

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-929

STATISTICAL REVIEW(S)

6/12/06



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation Clinical Studies Addendum

NDA/Serial Number: NDA 21-929
Drug Name: SYMBICORT (Combination of budesonide 80 µg and formoterol 4.5 µg, per puff) administered as two puffs, BID
Indication(s): SYMBICORT is proposed to be indicated for the treatment of asthma in patients 12 years of age and older
Applicant: AstraZeneca
Date(s): Applicant's letter date: September 23, 2005
Review Priority: Standard

Biometrics Division: Biometrics Division 2
Statistical Reviewer: Ted Guo, Ph.D., Biometrics Division 2
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Project Manager: Colette Jackson (ODE II)

Keywords: NDA review, clinical studies

Last modified: 6/12/2006

Introduction

This addendum is in response to the sponsor submission to NDA 21-929 on May 9, 2006 in response to a request for information from the Division.

Analyses Excluding Patients with Asthma Events Identified on CRF Who Should Have Been Withdrawn From the Study But Were Not

It is the Division's interest to evaluate the effect on the efficacy outcome contributed by patients with Asthma Events identified on CRF who should have been withdrawn from the study but were not. The patients' withdrawal was considered in the original protocol to be the primary efficacy variable. Even though the sponsor changed it to a secondary efficacy variable in the protocol amendment, it remains very important to the Division for the efficacy evaluation. These patients need to be identified and their efficacy results reported in a clear fashion. Unfortunately, identification of the subjects who qualified for withdrawal according to the protocol-specified criteria but who were ultimately not withdrawn was not possible using the information in the original submission. This triggered the Agency's 4/28/06's inquiry.

The analyses included in this report are based on data submitted on 5/9/06 by AstraZeneca in response to the Agency's 4/28/06 inquiry. In the Agency's inquiry, the first question to the sponsor says the following:

FDA Question 1:

Provide, in written format, subject identification numbers for subjects who qualified for early withdrawal from the studies according to the protocol specified discontinuation criteria (as recorded on the ASTEXAC case report form). For each of these subjects, include the timepoint at which the discontinuation criteria were satisfied. Also, indicate whether each of these subjects was actually withdrawn and if so the timepoint at which the withdrawal occurred. In addition, provide this information electronically including the subject identification number (USUBJID and SUBJECT), the date the discontinuation criteria were satisfied, an indicator variable for the withdrawal status of each patient, and the date the withdrawal occurred. These dates should be consistent with the date in the variable `_TERM_DT` in your disposition data set.

The sponsor submitted two SAS data sets named `_ASTEX.XPT` for Studies 716 and 717 in identical formats. The data set include the following variables:

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Table 1 Important variables in _ASTEX.XPT

VARIABLE	LABEL	MEANING
_EXATYPE	Type of Pre-defined Event	If event identified in the data, then _EXATYPE='CDS'. Else if event identified on CRF, then _EXATYPE='CRF'.
_EXA_SDT	Assessment Date	Asthma event date
_EXCRIT	Pre-defined Asthma Event Criteria	Pre-defined Asthma Event Criteria

Source: ... \N21929\N_000\2006-05-09\crt\datasets\sd-039-0716
 ... \N21929\N_000\2006-05-09\crt\datasets\sd-039-0717

Number of variables: 23

These data enables this reviewer to identify patients who met the CRF criteria but were not withdrawn from the study by merging these data with the patient demographic data in the original NDA submission. In this report, the term, **Subset**, is used to refer to these patients.

Reviewer's Remarks

All-data and subset analyses in the following text employ graphic techniques. P-value based inferential analyses were not considered for these analyses since they were exploratory. These analyses were focused on the primary efficacy variables. Within the premise of such consideration, this reviewer has the following comments.

From a visual comparison between the graphs based on all data and that based on the **Subset**, the numerical differences between treatments appear to be similar, and the ranks among the treatments appear to maintain the same order. These findings, though not based on rigorous statistical proof, suggest that overall statistical conclusions may not be changed by including or excluding those patients identified on the CRF who should have been withdrawn from the study, but were not. For Study 716, see Figures 1 and 2 for a visual comparison of pre-dosing FEV₁ percent change from baseline between all subjects and the **Subset**, Figures 3 and 4 and Tables 4 and 5 for the analogous comparison of pre-dosing FEV₁ change from baseline, Figures 5 and 6 for the mean change from baseline in pre-dosing FEV₁ (i.e., co-primary efficacy endpoint), Figures 7 and 8 for the 12-hour FEV₁ at the end of week 2 (i.e., co-primary efficacy endpoint), and Figures 9 and 10 for the 12-hour FEV₁ at the end of week 12. Analogous results for Study 717 are provided in Figures 12 through 20 and Tables 6 through 9.

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Study 716**Table 2 Number of patients ≥ 12 years (Study 716)**

PREMATURELY DISCONTINUED	TYPE OF PRE-DEFINED EVENT	TREATMENT				TOTAL
		SYM 80 BID	BUD 80 BID	FOR 4.5 BID	Placebo	
No	NOT ON CRF*	93	90	56	41	280
	CRF	12	13	23	19	67
	Total	105	103	79	60	347
Yes	NOT ON CRF*	7	5	10	12	34
	CRF	11	13	25	50	99
	Total	18	18	35	62	133
Total		123	121	114	122	480

Source: DEMO and _ASTEX (5/9/06) for patients aged ≥ 12

*: Patients not having pre-defined (asthma) events identified on CRF

Table 2, above, shows that 347 out of the 480 ITT patients (≥ 12) stayed in the study, among which 67 had pre-defined asthma events identified on CRF. Table 3, below, shows how many patients had specific asthma events. Note that most were associated with Criterion 4: nights with awakening.

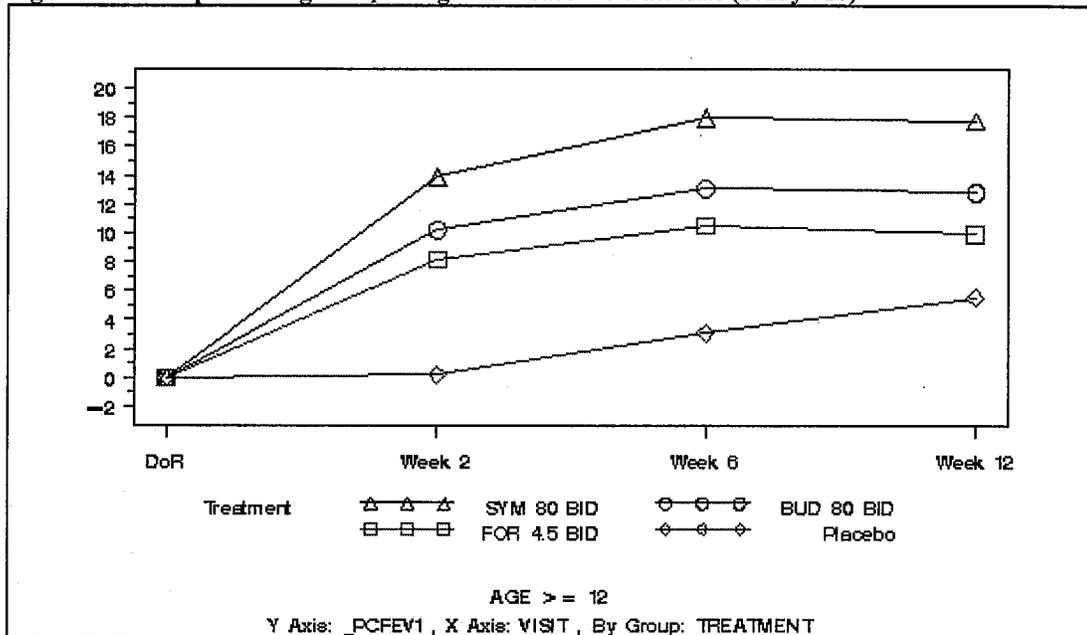
Table 3 Pre-defined asthma events (Study 716)

TREATMENT	PRE-DEFINED ASTHMA EVENT CRITERIA				TOTAL
	1- Decrease in FEV1	3- Decrease in Morning PEF	4- Nights with Awakening	5- Disallowed Treatment, 5a- Emergency Room Treatment	
SYM 80 BID	1		11		12
BUD 80 BID			13		13
FOR 4.5 BID	1	2	19	1	23
Placebo		1	18		19
Total	2	3	61	1	67

Source: DEMO and _ASTEX (5/9/06) for AGE ≥ 12 and DROPOUT='No' and _EXATYPE='CRF'

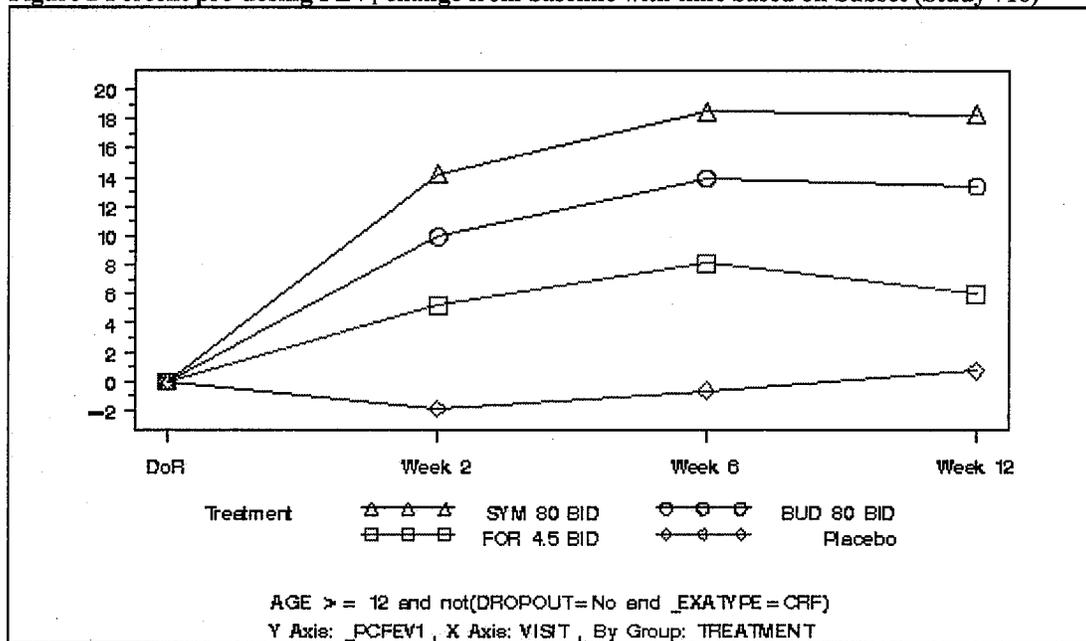
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Figure 1 Percent pre-dosing FEV₁ change from baseline with time (Study 716)



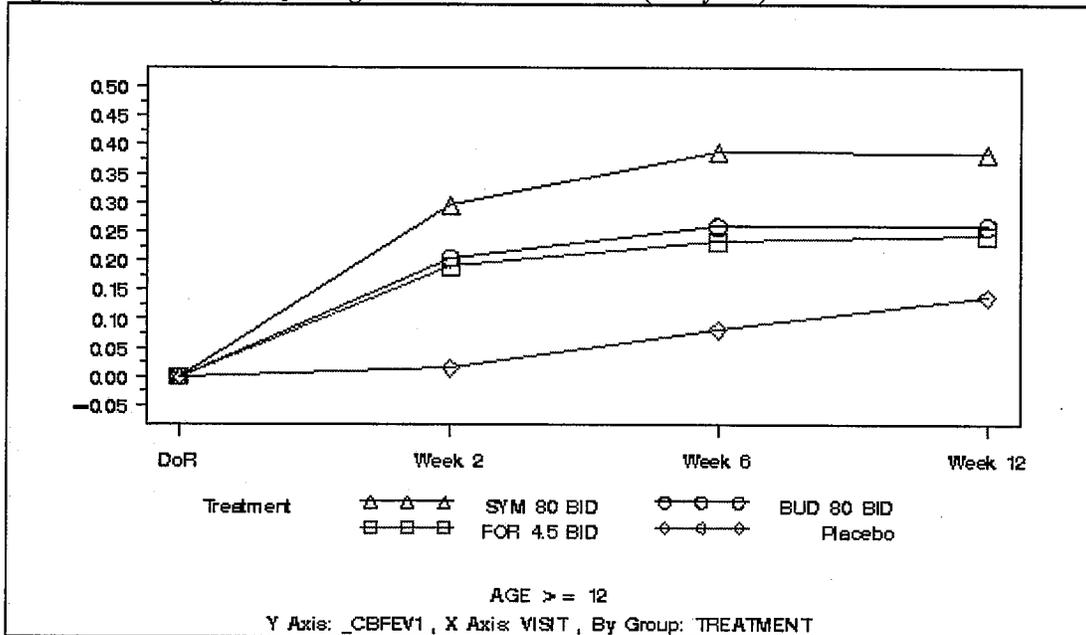
Source: PFT01_P11_1 for patients 12 years of age and older

Figure 2 Percent pre-dosing FEV₁ change from baseline with time based on Subset (Study 716)



Source: PFT01_P11_1 for patients 12 years of age and older and identified on CRF but were not withdrawn from the study

Figure 3 Pre-dosing FEV₁ change from baseline with time (Study 716)



Source: PFT01_P11_1 for patients 12 years of age and older

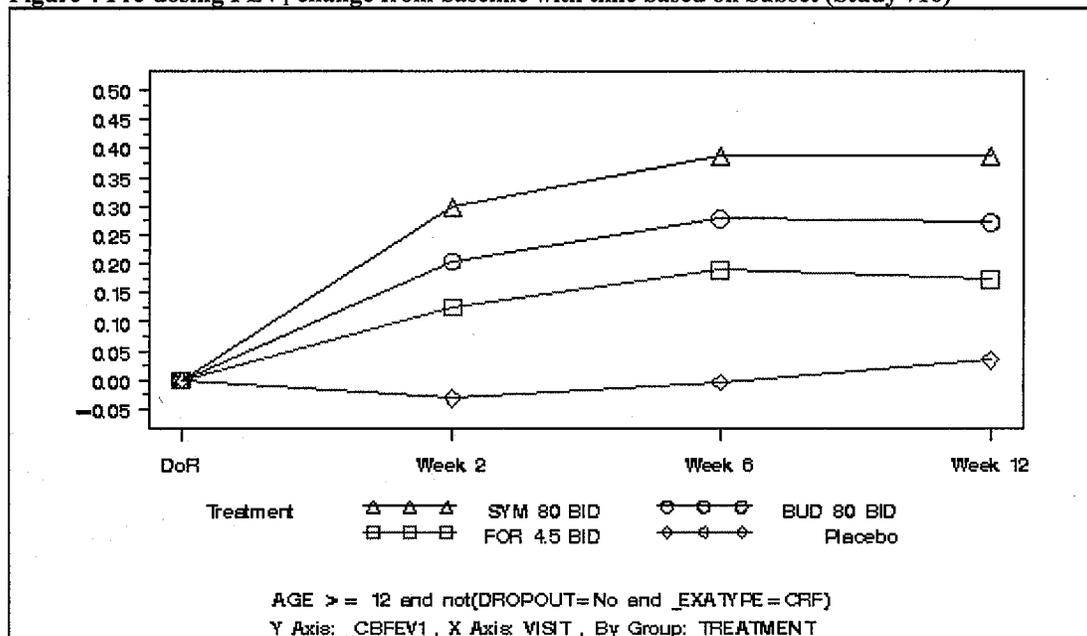
Table 4 Mean and Std. of Pre-dosing FEV₁ change from baseline with time (Study 716)

	DoR	Week 2		Week 6			Week 12			
	#Patients	#Patients	Mean	Std.	#Patients	Mean	Std.	#Patients	Mean	Std.
SYM 80 BID	129	136	0.28	0.37	128	0.37	0.37	114	0.37	0.36
BUD 80 BID	122	131	0.19	0.37	119	0.25	0.38	115	0.25	0.37
FOR 4.5 BID	114	126	0.18	0.39	99	0.22	0.42	88	0.23	0.39
Placebo	121	168	0.01	0.34	97	0.07	0.38	72	0.13	0.41
Overall	486	561	0.16	0.38	443	0.24	0.40	389	0.26	0.39

Source: PFT01_P11_1 for patients 12 years of age and older

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Figure 4 Pre-dosing FEV₁ change from baseline with time based on Subset (Study 716)



Source: PFT01_P11_1 for patients 12 years of age and older and identified on CRF but were not withdrawn from the study

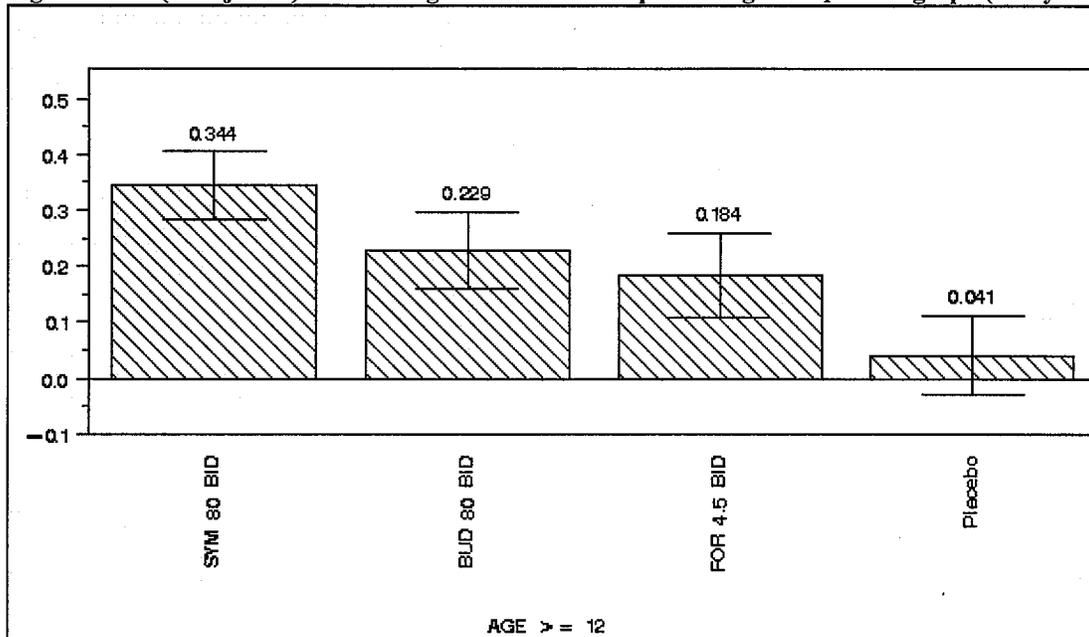
Table 5 Pre-dosing FEV₁ change from baseline with time based on Subset (Study 716)

	DoR	Week 2		Week 6			Week 12			
	#Patients	#Patients	Mean	Std.	#Patients	Mean	Std.	#Patients	Mean	Std.
SYM 80 BID	110	115	0.30	0.37	106	0.39	0.37	97	0.39	0.37
BUD 80 BID	103	111	0.20	0.37	96	0.28	0.38	96	0.27	0.38
FOR 4.5 BID	84	92	0.13	0.37	69	0.19	0.37	58	0.17	0.36
Placebo	95	132	-0.03	0.33	69	-0.00	0.35	47	0.04	0.34
Overall	392	450	0.15	0.38	340	0.24	0.40	298	0.25	0.39

Source: PFT01_P11_1 for patients 12 years of age and older and identified on CRF but were not withdrawn from the study

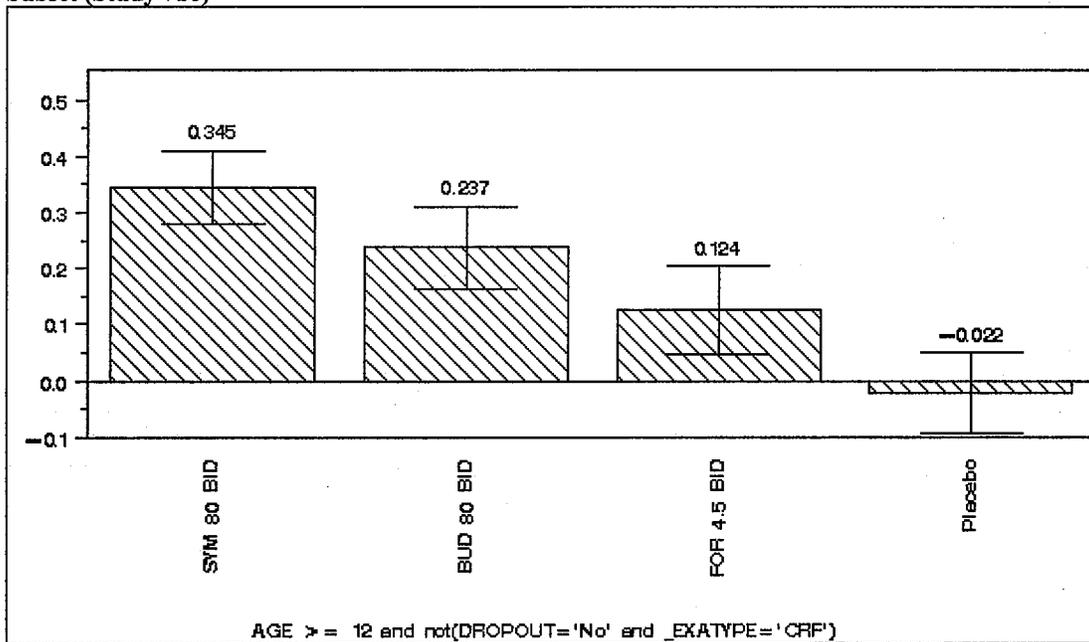
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Figure 5 Raw (unadjusted) mean change from baseline in pre-dosing FEV₁ in bar graph (Study 716)



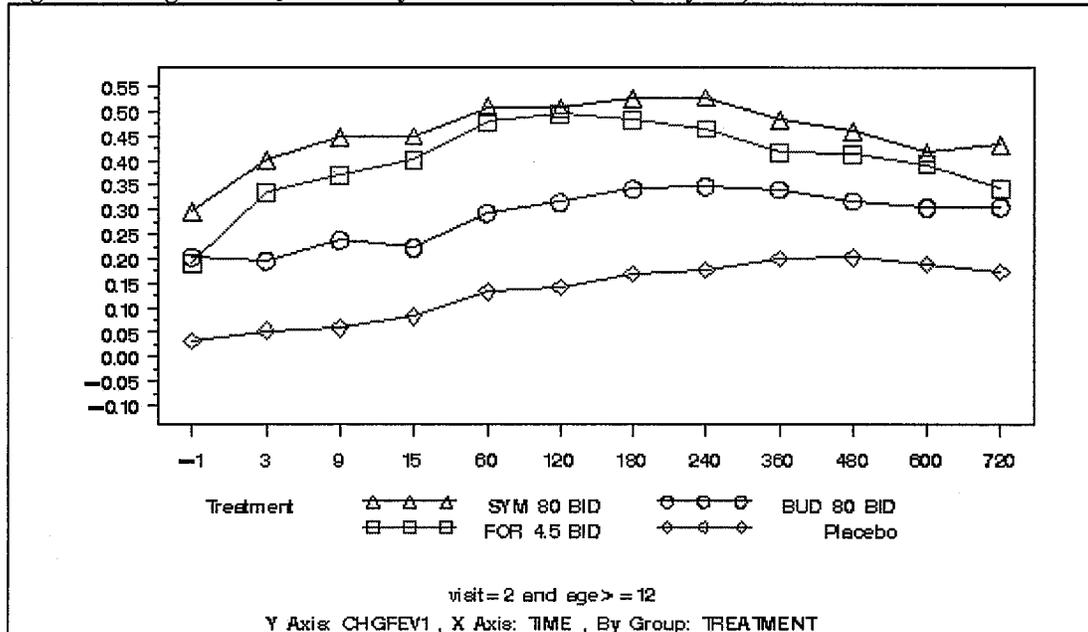
Source: PFT01_P12 for patients 12 years of age and older

Figure 6 Raw (unadjusted) mean change from baseline in pre-dosing FEV₁ in bar graph based on Subset (Study 716)



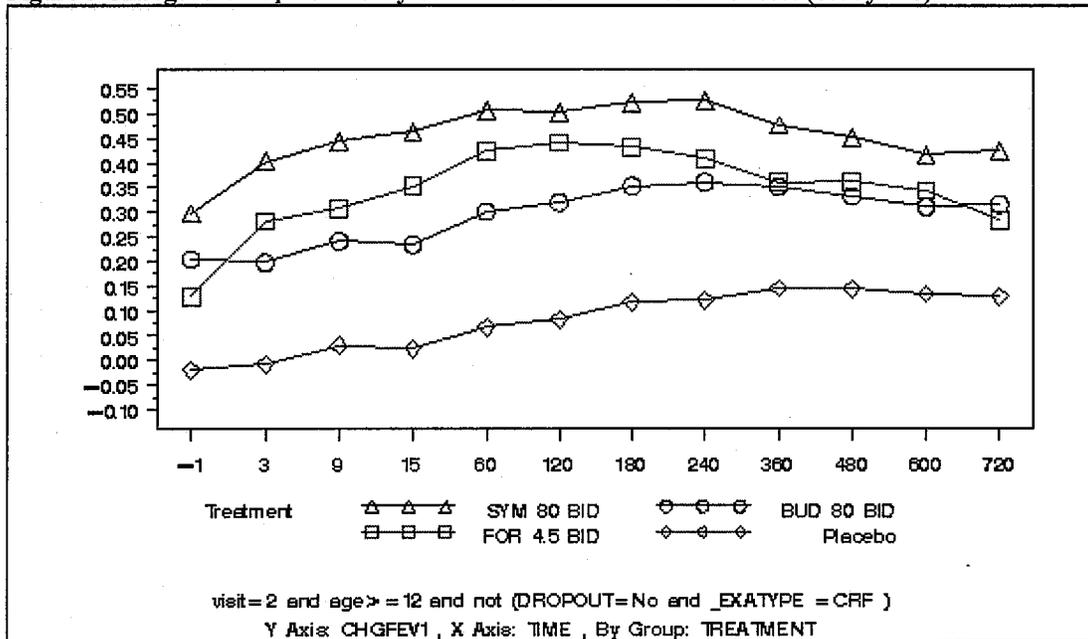
Source: PFT01_P12 for patients 12 years of age and older and identified on CRF but were not withdrawn from the study

Figure 7 Change in FEV₁ from study baseline at Week 2 (Study 716)



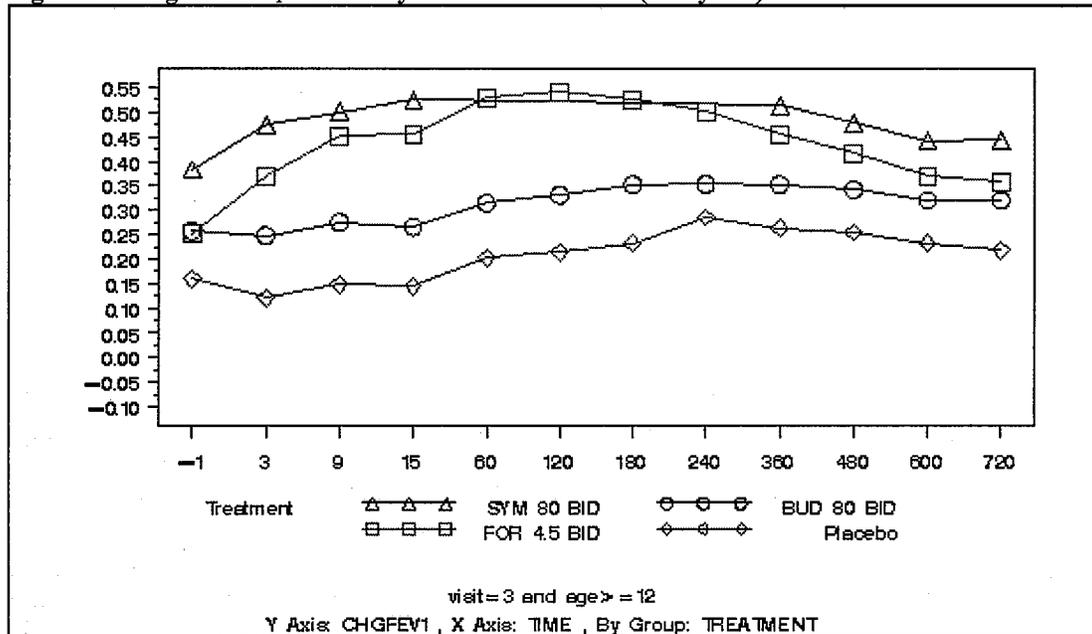
Source: PFT02_A1_1 for Week 2 and patients 12 years of age and older

Figure 8 Change in FEV₁ from study baseline at Week 2 based on Subset (Study 716)



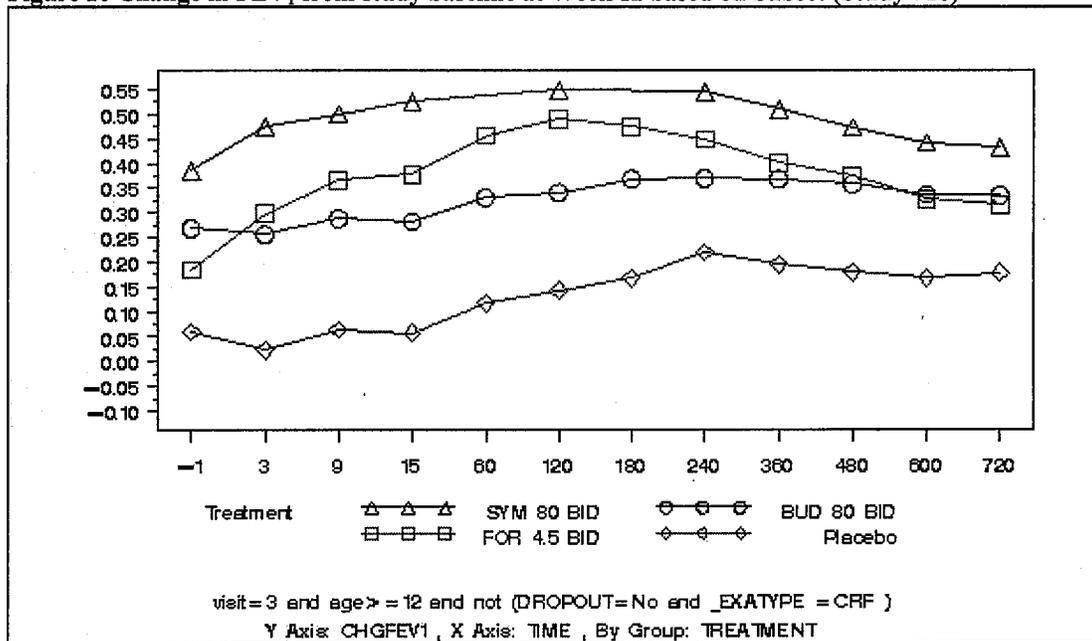
Source: PFT02_A1_1 for patients 12 years of age and older and identified on CRF but were not withdrawn from the study

Figure 9 Change in FEV₁ from study baseline at Week 12 (Study 716)



Source: PFT02_A1_1 for Week 12 and patients 12 years of age and older

Figure 10 Change in FEV₁ from study baseline at Week 12 based on Subset (Study 716)



Source: PFT02_A1_1 for patients 12 years of age and older and identified on CRF but were not withdrawn from the study

Study 717

Table 6 Number of patients (Study 717)

PREMATURELY DISCONTINUED	TYPE OF PRE-DEFINED EVENT	TREATMENT					TOTAL
		SYM 160 BID	BUD 160 BID	FOR 4.5 BID	BUD 160 + FOR 4.5	Placebo	
No	NOT ON CRF*	79	55	43	78	35	290
	CRF	18	23	17	8	15	81
	Total	97	78	60	86	50	371
Yes	NOT ON CRF*	8	6	12	13	6	45
	CRF	19	25	51	16	69	180
	Total	27	31	63	29	75	225
Total		124	109	123	115	125	596

Source: DEMO and _ASTEX (5/9/06) for patients

*: Patients not having pre-defined (asthma) events identified on CRF

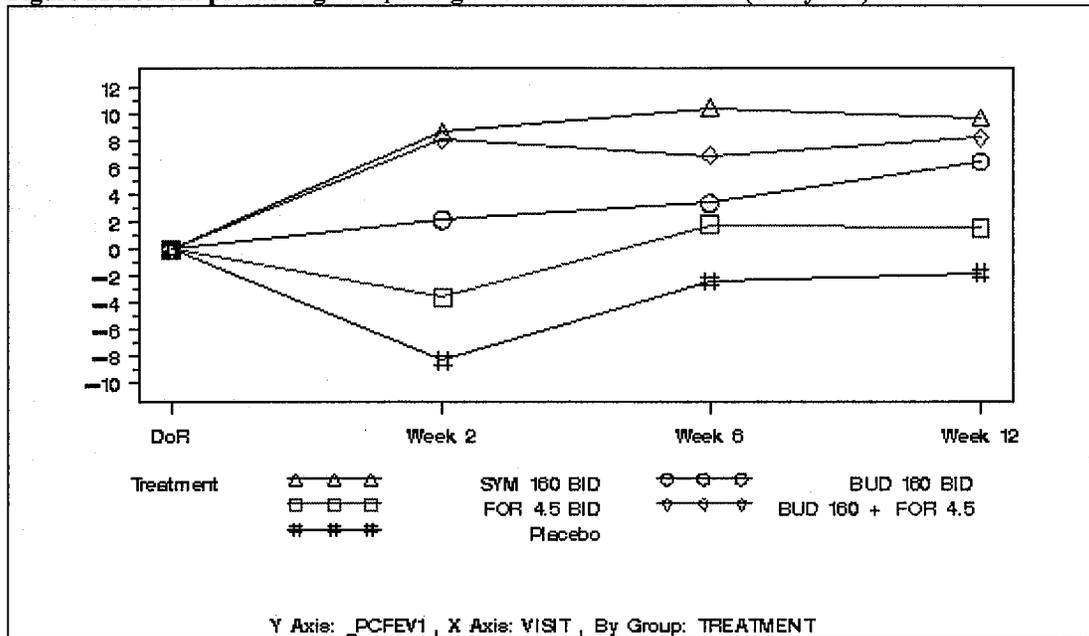
Table 6, above, shows that 371 out of the 596 ITT patients stayed in the study, among which 81 had pre-defined asthma events identified on CRF. Table 7, below, shows how many patients had specific asthma events. Note that most were associated with Criterion 4: nights with awakening.

Table 7 Pre-defined asthma events (Study 717)

TREATMENT	PRE-DEFINED ASTHMA EVENT CRITERIA						TOTAL
	1- Decrease in FEV1	2- Rescue Medication	3- Decrease in Morning PEF	4- Nights with Awakening	4- Nights with Awakening, 5- Disallowed Treatment, 5c- Disallowed Asthma Medication, 5d- Nebulized Bronchodilator, 5g- Other	5- Disallowed Treatment, 5c- Disallowed Asthma Medication, 5e- Steroids	
SYM 160 BID	2		1	14		1	18
BUD 160 BID			2	21			23
FOR 4.5 BID	5		1	10	1		17
BUD 160 + FOR 4.5	2		1	5			8
Placebo		1	1	13			15
Total	9	1	6	63	1	1	81

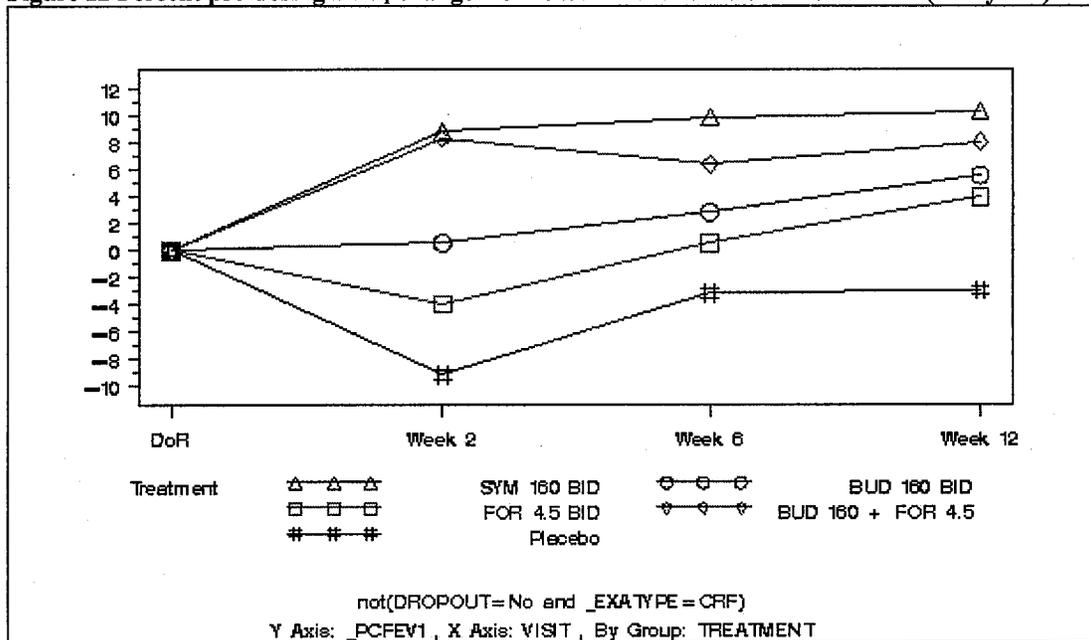
Source: DEMO and _ASTEX (5/9/06) for and DROPOUT='No' and _EXATYPE='CRF'

Figure 11 Percent pre-dosing FEV₁ change from baseline with time (Study 717)



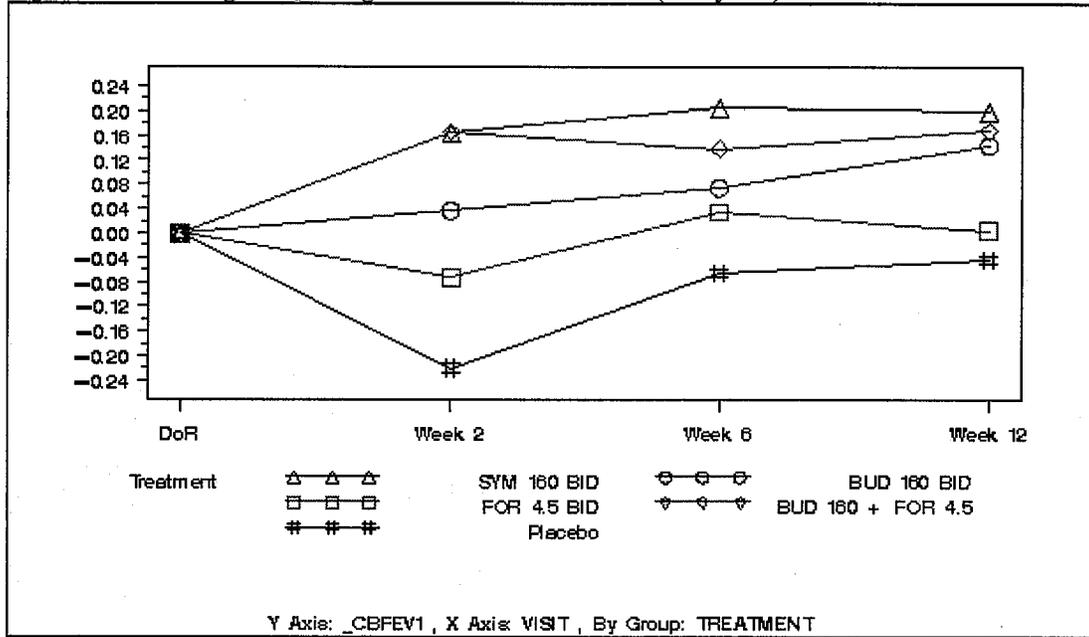
Source: PFT01_P11_1

Figure 12 Percent pre-dosing FEV₁ change from baseline with time based on Subset (Study 717)



Source: PFT01_P11_1 for patients identified on CRF but were not withdrawn from the study

Figure 13 Pre-dosing FEV₁ change from baseline with time (Study 717)



Source: PFT01_P11_1

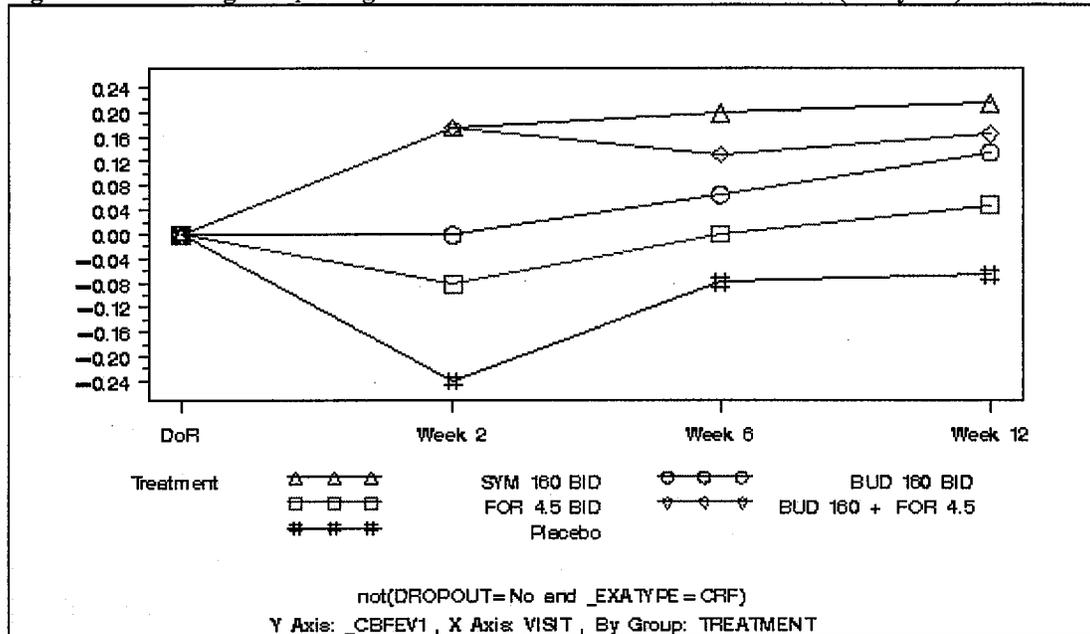
Table 8 Pre-dosing FEV₁ change from baseline with time (Study 717)

	DoR	Week 2		Week 6			Week 12			
	#Patients	#Patients	Mean	Std.	#Patients	Mean	Std.	#Patients	Mean	Std.
SYM 160 BID	118	128	0.17	0.32	114	0.21	0.28	105	0.20	0.33
BUD 160 BID	108	134	0.04	0.35	96	0.07	0.29	84	0.14	0.29
FOR 4.5 BID	116	139	-0.07	0.30	97	0.03	0.35	77	0.00	0.38
BUD 160 + FOR 4.5	111	124	0.17	0.28	106	0.14	0.34	97	0.17	0.30
Placebo	119	163	-0.22	0.43	77	-0.07	0.34	66	-0.04	0.34
Overall	572	688	0.00	0.38	490	0.09	0.33	429	0.11	0.34

Source: PFT01_P11_1

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Figure 14 Pre-dosing FEV₁ change from baseline with time based on Subset (Study 717)



Source: PFT01_P11_1 for patients identified on CRF but were not withdrawn from the study

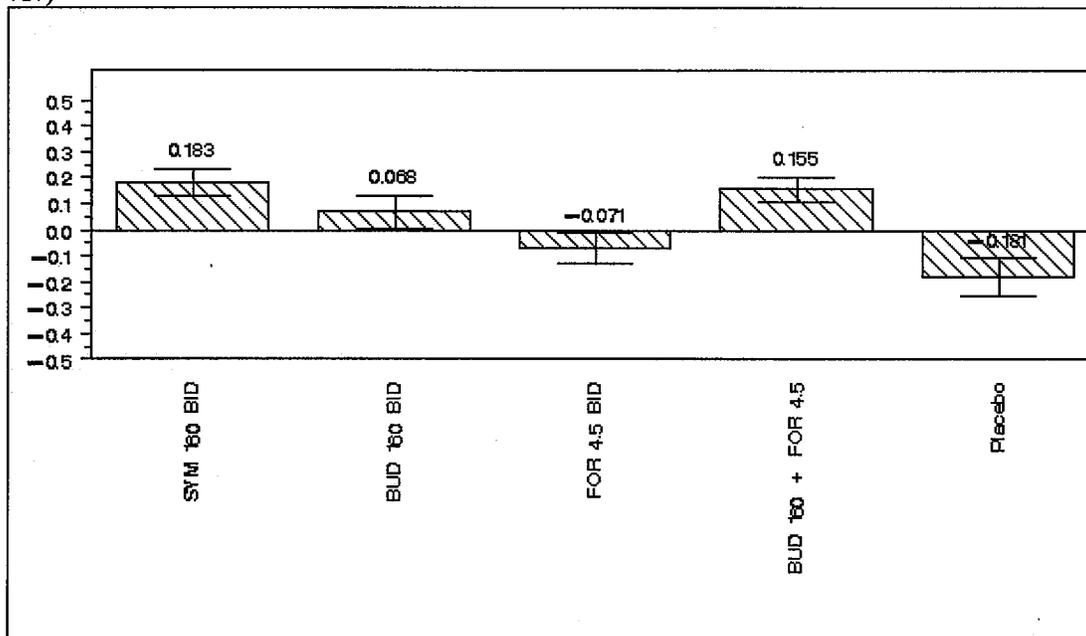
Table 9 Pre-dosing FEV₁ change from baseline with time based on Subset (Study 717)

	DoR	Week 2		Week 6			Week 12			
	#Patients	#Patients	Mean	Std.	#Patients	Mean	Std.	#Patients	Mean	Std.
SYM 160 BID	100	109	0.18	0.31	94	0.20	0.29	86	0.21	0.33
BUD 160 BID	85	102	-0.00	0.35	72	0.07	0.29	59	0.13	0.27
FOR 4.5 BID	99	117	-0.08	0.31	79	0.00	0.35	58	0.05	0.35
BUD 160 + FOR 4.5	103	112	0.18	0.27	98	0.13	0.34	87	0.17	0.30
Placebo	104	142	-0.24	0.45	62	-0.08	0.36	45	-0.07	0.33
Overall	491	582	-0.00	0.39	405	0.08	0.34	335	0.12	0.33

Source: PFT01_P11_1 for patients identified on CRF but were not withdrawn from the study

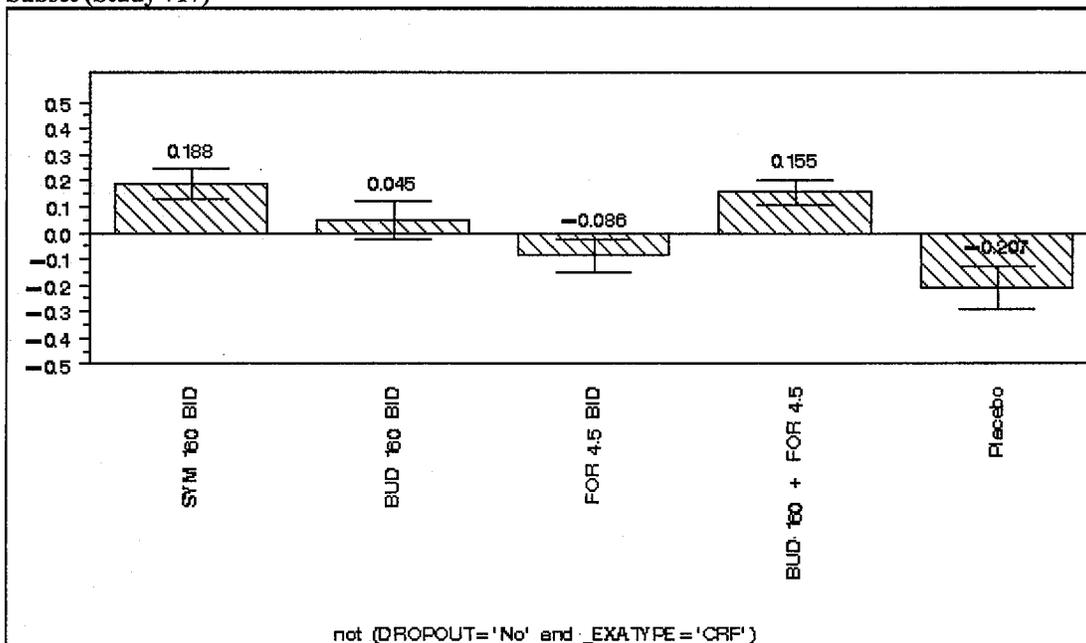
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Figure 15 Raw (unadjusted) mean change from baseline in pre-dosing FEV₁ in bar graph (Study 717)



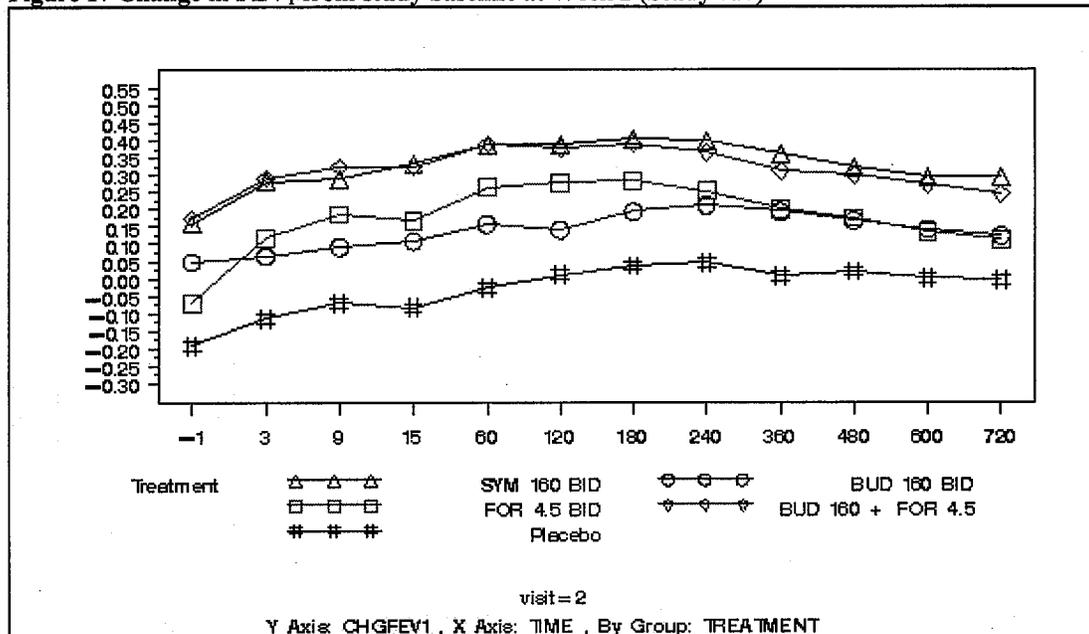
Source: PFT01_P12

Figure 16 Raw (unadjusted) mean change from baseline in pre-dosing FEV₁ in bar graph based on Subset (Study 717)



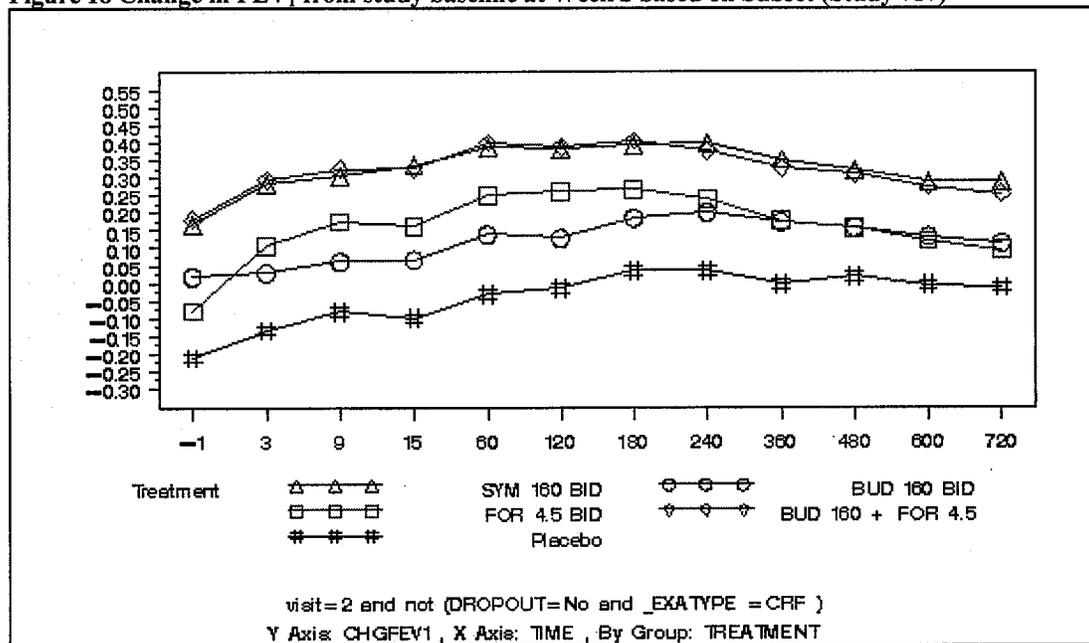
Source: PFT01_P12 for patients identified on CRF but were not withdrawn from the study

Figure 17 Change in FEV₁ from study baseline at Week 2 (Study 717)



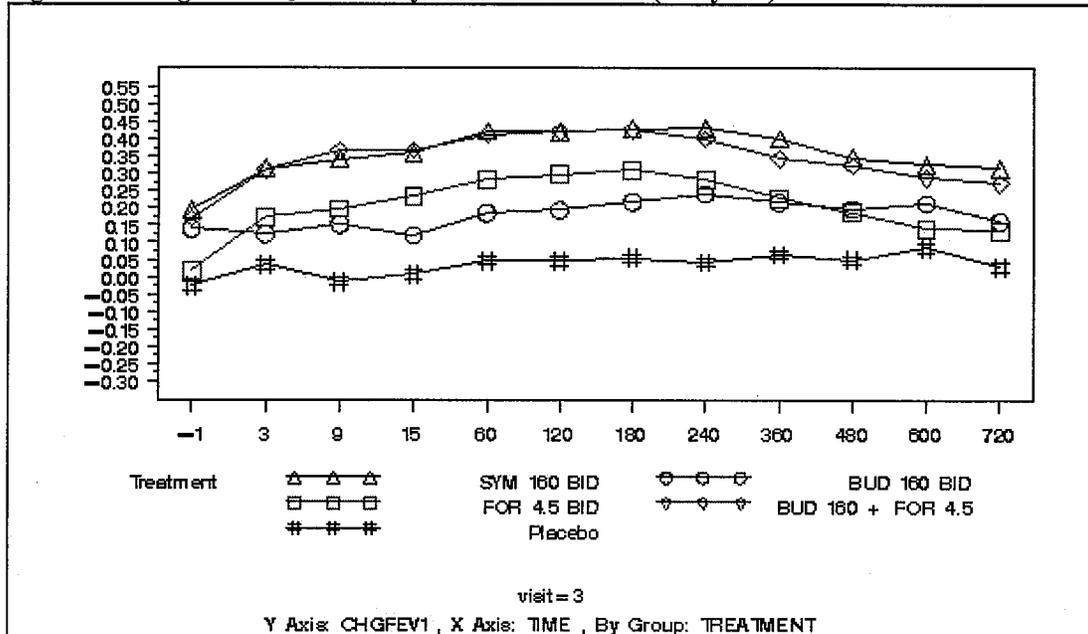
Source: PFT02_A1_1 for Week 2

Figure 18 Change in FEV₁ from study baseline at Week 2 based on Subset (Study 717)



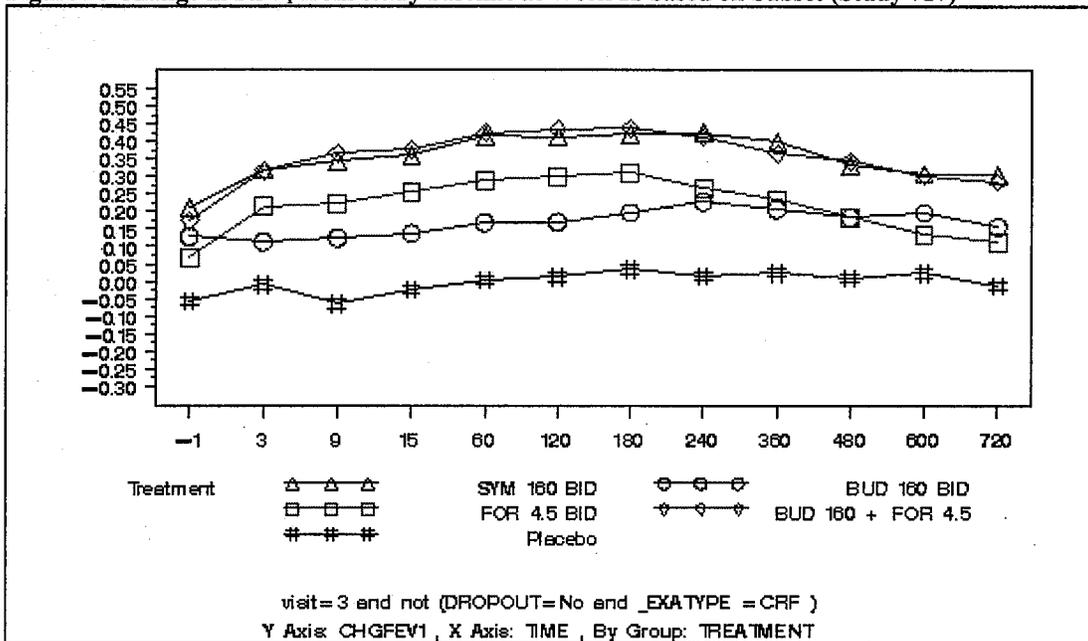
Source: PFT02_A1_1 for Week 2 for patients identified on CRF but were not withdrawn from the study

Figure 19 Change in FEV₁ from study baseline at Week 12 (Study 717)



Source: PFT02_A1_1 for Week 12

Figure 20 Change in FEV₁ from study baseline at Week 12 based on Subset (Study 717)



Source: PFT02_A1_1 for Week 12 for patients identified on CRF but were not withdrawn from the study

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/s/

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Addendum

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation Clinical Studies

NDA/Serial Number: NDA 21-929
Drug Name: SYMBICORT (Combination of budesonide 80 µg and formoterol 4.5 µg, per puff) administered as two puffs, BID
Indication(s): SYMBICORT is proposed to be indicated for the treatment of asthma in patients 12 years of age and older
Applicant: AstraZeneca
Date(s): Applicant's letter date: September 23, 2005
Review Priority: Standard

Biometrics Division: Biometrics Division 2
Statistical Reviewer: Ted Guo, Ph.D., Biometrics Division 2
Concurring Reviewers: Ruthanna Davi, M.S., Team Leader, Biometrics Division 2

Medical Division: Division of Pulmonary and Allergy Products (ODE II)
Clinical Team: Peter Stark, M.D., Medical Officers (ODE II)
Project Manager: Colette Jackson (ODE II)

Keywords: NDA review, clinical studies

Last modified: 5/23/2006

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 Figure 9 Mean change in pre-dosing FEV₁ from baseline by treatment and missing-visit status (Study 717)
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EXECUTIVE SUMMARY

Brief Overview of Clinical Studies

Symbicort® pMDI as a combination product of budesonide and formoterol is proposed to be indicated for the treatment of asthma in patients 12 years of age and older.

The primary objective of the pivotal studies in this NDA is to evaluate the effectiveness and safety of Symbicort® pMDI when comparing it with its components, budesonide (80 µg per puff via pMDI) and formoterol (4.5 µg per puff via dry power inhaler, Turbuhaler (TBH)), separately (Page 5, Section 4, SD-039-0716.pdf).

To demonstrate the effectiveness of SYMBICORT, the sponsor submitted two Phase III pivotal studies, Studies SD-039-716 (briefly 716) and SD-039-717 (briefly 717) that compared SYMBICORT with each of its components. These studies had similar designs.

They were phase III randomized, double-blind, double-dummy, placebo-controlled trials. The study drug was administered as 2 actuations twice daily. The study time line comprised a screening visit, a 14 (±7) day single-blind placebo run-in period, and a 12-week double-blind treatment period (Pages 35-36, Section 5.1, SD-039-0716.pdf).

For Study 716, at the randomization visit (Visit 2) the patient was randomized to one of the following treatment groups:

1. SYMBICORT pMDI (budesonide/formoterol) 80/4.5 mg (delivered dose) per actuation x 2 actuations administered twice daily (bid), and placebo TBH, 2 inhalations administered bid.
2. Budesonide pMDI 80 mg (delivered dose) per actuation x 2 actuations administered bid, and placebo TBH 2 inhalations administered bid.
3. Formoterol TBH 4.5 mg (delivered dose) per inhalation x 2 inhalations administered bid, and placebo pMDI 2 actuations administered bid.
4. Placebo pMDI, 2 actuations administered bid, and placebo TBH 2 inhalations administered bid.

See Section 4, SD-039-0716.pdf. Study 717 was designed in the same fashion with the following differences:

- Study 716 began with a placebo run-in period, while Study 717 started with a single-blind budesonide run-in period.
- The budesonide dose level in Study 717 was twice that in Study 716.
- Study 717 had an additional treatment arm: both budesonide and formoterol were administered separately rather than in the form of a combination drug (i.e. SYMBICORT).

For comparisons among the above treatments, two different primary efficacy variables were used. These primary efficacy variables were pre-specified by the sponsor.

- To compare Symbicort® with budesonide, the baseline-adjusted mean 12-hour FEV₁ was used to show the bronchodilatory effect contributed by formoterol.
- To compare Symbicort® with formoterol, the pre-dosing FEV₁ was used to show the anti-inflammatory effect contributed by budesonide.

The following table describes the main comparisons the sponsor intended to make.

Table 1 Main comparisons between treatments

COMPARISON	EFFECT TO TEST	EFFICACY VARIABLE TO USE
Symbicort® vs. budesonide*	Bronchodilatory effect of formoterol	Baseline-adjusted mean 12-hour FEV ₁ (AUC)
Symbicort® vs. placebo	Bronchodilatory effect of Symbicort	
Formoterol vs. placebo	Bronchodilatory effect of formoterol	
Symbicort® vs. formoterol*	Anti-inflammatory effect of budesonide	pre-dosing FEV ₁
Symbicort® vs. placebo	Anti-inflammatory effect of Symbicort	
Budesonide vs. placebo	Anti-inflammatory effect of budesonide	

*pre-specified primary efficacy comparison

All these tests were expected to demonstrate a statistically significant outcome for adequate demonstration of the efficacy of Symbicort to have been achieved.

This reviewer’s evaluation of the drug effectiveness is focused on whether the superiority of Symbicort® to its components can be demonstrated based on the sponsor’s data. Since no specific safety endpoints or hypotheses were identified by the medical division for formal statistical investigation, the safety of SYMBICORT was not the focus of this statistical review.

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Statistical Issues and Findings

The efficacy comparisons for studies 716 and 717 are described in Table 2 and consistently demonstrate the efficacy of SYMBICORT relative to each of its components and relative to placebo.

Table 2 Efficacy findings based on 12-week baseline-adjusted mean FEV₁ and pre-dosing FEV₁ (Studies 716 and 717 compared)

STATISTICAL COMPARISON: TEST OF BRONCHODILATORY EFFECT BY FORMOTEROL			STUDY 716	STUDY 717	FINDINGS CONSISTENTLY POSITIVE ACROSS STUDIES
Symbicort (80 or 160) BID vs.	Budesonide (80 or 160) BID	Efficacy variable is Week-2 baseline-adjusted AUC of FEV ₁	P=0.0003	P<0.0001	Yes
Formoterol 4.5 BID	placebo		P<0.0001	P<0.0001	Yes

STATISTICAL COMPARISON: TEST OF ANTI-INFLAMMATORY EFFECT BY BUDESONIDE			STUDY 716	STUDY 717	FINDINGS CONSISTENTLY POSITIVE ACROSS STUDIES
Budesonide (80 or 160) BID vs.	Formoterol 4.5 BID	Efficacy variable is treatment-period pre-dosing FEV ₁	P=0.0012	P<0.0001	Yes
Budesonide (80 or 160) BID vs.	placebo		P=0.0005	P<0.0001	Yes

STATISTICAL COMPARISON: EVALUATE EFFICACY OF SYMBICORT			STUDY 716	STUDY 717	FINDINGS CONSISTENTLY POSITIVE
Symbicort vs.	placebo	Efficacy variable is Week-2 baseline-adjusted AUC of FEV ₁	P<0.0001	P<0.0001	Yes
		Efficacy variable is treatment-period pre-dosing FEV ₁	P<0.0001	P<0.0001	Yes

Conclusions and Recommendations

Efficacy Conclusions:

Consistently across Studies 716 and 717, Symbicort® was shown to be statistically superior to its components and placebo.

Recommendations:

Overall, Symbicort®, administered two actuations via pMDI, BID, is recommended for approval.

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INTRODUCTION

OVERVIEW

Budesonide and formoterol are marketed in the United States and internationally for the treatment of asthma. Outside the US, SYMBICORT (a combination of the two products) is currently available as a dry powder inhaler (SYMBICORT TBH). SYMBICORT, in a fixed-combination, is administered by pMDI (a pressurized metered-dose inhaler) has been developed for those who prefer to use a pMDI or those who are unable to use dry powder inhalation devices (Page 34, Section 3 Introduction, SD-039-0716.pdf).

The purpose of this NDA was to demonstrate that SYMBICORT pMDI, combining budesonide 80 µg and formoterol 4.5 µg, administered as 2 actuations (puffs) twice daily (BID), is a safe and effective maintenance treatment for asthma in patients 12 years of age and older with mild to moderate ICS-dependent asthma. In addition, in Study 717 only, an additional treatment arm was administered both budesonide and formoterol separately rather than in the form of a combination drug for comparison with the SYMBICORT arm to demonstrate similarity in efficacy and safety.

Scope of Statistical Review: Pivotal Efficacy Studies

To demonstrate the effectiveness of SYMBICORT, the sponsor submitted two Phase III pivotal studies, Studies SD-039-716 (briefly 716) and SD-039-717 (briefly 717) that compared SYMBICORT with each of its components, budesonide and formoterol. These studies had similar designs.

Here is a description of the study design for Study 716:

Study 716 was phase III randomized, double-blind, double-dummy, placebo-controlled trial of SYMBICORT pMDI (fixed combination of 80 mg budesonide and 4.5 mg formoterol per actuation, administered as 2 actuations twice daily) versus its monoproducts, **budesonide** pMDI 80 mg per actuation, administered as 2 actuations twice daily and **formoterol** Turbuhaler (TBH), 4.5 mg per inhalation, administered as 2 inhalations twice daily, in children (≥ 6 years of age) and adults with asthma. The study comprised a screening visit, a 14 (± 7) day single-blind placebo run-in period, and a 12-week double-blind treatment period (Pages 35-36, Section 5.1, SD-039-0716.pdf).

For Study 716, at the randomization visit (Visit 2) the patient was randomized to one of the following treatment groups:

1. SYMBICORT pMDI (budesonide/formoterol) 80/4.5 mg (delivered dose) per actuation x 2 actuations administered twice daily (bid), and placebo TBH, 2 inhalations administered bid.
2. Budesonide pMDI 80 mg (delivered dose) per actuation x 2 actuations administered bid, and placebo TBH 2 inhalations administered bid.
3. Formoterol TBH 4.5 mg (delivered dose) per inhalation x 2 inhalations administered bid, and placebo pMDI 2 actuations administered bid.
4. Placebo pMDI, 2 actuations administered bid, and placebo TBH 2 inhalations administered bid.

See Section 4, SD-039-0716.pdf. Study 717 was designed in the same fashion with the following differences:

- Study 716 began with a placebo run-in period, while Study 717 started with a single-blind budesonide run-in period.
- The budesonide dose level in Study 717 was twice that in Study 716.
- Study 717 had an additional treatment arm: both budesonide and formoterol were administered separately rather than in the form of a combination drug (i.e. SYMBICORT).

For comparison among the above treatments, two different primary efficacy variables were used. These primary efficacy variables were pre-specified by the sponsor.

- To compare Symbicort® with budesonide, the baseline-adjusted mean 12-hour FEV₁ was used to show the bronchodilatory effect contributed by formoterol.
- To compare Symbicort® with formoterol, the pre-dosing FEV₁ was used to show the anti-inflammatory effect contributed by budesonide.

Table 3 Main comparisons between treatments

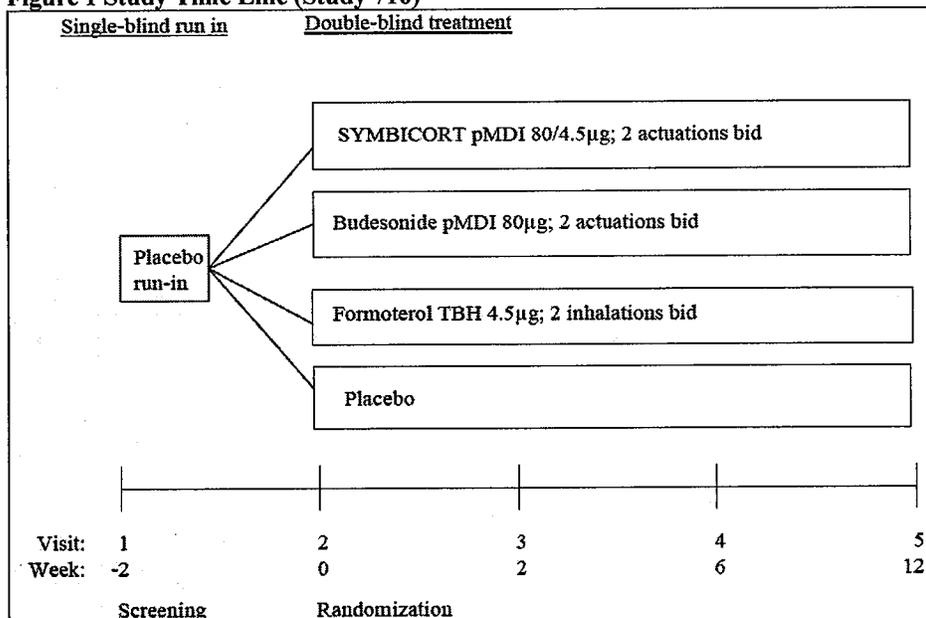
COMPARISON	EFFECT TO TEST	EFFICACY VARIABLE TO USE
Symbicort® vs. budesonide*	Bronchodilatory effect of formoterol	Baseline-adjusted mean 12-hour FEV ₁ (AUC)
Symbicort® vs. placebo	Bronchodilatory effect of Symbicort	
Formoterol vs. placebo	Bronchodilatory effect of formoterol	
Symbicort® vs. formoterol*	Anti-inflammatory effect of budesonide	pre-dosing FEV ₁
Symbicort® vs. placebo	Anti-inflammatory effect of Symbicort	
Budesonide vs. placebo	Anti-inflammatory effect of budesonide	

*pre-specified primary efficacy comparison

All these tests were expected to demonstrate a statistically significant outcome for adequate demonstration of the efficacy of Symbicort to have been achieved.

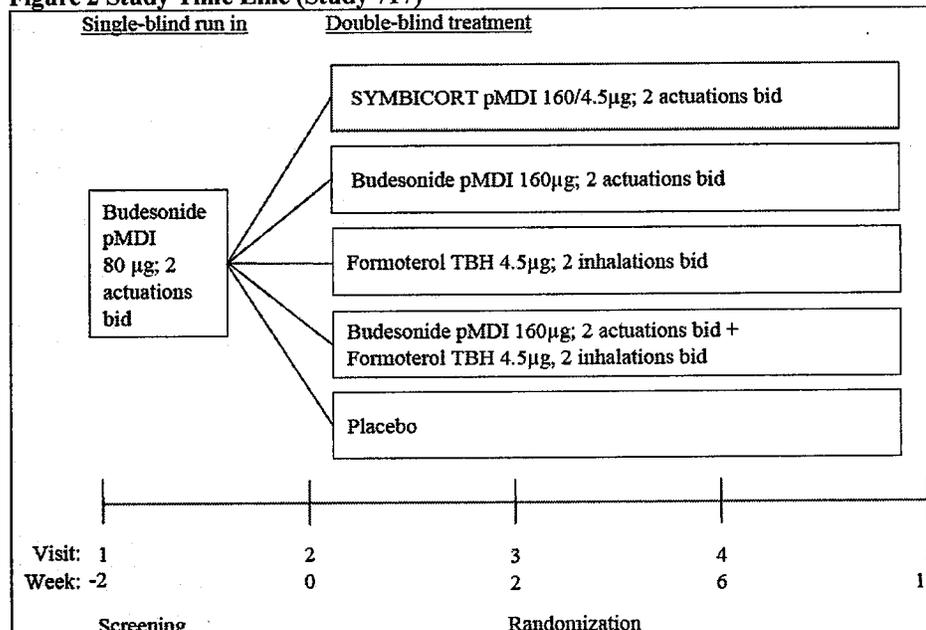
The time lines of the studies are shown in Figures 1 and 2.

Figure 1 Study Time Line (Study 716)



Source: Page 37, Section 5.1, SD-039-0716.pdf

Figure 2 Study Time Line (Study 717)



Source: Page 43, Section 5.1, SD-039-0717.pdf

DATA SOURCES

The sponsor submitted this application including the electronic datasets to the FDA Electronic Document Room (EDR). The submission is recorded in the EDR as indicated in Table 4, below. All the data submitted are in SAS v.5 transport format. The number of data files for the pivotal studies and the number of data files used in the statistical review are shown in Table 5.

Table 4 Data Source

DOCUMENT 2702535		
Application: N021929	Letter_Date: 23-Sep-2005	Stamp_Date: 23-Sep-2005
Incoming_Doc_Type: N	Sup_Modification_Type:	In_Doc_Type_Seq_No: 000
Company: ASTRAZENECA PHARMS		
Drug: SYMBICORT		

Source: EDR of FDA

Table 5 Sponsor's Data Submitted

PATH/LOCATION	NO. DATA FILES SUBMITTED	NO. DATA FILES USED IN STATISTICAL REVIEW
\\Cdsub1\N21929\N_000\2005-09-23\crt\datasets\SD-039-0716	89	5
\\Cdsub1\N21929\N_000\2005-09-23\crt\datasets\SD-039-0717	90	5

The numbers of data files used in the statistical evaluation are shown in the third column. Given the large amount of data, this reviewer selected the file(s) containing the most relevant evidence for the efficacy of the drug.

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STATISTICAL EVALUATION

EVALUATION OF EFFICACY

Study Design and Endpoints

To demonstrate the effectiveness of SYMBICORT, the sponsor submitted two Phase III pivotal studies, Studies SD-039-716 (briefly 716) and SD-039-717 (briefly 717) that compared SYMBICORT with each of its components, budesonide and formoterol. These studies had similar designs.

Here is a description of the study design for Study 716:

Study 716 was phase III randomized, double-blind, double-dummy, placebo-controlled trial of SYMBICORT pMDI (fixed combination of 80 mg budesonide and 4.5 mg formoterol per actuation, administered as 2 actuations twice daily) versus its monoproducts, **budesonide** pMDI 80 mg per actuation, administered as 2 actuations twice daily and **formoterol** Turbuhaler (TBH), 4.5 mg per inhalation, administered as 2 inhalations twice daily, in children (≥ 6 years of age) and adults with asthma. The study comprised a screening visit, a 14 (± 7) day single-blind placebo run-in period, and a 12-week double-blind treatment period (Pages 35-36, Section 5.1, SD-039-0716.pdf).

For Study 716, at the randomization visit (Visit 2) the patient was randomized to one of the following treatment groups:

1. SYMBICORT pMDI (budesonide/formoterol) 80/4.5 mg (delivered dose) per actuation x 2 actuations administered twice daily (bid), and placebo TBH, 2 inhalations administered bid.
2. Budesonide pMDI 80 mg (delivered dose) per actuation x 2 actuations administered bid, and placebo TBH 2 inhalations administered bid.
3. Formoterol TBH 4.5 mg (delivered dose) per inhalation x 2 inhalations administered bid, and placebo pMDI 2 actuations administered bid.
4. Placebo pMDI, 2 actuations administered bid, and placebo TBH 2 inhalations administered bid.

See Section 4, SD-039-0716.pdf. Study 717 was designed in the same fashion with the following difference:

- Study 716 began with a placebo run-in period, while Study started with a single-blind budesonide run-in period.
- The budesonide dose level in Study 717 was twice that in Study 716.

- Study 717 had an additional treatment arm: both budesonide and formoterol were administered separately rather than in a combination drug (i.e. SYMBICORT).

For comparisons among the above treatments, two different primary efficacy variables were used. These primary efficacy variables were pre-specified by the sponsor.

- To compare Symbicort® with budesonide, the baseline-adjusted mean 12-hour FEV₁ was used to show the bronchodilatory effect contributed by formoterol.
- To compare Symbicort® with formoterol, the pre-dosing FEV₁ was used to show the anti-inflammatory effect contributed by budesonide.

Both tests were expected to demonstrate a statistically significant outcome for adequate demonstration of the efficacy of Symbicort to have been achieved.

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Patient Distributions of Demographic and Baseline Characteristics

This section describes the patients' dispositions by treatment and based on their demographic characteristics, the status of protocol compliance, and reasons for early withdrawal from the study.

Study 716

There were 511 intent-to-treat (ITT) patients in this study. The number of patients by the status of protocol compliance and treatment are shown in the Tables 6 and 7.

Table 6 Number of patients by the status of protocol compliance and treatment (Study 716)

PER PROTOCOL ANALYSIS SET	TREATMENT								TOTAL	
	SYM 80 BID		BUD 80 BID		FOR 4.5 BID		Placebo		N	%
	N	%	N	%	N	%	N	%		
Yes	118	90.77	113	88.98	110	89.43	118	90.08	459	89.82
No	12	9.23	14	11.02	13	10.57	13	9.92	52	10.18
Total	130	100.00	127	100.00	123	100.00	131	100.00	511	100.00

Source: DEMO (patients in all ages)

Table 7 Number of patients aged 12 years and older by the status of protocol compliance and treatment (Study 716)

PER PROTOCOL ANALYSIS SET FOR PATIENTS ≥12 YEARS	TREATMENT								TOTAL	
	SYM 80 BID		BUD 80 BID		FOR 4.5 BID		Placebo		N	%
	N	%	N	%	N	%	N	%		
Yes	118	95.93	113	93.39	110	96.49	118	96.72	459	95.63
No	5	4.07	8	6.61	4	3.51	4	3.28	21	4.38
Total	123	100.00	121	100.00	114	100.00	122	100.00	480	100.00

Source: DEMO (Patients aged ≥12 years)

The patients aged 12 years and older comprised 94% of the total ITT patients (480/511=0.94). Since the label claims is based on this group of patients and this is the pre-specified age group to be used in the primary efficacy analysis, they are the focus of the statistical evaluation.

The overall percentages of patients aged 12 years and older without major protocol violations across the treatment groups were found to be above 95%. The proportion of subjects aged 12 years and older who are included in the per protocol analysis set appears to be balanced across treatments.

Tables 8 and 9 display the number of subjects aged 12 years and older who withdrew early and the frequencies of each reason for early withdrawal, respectively.

Table 8 Number of completing patients by treatment (Study 716)

EARLY WITHDRAWAL	TREATMENT								TOTAL	
	SYM 80 BID		BUD 80 BID		FOR 4.5 BID		Placebo			
	N	%	N	%	N	%	N	%	N	%
Yes	18	14.63	18	14.88	35	30.70	62	50.82	133	27.71
No	105	85.37	103	85.12	79	69.30	60	49.18	347	72.29
Total	123	100.00	121	100.00	114	100.00	122	100.00	480	100.00

Source: DEMO, DISP (patient ages ≥ 12 years)

The overall percentage of the early withdrawals among all the subjects 12 years of age and older was 27.7%, representing nearly 1/3 of the subjects 12 years of age and older in this study. Such high rate of early withdrawals might be partially explained by the original study protocol: In the original study protocol, one of the co-primary efficacy variables was defined as the withdrawal due to pre-defined asthma event. It was reasonable to anticipate that such number could be relatively large in the formoterol and placebo groups – in order for this variable to be tangible enough to measure. The following table might somewhat justify or explain this reviewer's observation.

Table 9 Reasons reported for early withdrawal (Study 716)

MAIN REASONS FOR* EARLY WITHDRAWAL	TREATMENT				TOTAL
	SYM 80 BID	BUD 80 BID	FOR 4.5 BID	Placebo	
	N	N	N	N	N
Adverse Event	4	3	3	11	21
Development of Study-Specific Discontinuation Criteria	9	8	21	40	78
Eligibility Criteria not Fulfilled	0	1	0	0	1
Subject not Willing to Continue Study	3	4	6	6	19
Other	2	2	5	5	14
Total	18	18	35	62	133

Source: DEMO, DISP (patient ages ≥ 12 years)

*: The listed reasons for early withdrawal are as reported by the sponsor in the electronic datasets. The number of early withdrawal appeared to be higher in the placebo group and possibly the formoterol group than in other groups. The most common reason for early withdrawal across treatments was “development of study-specific discontinuation criteria”. The number of early withdrawals due to adverse events appeared to be higher in the placebo group than in other groups, indicating the early withdrawal might not be closely associated with the active treatments.

Unfortunately no exact definitions or further explanations for the terms used to describe the reasons for early withdrawal in the electronic data sets have been found in the application. This reviewer was unable to interpret exactly what the listed reasons mean except for those self-explanatory ones, such as “adverse event.” Therefore, it is difficult to further analyze the early-withdrawal data for the reasons stated above.

Tables 10 through 13 are populated by the numbers and percentages of patients by treatment and demographic characteristics, such as race and sex. No obvious imbalances in these factors across treatment groups were observed.

Table 10 Number of patients by treatment and race (Study 716)

RACE	TREATMENT								TOTAL	
	SYM 80 BID		BUD 80 BID		FOR 4.5 BID		Placebo			
	N	%	N	%	N	%	N	%	N	%
Black	9	7.32	11	9.09	11	9.65	8	6.56	39	8.13
Caucasian	108	87.80	102	84.30	100	87.72	111	90.98	421	87.71
Oriental			1	0.83	1	0.88	1	0.82	3	0.63
Other	6	4.88	7	5.79	2	1.75	2	1.64	17	3.54
Total	123	100.00	121	100.00	114	100.00	122	100.00	480	100.00

Source: DEMO (patient ages ≥ 12 years)

Table 11 Number of patients by treatment and sex (Study 716)

SEX	TREATMENT								TOTAL	
	SYM 80 BID		BUD 80 BID		FOR 4.5 BID		Placebo			
	N	%	N	%	N	%	N	%	N	%
Female	77	62.60	75	61.98	72	63.16	75	61.48	299	62.29
Male	46	37.40	46	38.02	42	36.84	47	38.52	181	37.71
Total	123	100.00	121	100.00	114	100.00	122	100.00	480	100.00

Source: DEMO (patient ages ≥ 12 years)

Table 12 Analysis of patient-age distribution by treatment (Study 716)

TREATMENT	#PATIENTS	MEAN	MIN	MAX	LOWER QUARTILE	UPPER QUARTILE
SYM 80 BID	130	35.64	6.00	77.00	20.00	50.00
BUD 80 BID	127	35.78	7.00	78.00	19.00	49.00
FOR 4.5 BID	123	33.44	7.00	73.00	18.00	46.00
Placebo	131	34.15	6.00	66.00	21.00	46.00
Overall	511	34.76	6.00	78.00	20.00	48.00

Source: DEMO (patients in all ages)

Table 13 Analysis of patient-age distribution by treatment for patients 12 years and older (Study 716)

TREATMENT	#PATIENTS	MEAN	MIN	MAX	LOWER QUARTILE	UPPER QUARTILE
SYM 80 BID	123	37.20	12.00	77.00	20.00	50.00
BUD 80 BID	121	37.12	12.00	78.00	19.00	49.00
FOR 4.5 BID	114	35.34	12.00	73.00	18.00	46.00
Placebo	122	36.07	12.00	66.00	21.00	46.00
Overall	480	36.45	12.00	78.00	23.00	48.00

Source: DEMO (patient ages ≥ 12 years)

The baseline was defined as the pre-dosing FEV₁ on the day of randomization. The following tables show the baseline FEV₁ by treatment. The baseline FEV₁ was used in the sponsor's statistical analyses as a covariate.

Table 14 Baseline FEV₁ (Study 716)

TREATMENT	#PATIENTS	MEAN	STD
SYM 80 BID	129	2.36	0.63
BUD 80 BID	122	2.29	0.60
FOR 4.5 BID	112	2.39	0.63
Placebo	118	2.40	0.64

Source: PFT01_P12 (patients in all ages)

Table 15 Baseline FEV₁ (Study 716)

TREATMENT	#PATIENTS	MEAN	STD
SYM 80 BID	122	2.40	0.62
BUD 80 BID	116	2.32	0.60
FOR 4.5 BID	105	2.41	0.63
Placebo	111	2.43	0.64

Source: PFT01_P12 (patient ages ≥ 12 years)

The baseline average scores appear to be balanced across the treatment groups.

Study 717

There were 596 ITT patients in this study. The number of patients by the status of protocol compliance and treatment are shown in Tables 16 and 17.

Table 16 Number of patients by the status of protocol compliance and treatment (Study 717)

PER PROTOCOL ANALYSIS SET	TREATMENT										TOTAL	
	SYM 160 BID		BUD 160 BID		FOR 4.5 BID		BUD 160 + FOR 4.5		Placebo		N	%
	N	%	N	%	N	%	N	%	N	%		
Yes	108	87.10	97	88.99	109	88.62	107	93.04	110	88.00	531	89.09
No	16	12.90	12	11.01	14	11.38	8	6.96	15	12.00	65	10.91
Total	124	100.00	109	100.00	123	100.00	115	100.00	125	100.00	596	100.00

Source: DEMO (patients in all ages)

The overall percentages of patients without major protocol violations across the treatment groups were found to be above 89%. The proportion of subjects who are included in the pre protocol analysis set appears to be balanced across treatments.

Tables 18 and 19 display the number of subjects withdrawn early and the frequencies of each reason for early withdrawal.

Table 17 Number of completing patients by treatment (Study 717)

EARLY WITHDRAWAL	TREATMENT										TOTAL	
	SYM 160 BID		BUD 160 BID		FOR 4.5 BID		BUD 160 + FOR 4.5		Placebo		N	%
	N	%	N	%	N	%	N	%	N	%		
Yes	27	21.77	31	28.44	63	51.22	29	25.22	75	60.00	225	37.75
No	97	78.23	78	71.56	60	48.78	86	74.78	50	40.00	371	62.25
Total	124	100.00	109	100.00	123	100.00	115	100.00	125	100.00	596	100.00

Source: DEMO, DISP

The overall percentage of the early withdrawals among all the patients was 37.8%, representing over 1/3 of the total patients in this study. Such high rate of early withdrawals might be partially explained by the original study protocol: In the original study protocol, one of the co-primary efficacy variables was defined as the withdrawal due to pre-defined asthma event. It was reasonable to anticipate that such number could be relatively large in the formoterol and placebo groups – in order for this variable to be tangible enough to measure. The following table might somewhat justify or explain this reviewer’s observation.

Table 18 Reasons reported for early withdrawal (Study 717)

MAIN REASONS FOR* EARLY WITHDRAWAL	TREATMENT					TOTAL N
	SYM 160 BID	BUD 160 BID	FOR 4.5 BID	BUD 160 + FOR 4.5	Placebo	
	N	N	N	N	N	
Adverse Event	8	4	5	9	4	30
Development of Study-Specific Discontinuation	13	22	44	13	62	154
Eligibility Criteria not Fulfilled	2		2	1	1	6
Subject Lost to Follow-up	1		1	2		4
Subject not Willing to Continue Study	3	2	7	1	6	19
Other		3	4	3	2	12
Total	27	31	63	29	75	225

Source: DEMO, DISP

*: The listed reasons for early withdrawal are as reported by the sponsor in the electronic datasets. The number of early withdrawals was high in all groups but highest in the placebo (60%) and formoterol (51%) groups. Such numbers for the formoterol and placebo groups, on average, are about two fold of those for the other groups. The majority of the early withdrawals were due to **Development of Study-Specific Discontinuation**.

Unfortunately no exact definitions or further explanations for the terms used to describe the reasons for early withdrawal in the electronic data sets have been found in the application. This reviewer was unable to interpret exactly what the listed reasons mean except for those self-explanatory ones, such as “adverse event.” Therefore, it is difficult to further analyze the early-withdrawal data for the reasons stated above.

Tables 19 through 21 are populated by the numbers and percentages of patients by treatment and demographic characteristics, such as race and sex. No obvious imbalances in these factors across treatment groups were observed.

Table 19 Number of patients by treatment and race (Study 717)

RACE	TREATMENT										TOTAL	
	SYM 160 BID		BUD 160 BID		FOR 4.5 BID		BUD 160 + FOR 4.5		Placebo			
	N	%	N	%	N	%	N	%	N	%	N	%
Black	18	14.52	17	15.60	21	17.07	20	17.39	20	16.00	96	16.11
Caucasian	98	79.03	84	77.06	91	73.98	89	77.39	101	80.80	463	77.68
Oriental			3	2.75	3	2.44	2	1.74	1	0.80	9	1.51
Other	8	6.45	5	4.59	8	6.50	4	3.48	3	2.40	28	4.70
Total	124	100.00	109	100.00	123	100.00	115	100.00	125	100.00	596	100.00

Source: DEMO

Table 20 Number of patients by treatment and sex (Study 717)

SEX	TREATMENT										TOTAL	
	SYM 160 BID		BUD 160 BID		FOR 4.5 BID		BUD 160 + FOR 4.5		Placebo			
	N	%	N	%	N	%	N	%	N	%	N	%
Female	80	64.52	71	65.14	80	65.04	65	56.52	72	57.60	368	61.74
Male	44	35.48	38	34.86	43	34.96	50	43.48	53	42.40	228	38.26
Total	124	100.00	109	100.00	123	100.00	115	100.00	125	100.00	596	100.00

Source: DEMO

Table 21 Analysis of patient-age distribution by treatment (Study 717)

TREATMENT	#PATIENTS	MEAN	MIN	MAX	LOWER QUARTILE	UPPER QUARTILE
SYM 160 BID	124	41.75	12.00	74.00	30.50	52.50
BUD 160 BID	109	40.70	12.00	80.00	30.00	51.00
FOR 4.5 BID	123	39.99	12.00	87.00	28.00	50.00
BUD 160 + FOR 4.5	115	40.26	13.00	75.00	28.00	51.00
Placebo	125	41.94	12.00	75.00	33.00	53.00
Overall	596	40.95	12.00	87.00	30.00	51.50

Source: DEMO

The baseline was defined as the pre-dosing FEV₁ on the day of randomization. The following tables show the baseline FEV₁ by treatment. The baseline FEV₁ was used in the sponsor's statistical analyses as a covariate.

Table 22 Baseline FEV₁ (Study 717)

TREATMENT	#PATIENTS	MEAN	STD
SYM 160 BID	117	2.23	0.72
BUD 160 BID	108	2.30	0.64
FOR 4.5 BID	114	2.19	0.59
BUD 160 + FOR 4.5	111	2.23	0.62
Placebo	116	2.29	0.69

Source: PFT01_P12

The baseline average scores appear to be balanced across the treatment groups.

Statistical Methodologies

Statistical Analyses

Statistical Hypotheses

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

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

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

Rejection of this hypothesis required that SYMBICORT pMDI be superior to budesonide at the 5% level with respect to baseline-adjusted average 12-hour FEV₁ and also that SYMBICORT pMDI be superior to formoterol at the 5% level with respect to pre-dosing FEV₁. If H_{1null} was rejected, then testing was to continue.

Next, budesonide was to be tested versus placebo for pre-dosing FEV₁, and formoterol was to be tested versus placebo for baseline-adjusted average 12-hour FEV₁. 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 (Page 88, Section 5.7.2.1 Co-primary variables, SD-039-0716.pdf).”

The use of co-primary efficacy variables

“To support the primary objective, efficacy was determined by the co-primary endpoints of baseline-adjusted 12-hour FEV₁ and pre-dosing FEV₁. Together, the use of these co-primary variables was planned to demonstrate the superior efficacy profile of SYMBICORT pMDI over each of its monoprotect components. Baseline-adjusted average 12-hour FEV₁ was used to demonstrate the bronchodilatory effect of SYMBICORT pMDI, largely contributed by the formoterol component. Thus, it was expected that SYMBICORT pMDI would be statistically significantly more efficacious than budesonide alone in this variable.

Pre-dosing FEV₁ was used to demonstrate the stabilizing, anti-inflammatory effect of SYMBICORT pMDI, largely contributed by the budesonide component. Thus, it was expected that SYMBICORT pMDI would be statistically significantly more efficacious than formoterol alone in this variable.

As specified in the statistical analysis plan (SAP) (Appendix 12.1.9), the analyses of the secondary endpoints are primarily intended to show that SYMBICORT pMDI and each of its components differ from placebo in terms of improvement in efficacy and patient

reported outcomes (PROs). In addition, the analyses of the secondary endpoints are intended to describe the relationship between SYMBICORT pMDI and its components in terms of efficacy and PROs and to characterize the safety profile of SYMBICORT pMDI relative to its components and to placebo (Page 87, Section 5.7 Statistical methods and determination of sample size, SD-039-0716.pdf).”

Primary statistical analysis methods for the primary efficacy variables

Co-primary variable 1: Baseline-adjusted average 12-hour FEV₁

For the primary analysis of baseline-adjusted average 12-hour FEV₁ at the end of Week 2 LOCF time point (using WV Pre-CF extrapolation), SYMBICORT pMDI was compared to budesonide using the efficacy analysis set for subjects ≥ 12 years of age with an ANCOVA (analysis of covariance) model, adjusting for the fixed factors of center and treatment and for the covariate of baseline (Visit 2 pre-dosing) FEV₁. Treatment comparisons (LS mean differences, 95% confidence intervals, and p-values) were made by formulating contrasts within the context of this model.

Detailed description of WV Pre-CF extrapolation can be found in the Appendix.

Co-primary variable 2: Pre-dosing FEV₁

For the primary analysis of change from baseline to the average pre-dosing FEV₁ value over the double-blind treatment period, SYMBICORT pMDI was compared to formoterol using the efficacy analysis set for subjects ≥ 12 years of age with an ANCOVA model, adjusting for the fixed factors of center and treatment and for the covariate of baseline (Visit 2 pre-dosing) FEV₁. Treatment comparisons (LS mean differences, 95% confidence intervals, and p-values) were made by formulating contrasts within the context of this model (Page 93, Section 5.7.4.1 Primary statistical analysis methods for the primary efficacy variables, SD-039-0716.pdf).

Note that the definition for pre-dosing FEV₁ eliminates the need to formally impute missing values, because the averaging of pre-dosing FEV₁ only counts on non-missing FEV₁ values. This approach assumes that each subject’s missing values, if observed, would, on average, have been equal to the average of that subject’s observed values.

Study 716

Evaluation of the bronchodilatory effect of Symbicort® contributed by formoterol

ANCOVA (analysis of covariance) was done by this reviewer to evaluate the bronchodilatory effect of Symbicort® contributed by formoterol. For this purpose, Week-2 baseline-adjusted average 12-hour FEV₁ was analyzed as the efficacy variable using the methods pre-specified for the primary efficacy comparison. As the primary comparison, **SYM 80 BID** was compared with **BUD 80 BID**. Other outcomes of the analysis were secondary. Only patients aged 12 years and older were included in the analysis.

Tables 24 through 26 provide selected results from the ANCOVA using SAS. The data source was PFT02_A2, a subset analysis data set based on the sponsor's data set _PFT02. PFT02_A2 was created by using the primary efficacy variable with WV Pre-CF (within-visit pre-dosing value carried forward) treatment of missing data.

Table 23 Number of patients included in the analysis (Study 716)

NUMBER OF PATIENTS IN DATA SETS		
PFT02	Sponsor's efficacy data	511
PFT02_A2	Subset of _PFT02 using WV Pre-CF for missing data	457
	Subset of PFT02_A2 for patients aged ≥ 12 years	431

Source: PFT02_A2 for patients aged ≥ 12 years. PFT02_A2 is a subset of _PFT02 where _TIMEPTX="Week 2" and _STMPT=720.

Reviewer's Comment:

Note from Table 23 that the number of patients used in the analysis is 10% (457/511) smaller than the 511 ITT patients. It appears that the sponsor did not report data for all subjects even when the missing data were handled using WV Pre-CF approach. This discrepancy may explain the quantitative differences in the efficacy results described in this review and those presented by the sponsor in the study report. However, the statistical conclusions from the efficacy analyses presented here are not different from those present in the study report.

Table 24 ANCOVA Tests of fixed effects (Study 716)

TYPE 3 TESTS OF FIXED EFFECTS				
Effect	Num DF	Den DF	F Value	Pr > F
TREATMENT	3	372	16.82	<.0001
CENTER	54	372	1.70	0.0025
BFEV1	1	372	0.75	0.3862

Source: PFT02_A2 for patients aged ≥ 12 years

Table 25 ANCOVA Least squares means* (Study 716)

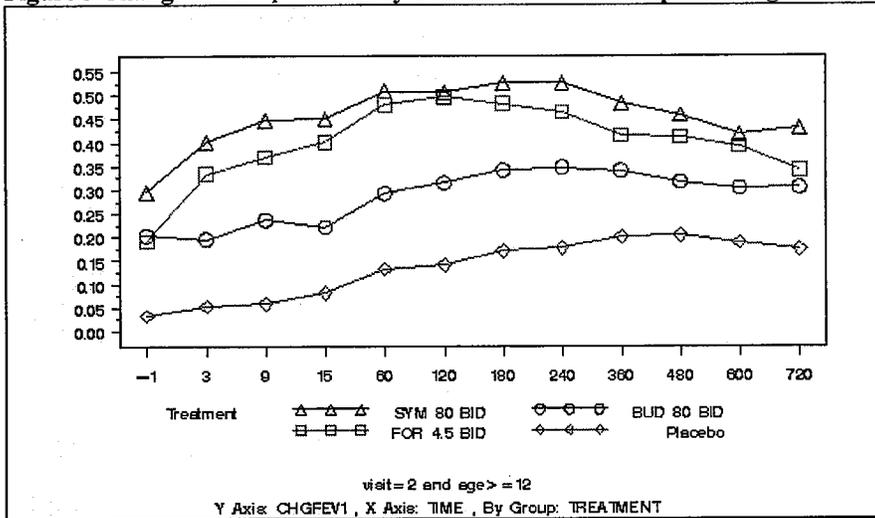
TREATMENT	ESTIMATE	STANDARD ERROR	DF	T VALUE	PR > T	ALPHA	LOWER	UPPER
SYM 80 BID	0.4417	0.03785	372	11.67	<.0001	0.05	0.3672	0.5161
BUD 80 BID	0.2679	0.03893	372	6.88	<.0001	0.05	0.1913	0.3444
FOR 4.5 BID	0.3836	0.04093	372	9.37	<.0001	0.05	0.3031	0.4641
Placebo	0.1064	0.04226	372	2.52	0.0122	0.05	0.02333	0.1895

Source: PFT02_A2 for patients aged ≥ 12 years

*: LS means of baseline-adjusted average 12-hour FEV₁ at Week 2 using the WV Pre-CF approach for missing data

Figure 3 depicts the average changes in FEV₁ at Week 2 from study baseline (pre-dosing FEV₁ at randomization) for the 454 patients aged 12 and older.

Figure 3 Change in FEV₁ from study baseline at Week 2 for patients aged 12 and older (Study 716)



Source:
PFT02_A1_1
(454 patients'
data used)

Symbicort appeared to have larger AUC than budesonide did, and both Symbicort and formoterol appeared to have larger AUC than placebo did.

Table 26 ANCOVA differences of least squares means (Study 716)

DIFFERENCES OF LEAST SQUARES MEANS									
Treatment	Treatment	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
SYM 80 BID	BUD 80 BID	0.1738	0.04724	372	3.68	0.0003*	0.05	0.08089	0.2667
SYM 80 BID	FOR 4.5 BID	0.05807	0.04887	372	1.19	0.2355	0.05	-0.03803	0.1542
SYM 80 BID	Placebo	0.3352	0.05018	372	6.68	<.0001	0.05	0.2366	0.4339
BUD 80 BID	FOR 4.5 BID	-0.1157	0.04965	372	-2.33	0.0203	0.05	-0.2133	-0.01809
BUD 80 BID	Placebo	0.1614	0.05080	372	3.18	0.0016	0.05	0.06156	0.2613
FOR 4.5 BID	Placebo	0.2772	0.05243	372	5.29	<.0001	0.05	0.1741	0.3802

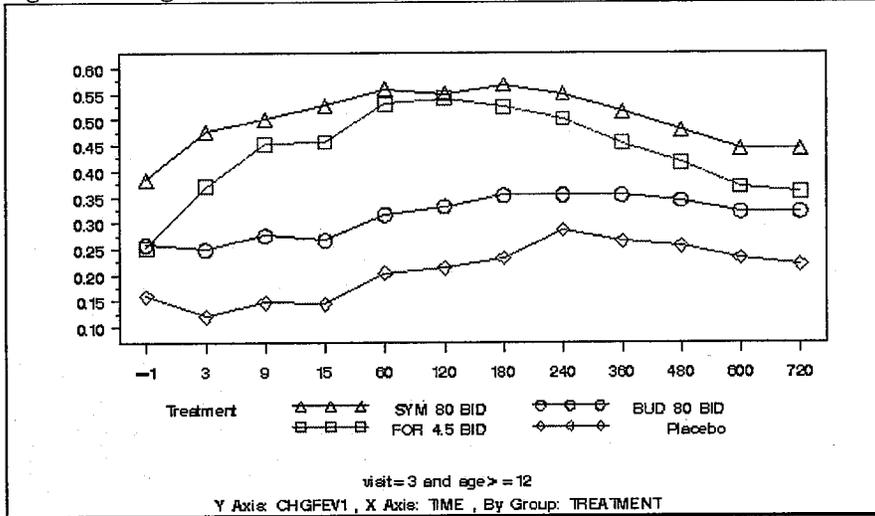
Source: PFT02_A2 for patients aged ≥12 years. *primary efficacy comparison

The comparison between SYM 80 BID and BUD 80 BID demonstrated that SYM 80 BID was statistically superior to BUD 80 BID with a p-value of 0.0003, showing a statistically significant bronchodilatory effect of Symbicort® contributed by formoterol. Formoterol itself was shown to be statistically superior to placebo with a p-value of <0.0001.

Figure 4 depicts the changes in FEV₁ at Week 12 from study baseline (pre-dosing FEV₁ at randomization) for patients aged 12 and older. This graphic incorporates data from 357 subjects (rather than the 454 incorporated into Figure 3). Assuming that subjects who are included in Figure 3 but not in Figure 4 would not have expressed values very

different from those included in both graphics, this graph shows that the differences among treatments are similar with those from Week 2 data.

Figure 4 Change in FEV₁ from study baseline at Week 12 for patients aged 12 and older (Study 716)



Source:
PFT02_A1_1
(357 patients'
data used)

Evaluation of the anti-inflammatory effect of Symbicort® contributed by budesonide

ANCOVA (analysis of covariance) was done by this reviewer to evaluate the anti-inflammatory effect of Symbicort® contributed by budesonide. For this purpose, the change from baseline in pre-dosing FEV₁ to the average over the treatment period was analyzed as the efficacy variable using the methods pre-specified for the primary efficacy comparison. As the primary comparison, **SYM 80 BID** was compared with **FOR 4.5 BID**. Other outcomes of the analysis were secondary. Only patients aged 12 years and older were included in the analysis.

Tables 30 through 32 provide selected results from the ANCOVA using SAS. The data source was PFT02_P12, a subset analysis data set based on the sponsor's data set _PFT01. PFT02_P12 was created by subsetting _PFT01 using the data of treatment-period average pre-dosing FEV₁ (_TIMEPTX= "Trt Avg Post-dosing"). Tables 28 and 29 and Figure 5 include unadjusted results for pre-dosing FEV₁ and change from baseline in pre-dosing FEV₁.

Table 27 Number of patients included in the analysis (Study 716)

NUMBER OF PATIENTS IN DATA SETS		
PFT01	Sponsor's efficacy data	511
PFT02_P12	Subset of PFT01 using Trt Avg Post-dosing	481
	Subset of PFT01 using Trt Avg Post-dosing for patients aged ≥12 years	454

Source: _PFT01, PFT02_P12, a subset of _PFT01 where _TIMEPTX="Trt Avg Pre-dosing".

Reviewer’s Comment:

Note from Table 27 that the number of patients used in the analysis is 11% (454/511) smaller than the 511 ITT patients. It appears that the sponsor did not report data for all subjects for treatment-period average pre-dosing FEV₁. This discrepancy may explain the quantitative differences in the efficacy results described in this review and those presented by the sponsor in the study report. The statistical conclusions from the efficacy analyses presented here are not different from those present in the study report.

Table 28 Unadjusted pre-dosing FEV₁ (Study 716)

TREATMENT	#PATIENTS	MEAN	STD
SYM 80 BID	122	2.74	0.67
BUD 80 BID	116	2.55	0.65
FOR 4.5 BID	105	2.59	0.73
Placebo	111	2.47	0.76

Source: PFT01_P12 for patients aged ≥12 years

Table 29 Unadjusted change from baseline in pre-dosing FEV₁ (Study 716)

TREATMENT	#PATIENTS	MEAN	STD
SYM 80 BID	122	0.34	0.34
BUD 80 BID	116	0.23	0.37
FOR 4.5 BID	105	0.18	0.39
Placebo	111	0.04	0.38

Source: PFT01_P12 for patients aged ≥12 years

The same information shown in above table can be visualized in the following graph.

Figure 5 Unadjusted change from baseline in pre-dosing FEV₁ in graph (Study 716)

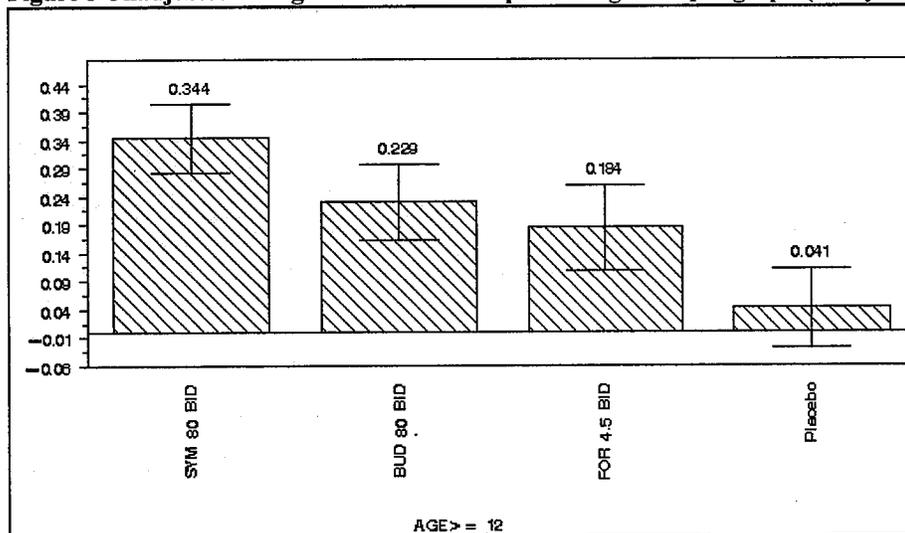


Table 30 ANCOVA Tests of fixed effects (Study 716)

TYPE 3 TESTS OF FIXED EFFECTS				
Effect	Num DF	Den DF	F Value	Pr > F
TREATMENT	3	395	13.56	<.0001
CENTER	54	395	1.30	0.0855
_BFEV1	1	395	0.95	0.3309

Source: PFT01_P12 for patients aged ≥ 12 years

Table 31 ANCOVA Least squares means (Study 716)

LEAST SQUARES MEANS*									
Effect	Treatment	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
TREATMENT	SYM 80 BID	0.3203	0.03856	395	8.31	<.0001	0.05	0.2445	0.3961
TREATMENT	BUD 80 BID	0.1845	0.03936	395	4.69	<.0001	0.05	0.1071	0.2619
TREATMENT	FOR 4.5 BID	0.1586	0.04139	395	3.83	0.0001	0.05	0.07727	0.2400
TREATMENT	Placebo	0.01131	0.04052	395	0.28	0.7803	0.05	-0.06835	0.09097

Source: PFT02_P12 for patients aged ≥ 12 years

*: LS means of change from baseline in pre-dosing FEV₁

Table 32 ANCOVA differences of least squares means (Study 716)

TREATMENT	TREATMENT	ESTIMATE	STANDARD ERROR	DF	T VALUE	PR > T	ALPHA	LOWER	UPPER
SYM 80 BID	BUD 80 BID	0.1359	0.04819	395	2.82	0.0051	0.05	0.04111	0.2306
SYM 80 BID	FOR 4.5 BID	0.1617	0.04967	395	3.26	0.0012*	0.05	0.06403	0.2593
SYM 80 BID	Placebo	0.3090	0.04862	395	6.36	<.0001	0.05	0.2134	0.4046
BUD 80 BID	FOR 4.5 BID	0.02583	0.05037	395	0.51	0.6084	0.05	-0.07320	0.1249
BUD 80 BID	Placebo	0.1732	0.04910	395	3.53	0.0005	0.05	0.07662	0.2697
FOR 4.5 BID	Placebo	0.1473	0.05070	395	2.91	0.0039	0.05	0.04766	0.2470

Source: PFT02_P12 for patients aged ≥ 12 years. * primary efficacy comparison

The comparison between SYM 80 BID and FOR 4.5 BID demonstrated that SYM 80 BID was statistically superior to FOR 4.5 BID with a p-value of 0.0012, showing a statistically significant anti-inflammatory effect of Symbicort® contributed by budesonide.

Study 717

Evaluation of the bronchodilatory effect of Symbicort® contributed by formoterol

ANCOVA (analysis of covariance) was done by this reviewer to evaluate the bronchodilatory effect of Symbicort® contributed by formoterol. For this purpose, Week-2 baseline-adjusted average 12-hour FEV₁ was analyzed as the efficacy variable using the methods pre-specified for the primary efficacy comparison. As the primary comparison, **SYM 160 BID** was compared with **BUD 160 BID**. Other outcomes of the analysis were secondary.

Tables 34 through 36 provide selected results from the ANCOVA using SAS. The data source was PFT02_A2, a subset analysis data set based on the sponsor's data set _PFT02. PFT02_A2 was created by using the primary efficacy variable with WV Pre-CF (within-visit pre-dosing value carried forward) treatment of missing data.

Table 33 Number of patients included in the analysis (Study 717)

NUMBER OF PATIENTS IN DATA SETS			
PFT02	Sponsor's efficacy data	596	
PFT02_A2	Subset of _PFT02 using WV Pre-CF for missing data	526	
	#Patients in PFT02_A2 by treatment	No.	%
	SYM 160 BID	113	21.48
	BUD 160 BID	100	19.01
	FOR 4.5 BID	107	20.34
	BUD 160 + FOR 4.5	108	20.53
	Placebo	98	18.63
	Total	526	100

Source: _PFT02; PFT02_A2, a subset of _PFT02 where _TIMEPTX="Week 2" and _STMPT=720.

Reviewer's Comment:

Note from Table 33 that the number of patients used in the analysis is 12% (526/596) smaller than the 596 ITT patients. It appears that the sponsor did not report data for all subjects even when the missing data were handled using **WV Pre-CF** approach. This discrepancy may explain the quantitative differences in the efficacy results described in this review and those presented by the sponsor in the study report. The statistical conclusions from the efficacy analyses presented here are not different from those presented in the study report.

Table 34 ANCOVA Tests of fixed effects (Study 717)

TYPE 3 TESTS OF FIXED EFFECTS				
Effect	Num DF	Den DF	F Value	Pr > F
TREATMENT	4	451	25.50	<.0001
CENTER	74	451	1.09	0.2943
BFEV1	1	451	0.00	0.9464

Source: PFT02_A2

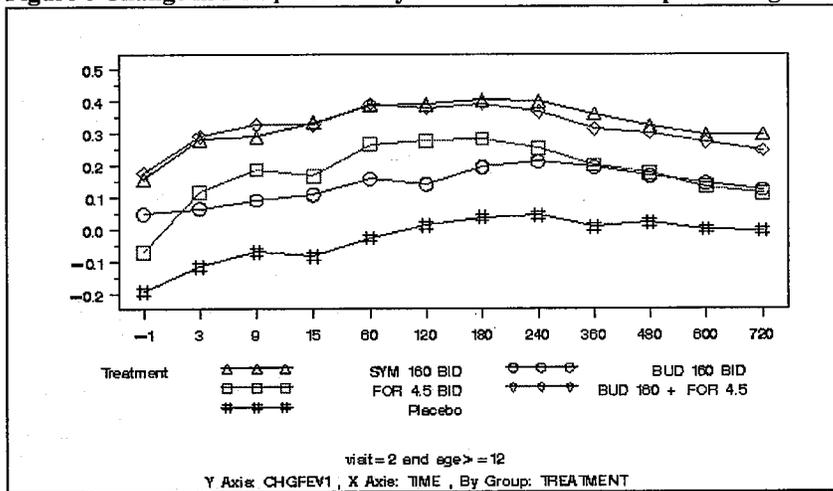
Table 35 ANCOVA Least squares means* (Study 717)

TREATMENT	ESTIMATE	STANDARD ERROR	DF	T VALUE	PR > T	ALPHA	LOWER	UPPER
SYM 160 BID	0.3421	0.03239	451	10.56	<.0001	0.05	0.2785	0.4058
BUD 160 BID	0.1522	0.03396	451	4.48	<.0001	0.05	0.08542	0.2189
FOR 4.5 BID	0.1896	0.03284	451	5.77	<.0001	0.05	0.1251	0.2542
BUD 160 + FOR 4.5	0.3084	0.03314	451	9.31	<.0001	0.05	0.2433	0.3736
Placebo	-0.06291	0.03437	451	-1.83	0.0679	0.05	-0.1305	0.004640

Source: PFT02_A2. *: LS means of baseline-adjusted average 12-hour FEV₁ at Week 2 using the WV Pre-CF approach for missing data

Figure 6 depicts the changes in FEV₁ at Week 2 from study baseline (pre-dosing FEV₁ at randomization) for the 566 patients.

Figure 6 Change in FEV₁ from study baseline at Week 2 for patients aged 12 and older (Study 717)



Source: PFT02_A1_1 (566 patients' data used)

Symbicort appeared to show a greater AUC than budesonide. Symbicort also appeared to have similar effect as its components taken separately at the same time. Symbicort components and formoterol had greater AUC than placebo.

Table 36 ANCOVA differences of least squares means (Study 717)

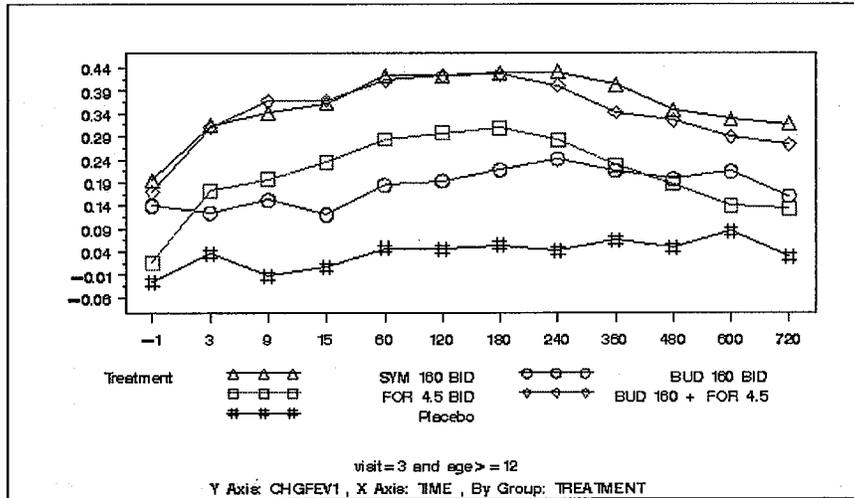
TREATMENT	TREATMENT	ESTIMATE	STANDARD ERROR	DF	T VALUE	PR > T	ALPHA	LOWER	UPPER
SYM 160 BID	BUD 160 BID	0.1899	0.04443	451	4.28	<.0001*	0.05	0.1026	0.2773
SYM 160 BID	FOR 4.5 BID	0.1525	0.04394	451	3.47	0.0006	0.05	0.06615	0.2389
SYM 160 BID	BUD 160 + FOR 4.5	0.03369	0.04391	451	0.77	0.4433	0.05	-0.05261	0.1200
SYM 160 BID	Placebo	0.4050	0.04447	451	9.11	<.0001	0.05	0.3176	0.4924
BUD 160 BID	FOR 4.5 BID	-0.03745	0.04467	451	-0.84	0.4023	0.05	-0.1252	0.05033
BUD 160 BID	BUD 160 + FOR 4.5	-0.1563	0.04426	451	-3.53	0.0005	0.05	-0.2432	-0.06928
BUD 160 BID	Placebo	0.2151	0.04523	451	4.76	<.0001	0.05	0.1262	0.3040
FOR 4.5 BID	BUD 160 + FOR 4.5	-0.1188	0.04449	451	-2.67	0.0078	0.05	-0.2062	-0.03138
FOR 4.5 BID	Placebo	0.2525	0.04483	451	5.63	<.0001	0.05	0.1644	0.3406
BUD 160 + FOR 4.5	Placebo	0.3713	0.04496	451	8.26	<.0001	0.05	0.2830	0.4597

Source: PFT02_A2. *primary efficacy comparison

The comparison between SYM 160 BID and BUD 160 BID demonstrated that SYM 80 BID was statistically superior to BUD 80 BID with a p-value of less than 0.0001, showing a statistically significant bronchodilatory effect of Symbicort® contributed by formoterol. Formoterol itself was shown to be statistically superior to placebo with a p-value of <0.0001.

Figure 7 depicts the changes in FEV₁ at Week 12 from study baseline (pre-dosing FEV₁ at randomization). This graphic incorporates data from 395 subjects (rather than the 566 incorporated into Figure 6). Assuming that subjects who are included in Figure 6 but not in Figure 7 would not have expressed values very different from those included in both graphics, this graph shows that the differences among treatments are similar with those from week 2 data.

Figure 7 Change in FEV₁ from study baseline at Week 12 for patients aged 12 and older (Study 717)



Source: PFT02_A1_1 (395 patients' data used)

Evaluation of the anti-inflammatory effect of Symbicort® contributed by budesonide

ANCOVA (analysis of covariance) was done by this reviewer to evaluate the anti-inflammatory effect of Symbicort® contributed by budesonide. For this purpose, the change from baseline in pre-dosing FEV₁ to the average over the treatment period was analyzed as the efficacy variable using the methods pre-specified for the primary efficacy comparison. As the primary comparison, SYM 160 BID was compared with FOR 4.5 BID. Other outcomes of the analysis were secondary.

Tables 38 through 40 provide selected results from the ANCOVA using SAS. The data source was PFT02_P12, a subset analysis data set based on the sponsor's data set _PFT01. PFT02_P12 was created by subsetting _PFT01 using the data of treatment-period average pre-dosing FEV₁ (_TIMEPTX="Trt Avg Post-dosing").

Table 37 Number of patients included in the analysis (Study 717)

NUMBER OF PATIENTS IN DATA SETS		
PFT01	Sponsor's efficacy data	596
PFT02_P12	Subset of _PFT01 using Trt Avg Post-dosing	566

Source: _PFT01; PFT02_P12, a subset of _PFT01 where _TIMEPTX="Trt Avg Predose".

Reviewer's Comment:

Note that the number of patients used in the analysis is 5% (566/596) smaller than the 596 ITT patients. It appears that the sponsor did not report all the data for treatment-period average pre-dosing FEV₁. This discrepancy should be noted.

Table 38 ANCOVA Tests of fixed effects (Study 717)

TYPE 3 TESTS OF FIXED EFFECTS				
Effect	Num DF	Den DF	F Value	Pr > F
TREATMENT	4	486	25.57	<.0001
CENTER	74	486	0.87	0.7626
BFEV1	1	486	8.68	0.0034

Source: PFT01_P12

Table 39 ANCOVA Least squares means* (Study 717)

TREATMENT	ESTIMATE	STANDARD ERROR	DF	T VALUE	PR > T	ALPHA	LOWER	UPPER
SYM 160 BID	0.1906	0.03271	486	5.83	<.0001	0.05	0.1263	0.2549
BUD 160 BID	0.06860	0.03381	486	2.03	0.0430	0.05	0.002169	0.1350
FOR 4.5 BID	-0.07386	0.03271	486	-2.26	0.0244	0.05	-0.1381	-0.00960
BUD 160 + FOR 4.5	0.1516	0.03343	486	4.53	<.0001	0.05	0.08590	0.2173
Placebo	-0.1814	0.03281	486	-5.53	<.0001	0.05	-0.2459	-0.1169

Source: PFT02_P12 for patients

*: LS means of change from baseline in pre-dosing FEV₁

Table 40 ANCOVA differences of least squares means (Study 717)

TREATMENT	TREATMENT	ESTIMATE	STANDARD ERROR	DF	T VALUE	PR > T	ALPHA	LOWER	UPPER
SYM 160 BID	BUD 160 BID	0.1220	0.04421	486	2.76	0.0060	0.05	0.03513	0.2089
SYM 160 BID	FOR 4.5 BID	0.2645	0.04374	486	6.05	<.0001*	0.05	0.1785	0.3504
SYM 160 BID	BUD 160 + FOR 4.5	0.03902	0.04412	486	0.88	0.3769	0.05	-0.04767	0.1257
SYM 160 BID	Placebo	0.3720	0.04317	486	8.62	<.0001	0.05	0.2872	0.4568
BUD 160 BID	FOR 4.5 BID	0.1425	0.04445	486	3.20	0.0014	0.05	0.05512	0.2298
BUD 160 BID	BUD 160 + FOR 4.5	-0.08299	0.04420	486	-1.88	0.0610	0.05	-0.1698	0.003859
BUD 160 BID	Placebo	0.2500	0.04382	486	5.71	<.0001	0.05	0.1639	0.3361
FOR 4.5 BID	BUD 160 + FOR 4.5	-0.2254	0.04451	486	-5.07	<.0001	0.05	-0.3129	-0.1380
FOR 4.5 BID	Placebo	0.1075	0.04344	486	2.48	0.0136	0.05	0.02218	0.1929
BUD 160 + FOR 4.5	Placebo	0.3330	0.04410	486	7.55	<.0001	0.05	0.2463	0.4196

Source: PFT02_P12

*primary efficacy comparison

The comparison between SYM 160 BID and FOR 4.5 BID demonstrated that SYM 160 BID was statistically superior to FOR 4.5 BID with a p-value of less than 0.0001, showing a statistically significant anti-inflammatory effect of Symbicort® contributed by budesonide.

FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Evaluation of early-withdrawal effect on change from baseline in pre-dosing FEV₁ and on baseline-adjusted Week-2 AUC of FEV₁

To explore the effect of early-withdrawal, the Division requested that the sponsor provide information about patients who should have been withdrawn but actually were not. This request can be found in the facsimile of 4/28/06. The sponsor responded on 5/9/06 (See folder \\CDSESUB1\N21929\N_000\2006-05-09, EFR). Due to time constraints, the evaluation of this response is not included in this report. It may be included in a future addendum to address this issue. Any statistical findings resulting from the evaluation of the sponsor's response of 5/9/06 may affect the conclusions of this report.

Evaluation of missing data of pre-dosing FEV₁

To evaluate the impact of missing observations on the efficacy outcome, this reviewer performed sensitivity analyses. Most missing observations occurred after the first two weeks of the study. Therefore, it is important to evaluate the effect of missing observations for the co-primary efficacy variable: the change from baseline in pre-dosing FEV₁.

Note that the efficacy data include Weeks 2, 6 and 12 pre-dosing FEV₁ values. Most patients had three observations (i.e., one for each measurement time point); some only had one or two observations. Table 41 and 43 show the numbers of patients by treatment and the status of missing visits for studies 716 and 717, respectively. Table 42 and Figure 8 and Table 44 and Figure 9 show the average changes in pre-dosing FEV₁ from baseline in the subgroups with and without complete data for studies 716 and 717, respectively.

Study 716

Table 41 Number of patients by treatment and missing-visit status (Study 716)

PATIENT HAD MISSING VISITS	#AVAILABEL WEEKS DATA	TREATMENT				TOTAL
		SYM 80 BID	BUD 80 BID	FOR 4.5 BID	Placebo	
		N	N	N	N	
No	3	108	104	79	58	349
Yes	1	8	9	15	24	56
	2	6	3	10	21	40
Total		122	116	104	103	445

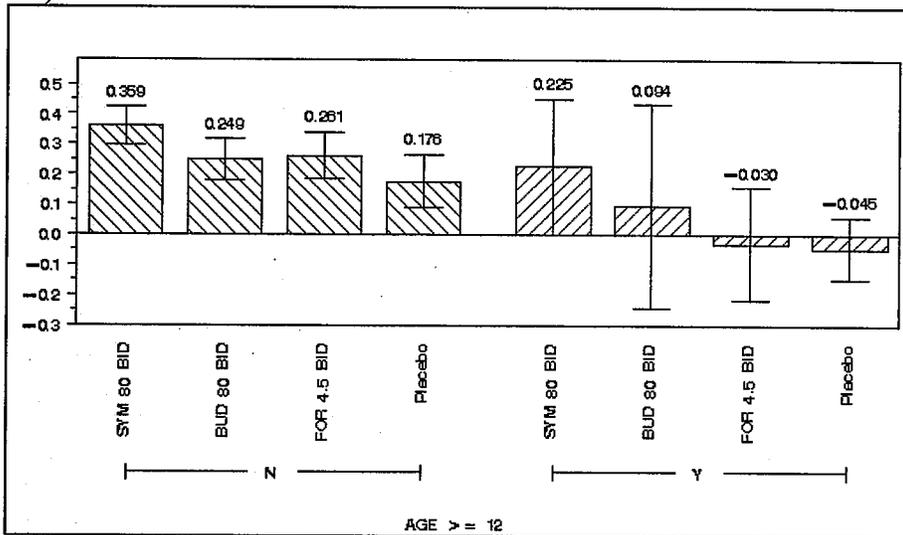
Source: PFT01_P11_3 (derived from PFT01_1)

Table 42 Mean change in pre-dosing FEV₁ from baseline by treatment and missing-visit status (Study 716)

PATIENT HAD MISSING VISITS	TREATMENT							
	SYM 80 BID		BUD 80 BID		FOR 4.5 BID		Placebo	
	Chg FEV ₁	N	Chg FEV ₁	N	Chg FEV ₁	N	Chg FEV ₁	N
N	0.359	108	0.249	104	0.261	79	0.176	58
Y	0.225	14	0.094	12	-0.030	25	-0.045	45

Source: PFT01_P11_3

Figure 8 Mean change in pre-dosing FEV₁ from baseline by treatment and missing-visit status (Study 716)



Source: PFT01_P11_3

This graph shows that, for the patients with all three complete visits, Symbicort had a numerically greater average change in pre-dosing FEV₁ than formoterol. Both Symbicort and budesonide had greater average changes in pre-dosing FEV₁ than placebo. Such trends were maintained for those with one or two missing visits.

Study 717

Table 43 Number of patients by treatment and missing-visit status (Study 717)

PATIENT HAD MISSING VISITS	#AVAILABLE WEEKS DATA	TREATMENT					TOTAL
		SYM 160 BID	BUD 160 BID	FOR 4.5 BID	BUD 160 + FOR 4.5	Placebo	
		N	N	N	N	N	
N	3	94	76	63	87	50	370
Y	1	15	19	30	10	38	112
	2	8	9	14	12	14	57
Total		117	104	107	109	102	539

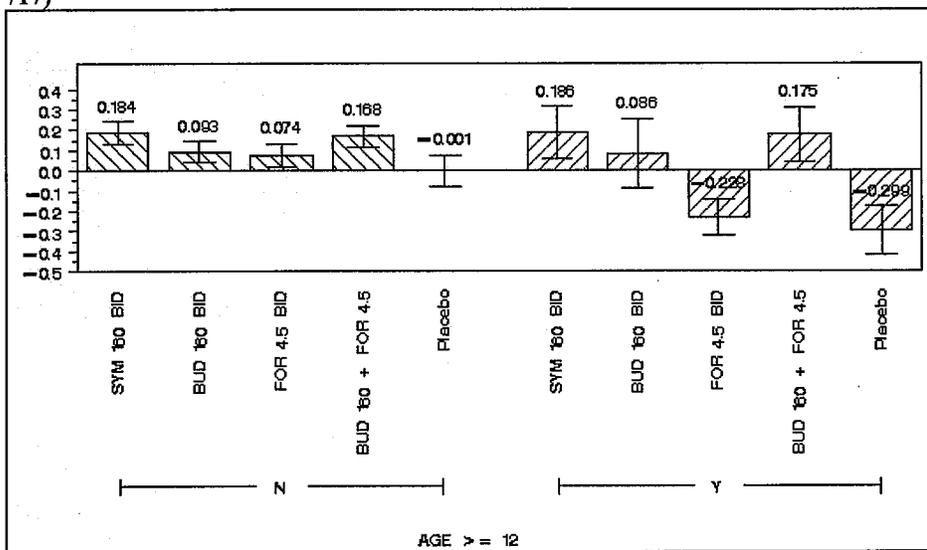
Source: PFT01_P11_3 (derived from PFT01_1)

Table 44 Mean change in pre-dosing FEV₁ from baseline by treatment and missing-visit status (Study 717)

PATIENT HAD MISSING VISITS	TREATMENT									
	SYM 160 BID		BUD 160 BID		FOR 4.5 BID		BUD 160 + FOR 4.5		Placebo	
	Chg FEV ₁	N								
N	0.184	94	0.093	76	0.074	63	0.168	87	-0.001	50
Y	0.186	23	0.086	28	-0.228	44	0.175	22	-0.299	52

Source: PFT01_P11_3

Figure 9 Mean change in pre-dosing FEV₁ from baseline by treatment and missing-visit status (Study 717)



Source: PFT01_P11_3

This graph shows that, for the patients with all three complete visits, Symbicort had a numerically greater average change in pre-dosing FEV₁ than formoterol. Both Symbicort and budesonide had greater average changes in pre-dosing FEV₁ than placebo. Symbicort and its components taken separately at the same time were similar. Such trends were maintained for those with one or two missing visits.

Results and Conclusions

The effectiveness of Symbicort was evaluated based on two co-primary efficacy variables: (1) baseline-adjusted mean 12-hour FEV₁ at Week 2 and (2) mean change in pre-dosing FEV₁ from study baseline over entire double-blind study period.

From Table 45, Symbicort was shown to be statistically superior to its components. Symbicort was also shown to be superior to placebo. Table 45 is identical to Table 2. In

addition, the components of Symbicort, budesonide and formoterol were also shown to be superior to placebo.

Table 45 Efficacy findings based on 12-week baseline-adjusted mean FEV₁ and pre-dosing FEV₁ (Studies 716 and 717 compared)

STATISTICAL COMPARISON: TEST OF BRONCHODILATORY EFFECT BY FORMOTEROL			STUDY 716	STUDY 717	FINDINGS CONSISTENTLY POSITIVE ACROSS STUDIES
Symbicort (80 or 160) BID vs.	Budesonide (80 or 160) BID	Efficacy variable is Week-2 baseline-adjusted AUC of FEV ₁	P=0.0003	P<0.0001	Yes
Formoterol 4.5 BID	placebo		P<0.0001	P<0.0001	Yes

STATISTICAL COMPARISON: TEST OF ANTI-INFLAMMATORY EFFECT BY BUDESONIDE			STUDY 716	STUDY 717	FINDINGS CONSISTENTLY POSITIVE ACROSS STUDIES
Budesonide (80 or 160) BID vs.	Formoterol 4.5 BID	Efficacy variable is treatment-period pre-dosing FEV ₁	P=0.0012	P<0.0001	Yes
Budesonide (80 or 160) BID vs.	placebo		P=0.0005	P<0.0001	Yes

STATISTICAL COMPARISON: EVALUATE EFFICACY OF SYMBICORT			STUDY 716	STUDY 717	FINDINGS CONSISTENTLY POSITIVE
Symbicort vs.	placebo	Efficacy variable is Week-2 baseline-adjusted AUC of FEV ₁	P<0.0001	P<0.0001	Yes
		Efficacy variable is treatment-period pre-dosing FEV ₁	P<0.0001	P<0.0001	Yes

CONCLUSIONS AND RECOMMENDATIONS

Efficacy Conclusions:

Consistently across Studies 716 and 717, Symbicort® was shown to be statistically superior to its components and placebo.

Recommendations:

Overall, Symbicort®, administered two actuations via pMDI, BID, is recommended for approval.

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Appendix

Imputation method for missing data: Sponsor's description

The following description of imputation of missing data can be found in the study report, SD-039-0716.PDF, Section 5.5.3.2 Primary variables: baseline-adjusted average 12-hour FEV₁ and predose FEV₁.

Missing values within a 12-hour profile were classified into 2 categories:

- “Bounded” missing data occurred when one or more planned values were missing between a pair of non-missing values. Bounded missing values were replaced with value determined by straight-line interpolation connecting the two non-missing points. In terms of the AUC calculation, this had the effect of ignoring bounded missing data.
- “Unbounded” missing data occurred when one or more planned values were missing after a non-missing value(s) and until the end of the planned set of spirometry maneuvers at that visit. For unbounded missing data, the following 2 extrapolation techniques were used separately for imputation:
 1. Carry forward the predose FEV₁ value from that visit to all successive protocol-specified planned time points at that visit, hereafter referred to as “within-visit predose value carried forward” or “WV Pre-CF.” This method is conservative when comparing SYMBICORT pMDI to budesonide because it discounts any acute bronchodilatory effect of formoterol and therefore this method of extrapolation was selected a priori to be used in the primary analysis of efficacy for this variable.
 2. Carry forward the FEV₁ value from the last non-missing measurement at that visit to all successive protocol-specified time points at that visit, hereafter referred to as “within-visit last observation carried forward” or “WV LOCF.” This method of extrapolation was used in sensitivity analyses of this variable.

(Page 110, SD-039-0716.PDF)

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Division's inquiry of 4/28/06 via facsimile

NDA 21-929
Symbicort

We are reviewing your NDA submission dated September 23, 2005, and we have the following requests in order to facilitate our review. The following requests pertain to studies 716 and 717.

1. Provide, in written format, subject identification numbers for subjects who qualified for early withdrawal from the studies according to the protocol specified discontinuation criteria (as recorded on the ASTEXAC case report form). For each of these subjects, include the time point at which the discontinuation criteria were satisfied. Also, indicate whether each of these subjects was actually withdrawn and if so the time point at which the withdrawal occurred. In addition, provide this information electronically including the subject identification number (USUBJID and SUBJECT), the date the discontinuation criteria were satisfied, an indicator variable for the withdrawal status of each patient, and the date the withdrawal occurred. These dates should be consistent with the date in variable `_TERM_DT` in your disposition data set.
2. Provide analyses and figures describing the co-primary efficacy endpoint, baseline-adjusted 12-hour FEV1, at the week 12 time point including only subjects who never qualified for withdrawal from the study as recorded on ASTEXAC case report form irrespective of whether the subject continued in the study or not. The figures should be similar to that displayed as Figure 3 in your proposed label. The analyses should be similar to those provided in Tables 27 and 28 in Section 7.2.1.1 of the study report for study 716; and in Tables 28 and 29 in Section 7.2.1.1 of the study report for study 717.
3. If the number of subjects described as a result of comment 1 is different from the information included in Table 41 in Section 7.2.2.1 of the study report for study 716 or Table 38 in Section 7.2.2.1 for study 717, provide an updated version of these tables.

If there are any questions, please contact Colette Jackson, Project Manager, at 301-796-1230.

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/s/

Ted Guo
5/23/2006 01:36:20 PM
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NDA 21-929 Statistical review

Ruth Davi
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