable dose for dose in the range of 4.5 to 18 mg. A similar pattern of results was seen for the secondary endpoints of maximum FEV1 and FEV1 at 12 hours. There was evidence of a dose-response relationship for onset of effect for both drug products. Across the dose range studied, urinary excretion of unchanged formoterol increased proportionally with increasing dose regardless of administration method, although systemic exposure to formoterol with Symbicort was approximately 35% greater than that with Oxis TBH. The difference in systemic exposure was unexplained.

10.1.2 Study SD-039-0716. Twelve-week safety and efficacy study using Symbicort (80/4.5 mcg) versus its monoproducts (budesonide MDI and formoterol TBH) in adolescents and adults (≥12 years) and children (6-11 years) with asthma

Protocol #:	SD-039-0716
Title:	A Twelve-Week, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Trial of SYMBICORT® pMDI (80/4.5 mcg) versus its Monoproducts (budesonide and formoterol) in Children (≥6 Years of Age) and Adults with Asthma – SPRUCE 80/4.5
Study Dates:	First subject enrolled:: July 31, 2002 Last subject completed: September 24, 2003
Sites:	Adults and adolescents ≥12 years: 63 centers in the United States Children 6 and 11 years: subset of 15 centers
IRB:	Each study site had a separate IRB. A listing was provided.
Ethics:	The study report states that the study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements and the AstraZeneca policy on Bioethics.

Source: M5, SD-039-0716.pdf

10.1.2.1 Protocol

10.1.2.1.1 Objectives

Primary: To compare the safety and efficacy (including health-related quality of life [HRQOL] and patient satisfaction variables) of Symbicort MDI (budesonide/formoterol 80/4.5 mcg per puff) administered as 2 puffs twice daily, to that of budesonide MDI (80 mcg per puff) alone and to that of formoterol DPI (4.5 mcg per inhalation), both administered as 2 inhalations twice daily, in patients ≥12 years of age with asthma.

Secondary: To compare the safety, efficacy (including HRQOL and patient satisfaction variables), and onset of effect of all 3 active products alone relative to placebo in patients with asthma.

10.1.2.1.2 Amendments and Post-Hoc Changes

The original protocol was dated May 6, 2002. Three amendments were made: on June 20, 2002, September 8, 2002, and January 8, 2003. The latter two amendments were made after enrollment of the first patient on July 31, 2002. The first amendment (June 29, 2002) made a number of modifications to the entry criteria. The second amendment (September 8, 2002) was made to address the issue of AE causality, modify the immunotherapy restrictions, and make minor administrative modifications.

The third amendment, dated January 8, 2003, was made to reflect AZ's decision to elevate pre-dose FEV_1 from a secondary to a co-primary variable, and to demote withdrawals due to pre-defined asthma events from a primary to a secondary variable. With this amendment, several other changes were made to clarify the pre-defined asthma events. [M5, Appendix 12.1.1, pp 7931-7996; SD-039-0716.pdf]

Reviewer's Comment: The 3rd amendment to the protocol, which elevated one co-primary variable and demoted another while the study was underway, is the subject of several sets of comments throughout the review of this study [and also, study 717]. See Variables/Endpoints and Results sections for details.

10.1.2.1.3 Summary of the Study Design

This was a randomized, double-blind, double-dummy, placebo-controlled trial comparing the efficacy and safety of Symbicort MDI (80/4.5 mcg formulation) with its pharmacologic monoproducts, budesonide MDI (80 mcg) and formoterol (Oxis) Turbuhaler, and placebo, in adolescents and adults (≥12 years of age) and a subset of children (6 to 11 years of age) with mild-moderate asthma (for ≥12 years: FEV_1 on ICS therapy 60% to 90% predicted; for <12 years: ≥75% predicted). Randomization was stratified by age group (<12 years old and ≥12 years). The study comprised a screening visit, a 14 (±7) day single-blind placebo run-in period, and a 12-week double-blind treatment period.

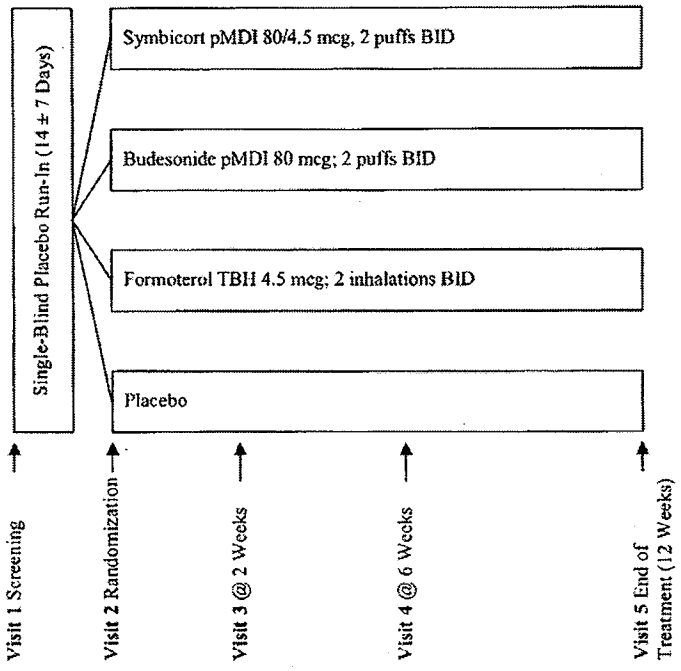

Figure 16. SD-039-0716, Flow chart of study treatments

Source: Protocol Amendment 4, p8018; SD-039-0716.pdf

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10.1.2.1.4 Population

Eligibility criteria included males and females (using contraception, if of childbearing potential) with asthma (by ATS criteria, with history for at least 6 months) who were at least 12 years of age (all centers) or, in a subset of centers, between the ages of 6 and 11 years; who were chronically treated with a low to medium dose of a qualifying inhaled corticosteroid (ICS) (Table 50); and whose FEV_1 on ICS therapy was between 60% to 90% predicted (≥12 years) or ≥75% predicted (<12 years). Patients ≥12 years of age had to demonstrate reversibility of FEV_1 of at least 12% and ≥0.20 L from the pre-albuterol baseline value within 15 to 30 minutes after administration of a standard dose of fast-acting $beta_2$-agonist (albuterol MDI, 2 to 4 actuations [90 mcg per actuation], with or without a spacer, or after administration of up to 2.5 mg nebulized albuterol if required). Patients <12 years of age had to show reversibility of ≥12% only. If receiving immunotherapy, patients had to on a maintenance IT regimen. Qualification for randomization was based on lung function and asthma symptoms scores during the run-in period, as discussed below. [p96-7]

Exclusion criteria included: severe asthma; hospitalization or required emergency treatment for asthma more than once within the previous 6 months; systemic corticosteroids within 4 weeks; malignancy within 5 years (except basal cell carcinoma); significant disease or disorder which, in the opinion of the investigator, could either put the subject at risk or influence the subject's ability to participate or the results of the study; known hypersensitivity to $beta_2$-agonists, budesonide, formoterol, or (inhaled) lactose; treatment with a beta-blocker (including eye drops); >10-pack-year history of smoking; or, participated another investigational study within 4 weeks or in a previous Symbicort trial. [p98-9]

Table 50. SD-039-0716, Qualifying ICS

Qualifying ICS	Dosage Range (mcg/day)
Beclomethasone dipropionate (CFC MDI)	168 – 630
Beclomethasone dipropionate (HFA MDI)	80 – 240
Budesonide	200 – 600
Budesonide (nebulized)	250 - 750
Flunisolide	500 – 1500
Fluticasone (CFC MDI)	88 – 440
Fluticasone (Diskus)	100 – 500
Triamcinolone acetonide	400 – 120
Source: p97. SD-039-0716.pdf	

Qualification for randomization was based on: normal screening labs, ECG, and Holter; lack of URI symptoms or need for systemic corticosteroids during baseline or at randomization; an FEV_1 between ≥50% to 85% predicted (≥12 years) or ≥75% predicted (<12 years); and daytime or nighttime asthma symptom scores (on an electronic diary) greater than 0 on at least 3 days of the 7-day qualification period. [p97-8]

10.1.2.1.5 Conduct

After qualification, patients were required to discontinue all asthma medications and enter a 2-week single-blind run-in placebo MDI treatment period. At Visit 2, eligible patients were randomized to one of the following double-blind, double-dummy treatments:

- Symbicort MDI (80/4.5) 2 actuations + placebo TBH 2 inhalations, administered BID
- Budesonide MDI (80) 2 actuations + placebo TBH 2 inhalations, administered BID
- Formoterol TBH (4.5) 2 inhalations + placebo MDI 2 actuations , administered BID
- Placebo MDI, 2 actuations + placebo TBH 2 inhalations , administered BID

Table 51. SD-039-0716, Investigational products

Product	Delivered dose	Manufacturer	Batch Number
Run-in treatment			
Placebo MDI		AstraZeneca Charnwood, UK and/or Dunkerque, France	P6349, P6351
Randomized treatment			
Actives			
SYMBICORT MDI	80 mcg budesonide and 4.5 mcg formoterol per actuation	AstraZeneca Charnwood, UK and/or Dunkerque, France	P6037, P6501A
Budesonide MDI	80 mcg per actuation	AstraZeneca Charnwood, UK and/or Dunkerque, France	P6456
Formoterol (Oxis) TBH	4.5 mcg per inhalation. (M2 TBH)	AstraZeneca Södertälje, Sweden	P6474, P6508, P6624
Placebos			
Placebo MDI		AstraZeneca Charnwood, UK and/or Dunkerque, France	P6204, P6349, P6490, P6491
Placebo TBH	(M2 TBH)	AstraZeneca Södertälje, Sweden	P6476, P6512, P6625, P6677
Rescue medication			
Albuterol MDI	90 mcg per actuation	Commercially available; supplied by AstraZeneca	ABL97A and ABP33A
Local anesthetic			
EMLA cream	Cream for topical application used as needed prior to phlebotomy	AstraZeneca	203083, 211051, 301148, 302074

Source: p102; SD-039-0716.pdf

Allowed medications included intranasal corticosteroids, if used prior to screening. Nasal cromolyn was permitted at any time. Rescue medication was a generic albuterol MDI.

Patients could be discontinued for any the following reasons: development of an exclusion criterion; AE, occurrence of a pre-defined asthma event; voluntary discontinuation; or, lost to follow-up. Withdrawals due to pre-defined asthma events were originally a co-primary efficacy variable for evaluation of the controller effect of the corticosteroid component (Symbicort minus formoterol comparison). With Amendment 3, this variable was demoted to a secondary variable. [p156]

Pre-defined asthma events were defined as:

1. For patients ≥12 years, a decrease in morning pre-dose FEV_1 of ≥20% from the pre-dose FEV_1 at randomization, or a decrease to <45% predicted.

   For patients <12 years of age, a decrease in morning pre-dose FEV_1 of ≥20% from the pre-dose FEV_1 at randomization, or to <60% of predicted.
2. For patients ≥12 years, use of ≥12 actuations of albuterol/day on 3 or more days within 7 consecutive days.

   For patients <12 years of age, use of ≥8 actuations of albuterol/day on 3 or more days within 7 consecutive days.
3. 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.
4. Two or more nights with awakening due to asthma, which required rescue medication use within 7 consecutive days.
5. Clinical exacerbation requiring emergency treatment, hospitalization, or use of asthma medication not allowed by the protocol.

Events meeting any of these criteria were to be recorded on the asthma exacerbation (ASTEXAC) CRF. Patients meeting criteria **1**, **2**, **3** or **5** were to be withdrawn from the trial. However, if the pre-defined asthma event was based solely on criterion **4**, the investigator could determine whether the patients should remain in the trial. [p100-1]

Reviewer's Comments:

1. ***Withdrawals due to pre-specified asthma events was originally a co-primary variable for evaluation of the controller effect of the corticosteroid component. See Variables/Endpoints and Results sections for details and discussion of these changes.***
2. ***It is also important to note that several of the predefined qualifying events were diary- or spirometry-related. As such, they could have been entered into the spirometry or electronic diary data but not necessarily transposed into the CRF (the predefined methodology for capturing events). This created a second set of problems with how to deal with variability in the data sets. Please see the Results section for further discussion.***

Spirometry was performed using daily-calibrated spirometers that met ATS standards, and spirometry measurements followed ATS guidelines. Spirometry measurements within 6 hours after albuterol use were excluded. Serial spirometry was performed at the randomization visit, at 2 weeks, and at the end of treatment (Visits 2, 3, and 5). At these visits, spirometry was performed at the following timepoints after dosing was completed: 3 (±1), 9 (±1), 15 (±1), 60 (±5), 120 (±10), 180 (±10), 240 (±10), 360 (±10), 480 (±10), 600 (±10) and 720 (±10) minutes (permitted time window in parenthesis).

Table 52. SD-039-0716, Summary of Study Activities by Visit

VISIT NUMBER	1	2	3	4	5
Treatment Week	-2	0	2	6	12
Informed Consent (and Assent, if required) obtained	X				
Inclusion/Exclusion Criteria reviewed	X	X			
Comprehensive Physical Examination (includes pulse, blood pressure, height, weight, temperature))	X[a]				X
Brief Physical Examination (includes pulmonary auscultation, pulse & blood pressure)		X	X	X	
Medical History	X				
12-Lead Electrocardiogram[b]	X[c]	X	X	X	X
Blood Laboratory Assessments (includes pregnancy testing, as required)	X[d]		X[e]		X[e]
Dispense Single-Blinded Run-In Medication @ V. 1 and Retrieve @ V. 2	X	X			
Dispense Rescue Medication (as needed); Instruct in Proper Use & Documentation of Use	X	X	X	X	
Dispense Peak Flow Meter & Instruct in Use & Care and Documentation of Measurements	X				
Dispense Diary & Instruct in Use & Completion	X				
Review Diary & Peak Flow Meter Use, Retrieve Data		X	X	X	X[f]
Holter Monitoring, 24-hour	X[c,g]		X[h]		
Adverse Events Assessment (including review of subject notebook at all visits)		X	X	X	X[i]
Spirometry	X[j]			X[k]	
Randomize @V. 2; Dispense Study Medication, Instruct in Proper Use & Documentation		X	X	X	
Collect Study Medication Dispensed at Previous Visit, Review Use & Documentation			X	X	X
12-Hour Serial Spirometry		X	X		X
Instruct/Remind Subject of Allowed/Disallowed Medications, Including Withholding Medications Prior to Each Study Visit	X	X	X	X	
Global Assessments					X
Health Outcomes Questionnaires (see Table 2, Section 5.6 for specifics.)		X	X	X	X

[a] Temperature only recorded at Visit 1

[b] Following Visit 1, all ECGs should be obtained between 1-2 hours after dosing with study drug.

[c] Report must be received and assessed prior to Visit 2, as described in Section 5.5.2. or 5.5.3.

[d] Results must be reviewed prior to Visit 2.

[e] Blood for glucose and potassium only at Visit 3; should be drawn 1-2 hours after morning dose of study drug at Visits 3 & 5.

[f] Retrieve electronic diary.

[g] Must be completed approximately 1 week prior to Visit 2.

[h] Must be completed within 1 week (before or after) of Visit 3.

[i] A follow-up phone call to assess for additional adverse events is required approximately 1 week after Visit 5.

[j] Spirometry and reversibility criteria to be met according to Sections 4.1.1., criteria 3 & 4, and 5.4.1.3.

[k] Pre-dose and 2-hour post-dose spirometry measurements only.

Source: p8019; SD-039-0716.pdf

10.1.2.1.6 Safety Evaluations

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 (≥12 years of age only), physical examinations, and vital signs.

10.1.2.1.7 Efficacy and Compliance Evaluations

Co-primary efficacy variables:

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 was used to demonstrate the bronchodilator effect of the formoterol component (Comparison: Symbicort minus budesonide). Pre-dose FEV_1 was used to demonstrate the stabilizing, anti-inflammatory effect of the budesonide component (Comparison: Symbicort minus formoterol). Although patients 6-12 years of age were randomized in a subset of centers, the primary efficacy evaluation was performed in patients ≥12 years of age.

Reviewer's Note: With Amendment 3, withdrawals due to asthma exacerbation was demoted from a co-primary to a secondary efficacy variable, and pre-dose FEV_1 was elevated from a secondary to a co-primary efficacy variable for evaluation of the contribution of the corticosteroid (budesonide) component to the combination drug product (Symbicort minus formoterol comparison). At the pre-NDA meeting, the applicant called attention to this change, which was carried out for both pivotal efficacy studies 716 and 717, and asked if the Division had any concerns. AstraZeneca stated that this change was carried out prior to any data being transferred to them, without unblinding any study personnel, and early in the course of the studies. The reason given for the change was that investigators were confused about whether patients who met withdrawal criteria were required to be withdrawn from the study or whether they could continue at the investigator's discretion; apparently, some patients who should have been discontinued because they met withdrawal criteria were not discontinued because investigators judged them to be clinically stable. Since pre-dose FEV_1 had been collected on all patients, the change was made. Please see the Results section for a discussion of effect of these changes.

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, and subject perception of onset of effect during spirometry using a Patient Perception of Onset of Effect Question [POE] administered prior to each spirometry assessment during the first hour),
- Diary variables (morning and evening PEF, nighttime and daytime asthma symptom scores, nighttime awakenings, rescue medication use, and subject perception of onset of effect using the Onset of Effect Questionnaire [OEQ]).

Baseline-adjusted FEV_1 was an average change from baseline in FEV_1 over 12 hours post-dose, weighted proportionally to time, at Visits 2, 3, and 5. This was calculated as the area between the FEV_1-over-time curve and the baseline FEV_1 value (AUC), divided by observation time. For

these calculations, the pre-dose FEV_1 value on the day of randomization (Visit 2) was used as baseline, and the 1st time point used in calculations was the ordered pair (0, baseline FEV1). The AUC was calculated with the trapezoidal method, using the actual times of measurements relative to dosing on the day of the serial spirometry visit. Extrapolation based on available data was used to impute missing values depending upon whether the data was bounded or unbounded, and alternative methodology served as sensitivity analyses. The primary time point for this analysis was the end of Week 2 (Visit 3). [p 109-12]

The primary derived variable for analysis of pre-dose FEV_1 was the change from baseline to the average over the treatment period. Baseline was defined as the pre-dose FEV_1 value measured on the day of randomization (Visit 2). The average over the treatment period was defined as the mean of all available pre-dose FEV_1 values from scheduled visits during the double-blind treatment period. [p113]

Treatment compliance was assessed using an electronic diary for recording of twice daily use of medications and other study variables. The diary captured the following variables: morning and evening peak expiratory flows (PEFs) (L/min) using a [redacted] Peak Flow Meter, daily asthma symptom scores during the day and night (on a scale of 0 to 3 where 0 = none, 1 = mild symptoms that are easily tolerated, 2 = moderate symptoms causing interference with daily activities, and 3 = severe symptoms causing inability to perform daily activities or sleep), daily nighttime awakenings due to asthma symptoms (Yes/No), daily rescue medication use (number of inhalations), and weekly subject perception of onset of effect using an Onset of Effect Questionnaire. The OEQ was completed weekly using a 5-point scale from strongly agree to strongly disagree to the following 5 statements:

1. During the past week, you could tell your study medication was working.
2. During the past week, you could feel your study medication begin to work right away.
3. During the past week, you felt physical sensations shortly after taking your study medication that reassured you that it was working.
4. During the past week, your study medication worked as quickly as your albuterol.
5. During the past week, you were satisfied with how quickly you felt your study medication begin to work.

Patient reported outcome (PRO) measures were also performed using the AQLQ (≥18 years), PAQLQ (7 to <18 years), Patient Satisfaction with Asthma Medication Questionnaire (PASM) (≥18 years), and the MOS Sleep scale (≥18 years).

10.1.2.1.8 Statistical Plan

Sample size:

A sample size estimation of 105 evaluable patients ≥12 years of age per treatment group was based on 95% power to detect a true mean difference between treatment groups of 0.25 L for the co-primary efficacy variables with for each variable, assuming a population standard deviation of 0.50 L, a 2-group t-test, and a 5% two-sided significance level for each test. Allowing for up to 5% of patients to be unevaluable, the study needed to randomize 112 patients ≥12 years of age per treatment group, or 448 patients ≥12 years of age overall. The protocol allowed for randomization of up to 92 patients 6 to <12 years of age.

Analysis sets:

The efficacy analysis set (EAS) was based on a modified ITT population, which included all randomized patients who had a randomization code, received at least one dose of study medication, and had sufficient data for at least on co-primary endpoint to be calculated. The primary efficacy analyses were based on the EAS population ≥12 years of age. Secondary efficacy analyses were performed using the EAS of all ages and per-protocol (PP) analysis sets. [p144]

Safety variables were analyzed with descriptive statistics, shift tables, and ANCOVA models using all patients who received at least one dose of study medication (safety analysis set).

Co-primary variables:

Each co-primary variable was analyzed by formulating contrasts within an analysis of covariance (ANCOVA) model, adjusting for the fixed factors of center and treatment and for the covariate of baseline FEV_1. For the comparison of Symbicort MDI to budesonide, baseline-adjusted average 12-hour FEV_1 was analyzed at Week 2, last observation carried forward (LOCF). For the comparison of Symbicort MDI to formoterol, pre-dose FEV_1 was analyzed as a change from baseline to the average over the double-blind treatment period. [p58]

To maintain a Type I error of no greater than 5%, a sequential approach was taken to hypothesis testing and the interpretation of unadjusted p-values. The following hypothesis was tested at the 5% level as the primary hypothesis:

H_{1null}: (SYMBICORT = Budesonide) OR (SYMBICORT = Formoterol)

H_{1alt}: (SYMBICORT ≠ Budesonide) AND (SYMBICORT ≠ Formoterol)

"The Rejection of this hypothesis required that SYMBICORT pMDI be superior to budesonide at the 5% level with respect to baseline-adjusted average 12-hour FEV_1 and also that SYMBICORT pMDI be superior to formoterol at the 5% level with respect to pre-dose FEV_1. If H_{1null} was rejected, then testing was to continue. Next, budesonide was to be tested versus placebo for pre-dose FEV_1, and formoterol was to be tested versus placebo for baseline-adjusted average 12-hour FEV_1. Each test was to be performed at the 5% level. Lastly, SYMBICORT pMDI was to be tested versus placebo for both of the co-primary endpoints as descriptive information." [p141]

Secondary variables:

Three outcome variables were prespecified as key secondary variables: 1) asthma symptoms as measured by percent of symptom-free days, 2) number of patients who experienced a pre-defined asthma event, and 3) the overall score from the AQLQ(S). The Simes-Hommel step-up method was used to control for multiplicity of testing at 5%, with the primary comparison as Symbicort MDI versus placebo, as follows: "The first step using the Simes-Hommel test was to rank the p-values for the three tests. If the largest of the three is ≤0.05, then the null hypothesis that Symbicort MDI = placebo was to be rejected for all three variables. If the largest p-value was not .0.05 but the second largest p-value was ≤0.025, then the null hypotheses that Symbicort MDI = placebo would be rejected for the remaining two variables. If the second largest p-value was not .0.025 but the final p-value was ≤0.017, then the null hypothesis that Symbicort MDI = placebo would be rejected for the final variable only." [p141-2]

10.1.2.2 Results

10.1.2.2.1 Description of the Study Population

10.1.2.2.1.1 Disposition

Of 1092 screened asthma patients, a total of 511 patients from 56 centers were randomized (ITT). All randomized patients received at least one study treatment (SAS) and provided at least one efficacy observation (EAS all ages), i.e. had sufficient data for at least one co-primary endpoint to be calculated. The primary efficacy analysis set, a subset of the EAS all ages, included 480 patients ≥12 years of age (EAS ≥12). The ITT population included a total of 35 patients who were screened more than once and later randomized: 7 Symbicort, 4 budesonide, 12 formoterol, and 12 placebo. Over half of all centers contributed 12 to 20 patients each. The per-protocol (PP) analysis set included 459 patients: 52 patients were excluded from this set (31 were <12 years of age; 1 had unacceptable FEV_1 reversibility at Visit 1; 18 were not treated with consistent ICS at entry; 1received disallowed medication after Visit 1; 1 had unacceptable asthma symptom score during run-in). [p167-70]

Reasons for discontinuation are shown in Table 53. The withdrawal rate was highest in the placebo group (51%), followed by the formoterol group (32%), and the Symbicort and budesonide groups (15%). The most common reason for withdrawal was due to study-specific discontinuation criteria (i.e., withdrawals due to pre-defined asthma events): highest in the placebo and formoterol groups (33.6% and 20.3%, respectively), followed by the Symbicort and budesonide groups (7.7% and 6.3%, respectively). The number of withdrawals due to development of pre-defined asthma events was originally a primary variable to evaluate the contribution of the budesonide component to the combination drug product (Symbicort minus formoterol comparison), but demoted to a secondary efficacy variable when pre-dose FEV_1 was upgraded. The reason given for the change was that investigators were confused about whether patients who met withdrawal criteria were required to be withdrawn from the study or whether they could continue at the investigator's discretion; apparently, some patients who should have been discontinued because they met withdrawal criteria were not discontinued because investigators judged them to be clinically stable. Since pre-dose FEV_1 had been collected on all patients, the change was made. Since this change was performed while studies were ongoing, understanding the nature and frequency of withdrawals becomes an important issue for evaluation the contribution of withdrawals to the results and interpretation of this study.

The applicant states that the higher withdrawal rate in the placebo group was due to both a greater rate of withdrawals due to study-specific discontinuation criteria, and also a greater rate of discontinuations due to adverse events, which were higher in the placebo group (9.2%) than in the other treatment groups (3.8% Symbicort, 2.4% budesonide, 2.4% formoterol). [p111-3] In addition, a higher percentage of patients in the placebo group (5.3%) experienced an AE of asthma compared to 0%, 1.6%, and 3.3% for Symbicort, budesonide and formoterol, respectively. Asthma adverse events that either qualified patients for withdrawal or lead to withdrawal were evaluated as part of this review, and described in later sections.

Not surprisingly, the predominance of withdrawals in the placebo group were in patients who had poorer asthma control and lower baseline mean FEV_1 values, as the baseline mean for the

subgroup of placebo patients remaining at Week 12 (2.66 L) was notably higher than those for the active treatment groups (Symbicort 2.40 L, budesonide 2.32 L, formoterol 2.45 L). [p201-2]

Implications from the withdrawal pattern are limited by the uneven application of the pre-defined asthma event qualifying criteria. Nevertheless, 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. In addition, in this study in less severe asthmatics the frequency of withdrawals due to an asthma event was similar in the Symbicort and budesonide treatment arms, implying that the addition of formoterol to budesonide does not add much to the benefit of budesonide as a controller drug in the prevention of asthma exacerbations [and this observation was borne out by the CRF data]. This is discussed further within the discussion of qualifying pre-defined asthma events in the Secondary Variables section.

Table 53. SD-039-0716, Reasons for Discontinuation

	Symbicort n=130	Budesonide n=127	Formoterol n=123	Placebo n=131	Total n=511
All randomized patients (Applicant's analyses)					
Randomized / took study med	130	127	123	131	511
Completed	110	108	84	64	366
Discontinued	20 (15.4)	19 (15.0)	39 (31.7)	67 (51.1)	145 (28.4)
Reasons for Discontinuation					
Developed study-specific discontinuation criteria [a]	10 (7.7)	8 (6.3)	25 (20.3)	44 (33.6)	87 (17.0)
Adverse event	5 (3.8)[b]	3 (2.4)	3 (2.4)	12 (9.2)	23 (4.5)[b]
Not willing to continue	3 (2.3)	5 (3.9)	6 (4.9)	6 (4.6)	20 (3.9)
Eligibility criteria not fulfilled	0	1 (0.8)	0	0	1 (0.2)
Lost to follow-up	0	0	0	0	0
Other	2 (1.5)	2 (1.6)	5 (4.1)	5 (3.8)	14 (2.7)
Efficacy Subset of patients ≥12y (From Dr. Guo)					
Randomized / took study med	123	121	114	122	480
Completed	105	103	79	60	347
Discontinued	18 (14.6)	18 (14.9)	35 (30.7)	62 (50.8)	133 (27.7)
Developed study-specific discontinuation criteria	9	8	21	40	74
Adverse event	4	3	3	11	21

Note: This table includes data from the applicant's analyses and from the FDA statistician.
[a] Represents withdrawals due to pre-defined asthma events.
[b] Includes 22 DAEs that occurred during treatment and 1 DAE that occurred post-treatment.

Sources: Table 17, p 166; SD-039-716.pdf. Data for efficacy subset from FDA statistician, Dr. Ted Guo (DEMO, DISP, patients ≥12 years).

10.1.2.2.1.2 Demographics and Baseline Characteristics

Demographics and key baseline characteristics for the ITT/efficacy/safety population are shown in Table 54, which shows that the treatment groups were similar, and their baseline characteristics including disease severity (daily ICS dose, mean pre-dose FEV_1, and percent reversibility) were comparable. The study population was approximately 90% Caucasian, 40% males and 60% females, a mean age of 35 years (range 6 to 78 years), and 31/511 <12 years of age and 480/511 ≥12 years of age. All except 1 had asthma controlled by a regimen of ICS prior to entry, and asthma medication use was similar between treatment groups. The average length

of asthma history was 19 years. At screening, the mean pre-dose FEV_1 was 2.5 L and mean percent reversibility was 18.9% (range 10.3% to 62.6%). At baseline, the mean percent predicted FEV_1 for most patients was in the mild-to-moderate range (75.7 % predicted) while being treated with an average ICS dose of 341.5 mcg daily (range 80 to 1200 mcg a day). [p178]

Table 54. SD-039-0716, Demographic and key baseline characteristics, ITT

	Symbicort n=130	Budesonide n=127	Formoterol n=123	Placebo n=131	Total n=511
Sex (n, %)					
Male	50 (38.5)	50 (39.4)	46 (37.4)	55 (42.0)	201 (39.3)
Female	50 (38.5)	77 (60.6)	77 (62.6)	76 (58.0)	310 (60.7)
Age (yr)					
Mean (SD)	35.6 (16.6)	35.8 (16.7)	33.4 (16.9)	34.1 (15.7)	34.8 (16.4)
Median	36.5	38.0	32.0	34.0	35.0
Range	6 to 77	7 to 78	7 to 73	6 to 66	6 to 78
Age group (yr), (n, %)					
6 to <12	7 (5.4)	6 (4.7)	9 (7.3)	9 (6.9)	31 (6.1)
≥12	123 (94.6)	121 (95.3)	114 (92.7)	122 (93.1)	480 (93.9)
12 to <16	12 (9.2)	14 (11.0)	15 (12.2)	11 (8.4)	52 (10.2)
16 to <65	108 (83.1)	103 (81.1)	92 (74.8)	110 (84.0)	413 (80.8)
65 to <75	2 (1.5)	3 (2.4)	7 (5.7)	1 (0.8)	13 (2.5)
≥75	1 (0.8)	1 (0.8)	0	0	2 (0.4)
Race (n, %)					
Caucasian	113 (86.9)	107 (84.3)	107 (87.0)	119 (90.8)	446 (87.3)
Black	11 (8.5)	12 (9.4)	13 (10.6)	8 (6.1)	44 (8.6)
Oriental	1 (0.8)	1 (0.8)	1 (0.8)	2 (1.5)	4 (0.8)
Other	6 (4.6)	7 (5.5)	2 (1.6)	2 (1.5)	17 (3.3)
ICS use at entry (mcg/day) [a]					
N	130	126	123	131	510
Mean (SD)	345.4 (156.2)	352.6 (189.3)	328.7 (173.3)	339.0 (183.1)	341.5 (175.6)
Min, Max	80, 1000	88, 1200	88, 1200	80, 1000	80, 1200
Years since diagnosis	19.4 (12.7)	18.8 (13.0)	18.6 (12.4)	19.7 (13.8)	19.2 (13.0)
Screening (Visit 1, pre-bronchodilator) (mean, SD)					
FEV_1 (L)	2.5 (0.64)	2.5 (0.61)	2.5 (0.62)	2.5 (0.67)	2.5 (0.64)
FEV_1 % predicted	76.3 (9.48)	75.6 (7.96)	76.5 (8.22)	74.3 (8.82)	75.7 (8.67)
Percent reversibility in FEV_1					
N	130	127	122	131	510
Mean (SD)	18.2 (7.4)	19.3 (6.7)	18.8 (7.6)	19.4 (8.9)	18.9 (7.7)
Median	15.4	17.6	16.0	15.7	16.0
Baseline (Visit 2, pre-dose) (mean, SD)					
FEV_1 (L)	2.4 (0.63)	2.3 (0.61)	2.4 (0.64)	2.3 (0.66)	2.3 (0.63)
FEV_1 % predicted	71.6 (11.41)	70.8 (10.69)	71.5 (10.39)	71.2 (11.10)	71.3 (10.89)
Run-in period average (mean, SD)					
Morning PEF (L/min)	342.1 (97.7)	346.4 (85.1)	350.5 (89.0)	340.7 (95.2)	345.1 (91.8)
Daily rescue medication[b]	2.7 (2.4)	2.9 (2.8)	2.7 (2.7)	2.6 (2.7)	2.7 (2.6)
Daytime asthma symptom score [c]	1.2 (0.5)	1.1 (0.5)	1.1 (0.5)	1.1 (0.5)	1.1 (0.5)
Nighttime asthma symptom score [c]	1.1 (0.5)	1.1 (0.5)	1.0 (0.5)	1.1 (0.5)	1.1 (0.5)

	Symbicort n=130	Budesonide n=127	Formoterol n=123	Placebo n=131	Total n=511
a Baseline ICS is defined as the last ICS dose reported prior to run-in. b Nighttime and daytime rescue medication use. c Symptoms rated on a scale of 0=none, 1=mild, 2=moderate, 3=severe.					
Source: T19, p172-3; SD-039-716.pdf					

10.1.2.2.1.3 Compliance

Medication compliance, shown in Table 55, was high during both the run-in and treatment periods. The table shows compliance calculated in 2 ways.

Table 55. SD-039-0716, Study Medication Compliance, ITT

	Symbicort n=130	Budesonide n=127	Formoterol n=123	Placebo n=131	Total n=511
Run-in					
N	130	127	123	131	511
Compliance using diary entries [a]					
Mean (SD)	99.3 (2.26)	98.7 (4.51)	99.2 (2.23)	99.0 (2.80)	99.1 (3.09)
<80% (n,%)	0	2 (1.6)	0	0	2 (0.4)
>80% (n,%)	130 (100.0)	125 (98.4)	123 (100)	131 (100)	509 (99.6)
Compliance using days on treatment [b]					
Mean (SD)	91.7 (8.46)	91.4 (10.81)	91.9 (8.79)	91.3 (6.80)	91.6 (8.79)
<80% (n,%)	8 (6.2)	7 (5.5)	7 (5.7)	11 (8.4)	33 (6.5)
>80% (n,%)	122 (93.8)	120 (94.5)	116 (94.3)	120 (91.6)	478 (93.5)
Treatment period					
N	130	126	120	126	502
Compliance using diary entries [a]					
Mean (SD)	98.9 (1.98)	98.6 (2.36)	98.7 (2.27)	99.2 (1.74)	98.9 (2.11)
<80% (n,%)	0	0	0	0	0
>80% (n,%)	130 (100.0)	126 (99.2)	120 (97.6)	126 (96.2)	502 (98.2)
NA	0	0 1 (0.8)	3 (2.4)	5 (3.8)	9 (1.8)
Compliance using days on treatment [b]					
Mean (SD)	91.4 (13.43)	90.6 (11.80)	89.7 (12.87)	91.0 (9.17)	90.7 (11.91)
<80% (n,%)	13 (10.0)	13 (10.2)	19 (15.4)	17 (13.0)	62 (12.1)
>80% (n,%)	117 (90.0)	113 (89.0)	101 (82.1)	109 (83.2)	440 (86.1)
NA	0	0 1 (0.8)	3 (2.4)	5 (3.8)	9 (1.8)
a Medication compliance using diary entries = [Total (Yes) study medication intakes recorded in diary (am or pm) / total (Yes/No) intakes recorded] x 100. b Medication compliance using days on treatment = [Total (Yes) study medication intakes recorded in diary (am or pm) / (days on treatment-0.5) x 2] x 100. Randomization (Day 1) was excluded from compliance calculations; Patients who discontinued on the day of randomization were excluded from all calculations during the double-blind treatment period. NA Not available due to subject withdrawal on the day of randomization. Nine (9) patients discontinued treatment on the day of randomization after receiving randomized treatment.					
Source: T21, p176; SD-039-716.pdf					

10.1.2.2.1.4 Concomitant Medications

Review of tables of concomitant medications during run-in and treatment phases revealed few differences among treatment groups with regard to use of concomitant medications. During the course of the study, 90.4% (462) patients used concomitant medications not related to asthma; use of these medications was similar among treatment groups. During the course of the study,

80.8% (413) of patients used concomitant medications to treat asthma, most commonly a short-acting beta-agonist (79.8%). The percent of patients using a short-acting beta-agonist was similar among treatment groups (82.3% Symbicort, 81.1% budesonide, 78% formoterol, 77.9% placebo). [p179]

10.1.2.2.2 Efficacy

10.1.2.2.2.1 Primary Variables

Efficacy was evaluated only in patients ≥12 years of age (EAS ≥12). 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.

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.

10.1.2.2.2.1.1 Baseline-adjusted average 12-hour FEV_1

Baseline-adjusted average 12-hour FEV_1 at Week 2 in patients ≥12 years was the primary variable/endpoint/population for evaluation of the contribution of the LABA (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 and treatment comparisons at Week 2 (primary endpoint) and End of Treatment (12 weeks, secondary endpoint) are shown in Table 56 and Table 57, respectively. 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 study end were quite similar to the primary results, implying that the combination maintained efficacy throughout the study treatment period.

The sponsor 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. Treatment by center interaction was explored, employing

several methodologies. Mean baseline-adjusted average 12-hour FEV_1 by center was plotted for Symbicort (y-axis) versus budesonide (x-axis). Outlier centers were identified and excluded from a sensitivity analysis. Results were consistent with the main analysis. In a second analysis, the applicant added center-by-treatment interaction to the statistical model. Using this approach, the model was statistically significant (p=0.030). Since treatment means were not all estimable in this model, small centers (<10 patients) were pooled, and the model re-analyzed. In this model, center-by-treatment was no longer significant (p=0.120). Using this same model, the results were again consistent with the main analysis.

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 17. 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 18, Figure 19, and Figure 20, 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 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 56. SD-039-0716, Baseline-adjusted average 12-hour FEV_1 (L), Treatment Means (EAS ≥12)

Treatment	N	Baseline FEV_1 (L)	Week 2 LOCF		End of Treatment	
			Observed value	From ANCOVA	Observed value	From ANCOVA
		Mean (SD)	Mean (SD)	LS Mean (SEM) (95% CI)	Mean (SD)	LS Mean (SEM) (95% CI)
Symbicort	**123**	**2.40** (0.62)	**0.47** (0.37)	**0.45** (0.04) **(0.38, 0.52)**	0.50 (0.37)	0.48 (0.04) (0.41, 0.55)
Budesonide	**121**	**2.33** (0.62)	**0.30** (0.35)	**0.26** (0.04) **(0.19, 0.34)**	0.32 (0.37)	0.28 (0.04) (0.21, 0.35)
Formoterol	114	2.38 (0.64)	0.40 (0.39)	0.38 (0.04) (0.31, 0.45)	0.41 (0.39)	0.39 (0.04) (0.31, 0.46)
Placebo	122	2.39 (0.65)	0.12 (0.33)	0.10 (0.04) (0.03, 0.17)	0.12 (0.35)	0.10 (0.04) (0.02, 0.17)

*Treatment means 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: T27, T29, p190-1; SD-039-0716

Table 57. SD-039-0716, Baseline-adjusted average 12-hour FEV_1 (L), Treatment Comparisons (EAS ≥12)

Treatment Comparisons*	Week 2			End of Treatment		
	LS Mean (SEM)	95% CI	p-value	LS Mean (SEM)	95% CI	p-value
Symbicort minus Placebo	0.35 (0.04)	(0.26, 0.44)	<0.001	0.39 (0.05)	(0.30, 0.47)	<0.001
Symbicort minus Budesonide	**0.18 (0.04)**	**(0.09, 0.27)**	**<0.001**	0.20 (0.05)	(0.11, 0.29)	<0.001
Symbicort minus Formoterol	0.07 (0.05)	(-0.02, 0.16)	0.148	0.09 (0.05)	(0.00, 0.19)	0.043
Budesonide minus Placebo	0.17 (0.04)	(0.08, 0.25)	<0.001	0.19 (0.04)	(0.10, 0.28)	<0.001
Formoterol minus Placebo	0.28 (0.05)	(0.19, 0.37)	<0.001	0.29 (0.05)	(0.20, 0.38)	<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: T28, T30, p190-1; SD-039-0716						

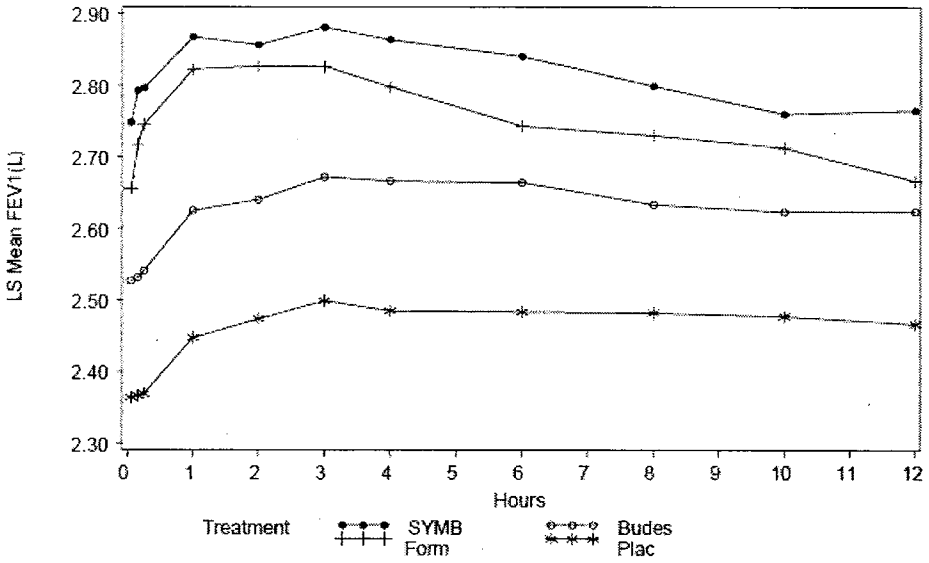

Figure 17. SD-039-0716, LS mean FEV_1 values at Week 2 LOCF, (EAS ≥12)

Source: F4, p193; SD-039-0716

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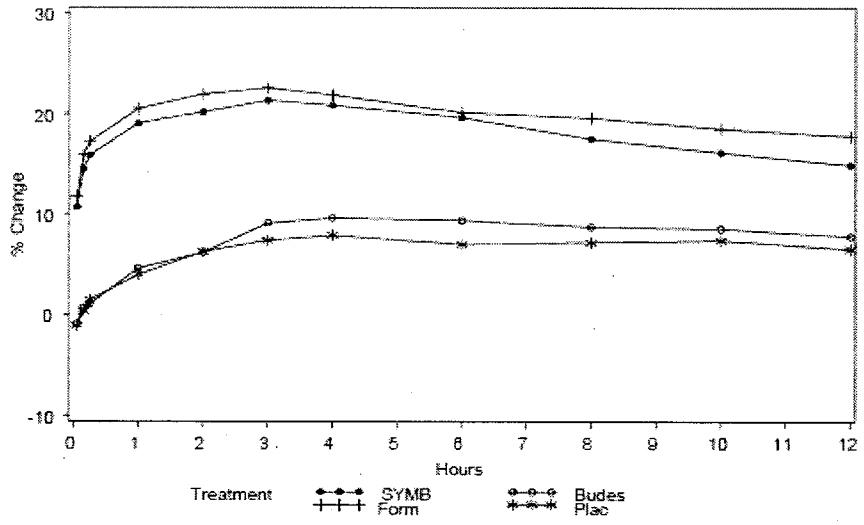

Figure 18. SD-039-0716, Mean percent change from baseline in FEV_1 on Day of Randomization, (EAS ≥12)

Source: F5, p194; SD-039-0716

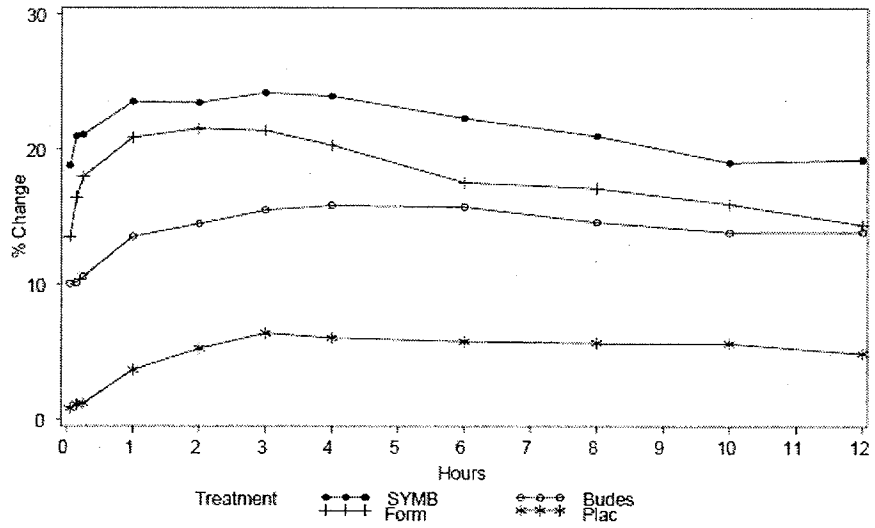

Figure 19. SD-039-0716, Mean percent change from baseline in FEV_1 at Week 2 LOCF, (EAS ≥12)

Source: F6, p195; SD-039-0716

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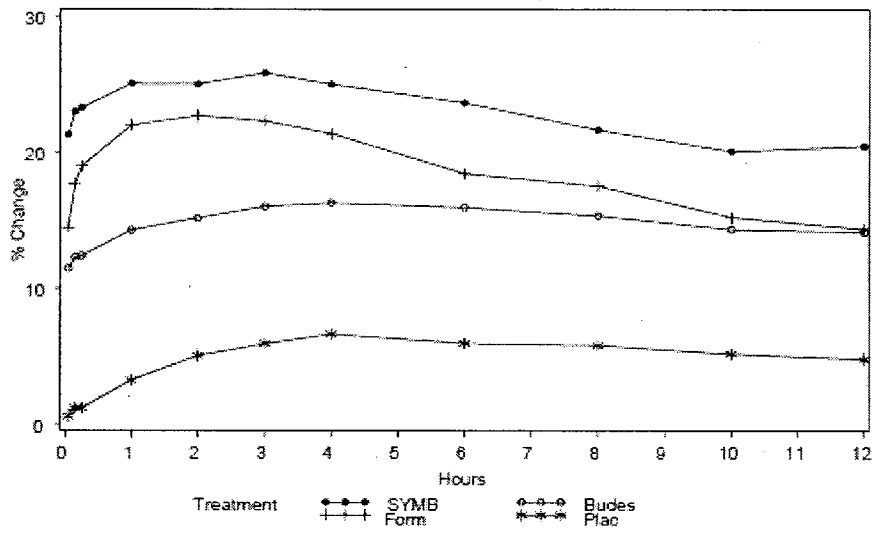


Figure 20. SD-039-0716, Mean percent change from baseline in FEV_1 at End of treatment LOCF, (EAS ≥12)

Source: F7, p196; SD-039-0716

10.1.2.2.2.1.2 Pre-dose FEV_1

The change from baseline in average pre-dose FEV_1 averaged over the treatment period in patients ≥12 years (EAS ≥12) was the primary endpoint for evaluation of the contribution of the corticosteroid (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 58 and Table 59, respectively. The primary comparison of Symbicort to formoterol was significant (p=0.001), and is shown **bolded** in Table 59. The three comparisons between Symbicort to placebo and each mono- component product to placebo were significant, providing study assay sensitivity.

Secondary analyses included change from baseline in pre-dose FEV_1 at each visit, shown graphically in Figure 21, including Week 2 (S-F comparison for observed cases: p=0.027), Week 6 (S-F comparison for observed cases: p=0.007), and Week 12 (S-F comparison for observed cases: p=0.026) visits, 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). 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. This figure also depicts visually the effect of withdrawals on pre-dose FEV_1 over the course of the study for the placebo group, and how the choice of primary endpoint tended to minimize the effect of withdrawal. Treatment comparisons at various time points over the course of the study are shown in Table 60. No clear trend in results may be seen over time except for the comparisons to placebo, as expected based on the gradual improvement in FEV_1 for the placebo group over time.

Since there were a large number of withdrawals during the study (Table 53), 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 co-primary variables/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 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 53, the numbers of patients involved varies by treatment group, with the majority of patients being in the placebo group, and to a lesser extent the formoterol group. Fewer patients were involved when considering the primary comparison between Symbicort and formoterol than when considering secondary comparisons between any active and placebo, and we considered the numbers to be too small to be of overall concern.

We assessed the impact of withdrawals by examining the corresponding drift in baseline FEV_1 from Week 2 to Week 12 may be seen in Table 61. For convenience, the numbers of patients enrolled at ITT, Week 2, Week 6, 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 two (budesonide-containing) treatment groups. Both the placebo and formoterol groups showed a gradual increase in baseline FEV_1 throughout the treatment period. By Week 12, the baseline mean for the remaining placebo patients (2.66 L) was notably higher than those for the active treatment groups (Symbicort 2.40 L, budesonide 2.32 L, formoterol 2.45 L), implying that the predominance of withdrawals in the placebo group were in patients who had poorer asthma control and lower baseline mean FEV_1 values. These results appear to correlate with the higher rate of withdrawals due to pre-defined asthma events (shown in Table 53) in the placebo group, as patients with lower baseline would be expected to experience more asthma-related adverse events and therefore would be more likely to be withdrawn. Interestingly, this did not match as well for the formoterol group, in which an intermediate number of patients (but more than for either budesonide-containing group) withdrew and withdrew due to a predefined adverse event, but the baseline mean FEV_1 rose only slightly for patients still enrolled at Week 12 compared to those enrolled at Week 2. Because withdrawals in placebo patients were in patients who had lower baseline pre-dose FEV_1, it is likely that this would driven the results to favor the placebo group, thereby making it harder to

show treatment differences from placebo. This correlates with what is seen for results over the time course of the study, as shown in Figure 21 and the observed pre-dose FEV_1 values at Week 12 (Table 61). The observed pre-dose FEV_1 values at Week 12 for the placebo and formoterol treatment groups were similar to that for the Symbicort group, with the impact being smaller treatment group differences at Week 12 (S-B 0.18 L, S-F 0.06 L, S-P 0.34 L, B-P 0.16 L, F-P 0.28 L) than at Week 2. [T32, p202]

Results across age, sex, and race were explored in separate analyses and were similar to the primary analysis. There were too few patients <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. Treatment by center interaction was explored, employing several methodologies. Mean baseline-adjusted average 12-hour FEV_1 by center was plotted for Symbicort (y-axis) versus budesonide (x-axis). Outlier centers were identified and excluded from a sensitivity analysis. Results were consistent with the main analysis. In a second analysis, the applicant added center-by-treatment interaction to the statistical model. Using this approach, the model approached statistical significance (p=0.087). Since treatment means were not all estimable in this model, small centers (<10 patients) were pooled, and the model re-analyzed. In this model, center-by-treatment was no longer significant (p=0.290). Using this same model, the results were consistent with the main analysis.

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.

Table 58. SD-039-0716, Pre-dose FEV_1 (L), Treatment Means (EAS ≥12)

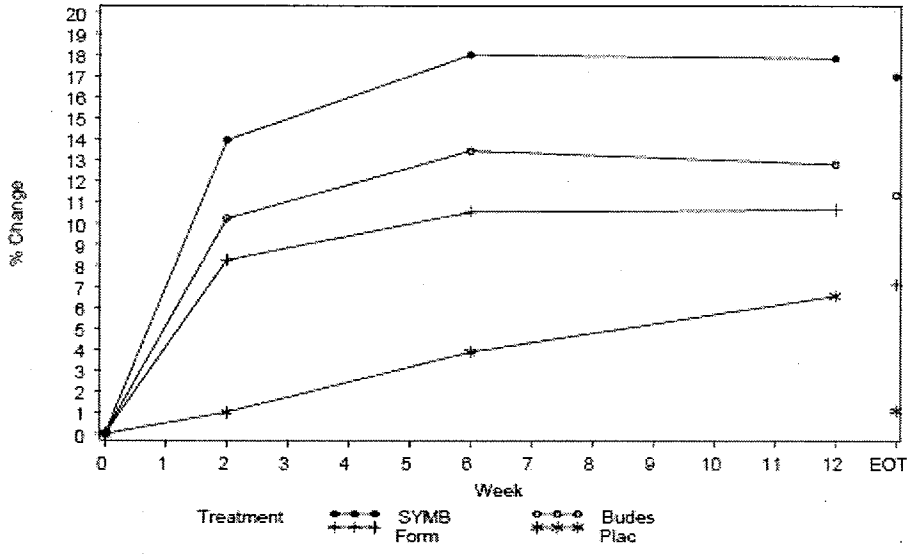
Treatment	N	Baseline FEV_1 (L)	Treatment period*			
			Observed value	Change from baseline	From ANCOVA	
		Mean (SD)	Mean (SD)	Mean (SD)	LS Mean (SEM)	95% CI
Symbicort	**122**	**2.40** (0.62)	**2.74** (0.67)	**0.34** (0.34)	**0.32** (0.04)	**(0.24, 0.40)**
Budesonide	116	2.32 (0.60)	2.55 (0.65)	0.23 (0.37)	0.18 (0.04)	(0.11, 0.26)
Formoterol	**105**	**2.41** (0.63)	**2.59** (0.73)	**0.18** (0.39)	**0.16** (0.04)	**(0.08, 0.24)**
Placebo	111	2.43 (0.64)	2.47 (0.76)	0.04 (0.38)	0.01 (0.04)	(-0.07, 0.09)
*Mean of all pre-dose FEV_1 values obtained during the double-blind treatment period (EAS ≥12 yr)						
Source: T33, p199; SD-039-0716						

Table 59. SD-039-0716, Pre-dose FEV_1 (L), Treatment Comparisons (EAS ≥12)

Comparison*	ANCOVA		
	LS Mean (SEM)	95% CI	p-value
Symbicort minus Placebo	0.31 (0.05)	(0.21, 0.40)	<0.001
Symbicort minus Budesonide	0.14 (0.05)	(0.04, 0.23)	0.005
Symbicort minus Formoterol	**0.16** (0.05)	**(0.06, 0.26)**	**0.001**
Budesonide minus Placebo	0.17 (0.04)	(0.08, 0.27)	<0.001
Formoterol minus Placebo	0.15 (0.05)	(0.05, 0.25)	0.004
*Treatment comparisons for change from baseline to the entire double-blind treatment period (EAS ≥12 yr)			
Source: T34, p199; SD-039-0716			

Table 60. SD-039-0716, Pre-dose FEV_1 Treatment Comparisons at Various Study Timepoints (EAS≥12)

Treatment Comparisons*	Week 2		Week 12		End of Treatment*	
	LS Mean	95% CI	LS Mean	95% CI	LS Mean	95% CI
Symbicort minus Placebo	0.28	(0.18, 0.37)	0.23	(0.11, 0.35)	0.34	(0.23, 0.45)
Symbicort minus Budesonide	0.12	(0.12, 0.21)	0.15	(0.04, 0.25)	0.15	(0.05, 0.26)
Symbicort minus Formoterol	0.11	(0.01, 0.21)	0.13	(0.02, 0.24)	0.20	(0.09, 0.31)
Budesonide minus Placebo	0.16	(0.06, 0.26)	0.08	(-0.04, 0.21)	0.19	(0.08, 0.29)
Formoterol minus Placebo	0.16	(0.06, 0.26)	0.10	(-0.03, 0.23)	0.14	(0.03, 0.25)
*End of Treatment was defined as Week 12, LOCF						
Source: T11.2.2.4.2, p2232; SD-039-0716						



	Wk 2 N	Wk 6 N	Wk 12 N	EOT N
SYMB	122	114	108	122
Budes	116	107	107	116
Form	105	89	80	105
Place	111	80	62	111

Figure 21. SD-039-0716, Mean percent change from baseline in pre-dose FEV_1 by visit (EAS ≥12 yr)

EOT = End of Treatment: defined as the pre-dose FEV_1 value from the last available visit after receiving randomized treatment.

Source: F8, p203; SD-039-0716

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Table 61. SD-039-0716, Shift in Baseline Pre-dose FEV_1 (L) over the Study (EAS ≥12)

Treatment	ITT	Week 2		Week 6		Week 12[1]			Comp[1]
		N	Baseline Mean (SD)	N	Baseline Mean (SD)	N	Baseline Mean (SD)	Observed Mean (SD)	N
Symbicort	130	122	2.40 (0.62)	114	2.40 (0.63)	108	2.40 (0.63)	2.79 (0.68)	110
Budesonide	127	116	2.32 (0.60)	107	2.32 (0.61)	107	2.32 (0.61)	2.58 (0.63)	108
Formoterol	123	105	2.41 (0.63)	89	2.42 (0.61)	80	2.45 (0.57)	2.70 (0.71)	84
Placebo	131	111	2.43 (0.64)	80	2.55 (0.64)	62	2.66 (0.62)	2.82 (0.72)	64

[1] 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 53).

Source: T11.2.2.4.1, p2231; T37, p201; SD-039-0716

10.1.2.2.2.2 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 with continuous beta-agonist use. However, in addition to the expected LABA bronchodilator benefits, the addition of formoterol to budesonide did not appear to have much effect on secondary variables.

It should be noted that the Symbicort results in this study differ from the results found in study 717 in moderate to severe asthmatics, in addition to the prevention [or delay] of tachyphylaxis the Symbicort and free combination treatment arms improved beyond either of the two monoproduct arms with regard to multiple secondary endpoints.

10.1.2.2.2.2.1 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 62 for all patient population strata. Treatment group comparisons for the EAS ≥12 population are shown in Table 63. In the EAS ≥12 population, the percentage of patients with at least 1 pre-defined asthma event was lower in the Symbicort (18.7%) and budesonide (21.5%) groups than in the formoterol (42.1%) and placebo (56.6%) groups. The most commonly met criterion was nighttime awakenings due to asthma; however, no one criterion was responsible for 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 all active treatments compared to placebo. Kaplan-Meier curves for time (days) to first event (EAS ≥12) are shown in Figure 22. The time to the first pre-defined asthma event was longest and similar for Symbicort and budesonide, followed by formoterol and placebo. [p207-8]

Formoterol treatment alone appeared to fare only a little better than placebo, implying that when used alone it has no benefit as a controller medication in prevention of exacerbations. The frequency of and time to qualifying asthma events were similar in the Symbicort and budesonide treatment arms including the percent of patients who experienced a drop in FEV_1. The implication is that in a population of less severe asthmatics such as this, the addition of formoterol to budesonide adds little for control of a series of asthma indices that are often used to evaluate the status of patients and are often indicative of exacerbations.

Table 62. SD-039-0716, Number and percentage of patients with a CRF pre-defined asthma event

Criteria	Treatment group, n (%)				
	Symbicort	Budesonide	Formoterol	Placebo	Total
EAS All	130	127	123	131	511
Pre-defined asthma event	26 (20.0)	27 (21.3)	52 (42.3)	74 (56.5)	179 (35.0)
Time to Event (Mean days)	27.8	23.3	24.1	21.5	23.5
EAS 6 to <12 population	7	6	9	9	31
Pre-defined asthma event	3 (42.9)	1 (16.7)	4 (44.4)	5 (55.6))	13 (41.9)
Time to Event (Mean days)	55.3	41.0	28.5	29.0	35.8
EAS ≥12 population	123	121	114	122	480
Pre-defined asthma event	23 (18.7)	26 (21.5)	48 (42.1)	69 (56.6)	166 (34.6)
Time to Event (Mean days)	24.2	22.6	23.8	21.0	22.5
Criterion 1: Decrease in FEV_1	3 (2.4)	3 (2.5)	11 (9.6)	9 (7.4)	26 (5.4)
Criterion 2: Rescue medication	1 (0.8)	3 (2.5)	1 (0.9)	3 (2.5)	8 (1.7)
Criterion 3: Decrease in AM PEF	3 (2.4)	1 (0.8)	8 (7.0)	14 (11.5)	26 (5.4)
Criterion 4: Nighttime awakening	17 (13.8)	20 (16.5)	31 (27.2)	52 (42.6)	120 (25.0)
Criterion 5: Clinical exacerbation:	1 (0.8)	3 (2.5)	5 (4.4)	20 (16.4)	29 (6.0)
ER treatment	1 (0.8)	1 (0.8)	1 (0.9)	1 (0.8)	4 (0.8)
Hospitalization	0	0	0	0	0
Disallowed asthma medication:	1 (0.8)	3 (2.5)	4 (3.5)	20 (16.4)	28 (5.8)
• Nebulized bronchodilator	1 (0.8)	1 (0.8)	1 (0.9)	7 (5.7)	10 (2.1)
• Steroid	1 (0.8)	2 (1.7)	3 (2.6)	15 (12.3)	21 (4.4)
• Leukotriene modifier	1 (0.8)	0	0	0	1 (0.2)
• Other	0	1 (0.8)	1 (0.9)	5 (4.1)	7 (1.5)
Data derived from ASTEXAC in CRF					
Source: T41, p206; T11.2.3.1.1, p2258-63; SD-039-0716					

Table 63. SD-039-0716, Treatment comparisons for percentage of patients with at least 1 CRF pre-defined asthma event (EAS ≥12)

Comparison*	Odds ratio	95% CI	P-value
Symbicort vs Placebo	**0.18**	**(0.10, 0.31)**	**<0.001**
Symbicort vs Budesonide	0.84	(0.45, 1.57)	0.587
Symbicort vs Formoterol	**0.32**	**(0.18, 0.57)**	**<0.001**
Budesonide vs Placebo	0.21	(0.12, 0.37)	<0.001
Formoterol vs Placebo	0.56	(0.33, 0.94)	0.027
*The applicant states that as a secondary variable, the comparison of Symbicort to placebo is the prespecified primary comparison. However, as a former primary variable, the comparison to formoterol is of most interest. Both are **bolded**.			
Source: T42, p207; SD-039-0716			

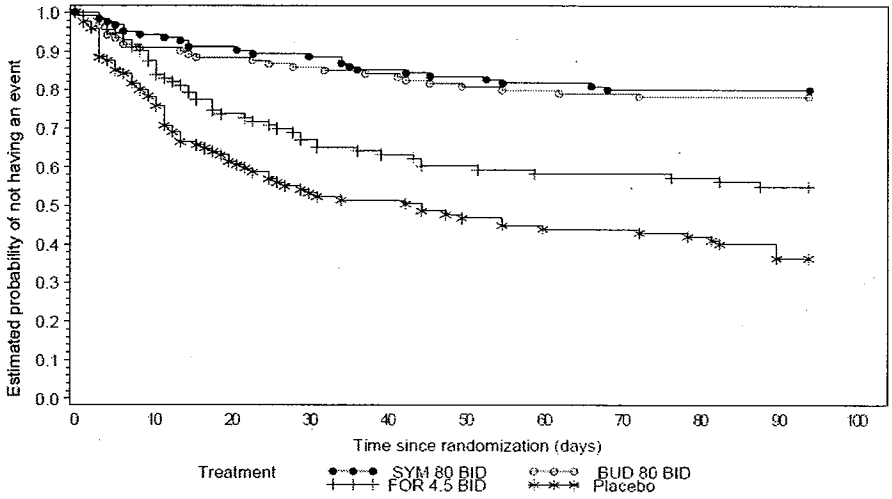

Figure 22. SD-039-0716, Kaplan-Meier curves of time (days) to first CRF pre-defined asthma event (EAS ≥12)*

*This figure shows the results for the EAS ≥12 population. The Kaplan-Meier curves for all ages was almost identical to those above. [F11.2.3.2.5.2, p2410]

Source: F11.2.3.2.5.1, p2409; SD-039-0716

Withdrawals due to pre-defined asthma events

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. [p209] The results (Table 64) are comparable to those of the CRF pre-defined asthma events [*see above*].

Table 64. SD-039-0716, Withdrawals due to pre-defined asthma event

Criteria	Treatment group, n (%)				
	Symbicort	Budesonide	Formoterol	Placebo	Total
EAS All	130	127	123	131	511
Pre-defined asthma event	10 (7.7)	8 (6.3)	25 (20.3)	44 (33.6)	87 (17.0)
Time to Event (Mean days)	29.6	18.3	25.3	22.4	23.7
EAS 6 to <12 population	7	6	9	9	31
Pre-defined asthma event	1 (14.3)	0	4 (44.4)	4 (44.4)	9 (29.0)
Time to Event (Mean days)	57.0	0	28.5	31.5	33.0
EAS ≥12 population	123	121	114	122	480
Pre-defined asthma event	9 (7.3)	8 (6.6)	21 (18.4)	40 (32.8)	78 (16.3)
Time to Event (Mean days)	26.6	18.3	24.7	21.5	22.6
Criterion 1: Decrease in FEV_1	1 (0.8)	3 (2.5)	9 (7.9)	12 (9.8)	26 (5.2)
Criterion 2: Rescue medication	2 (1.6)	3 (2.5)	2 (1.8)	3 (2.5)	10 (2.1)
Criterion 3: Decrease in AM PEF	3 (2.4)	1 (0.8)	5 (4.4)	11 (9.0)	20 (4.2)
Criterion 4: Nighttime awakening	4 (3.3)	4 (3.3)	7 (6.1)	22 (18.0)	37 (7.7)
Criterion 5: Clinical exacerbation:	1 (0.8)	1 (0.8)	6 (5.3)	14 (11.5)	22 (4.6)
ER treatment	1 (0.8)	0	2 (1.8)	1 (0.8)	4 (0.8)
Hospitalization	0	0	0	0	0
Disallowed asthma medication	1 (0.8)	1 (0.8)	6 (5.3)	14 (11.5)	22 (4.6)

Source: T11.2.3.3.1, p2411-16; SD-039-0716

10.1.2.2.2.2.2 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 23 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 65. As expected, neither budesonide nor placebo showed much bronchodilatory effect. While similar percents of patients in the Symbicort MDI and Oxis TBH groups achieved a 15% improvement in FEV_1 after 60 minutes (61% Symbicort, 62% Oxis), 57% of the Oxis compared to 49% of the Symbicort patients achieved a 15% improvement in FEV_1 within 15 minutes, the pre-specified time point of comparison. None of these results are surprising. Formoterol, whether administered as a single ingredient or in combination with budesonide, is a bronchodilator.

On the last day of treatment, 56% of the Oxis compared to 62% of the Symbicort patients achieved a 15% improvement in FEV_1 within 15 minutes, and 62% of the Oxis compared to 67% of the Symbicort patients achieved a 15% improvement in FEV_1 within 60 minutes. The results may reflect a small formoterol tachyphylaxis-sparing effect of the budesonide component.

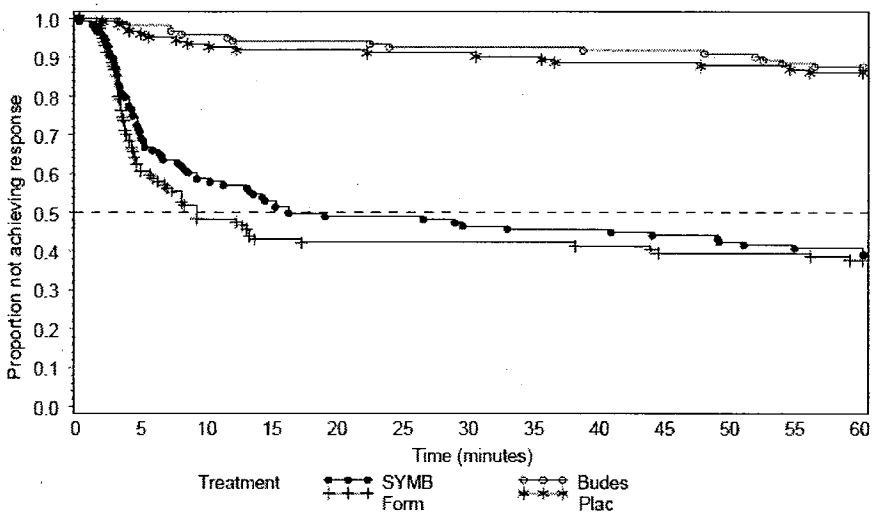

Figure 23. SD-039-0716, Kaplan-Meier plot of time to 15% improvement in FEV_1 during the first 60 minutes after first dose, Day 1 (EAS ≥12)

Source: F10 p211; SD-039-0716

Table 65. SD-039-0716, Number (%) of patients achieving 15% improvement in FEV_1 (EAS ≥12)

Estimated time	Symbicort n=123	Budesonide n=121	Formoterol n=114	Placebo n=122
Within 3 minutes	21 (17.1)	1 (0.8)	23 (20.2)	2 (1.6)
Within 9 minutes	51 (41.5)	5 (4.1)	59 (51.8)	8 (6.6)
Within 15 minutes*	**60 (48.8)**	**7 (5.8)**	**65 (57.0)**	**10 (8.2)**
Within 60 minutes	75 (61.0)	15 (12.4)	71 (62.3)	17 (13.9)
Longer than 60 minutes	21 (17.1)	31 (25.6)	16 (14.0)	19 (15.6)
Less than 15% improvement	27 (22.0)	75 (62.0)	27 (23.7)	86 (70.5)
*The 15-minute time point was pre specified as the primary time point for comparison.				
Source: T43 p212; SD-039-0716				

10.1.2.2.2.2.3 Morning and Evening PEF

Table 66 summarizes the morning and evening PEF parameters. All 3 active treatments (Symbicort, budesonide, and formoterol) showed a greater increase from baseline in morning and evening PEF than placebo, although Symbicort showed greater change from baseline than either budesonide or formoterol. [p230-2] These results are comparable to the pre-dose FEV_1 results, in which patients on Symbicort had higher pre-dose FEV1s than patients on budesonide or formoterol alone, but the results do not exactly match with those of the qualifying pre-defined events, for which Symbicort and budesonide gave comparable results.

Table 66. SD-039-0716, Mean Morning and Evening PEF (EAS ≥12)

	N	Baseline	Observed value	Change from baseline
Morning PEF (L/min)				
Symbicort	123	349.9	396.0	46.0
Budesonide	119	353.3	374.6	21.3
Formoterol	111	358.5	379.0	20.5
Placebo	117	350.3	350.6	0.3
Evening PEF (L/min)				
Symbicort	123	370.4	405.9	35.4
Budesonide	119	368.8	382.5	13.7
Formoterol	111	374.4	389.5	15.1
Placebo	116	364.2	365.8	1.6
Source: T56, p230; SD-039-0716				

10.1.2.2.2.2.4 Asthma symptoms

Table 67 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. While it is correct that Symbicort showed a greater reduction from baseline compared with placebo for all parameters, it should be noted that Symbicort and budesonide had comparable results, with less improvement in all but awakening free nights with formoterol compared to either Symbicort or budesonide. Again, the addition of formoterol to budesonide adds little in the way of asthma symptom control.

The study report notes that improvement with Symbicort treatment relative to placebo was seen within 1 day of the first dose. [p232-6]

Table 67. SD-039-0716, Asthma symptom scores (EAS ≥12)

Asthma symptom scores	N	Baseline	Observed value	Change from baseline
Average daily symptom score (0-3)				
Symbicort	123	1.13	0.70	-0.43
Budesonide	119	1.10	0.70	-0.40
Formoterol	111	1.07	0.82	-0.25
Placebo	117	1.12	1.02	-0.10
Daytime symptom score (0-3)				
Symbicort	123	1.15	0.75	-0.39
Budesonide	119	1.13	0.75	-0.39
Formoterol	111	1.11	0.88	-0.23
Placebo	117	1.14	1.03	-0.11
Nighttime symptom score (0-3)				
Symbicort	123	1.12	0.64	-0.48
Budesonide	119	1.07	0.65	-0.42
Formoterol	111	1.03	0.77	-0.27
Placebo	117	1.11	1.0	-0.10
Symptom free days (% of days)				
Symbicort	123	6.7	30.8	24.1
Budesonide	119	8.7	31.4	22.7

Asthma symptom scores	N	Baseline	Observed value	Change from baseline
Formoterol	111	10.3	24.1	13.8
Placebo	117	7.1	12.2	7.1
Awakening free nights (% of nights)				
Symbicort	123	71.0	92.5	21.6
Budesonide	119	69.3	90.6	21.3
Formoterol	111	70.2	89.2	19.0
Placebo	117	69.5	82.8	13.3
Source: T58, p233; SD-039-0716				

10.1.2.2.2.2.5 Rescue medicine use

Table 68 summarizes the parameters of rescue medication use for the different treatment arms. Symbicort showed a greater improvement from baseline compared with placebo for all parameters. In this parameter, the budesonide and formoterol mono-components had comparable results, but showed somewhat less improvement than Symbicort.

Table 68. SD-039-0716, Rescue medication use (EAS ≥12)

Rescue medication use	N	Baseline	Observed value	Change from baseline
Total number of daily inhalations				
Symbicort	123	2.75	0.91	-1.84
Budesonide	119	2.99	1.50	-1.49
Formoterol	111	2.75	1.31	-1.44
Placebo	117	2.57	2.58	0.01
Daytime number of inhalations				
Symbicort	123	1.66	0.60	-1.05
Budesonide	119	1.73	0.92	-0.82
Formoterol	111	1.63	0.81	-0.82
Placebo	116	1.49	1.51	0.02
Nighttime number of inhalations				
Symbicort	123	1.26	0.39	-0.87
Budesonide	119	1.44	0.66	-0.77
Formoterol	111	1.28	0.58	-0.70
Placebo	117	1.23	1.18	-0.05
Rescue med free days (% of days)				
Symbicort	123	30.7	71.9	41.2
Budesonide	119	27.7	58.1	30.4
Formoterol	111	33.1	61.7	28.7
Placebo	117	33.7	41.7	8.1
Source: T60, p237; SD-039-0716				

10.1.2.2.2.2.6 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. For the PAQLQ(S), there were too few patients to have meaningful results. Results for the MOS Sleep Scale and the PSAM Questionnaire were generally comparable to those for secondary endpoints, with a step-down to

the monoproducts and little change for placebo. Just as for other secondary endpoints (except rescue medication use) the addition of formoterol to budesonide added little to these measures of asthma control.

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 69. Consistent with other results, patients on placebo stayed about the same or worsened slightly, and the results for formoterol alone were not in the clinically relevant range. Whereas the overall score for budesonide was clinically relevant, the 95% confidence intervals did not exclude the MID of 0.5. However, the overall score for Symbicort was in the clinically relevant range and the 95% confidence intervals excluded the MID of 0.5. Results were generally similar for individual scores.

AQLQ[S] treatment comparisons for the overall score at the end of treatment are shown in Table 70. The overall score for the comparison of Symbicort to placebo was clinically relevant (0.84) and statistically significant (p-value <0.001), with 95% confidence intervals (0.58, 1.09) that excluded the MID of 0.5. Whereas the comparison of budesonide to placebo was clinically relevant and statistically significant, the comparison of formoterol to placebo was not clinically relevant.

Table 69. SD-039-0716, Overall 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	102	5.24	6.02	0.79	0.78	0.58, 0.98
Budesonide	99	5.09	5.82	0.73	0.62	0.42, 0.83
Formoterol	88	5.08	5.52	0.44	0.29	0.08, 0.51
Placebo	100	5.10	5.14	0.05	-0.06	-0.26, 0.15
Symptoms						
Symbicort	102	4.90	5.94	1.04	1.01	0.78, 1.24
Budesonide	99	4.78	5.75	0.97	0.85	0.62, 1.08
Formoterol	88	4.86	5.37	0.51	0.40	0.15, 0.64
Placebo	100	4.84	4.86	0.02	-0.08	-0.31, 0.16
Activity limitation						
Symbicort	103	5.63	6.17	0.54	0.52	0.32, 0.72
Budesonide	99	5.55	6.04	0.49	0.41	0.22, 0.61
Formoterol	88	5.50	5.81	0.31	0.15	-0.06, 0.36
Placebo	100	5.49	5.52	0.03	-0.07	-0.27, 0.13
Emotional function						
Symbicort	102	5.07	6.03	0.96	1.01	0.75, 1.27
Budesonide	99	4.66	5.56	0.89	0.70	0.44, 0.96
Formoterol	88	4.69	5.27	0.58	0.44	0.16, 0.71
Placebo	100	4.95	4.91	-0.04	-0.06	-0.32, 0.20

AQLQ	N	Baseline	End of Treatment			
			Observed value	Change from baseline	From ANCOVA	
					LS mean	95% CI
Environmental exposure						
Symbicort	102	5.35	5.83	0.48	0.46	0.26, 0.67
Budesonide	99	5.21	5.73	0.52	0.43	0.23, 0.64
Formoterol	88	5.13	5.48	0.35	0.18	-0.04, 0.40
Placebo	100	5.06	5.29	0.23	0.07	-0.14, 0.28
Source: T68, p247; SD-039-0716						

Table 70. SD-039-0716, AQLQ[S] treatment comparisons, overall scores, end of treatment

Comparison	LS mean	95% CI	p-value
AQLQ (S) Overall score			
Symbicort minus Placebo	0.84	0.58, 1.09	<0.001
Budesonide minus Placebo	0.68	0.42, 0.94	<0.001
Formoterol minus Placebo	0.35	0.08, 0.61	0.011
Symbicort minus Budesonide	0.16	-0.10, 0.41	0.234
Symbicort minus Formoterol	0.49	0.22, 0.75	<0.001
Source: T69, p248; SD-039-0716			

10.1.2.2.3 Safety

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

10.1.2.2.3.1 Exposure

Results for the extent of exposure (Table 71) among treatment groups in this study parallel the results for study discontinuations (Table 53) and withdrawals due to pre-defined asthma events (Table 64). There were more withdrawals in the placebo group, hence less exposure. While the exposure to Symbicort and budesonide dropped off in the last 2 weeks of the study, the exposure to all three active is considered adequate to assess safety and efficacy.

Table 71. SD-039-0716, Exposure ITT/SAS

Exposure	Symbicort n=130	Budesonide n=127	Formoterol n=123	Placebo n=131
Run-in (Mean days, SD)	12.7 (4.75)	12.4 (4.54)	13.3 (5.13)	12.0 (4.46)
Treatment period (Mean days, SD)	78.2 (19.30)	76.7 (22.26)	66.8 (29.88)	55.2 (33.64)
Treatment Period (n, %)				
Overall	130 (100)	127 (100)	123 (100)	131 (100)
At least 2 weeks	129 (99.2)	123 (96.9)	116 (94.3)	112 (85.5)
At least 4 weeks	122 (93.8)	115 (90.6)	99 (80.5)	87 (66.4)
At least 6 weeks	118 (90.8)	112 (88.2)	93 (75.6)	79 (60.3)
At least 8 weeks	115 (88.5)	112 (88.2)	88 (71.5)	70 (53.4)
At least 10 weeks	114 (87.7)	112 (88.2)	86 (69.9)	68 (51.9)
At least 12 weeks	87 (66.9)	90 (70.9)	74 (60.2)	59 (45.0)
Source: T74, p266; and T11.3.1.1.1.1, T11.3.1.2.1.1; SD-039-716.pdf				

10.1.2.2.3.2 Adverse events

An overall summary of AEs in this study is shown in Table 72. The overall percentage of patients with at least one adverse event was slightly lower in the formoterol and placebo groups

than in the Symbicort and budesonide groups, a pattern relatively consistent with the duration of exposure for each treatment group.

There were no deaths; 4 patients experienced a serious adverse event (SAE) during the treatment period: 2 each in the Symbicort (lobar pneumonia [E6023020]; left orbital fracture [E6009017]) and placebo (abdominal pain [E6010009]; intestinal obstruction [E6057008]) treatment groups. One Symbicort patient (lobar pneumonia) and both placebo patients with SAEs were discontinued from treatment, but the patient with the orbital fracture was not. None of the SAEs were determined by the investigators to be study drug-related.

A total of 22 patients had AEs leading to discontinuation (DAE) during the treatment period, more in the placebo than in any of the active treatment groups. Of these, one patient in the placebo group was between 6 and 12 years of age, and none were over 65 years of age. There was one pregnancy (E6023004) during the study: an 18 year old Caucasian in the Symbicort treatment group was withdrawn at Day 20. The patient delivered a healthy baby at term, with no reported problems for mother or infant except neonatal jaundice in the first week of life. [p262]

Table 73 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. Three patients on Symbicort, two on formoterol, and one on placebo were withdrawn due to a cardiac AE (see table and next paragraph for details). More patients in the placebo group (7) than the other treatment groups (0 Symbicort, 2 budesonide, 0 formoterol) were withdrawn due to worsening asthma or decrease in FEV_1.

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 74. No significant trends were identified. There were slightly more frequent cardiac AEs in the Symbicort (3.1%) than the other treatment groups; and none in patients ≥65 or in children <12 years of age. All of the cardiac AEs reported in the Symbicort and formoterol groups occurred within the first 28 days of treatment and all were reported from Holter or ECG findings. In the Symbicort group, 4 cardiac AEs were reported: ventricular extrasystole, non-sustained ventricular tachycardia, tachycardia, and 2nd-degree AV block (n=1 subject for each). In the formoterol group, 2 patients had atrial fibrillation. The study report mentions that 1 patient on formoterol had ECG ST-T wave changes, but the listing only shows two AE and the supporting tables do not show this (presumably, these changes were noted in one of the 2 patients with atrial fibrillation). Tachycardia was reported as an AE for 1 patient in the budesonide group, and ventricular extrasystole was reported as an AE for 1 patient in the placebo group.

Adverse events reported by ≥3% of patients in any treatment group during the treatment period are shown in Table 75. No significant safety trends were identified, with AEs generally similar across treatment groups except that a higher percentage of patients in the placebo group (5.3%) had an AE of asthma compared to 0%, 1.6%, and 3.3% for Symbicort, budesonide and formoterol, respectively. The Symbicort group reported pharyngolaryngeal pain and a higher percentage of patients in the budesonide group had influenza compared to the other treatment groups. One patient in the Symbicort group (E6023020) had oral candidiasis. Hoarseness was reported for 1 Symbicort patient (E6003015) and 2 budesonide patients (E6022010, E6023025). The overall incidence of throat irritation was also low (1.0%) and similar incidence across

treatment groups. The incidence of asthma was highest in the placebo group (5.3%), with none in the Symbicort group.

The overall pattern of AEs was similar for males and females, although more males (14.0%) than females (6.3%) reported headaches. The number of non-Caucasian patients was not high enough to allow determination of differences in the AE profile or for individual AEs across races. There were no SAEs, cardiac AEs, or asthma AEs among Black patients in the Symbicort group.

Table 72. SD-039-0716, Adverse event overview (ITT/SAS)

Number (%) of patients with an AE*	Symbicort n=130	Budesonide n=127	Formoterol n=123	Placebo n=131
Mean duration of exposure (days)	78.2	76.7	66.8	55.2
Any AE (during treatment)*	84 (64.6)	77 (60.6)	67 (54.5)	77 (58.8)
SAE	2 (1.5)	0	0	2 (1.5)
SAE leading to death	0	0	0	0
SAE leading to discontinuation	1 (0.8)	0	0	2 (1.5)
Discontinuations due to an AE	4 (3.1)	3 (2.4)	3 (2.4)	12 (9.2)
Other significant AEs	0	0	0	0
Total number of AEs				
Any AE	221	227	186	166
SAE	2	0	0	2
*Several patients had AEs in run-in or in the post-treatment phase, but only double-blind treatment period is shown. Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each category. See Table 73 for full listing.				
Source: T75, p268; and T11.3.2.1.4 p3868-70; SD-039-0716.pdf				

Table 73. SD-039-0716, Listing of SAEs and DAEs during all study phases* (SAS)

Identifier	DAE	Age	Sex	Race	AE Onset	SAE	DAE
Symbicort							
E6001012	Pneumonia	6	M	C	Post 32*		Yes
E6003015	Ventricular tachycardia (9-beat run)	57	M	C	16		Yes
E6009017	Left orbital fracture	55	M	--	3	Yes	**No**
E6022014	Ventricular extrasystoles	46	F	C	15		Yes
E6023020	Right lower lobe pneumonia (Patient also had SAE of left lobar pneumonia during post-treatment period)	15	F	C	66	Yes	Yes
E6034007	Asthma exacerbation (Patient subsequently re-enrolled and randomized to Symbicort treatment)	53	F	C	Run-in*		Yes
E6037023	AV block second degree (Holter)	20	F	C	14		Yes
Budesonide							
E6021009	Contact dermatitis	43	F	C	31		Yes
E6022001	Asthma exacerbation	17	F	C	4		Yes
E6034006	Asthma exacerbation	50	F	B	3		Yes
Formoterol							
E6017014	Atrial fibrillation	46	M	C	1		Yes
E6019010	Atrial fibrillation	63	F	C	15		Yes
E6052012	Bronchitis	45	F	C	21		Yes
Placebo							
E6001013	FEV_1 decreased	31	M	C	1		Yes
E6003020	Increased asthma	50	F	C	17		Yes

Identifier	DAE	Age	Sex	Race	AE Onset	SAE	DAE
E6003034	Increased asthma	36	F	C	8		Yes
E6010009	Abdominal pain	6	M	C	12	Yes	Yes
E6016005	Abnormal Holter (ventricular extrasystoles)	49	F	B	15		Yes
E6016014	Bronchitis	47	F	B	20		Yes
E6022009	Asthma exacerbation	45	F	C	41		Yes
E6034037	Asthma exacerbation	22	M	C	15		Yes
E6035007	Severe erosive gastritis (Patient subsequently re-enrolled and randomized to placebo treatment [E6035018])	40	F	C	Run-in* (not on run-in treatment)	Yes	Yes
E6049001	Asthma exacerbation	21	F	C	12		Yes
E6052001	Bronchitis	45	M	C	47		Yes
E6055013	Increased asthma	20	F	C	4		Yes
E6057008	Bowel obstruction	44	F	C	74	Yes	Yes
	Stomach ache Chest pain				11		
	Cough Sore throat				12		

* Includes run-in, double-blind treatment, and post-treatment periods. Post treatment period listing shows days into period. Onset day is not the same as day of withdrawal.

Source: S11.3.4.3, p5089-94; T11.3.5.5, p 5132-54; SD-039-0716.pdf

Table 74. SD-039-0716, 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)

SOC	Symbicort n=130	Budesonide n=127	Formoterol n=123	Placebo n=131
Mean duration of exposure (days)	78.2	76.7	66.8	55.2
Any AE (during treatment)	84 (64.6)	77 (60.6)	67 (54.5)	77 (58.8)
Infections and infestations	49 (37.7)	50 (39.4)	38 (30.9)	36 (27.5)
Respiratory, thoracic and mediastinal	26 (20.0)	19 (15.0)	18 (14.6)	27 (20.6)
Gastrointestinal	15 (11.5)	23 (18.1)	13 (10.6)	13 (9.9)
Nervous system	13 (10.0)	15 (11.8)	14 (11.4)	17 (13.0)
General disorders & administration site	8 (6.2)	7 (5.5)	12 (9.8)	8 (6.1)
Musculoskeletal and connective tissue	11 (8.5)	9 (7.1)	5 (4.1)	8 (6.1)
Injury, poisoning & procedural complications	7 (5.4)	9 (7.1)	4 (3.3)	4 (3.1)
Skin and subcutaneous tissue	5 (3.8)	7 (5.5)	4 (3.3)	2 (1.5)
Cardiac	4 (3.1)	1 (0.8)	2 (1.6)	1 (0.8)
Psychiatric	2 (1.5)	4 (3.1)	2 (1.6)	0
Ear and labyrinth	2 (1.5)	0	3 (2.4)	2 (1.5)
Reproductive system and breast	1 (0.8)	2 (1.6)	2 (1.6)	2 (1.5)
Eye	2 (1.5)	2 (1.6)	1 (0.8)	1 (0.8)
Investigations	0	1 (0.8)	1 (0.8)	2 (1.5)
Metabolism and nutrition	1 (0.8)	1 (0.8)	1 (0.8)	1 (0.8)
Immune system	1 (0.8)	0	1 (0.8)	1 (0.8)
Surgical and medical procedures	0	1 (0.8)	0	1 (0.8)
Blood and lymphatic system	0	0	0	1 (0.8)
Endocrine	0	0	1 (0.8)	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (0.8)	0	0	0
Renal and urinary	0	1 (0.8)	0	0

Source: T76, p270; SD-039-0716.pdf

Table 75. SD-039-0716, Adverse events reported by at least 3% of patients in any treatment group during the treatment period (ITT/SAS)

Preferred Term	Symbicort n=130	Budesonide n=127	Formoterol n=123	Placebo n=131
Mean duration of exposure (days)	78.2	76.7	66.8	55.2
Any AE (during treatment)	84 (64.6)	77 (60.6)	67 (54.5)	77 (58.8)
Nasopharyngitis	20 (15.4)	17 (13.4)	16 (13.0)	14 (10.7)
Headache	12 (9.2)	14 (11.0)	9 (7.3)	13 (9.9)
Pharyngolaryngeal pain	12 (9.2)	6 (4.7)	4 (3.3)	9 (6.9)
Sinusitis	9 (6.9)	7 (5.5)	6 (4.9)	7 (5.3)
Upper respiratory tract infection	7 (5.4)	10 (7.9)	8 (6.5)	3 (2.3)
Cough	7 (5.4)	3 (2.4)	5 (4.1)	5 (3.8)
Influenza	5 (3.8)	9 (7.1)	3 (2.4)	2 (1.5)
Dyspepsia	5 (3.8)	5 (3.9)	3 (2.4)	3 (2.3)
Asthma	0	2 (1.6)	4 (3.3)	7 (5.3)
Diarrhea	1 (0.8)	6 (4.7)	1 (0.8)	4 (3.1)
Back pain	4 (3.1)	3 (2.4)	3 (2.4)	1 (0.8)
Nausea	1 (0.8)	6 (4.7)	2 (1.6)	2 (1.5)
Viral upper respiratory tract infection	4 (3.1)	4 (3.1)	0	2 (1.5)
Gastroenteritis viral	3 (2.3)	1 (0.8)	4 (3.3)	1 (0.8)
Myalgia	5 (3.8)	1 (0.8)	0	3 (2.3)
Nasal congestion	2 (1.5)	4 (3.1)	2 (1.6)	1 (0.8)
Arthralgia	4 (3.1)	2 (1.6)	0	2 (1.5)

Source: T77, p272; SD-039-0716.pdf

10.1.2.2.3.3 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. One patient from the Symbicort treatment group (E6027025) had a post-study AE of anemia with the lowest hemoglobin level of 112g/L, and one patient from the Symbicort treatment group had an AE of diabetes and reached a maximum serum glucose of 12.93 mmol/L at week 2.

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 between the Symbicort and budesonide groups.

There were small decreases from baseline in mean serum potassium, similar between the Symbicort and formoterol groups. 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. Of patients identified as having potassium values <3.3 mmol/L or >5.5 mmol/L, 2 patients (E6055005 [budesonide] and E6036013 [formoterol]) had potentially significant changes in corrected QT compared to baseline; however, all corresponding QT values (corrected and uncorrected) were less than 450 msec and all ECGs were read as normal.

10.1.2.2.3.4 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 patients ≥12 years 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 35 patients had a QT, QTcB, or QTcF of ≥450 msec or a change from baseline of ≥60msec at least once during the study: 14 Symbicort, 10 budesonide, 7 formoterol, and 4 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, 8 patients had a QT/QTc of ≥450 msec, of whom 2 had a QT/QTc change of ≥60 msec (E6039011 and 6031011). In the budesonide group, 2 patients had a QT/QTc of ≥450 msec, neither of whom had a QT/QTc change of ≥60 msec. In the formoterol group, 6 patients had a QT/QTc of ≥450 msec, none of whom had a QT/QTc change of ≥ 60msec. In the placebo group, no patients had a QT/QTc of ≥450 msec. The remaining 19 patients had a change in QT or QTc of ≥60 msec but no QT or QTc value ≥450 msec (6 Symbicort, 8 budesonide, 1 formoterol, 4 placebo). [p297, T92, p 298-300]

Results of Holter examinations were available from 406 patients. 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 or treatment group differences. Five patients had heart rate abnormalities on Holter: 2 Symbicort and 1 budesonide patient had a shift in average heart rate from normal to high (>100 bpm) ; and 2 additional Symbicort patients had high baseline heart rates that remained high. Four patients developed ≥50 ventricular ectopic beats: 2 Symbicort, 1 budesonide, 1 placebo. Fourteen developed ≥50 supraventricular ectopic beats: 5 Symbicort, 4 budesonide, 3 formoterol, 2 placebo. Five patients were withdrawn due to having met protocol-specific Holter withdrawal criteria (2 Symbicort, 0 budesonide, 1 formoterol, and 2 placebo). Two patients remained in the study following cardiologist evaluation despite having met Holter withdrawal criteria (1 budesonide, 1 formoterol). Five patients did not meet withdrawal criteria but had clinically notable findings (3 budesonide, 2 formoterol).

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 (13 [10.6%]) and placebo groups (26 [19.8%]) had lung abnormalities reported on physical examination at the end of treatment compared to Symbicort (2 [1.5%]) and budesonide (7 [5.5%]). [T11.3.10.1.1, p 7123-4]

10.1.2.3 Summary and Conclusions

Study SD-039-0716 was a randomized, double-blind, double-dummy, placebo-controlled 12-week study comparing the efficacy and safety of Symbicort MDI (80/4.5 mcg dosage strength) with its pharmacologic monoproducts, budesonide MDI (80 mcg) and formoterol (Oxis)

Turbuhaler, and placebo, each administered as 2 inhalations BID, in 511 adolescents and adults (≥12 years of age) and a subset of 31 children (6 to 11 years of age) with mild-to-moderate asthma (for ≥12 years: FEV_1 on ICS therapy 60% to 90% predicted; for <12 years: ≥75% predicted). Randomization was stratified by age group (<12 years old and ≥12 years). The study comprised a screening visit, a 14 (±7) day single-blind placebo run-in period, and a 12-week double-blind treatment period. The study population was approximately 90% Caucasian, 40% males and 60% females, a mean age of 35 years (range 6 to 78 years), and 31/511 <12 years of age and 480/511 ≥12 years of age. All except 1 had asthma controlled by a regimen of ICS prior to entry. The average length of asthma history was 19 years. At screening, the mean pre-dose FEV_1 was 2.5 L and mean percent reversibility was 18.9% (range 10.3% to 62.6%). At baseline, the mean percent predicted FEV_1 for most patients was in the mild-to-moderate range (75.7 % predicted) while being treated with an average ICS dose of 341.5 mcg daily (range 80 to 1200 mcg a day). Treatment groups were well balanced at randomization.

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 (≥12 years of age only), 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 [*only those for patients ≥12 years are shown; similar criteria were included for younger patients*]: a decrease in morning pre-dose FEV_1 of ≥20% from the pre-dose FEV_1 at randomization, or a decrease to <45% 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). Although patients 6-12 years of age were randomized in a subset of centers, the primary efficacy evaluation was performed in patients ≥12 years of age. 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 71.3%. 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 mild to moderate asthmatics, the secondary endpoints speak clearly to the pharmacological differences between the two active ingredients and any added benefit from providing them in a fixed combination product. 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.

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. However, in addition to the expected LABA bronchodilator benefits, in this population the addition of formoterol to budesonide did not appear to have much effect on secondary variables. Formoterol did not add significantly to factors in key asthma control such as frequency and severity of exacerbations [as measured by the key secondary endpoint of pre-specified asthma events]. The only secondary endpoints supportive of an additive effect for formoterol were PEF endpoints.

It should be noted that the Symbicort results in this study differ from the results found in study **717** in moderate to severe asthmatics, in addition to the prevention [or delay] of tachyphylaxis the Symbicort and free combination treatment arms improved beyond either of the two monoproduct arms with regard to multiple secondary endpoints.

In summary, this study supports the efficacy of Symbicort. That said, except for AM and PM PEFR, in this study population there was little if any '*symbi*otic' relationship found for the components in the *Symbi*cort combination. It suggests that in milder populations the addition of a LABA does not provide controller effects, but only a bronchodilator effect.

10.1.3 Study SD-039-0717. Twelve-week safety and efficacy study using Symbicort (160/4.5 µg) versus its monoproducts (budesonide MDI and formoterol TBH) in adolescents and adults (≥12 Years of Age) with asthma

Protocol #:	SD-039-0717
Title:	Study SD-039-0717. A Twelve-Week, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Trial of SYMBICORT® (160/4.5 µg) versus its Monoproducts (budesonide and formoterol) in Adolescents (≥12 Years of Age) and Adults with Asthma – SPRUCE 160/4.5
Study Dates:	First subject enrolled:: 9 July 2002 Last subject completed: 29 January 2004
Sites:	Adults and adolescents ≥12 years: 84 Centers in the United States 24-hour Holter monitoring: subset of 23 centers
IRB:	Each study site had a separate IRB. A listing was provided.
Ethics:	The study report states that the study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements and the AstraZeneca policy on Bioethics.

Source: M5, SD-039-0717.pdf

10.1.3.1 Protocol

This study was quite similar in design to study SD-039-0**716**. Therefore, the only the differences between the study designs will be highlighted.

Like study 716, this was a randomized, double-blind, double-dummy, placebo-controlled efficacy and safety study. The study design was similar to study 716, except that the run-in period included single-blind treatment with budesonide instead of placebo, and this study used the 160/4.5 and 160 mcg per puff formulations of Symbicort and budesonide instead of the 80/4.5 and 160 mcg per puff formulations, respectively. Treatment arms also included the free combination of the monoproducts and placebo. This study did not include children, but rather, included only adolescents and adults ≥12 years of age. Whereas study SD-039-0716 included patients who had been on low to medium dose ICS and had FEV_1 of 60-90% percent predicted (for ≥12 years of age), the entry criteria for this study included asthma patients who had been on medium to high dose ICS and had FEV_1 of 45-85% percent predicted. Randomization was stratified by asthma severity, based on consistent use of moderate vs high dose ICS use prior to screening, as shown in Table 76. The study comprised a screening visit, a 2 (±1) week single-

blind run-in period of budesonide 160 mcg BID (budesonide 80 mcg, 2 actuations BID), and a 12-week double-blind treatment period. The study was performed contemporaneously to study 716.

Table 76. SD-039-0717, Definition of moderate- and high-dose ICS strata

ICS use*	Daily ICS dose at Visit 1 (mcg.day)	
	Moderate-dose stratum	High-dose stratum
Beclomethasone dipropionate (CFC)	540 – 840	>840
Beclomethasone dipropionate (HFA)	160 – 280	>280
Budesonide	400 – 600	>600
Flunisolide	1000 – 1999	≥2000
Fluticasone (CFC)	264 – 440	>440
Fluticasone (Diskus)	300 – 500	>500
Triamcinolone acetonide	800 – 1999	>2000
*Patients were required to have been on constant daily ICS for at least 4 weeks prior to study		
Source: p57, SD-039-0717.pdf		

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. PK was also performed in a subset of patients.

Just as for study 716, study 717 included a set of pre-defined criteria for withdrawal of patients due to an asthma event. The criteria were substantially the same, with only one minor difference from study 716 for criterion #1. 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.

Co-primary and secondary variables and endpoints were similar to those used for study 716.

Reviewer's Comment: The same Amendments were made for this study as for study 716, with a demotion of 'withdrawals due to a pre-defined asthma event' to a secondary endpoint and elevation of pre-dose FEV_1 to a primary endpoint. Therefore, this study has the same issues with regard to effects of the changes in one of the co-primary variables during the course of the study.

A listing of the investigational products and batch numbers used in this study is shown below.

Table 77. SD-039-0717, Investigational products

Product	Delivered dose	Manufacturer	Batch Number
Run-in treatment			
Budesonide MDI	80 mcg per actuation	AstraZeneca Charnwood, UK and/or Dunkerque, France	P6361, P64941
Randomized treatment			
Actives			
SYMBICORT MDI	160 mcg budesonide and 4.5 mcg formoterol per actuation	AstraZeneca Charnwood, UK and/or Dunkerque, France	P6040, P6041A, P6502A
Budesonide MDI	160 mcg per actuation	AstraZeneca Charnwood, UK and/or Dunkerque, France	P6363, P6364, P6388, P6495, P6611
Formoterol (Oxis) TBH	4.5 mcg per inhalation. (M2 TBH)	AstraZeneca Södertälje, Sweden	P6474, P6508, P6550, P6624
Placebos			
Placebo MDI		AstraZeneca Charnwood, UK and/or Dunkerque, France	P6254, P6349, P6351, P6490, P6491
Placebo TBH	(M2 TBH)	AstraZeneca Södertälje, Sweden	P6476, P6512, P6623, P6625, P6677
Rescue medication			
Albuterol MDI	90 mcg per actuation	Commercially available; supplied by AstraZeneca	ABL97A, ABZ93A
Local anesthetic			
EMLA cream	Cream for topical application used as needed prior to phlebotomy	AstraZeneca	203083, 211051, 301148, 302074

Source: T2.p55; SD-039-0717.pdf

10.1.3.2 Results

10.1.3.2.1 Description of the Study Population

10.1.3.2.1.1 Disposition

Of 1373 screened asthma patients, a total of 596 patients from 76 centers were randomized (ITT). All randomized patients received randomized treatment (SAS) and provided at least one efficacy observation (EAS), i.e. had sufficient data for at least one co-primary endpoint to be calculated; 213 received Holter monitoring; 131 had PK evaluations; 427 were in moderate-dose stratum; 169 were in high-dose stratum. The per-protocol (PP) analysis set included 526 patients: 70 patients were excluded from this set (6 unacceptable FEV_1 reversibility at Visit 1; 20 not treated with consistent ICS at entry; 1 received beta-blocker after Visit 1; 9 received disallowed medication after Visit 1; 7 had unacceptable asthma symptom score during run-in; 5 had unacceptable FEV_1 criteria for age at Visit 2; 28 were randomized to the wrong dose stratum; 2 had study blind broken during the study). The ITT population included a total of 26 patients who were screened more than once and later randomized: 7 Symbicort, 3 budesonide, 8

formoterol, 3 budesonide + formoterol, and 5 placebo. Over half of all centers contributed 6 to 20 patients each; many centers enrolled ≤5 patients. [p127]

Reasons for discontinuation are shown in Table 78. The overall withdrawal rate was 38% in this study. The withdrawal rate was highest in the placebo group (60%), followed by the formoterol group (51%), budesonide (28%), budesonide + formoterol (25%), and the Symbicort group (22%). The most common reason for withdrawal was due to study-specific discontinuation criteria (i.e., withdrawals due to pre-defined asthma events): highest in the placebo and formoterol groups (49.6% and 35.8%, respectively), followed by the budesonide (20.2%), then the budesonide + formoterol and Symbicort groups (11.3% and 10.5%, respectively). The number of withdrawals due to development of pre-defined asthma events was originally a primary variable to evaluate the contribution of the budesonide component to the combination drug product (Symbicort minus formoterol comparison), but demoted to a secondary efficacy variable when pre-dose FEV_1 was upgraded. The reason given for the change was that investigators were confused about whether patients who met withdrawal criteria were required to be withdrawn from the study or whether they could continue at the investigator's discretion; apparently, some patients who should have been discontinued because they met withdrawal criteria were not discontinued because investigators judged them to be clinically stable. Since pre-dose FEV_1 had been collected on all patients, the change was made. Since this change was performed while studies were ongoing, understanding the nature and frequency of withdrawals becomes an important issue for evaluation the contribution of withdrawals to the results and interpretation of this study.

Whereas in study 716 the higher discontinuation rate in the placebo group was due to both a greater rate of withdrawals due to study-specific discontinuation criteria, and also a greater rate of discontinuations due to adverse events, the contribution of adverse events was more evenly distributed across treatment groups in this study. As a result, the high discontinuation rate in both the placebo and formoterol groups was primarily due to the study-specific discontinuation criteria, thereby playing a more prominent role in discontinuations for this study than for study 716. To some extent this is not surprising, given the more severe asthma entry criteria for these patients. On the other hand, the number of patients withdrawn in these two groups is surprisingly high.

Unlike in study 716, where the predominance of withdrawals in the placebo group were in patients who had poorer asthma control and lower baseline mean pre-dose FEV_1 values, as evidenced by the baseline mean for the subgroup of placebo patients remaining at Week 12 being notably higher than those for the active treatment groups, in this study baseline pre-dose FEV_1 for patients remaining at Week 12 were similar among treatment groups. [T36, p161; SD-039-0717]

Implications from the withdrawal pattern are limited by the uneven application of the pre-defined asthma event qualifying criteria. Nevertheless, 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 little benefit in prevention of exacerbations. Whereas in study 716 the frequency of withdrawals due to an asthma event 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 culminating in withdrawal. Whereas in study 716 in less severe asthmatics the addition of a LABA did not appear to add benefit to budesonide in the prevention of asthma exacerbations

[and this observation was borne out by the CRF data], in this study the withdrawal events appear to show some benefit from the addition of formoterol [this observation also was borne out by the CRF data]. This is discussed further within the discussion of qualifying pre-defined asthma events in the Secondary Variables section.

Table 78. SD-039-0717, Reasons for Discontinuation (all randomized patients)

	Symbicort n=124	Budesonide n=109	Formoterol n=123	Bud+For n=115	Placebo n=125	Total n=596
Randomized / took study med	124	109	123	115	125	596
Completed	97	78	60	86	50	371
Discontinued	27 (21.7)	31 (28.4)	63 (51.2)	29 (25.2)	75 (60.0)	225 (37.8)
Reasons for Discontinuation						
Developed study-specific discontinuation criteria [a]	13 (10.5)	22 (20.2)	44 (35.8)	13 (11.3)	62 (49.6)	154 (25.8)
Adverse event	8 (6.5)	4 (3.7)	5 (4.1)	9 (7.8)	4 (3.2)	30 (5.0)
Not willing to continue	3 (2.4)	2 (1.8)	7 (5.7)	1 (0.9)	6 (4.8)	19 (3.2)
Eligibility criteria not fulfilled	2 (1.6)	0	2 (1.6)	1 (0.9)	1 (0.8)	6 (1.0)
Lost to follow-up	1 (0.8)	0	1 (0.8)	2 (1.7)	0	4 (0.7)
Other	0	3 (2.8)	4 (3.3)	3 (2.6)	2 (1.6)	12 (2.0)
[a] Represents withdrawals due to pre-defined asthma events.						
Sources: Table 18, p 125; SD-039-0717.pdf						

10.1.3.2.1.2 Demographics and Baseline Characteristics

Demographics and key baseline characteristics for the ITT/efficacy/safety population are shown in Table 79, which shows that the treatment groups were similar, and their baseline characteristics including disease severity (daily ICS dose, mean pre-dose FEV_1, and percent reversibility) were comparable. 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.

Table 79. SD-039-0717, Demographic and key baseline characteristics, ITT

	Symbicort n=124	Budesonide n=109	Formoterol n=123	Bud+For n=115	Placebo n=125	Total n=596
Sex (n, %)						
Male	44 (35.5)	38 (34.9)	43 (35.0)	50 (43.5)	53 (42.4)	228 (38.3)
Female	80 (64.5)	71 (65.1)	80 (65.0)	65 (56.5)	72 (57.6)	368 (61.7)
Age (yr)						
Mean (SD)	41.8 (15.5)	40.7 (14.2)	40.0 (16.4)	40.3 (14.7)	41.9 (15.2)	40.9 (15.2)
Median	41.5	42.0	41.0	40.0	43.0	41.0
Range	12 to 74	12 to 80	12 to 87	13 to 75	12 to 75	12 to 87

	Symbicort n=124	Budesonide n=109	Formoterol n=123	Bud+For n=115	Placebo n=125	Total n=596
Age group (yr), (n, %)						
12 to <16	6 (4.8)	3 (2.8)	12 (9.8)	5 (4.3)	4 (4.8)	32 (5.4)
16 to <65	107 (86.3)	102 (93.6)	102 (82.9)	104 (90.4)	112 (89.6)	527 (88.4)
65 to <75	11 (8.9)	3 (2.8)	8 (6.5)	5 (4.3)	6 (4.8)	33 (5.5)
≥75	0	1 (0.9)	0	1 (0.9)	1 (0.8)	4 (0.7)
Race (n, %)						
Caucasian	98 (79.0)	84 (77.1)	91 (74.0)	89 (77.4)	101 (80.8)	463 (77.7)
Black	18 (14.5)	17 (15.64)	21 (17.4)	20 (17.4)	20 (16.0)	96 (16.1)
Oriental	0	3 (2.8)	3 (2.4)	2 (1.7)	1 (0.8)	9 (1.5)
Other	8 (6.5)	5 (4.6)	8 (6.5)	4 (3.5)	3 (2.4)	28 (4.7)
ICS use at entry (ALL, mcg/day) [a]						
Mean (SD)	570 (225)	590 (252)	593 (237)	588 (245)	607 (269)	590 (245)
Min, Max	160, 1200	160, 1600	220, 1320	160, 1200	160, 1600	160, 1600
ICS use at entry (Moderate-dose stratum, mcg/day) [a]						
N	91	81	86	82	87	427
Mean (SD)	466 (120)	491 (202)	480 (146)	462 (136)	461 (132)	341 (148)
Min, Max	160, 1000	160, 1600	220, 1000	160, 1200	160, 1000	160, 1600
ICS use at entry (High-dose stratum, mcg/day) [a]						
N	33	28	37	33	38	169
Mean (SD)	858 (195)	896 (139)	857 (194)	899 (161)	941 (195)	887 (181)
Min, Max	320, 1200	320, 1000	320, 1320	320, 1200	660, 1000	320, 1600
Years since diagnosis	23.1 (15.1)	23.2 (16.0)	21.7 (15.3)	21.7 (13.4)	23.3 (15.0)	22.6 (15.0)
Screening (Visit 1, pre-bronchodilator) (mean, SD)						
FEV_1 (L)	2.2 (0.69)	2.3 (0.61)	2.1 (0.57)	2.2 (0.57)	2.2 (0.63)	2.2 (0.62)
FEV_1 % predicted	67.9 (10.48)	68.7 (10.74)	65.1 (10.30)	65.4 (10.16)	67.5 (10.73)	66.9 (10.54)
Percent reversibility in FEV_1						
Mean (SD)	20.5 (11.8)	22.7 (13.2)	24.4 (12.9)	22.6 (11.0)	21.1 (11.5)	22.2 (12.1)
Median	17.2	18.4	20.1	18.4	18.2	18.3
Baseline (Visit 2, pre-dose) (mean, SD)						
FEV_1 (L)	2.2 (0.72)	2.3 (0.63)	2.2 (0.60)	2.2 (0.61)	2.3 (0.68)	2.2 (0.65)
FEV_1 % predicted	67.5 (11.50)	70.0 (10.45)	67.5 (11.51)	66.9 (0.61)	68.7 (11.07)	68.1 (11.12)
Run-in period average (mean, SD)						
Morning PEF (L/min)	343.8 (92.2)	342.3 (90.4)	337.9 (91.6)	336.7 (95.4)	353.7 (107.2)	343.0 (95.6)
Daily rescue med.[b]	2.1 (2.0)	2.2 (2.7)	2.4 (2.2)	2.2 (2.1)	2.5 (2.5)	2.4 (2.3)
Daytime asthma symptom score [c]	1.0 (0.5)	1.1 (0.5)	1.1 (0.5)	1.1 (0.5)	1.1 (0.5)	1.1 (0.5)
Nighttime asthma symptom score [c]	0.9 (0.5)	1.0 (0.5)	0.9 (0.5)	0.9 (0.5)	1.0 (0.5)	1.0 (0.5)

a Patients were stratified by baseline ICS dose (moderate or high). Since a number of patients had more than one dose of ICS during the 28-day period preceding Visit 1, and some patients were changed from fixed dose LABA combinations to prepare for Visit 1, baseline ICS dose was defined as the last ICS dose prior to the 48-hour period preceding Visit 1.
b Nighttime plus daytime rescue medication use.
c Symptoms rated on a scale of 0=none, 1=mild, 2=moderate, 3=severe.

Source: T20, p131-2; SD-039-0717.pdf

10.1.3.2.1.3 Compliance

Medication compliance, shown in Table 80, was high during both the run-in and treatment periods. The table shows compliance calculated in 2 ways.

Table 80. SD-039-0717, Study Medication Compliance, ITT

	Symbicort n=124	Budesonide n=109	Formoterol n=123	Bud+For n=115	Placebo n=125	Total n=596
Run-in						
N	124	109	123	115	125	596
Compliance using diary entries [a]						
Mean (SD)	98.3 (5.42)	98.6 (3.31)	98.5 (5.79)	98.9 (2.56)	99.2 (2.89)	98.7 (4.25)
<80% (n,%)	2 (1.6)	0	1 (0.8)	0	1 (0.8)	4 (0.7)
>80% (n,%)	122 (98.4)	109 (100)	122 (99.2)	115 (100)	124 (99.2)	592 (99.3)
Compliance using days on treatment [b]						
Mean (SD)	90.2 (11.60)	89.3 (12.72)	89.5 (13.71)	90.1 (9.33)	88.7 (15.10)	89.6 (12.66)
<80% (n,%)	8 (6.5)	12 (11.0)	12 (9.8)	12 (10.4)	13 (10.4)	57 (9.6)
>80% (n,%)	116 (93.5)	97 (89.0)	111 (90.2)	103 (89.6)	112 (89.6)	539 (90.4)
Treatment period						
N	121	109	119	114	124	586
Compliance using diary entries [a]						
Mean (SD)	98.4 (2.87)	98.7 (2.07)	98.8 (2.77)	98.6 (2.38)	98.3 (5.18)	98.6 (3.28)
<80% (n,%)	0	0	0	0	1 (0.8)	1 (0.2)
>80% (n,%)	121 (97.6)	109 (100.0)	119 (96.7)	113 (98.3)	123 (98.4)	585 (98.2)
NA	3 (2.4)	0	4 (3.3)	1 (0.9)	1 (0.8)	9 (1.5)
Missing	0	0	0	1 (0.9)	0	1 (0.2)
Compliance using days on treatment [b]						
Mean (SD)	88.2 (11.98)	87.4 (15.93)	90.6 (13.34)	88.4 (14.98)	88.1 (14.82)	88.5 (14.23)
<80% (n,%)	25 (20.2)	23 (21.1)	16 (13.0)	22 (19.1)	23 (18.4)	109 (18.3)
>80% (n,%)	96 (77.4)	86 (78.9)	103 (83.7)	92 (80.0)	101 (80.8)	478 (80.2)
NA	3 (2.4)	0	4 (3.3)	1 (0.9)	1 (0.8)	9 (1.5)

a Medication compliance using diary entries = [Total (Yes) study medication intakes recorded in diary (am or pm) / total (Yes/No) intakes recorded] x 100.
b Medication compliance using days on treatment = [Total (Yes) study medication intakes recorded in diary (am or pm) / (days on treatment-0.5) x 2] x 100. Randomization (Day 1) was excluded from compliance calculations; Patients who discontinued on the day of randomization were excluded from all calculations during the double-blind treatment period.
NA Not available due to subject withdrawal on the day of randomization. Nine (9) patients discontinued treatment on the day of randomization after receiving randomized treatment.
Missing One patient had no diary data recorded on or after the day of randomization.
Source: T22, p135; SD-039-0717.pdf

10.1.3.2.1.4 Concomitant Medications

Review of tables of concomitant medications during run-in and treatment phases revealed few differences among treatment groups with regard to use of concomitant medications. During the course of the study, 87.1% (519) patients used concomitant medications not related to asthma; use of these medications was similar among treatment groups. During the course of the study, 95.3% (568) of patients used concomitant medications to treat asthma, most commonly a short-acting beta-agonist (94.6%). The percent of patients using a short-acting beta-agonist was similar among treatment groups (95.2% Symbicort, 94.5% budesonide, 95.9% formoterol, 95.7% budesonide + formoterol, 92.0% placebo). [p138-9]