

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-929

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW**Division Of Pulmonary and Allergy Drug Products (HFD-570)**

APPLICATION: NDA 21-929	TRADE NAME: Symbicort® Inhalation Aerosol
APPLICANT/SPONSOR: AstraZeneca	USAN NAME: Budesonide / formoterol fumarate dihydrate inhalation aerosol
MEDICAL OFFICER: Peter Starke, MD	CATEGORY: Inhaled corticosteroid and long-acting beta ₂ -agonist
TEAM LEADER:	ROUTE: Orally inhaled
DATE: April 29, 2008	

SUBMISSIONS REVIEWED IN THIS DOCUMENT

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
March 24, 2008		N-0010	PSUR coving the period from November 25, 2007 to February 24, 2008

RELATED APPLICATIONS

<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>

REVIEW SUMMARY:

This is a medical officer review of a PSUR submitted by AstraZeneca for Symbicort on March 24, 2008, coving the period from November 25, 2007 to February 24, 2008. Symbicort pMDI was approved in the US on July 21, 2006, and US market launch was in June 2007.

AstraZeneca states that Symbicort has not been withdrawn due to safety reasons in any country.

AstraZeneca estimates that approximately 8,100 subjects have been exposed to Symbicort in clinical studies during the period of this report. Of these, approximately 1,200 were receiving pMDI and approximately 6,900 were receiving TBH.

AstraZeneca estimates that from October 1 to December 31, 2007, the worldwide exposure for Symbicort pMDI and Symbicort TBH were 5.3 million and 242.7 million treatment days, respectively. The total worldwide exposure for Symbicort since launch is estimated as 3.8 billion treatment days.

AstraZeneca reports that during this PSUR period 114 case reports met the criteria for inclusion in the PSUR. The reports come from spontaneous reporting, regulatory authorities, the literature, and clinical trials. The reports included a total of 216 adverse events, of which 34 case reports and 70 events were considered serious. There were 6 deaths. Review of summary tables showed no new trends or safety signals that are not already labeled. There were 26 reports that could be related to lack of efficacy, and no specific device problems reported.

OUTSTANDING ISSUES:

None

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	☐ FILEABLE	☐ NOT FILEABLE
	☐ APPROVAL	☐ APPROVABLE ☐ NOT APPROVABLE
OTHER ACTION:	☒ NO ACTION	☐ COMMENTS TO APPLICANT

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Peter Starke
4/29/2008 01:58:26 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW Division Of Pulmonary and Allergy Drug Products (HFD-570)			
APPLICATION: NDA 21-929 APPLICANT/SPONSOR: AstraZeneca MEDICAL OFFICER: Peter Starke, M.D. TEAM LEADER: Lydia Gilbert McClain, MD DATE: April 12, 2007	TRADE NAME: Symbicort® Inhalation Aerosol, 80/4.5 & 160/4.5 mcg USAN NAME: Budesonide 80 or 160 mcg and formoterol fumarate dihydrate 4.5 mcg inhalation aerosol CATEGORY: Corticosteroid and long-acting beta agonist combination ROUTE: Orally inhaled		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
April 10, 2007	April 10, 2007		Additional questions regarding Pre-NDA briefing document
RELATED DOCUMENTS AND APPLICATIONS			
<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>	
September 23, 2005	NDA 21-929	NDA for Symbicort Inhalation Aerosol, Approved July 21, 2006	
February 9, 2007		Pre-NDA briefing document	
<u>REVIEW SUMMARY:</u> This is a review of several additional questions posed by AstraZeneca after receiving FDA comments regarding their pre-NDA briefing document for the addition of an _____ to Symbicort® Inhalation Aerosol, 80/4.5 & 160/4.5. Questions and comments are attached.			
<u>OUTSTANDING ISSUES:</u> Comments to be sent to sponsor.			

Appears This Way
On Original

1 Page(s) Withheld

X Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

Withheld Track Number: Medical-

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Peter Starke
4/16/2007 11:24:14 AM
MEDICAL OFFICER

Lydia McClain
4/16/2007 04:56:43 PM
MEDICAL OFFICER
I concur

MEDICAL OFFICER REVIEW Division Of Pulmonary and Allergy Drug Products (HFD-570)			
APPLICATION: NDA 21-929 APPLICANT/SPONSOR: AstraZeneca MEDICAL OFFICER: Peter Starke, M.D. TEAM LEADER: Lydia Gilbert McClain, MD DATE: March 27, 2007	TRADE NAME: Symbicort® Inhalation Aerosol, 80/4.5 & 160/4.5 mcg USAN NAME: Budesonide 80 or 160 mcg and formoterol fumarate dihydrate 4.5 mcg inhalation aerosol CATEGORY: Corticosteroid and long-acting beta agonist combination ROUTE: Orally inhaled		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
February 9, 2007	February 9, 2007		Pre-NDA briefing document
RELATED APPLICATIONS			
<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>	
September 23, 2005	NDA 21-929	NDA for Symbicort Inhalation Aerosol, Approved July 21, 2006	
<u>REVIEW SUMMARY:</u> This is a review of a pre-NDA briefing document from AstraZeneca for Symbicort® Inhalation Aerosol, 80/4.5 & 160/4.5, for the addition of an _____ AstraZeneca proposes to submit the results of one clinical study _____. The sNDA is planned for submission in the second quarter of 2007.			
<u>OUTSTANDING ISSUES:</u> Comments to be sent to sponsor.			

Appears This Way
On Original

5 Page(s) Withheld

6 Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Peter Starke
4/2/2007 12:39:32 PM
MEDICAL OFFICER

Lydia McClain
4/2/2007 01:40:32 PM
MEDICAL OFFICER
I concur

MEDICAL OFFICER REVIEW

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

APPLICATION: IND 63,394	TRADE NAME: Symbicort 80/4.5 & 160/4.5
APPLICANT/SPONSOR: AstraZeneca	USAN NAME: Budesonide & formoterol fumarate dehydrate inhalation aerosol
MEDICAL OFFICER: Peter Starke, MD	
TEAM LEADER: ---	CATEGORY: Corticosteroid and long-acting beta agonist combination
REVIEW DATE: August 8, 2006	ROUTE: Orally inhaled

SUBMISSIONS REVIEWED IN THIS DOCUMENT

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
May 15, 2006	May 18, 2006	N-487	Final study report for study SD-039-0728

RELATED APPLICATIONS

<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>
September 23, 2005	September 23, 2005	NDA 21-929 Symbicort NDA submission
January 19, 2006	January 19, 2006	NDA 21-929 4-month Safety Update

REVIEW SUMMARY:

This review covers a study SD-039-0728, a 52-week study which assessed the long-term safety of Symbicort MDI 160/4.5 administered as 2 or 4 actuations twice daily, as well as budesonide HFA-227 MDI 160 mcg 4 actuations twice daily, in 708 stable moderate-to-severe asthmatics ≥ 12 years of age, 443 of whom were randomized to high dose Symbicort (640/18 BID). The study was initiated in August of 2003, and the last subject completed treatment in February of 2005. The study report was finalized on February 27, 2006 and submitted to the IND in May of this year. Note that this occurred during the review period for NDA 21-929 for Symbicort 80/4.5 and 160/4.5, which was approved on July 21, 2006. Safety information from this study was submitted and reviewed as part of the 4-month safety update to the NDA. It was considered important because the study used the maximum to-be-approved dosage as well as a dosage twice the to-be-approved dose. Because of the safety issues with LABAs, and the specific safety issue noted for Foradil at double the approved dose, the study report was reviewed for any safety issues not revealed in the 4-month safety update.

There were no deaths. The percentages of patients with AEs were about the same, whereas the percentages of SAEs were higher in the 302/9 than the other treatment groups (4.7% Symbicort 640/18 BID; 9.1% Symbicort 320/9 BID; 3.8% Bud 640 BID). There was no clear pattern of SAEs by SOC or preferred term (PT) [Table 53, p178], although 1 patient on Symbicort 640/18 BID had atrial fibrillation. The overall percentages of patients with AEs were about the same (by PT) [Table S5]. However, the Symbicort 640/18 BID group experienced higher frequency of β_2 -agonist effects: tremor (6.8%) and muscle cramps (5.2%) than the other treatment groups. Pharyngolaryngeal pain was higher in both high dose budesonide groups, whereas oral candidiasis was higher for Symbicort 640/18 BID than for either 320/9 BID or budesonide 640 BID. The incidence of potentially asthma-related AEs was generally similar across treatment groups. Likewise, similar percentages of patients in the two Symbicort treatment groups experienced at least one asthma exacerbation (12.2% Symbicort 640/18 BID; 14.4% Symbicort 320/9 BID; 21.8% Bud 640 BID). The study summary states that the "overall incidence of AEs in the cardiac SOC and the incidence of individual cardiac-related PTs in the cardiac and investigations SOC were slightly higher in the Symbicort treatment groups than in the budesonide group; the majority of individual events were related to abnormalities detected during ECG and Holter monitoring and did not result in subject discontinuation. For cardiac and cardiac-related AEs, there were no consistent differences noted between the 2 SYMBICORT pMDI groups. There were no significant patterns of AEs emerging after longer periods of treatment for any of the treatment groups." At and beyond 6 months of treatment, treatment group comparisons showed lower mean values of 24-hour urinary cortisol for both treatment groups containing budesonide 640 BID than the treatment group containing 320 BID.

OUTSTANDING ISSUES: None. Based on review of these data, no labeling changes are indicated.

RECOMMENDED REGULATORY ACTION: None

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Peter Starke
8/8/2006 11:47:44 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-929
Submission Code	N-000
Letter Date	September 23, 2005
Stamp Date	September 23, 2005
PDUFA Goal Date	July 23, 2006
Reviewer Name	Peter Starke, MD
Review Completion Date	May 23, 2006
Established Name	Budesonide/formoterol inhalation aerosol
(Proposed) Trade Name	Symbicort® 80/4.5 and 160/4.5 Inhalation Aerosol
Therapeutic Class	Corticosteroid/long-acting beta-agonist sthma controller
Applicant	AstraZeneca LP
Priority Designation	S
Formulation	Pressurized metered dose inhaler
Dosing Regimen	2 inhalations of 80/4.5 or 160/4.5 mcg twice daily
Indication	Maintenance treatment of asthma
Intended Population	≥12 years of age

MEDICAL OFFICER REVIEW Division Of Pulmonary and Allergy Drug Products (HFD-570)		
APPLICATION: NDA 21-929 APPLICANT/SPONSOR: AstraZeneca MEDICAL OFFICER: Peter Starke, MD TEAM LEADER: -- PDUFA DATE: July 23, 2006	TRADE NAME: Symbicort 80/4.5 & 160/4.5 USAN NAME: Budesonide & formoterol fumarate dehydrate inhalation aerosol CATEGORY: Corticosteroid and long-acting beta agonist combination ROUTE: Orally inhaled	
SUBMISSIONS REVIEWED IN THIS DOCUMENT		
<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission/Comments</u>
September 23, 2005	September 23, 2005	Original submission
January 19, 2006	January 19, 2006	4-month Safety Update
March 16, 2006	March 16, 2006	Response to CMC questions
March 17, 2006	March 17, 2006	Response to Mid-cycle clinical comments including labeling with draft Boxed Warning
May 9, 2006	May 9, 2006	Response to information request of April 28, 2006 for clarification tables of patients in studies 716 and 717 who qualified for withdrawal due to a predefined asthma event
May 15, 2006	May 15, 2006	Submission A. Response to Clinical IR.
RECOMMENDED REGULATORY ACTION		
NDA: <u> X </u> APPROVAL <u> </u> APPROVABLE <u> </u> NOT APPROVABLE		
OTHER ACTION:		

Appears This Way
 On Original

Table of Contents

1	EXECUTIVE SUMMARY	10
1.1	RECOMMENDATION ON REGULATORY ACTION	10
1.2	RECOMMENDATION ON POSTMARKETING ACTIONS	10
1.2.1	Risk Management Activity	10
1.2.2	Required Phase 4 Commitments	10
1.2.3	Other Phase 4 Requests	10
1.3	SUMMARY OF CLINICAL FINDINGS	11
1.3.1	Brief Overview of Clinical Program	11
1.3.2	Efficacy	13
1.3.3	Safety	15
1.3.4	Dosing Regimen and Administration	15
1.3.5	Drug-Drug Interactions	16
1.3.6	Special Populations	16
2	INTRODUCTION AND BACKGROUND	18
2.1	PRODUCT INFORMATION	18
2.2	CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS	19
2.3	AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES	19
2.4	IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS	21
2.5	PRESUBMISSION REGULATORY ACTIVITY	22
2.6	OTHER RELEVANT BACKGROUND INFORMATION	23
3	SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES	23
3.1	CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE)	23
3.1.1	Device Overview	24
3.1.2	Formoterol fumarate	26
3.1.3	Budesonide	26
3.1.4	Other CMC issues	27
3.1.5	Device performance and reliability	28
3.2	ANIMAL PHARMACOLOGY/TOXICOLOGY	29
4	DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY	30
4.1	SOURCES OF CLINICAL DATA	30
4.2	TABLES OF CLINICAL STUDIES	30
4.3	REVIEW STRATEGY	31
4.4	DATA QUALITY AND INTEGRITY	33
4.5	COMPLIANCE WITH GOOD CLINICAL PRACTICES	35
4.6	FINANCIAL DISCLOSURES	35
5	CLINICAL PHARMACOLOGY	36
5.1	PHARMACOKINETICS	36
5.2	PHARMACODYNAMICS	37
5.3	EXPOSURE-RESPONSE RELATIONSHIPS	38
6	INTEGRATED REVIEW OF EFFICACY	38

6.1	INDICATION	38
6.1.1	Methods	38
6.1.2	General Discussion of Endpoints	40
6.1.3	Study Design	41
6.1.4	Efficacy Findings	45
6.1.5	Clinical Microbiology	55
6.1.6	Efficacy Conclusions	55
7	INTEGRATED REVIEW OF SAFETY	55
7.1	METHODS AND FINDINGS	56
7.1.1	Deaths	57
7.1.2	Other Serious Adverse Events	57
7.1.3	Dropouts and Other Significant Adverse Events	59
7.1.4	Other Search Strategies	62
7.1.5	Common Adverse Events	62
7.1.6	Less Common Adverse Events	68
7.1.7	Laboratory Findings	69
7.1.8	Vital Signs	71
7.1.9	Electrocardiograms (ECGs)	72
7.1.10	Immunogenicity	76
7.1.11	Human Carcinogenicity	76
7.1.12	Special Safety Studies	76
7.1.13	Withdrawal Phenomena and/or Abuse Potential	76
7.1.14	Human Reproduction and Pregnancy Data	77
7.1.15	Assessment of Effect on Growth	77
7.1.16	Overdose Experience	77
7.1.17	Postmarketing Experience	78
7.2	ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS	78
7.2.1	Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety	78
7.2.2	Description of Secondary Clinical Data Sources Used to Evaluate Safety	83
7.2.3	Adequacy of Overall Clinical Experience	85
7.2.4	Adequacy of Special Animal and/or In Vitro Testing	85
7.2.5	Adequacy of Routine Clinical Testing	85
7.2.6	Adequacy of Metabolic, Clearance, and Interaction Workup	85
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	85
7.2.8	Assessment of Quality and Completeness of Data	85
7.2.9	Additional Submissions, Including 4-Month Safety Update	85
7.3	SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS	91
7.4	GENERAL METHODOLOGY	91
7.4.1	Pooling Data Across Studies to Estimate and Compare Incidence	91
7.4.2	Explorations for Predictive Factors	92
7.4.3	Causality Determination	92
8	ADDITIONAL CLINICAL ISSUES	93
8.1	DOSING REGIMEN AND ADMINISTRATION	93

8.2	DRUG-DRUG INTERACTIONS	93
8.3	SPECIAL POPULATIONS.....	94
8.4	PEDIATRICS	94
8.5	ADVISORY COMMITTEE MEETING	95
8.6	LITERATURE REVIEW	95
8.7	POSTMARKETING RISK MANAGEMENT PLAN	95
8.8	OTHER RELEVANT MATERIALS	95
9	OVERALL ASSESSMENT.....	96
9.1	CONCLUSIONS	96
9.2	RECOMMENDATION ON REGULATORY ACTION	96
9.3	RECOMMENDATION ON POSTMARKETING ACTIONS	96
9.3.1	Risk Management Activity	96
9.3.2	Required Phase 4 Commitments.....	96
9.3.3	Other Phase 4 Requests.....	96
9.4	LABELING REVIEW	97
9.5	COMMENTS TO APPLICANT.....	97
10	APPENDICES	98
10.1	REVIEW OF INDIVIDUAL STUDY REPORTS	98
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.....	98
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.....	105
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 143	
10.1.4	Study SD-039-0726. A 12-week, safety and efficacy study evaluating Symbicort (80/4.5 mcg) 2 puffs once daily as maintenance therapy in asthmatics ≥16 years of age previously stable on Symbicort 80/4.5 mcg, 2 actuations BID.....	178
10.1.5	Study SD-039-0681	184
10.1.6	Study SD-039-0682	187
10.1.7	Study SD-039-0715. One-year safety study with Symbicort MDI 160/4.5 in asthmatics ≥12 years of age 190	
10.1.8	Study SD-039-0719. Six-month safety study with Symbicort MDI 160/4.5 in asthmatic children 6 to 11 years of age	204
10.2	LINE-BY-LINE LABELING REVIEW.....	215
	REFERENCES	216

Table of Tables

Table 1. Symbicort MDI Dosage Strengths.....	18
Table 2. NDA 21-929 Clinical Products.....	19
Table 3. Means for fine particle dose of budesonide as % of label claim for each dosage strength of Symbicort	27
Table 4. Summary data for clinical returns dose analysis.....	28
Table 5. Symbicort MDI Phase 3 Studies.....	30

Table 6. DSI Audit Sites and Results	34
Table 7. Listing of studies with financial interest disclosed.....	36
Table 8. Demographic and Other characteristics, Pivotal Phase 3 studies 716 and 717 (Pool 3*).....	45
Table 9. Studies 716 and 717, Baseline-adjusted average 12-hour FEV ₁ (L), Treatment Means*, Week 2.....	48
Table 10. Studies 716 & 717, Treatment Comparisons*, Baseline-adjusted average 12-hour FEV ₁ (L), Week 2.....	48
Table 11. Studies 716 and 717, AM Pre-dose FEV ₁ (L), Treatment Means*.....	49
Table 12. Studies 716 and 717, Treatment comparisons*, AM Pre-dose FEV ₁ (L), Average over study	50
Table 13. Studies 716 and 717, Pre-defined asthma events, Number and percentage of patients meeting predefined withdrawal criteria (CRF data).....	51
Table 14. Studies 716 and 717, Treatment comparison odds ratios, Pre-defined asthma events.....	53
Table 15. AQLQ[S] treatment comparisons for Symbicort minus placebo, overall scores, end of treatment.....	55
Table 16. Open-label Safety Studies 715 and 719, FEV ₁ (L) *, Treatment Means	55
Table 17. Adverse events during randomized treatment, Pivotal Phase 3 studies (Pool 3*)	56
Table 18. Overview of adverse events during randomized treatment, All Phase 3 studies (Pool 5*).....	57
Table 19. SAEs during randomized treatment, Pivotal Phase 3 studies (Pool 3*).....	58
Table 20. SAEs during randomized treatment, All Phase 3 studies (Pool 5*).....	58
Table 21. DAEs, Most commonly reported SOC/PTs, Pivotal Phase 3 studies (Pool 3*).....	60
Table 22. DAEs, Most commonly reported SOC/PTs, All Phase 3 studies (Pool 5*)	61
Table 23. PI AE table. AEs ≥3% in any Symbicort MDI group and higher than placebo, Pool 4*, BID treatment only, Patients ≥12 years	63
Table 24. ICS events of interest, All placebo-controlled Phase 3 studies (Pool 4*).....	64
Table 25. ICS events of interest, All Phase 3 studies (Pool 5*).....	64
Table 26. Beta-adrenergic events of interest, All placebo-controlled Phase 3 studies (Pool 4*).....	65
Table 27. Beta-adrenergic events of interest, All Phase 3 studies (Pool 5*)	66
Table 28. Cardiac events of interest, All placebo-controlled Phase 3 studies (Pool 4*).....	66
Table 29. Cardiac events of interest, All Phase 3 studies (Pool 5*)	67
Table 30. All placebo-controlled Phase 3 studies (Pool 4*).....	68
Table 31. Asthma and potentially asthma-related events of interest, All Phase 3 studies (Pool 5*)	68
Table 32. Mean 24-hour urinary cortisol results (nmol) (Mean, range)	71
Table 33. ECG findings, Pool 5 AM assessments	73
Table 34. Summary of QT, QTcB, and QTcF changes (msec), Pool 5 AM assessments	74
Table 35. Number of Subjects in Symbicort MDI Studies, by Pool.....	79
Table 36. Demographic characteristics, All Phase 2/3 studies (Pool 6)	81
Table 37. Demographic and Other characteristics, All Completed Phase 3 studies (Pool 5)	81
Table 38. Duration of Symbicort MDI Exposure, All Phase 2/3 studies (Pool 6).....	82
Table 39. Duration of Exposure, All Completed Phase 3 studies (Pool 5).....	82
Table 40. Duration of Exposure to Symbicort MDI by total daily dose, All Completed Phase 3 studies (Pool 5).....	83
Table 41. Studies submitted with 4-Month Safety Update.....	87
Table 42. 4MSU, Updated demographic and other characteristics, Symbicort and Budesonide groups, All completed Phase 3 studies (Pool 5)	87
Table 43. 4MSU, Cumulative duration of Symbicort MDI exposure, All Phase 2/3 studies (Pool 6).....	88
Table 44. 4MSU, Overview of adverse events during randomized treatment, All Phase 3 studies (Pool 5*).....	89
Table 45. 4MSU, SAEs, All Phase 3 studies (Pool 5*)	90
Table 46. SD-039-0728, Most commonly reported AEs by dose.....	90
Table 47. SD-039-0729, Possible crossover treatments	99
Table 48. SD-039-0729, Treatment means for average 12-hour FEV ₁ (ANCOVA results, LOCF).....	100
Table 49. SD-039-0729, Onset of treatment effect (≥15% increase in FEV ₁), by treatment	102

Table 50. SD-039-0716, Qualifying ICS	107
Table 51. SD-039-0716, Investigational products	108
Table 52. SD-039-0716, Summary of Study Activities by Visit	110
Table 53. SD-039-0716, Reasons for Discontinuation	115
Table 54. SD-039-0716, Demographic and key baseline characteristics, ITT.....	116
Table 55. SD-039-0716, Study Medication Compliance, ITT.....	117
Table 56. SD-039-0716, Baseline-adjusted average 12-hour FEV ₁ (L), Treatment Means (EAS ≥12)	119
Table 57. SD-039-0716, Baseline-adjusted average 12-hour FEV ₁ (L), Treatment Comparisons (EAS ≥12)	120
Table 58. SD-039-0716, Pre-dose FEV ₁ (L), Treatment Means (EAS ≥12).....	124
Table 59. SD-039-0716, Pre-dose FEV ₁ (L), Treatment Comparisons (EAS ≥12)	124
Table 60. SD-039-0716, Pre-dose FEV ₁ Treatment Comparisons at Various Study Timepoints (EAS ≥12)	125
Table 61. SD-039-0716, Shift in Baseline Pre-dose FEV ₁ (L) over the Study (EAS ≥12).....	126
Table 62. SD-039-0716, Number and percentage of patients with a CRF pre-defined asthma event	128
Table 63. SD-039-0716, Treatment comparisons for percentage of patients with at least 1 CRF pre-defined asthma event (EAS ≥12).....	129
Table 64. SD-039-0716, Withdrawals due to pre-defined asthma event	130
Table 65. SD-039-0716, Number (%) of patients achieving 15% improvement in FEV ₁ (EAS ≥12).....	131
Table 66. SD-039-0716, Mean Morning and Evening PEF (EAS ≥12)	132
Table 67. SD-039-0716, Asthma symptom scores (EAS ≥12)	132
Table 68. SD-039-0716, Rescue medication use (EAS ≥12).....	133
Table 69. SD-039-0716, Overall AQLQ(S) for patients ≥18 years of age	134
Table 70. SD-039-0716, AQLQ[S] treatment comparisons, overall scores, end of treatment.....	135
Table 71. SD-039-0716, Exposure ITT/SAS.....	135
Table 72. SD-039-0716, Adverse event overview (ITT/SAS).....	137
Table 73. SD-039-0716, Listing of SAEs and DAEs during all study phases* (SAS).....	137
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)	138
Table 75. SD-039-0716, Adverse events reported by at least 3% of patients in any treatment group during the treatment period (ITT/SAS)	139
Table 76. SD-039-0717, Definition of moderate- and high-dose ICS strata.....	144
Table 77. SD-039-0717, Investigational products	145
Table 78. SD-039-0717, Reasons for Discontinuation (all randomized patients).....	147
Table 79. SD-039-0717, Demographic and key baseline characteristics, ITT.....	147
Table 80. SD-039-0717, Study Medication Compliance, ITT	149
Table 81. SD-039-0717, Baseline-adjusted average 12-hour FEV ₁ (L), Treatment Means Week 2 (EAS)	152
Table 82. SD-039-0717, Baseline-adjusted average 12-hour FEV ₁ (L), Treatment Means at End of Treatment and at Week 12 (EAS)	152
Table 83. SD-039-0717, Baseline-adjusted average 12-hour FEV ₁ (L), Treatment Comparisons (EAS)	152
Table 84. SD-039-0717, Pre-dose FEV ₁ (L), Treatment Means (EAS).....	157
Table 85. SD-039-0717, Pre-dose FEV ₁ (L), Treatment Comparisons, Average over Double-blind Period (EAS)	157
Table 86. SD-039-0717, Pre-dose FEV ₁ Treatment Comparisons at Various Study Timepoints (EAS).....	157
Table 87. SD-039-0717, Shift in Baseline Pre-dose FEV ₁ (L) over the Study (EAS ¹).....	158
Table 88. SD-039-0717, Number and percentage of patients with a CRF pre-defined asthma event (EAS)	161
Table 89. SD-039-0717, Treatment comparisons for percentage of patients with at least 1 CRF pre-defined asthma event (EAS).....	161
Table 90. SD-039-0717, Withdrawals due to pre-defined asthma event (EAS).....	162
Table 91. SD-039-0717, Number (%) of patients achieving 15% improvement in FEV ₁ (EAS).....	164
Table 92. SD-039-0717, Mean Morning and Evening PEF (EAS).....	164

Table 93. SD-039-0717, Asthma symptom scores (EAS)	165
Table 94. SD-039-0717, Rescue medication use (EAS)	165
Table 95. SD-039-0717, AQLQ(S) for patients ≥18 years of age	167
Table 96. SD-039-0717, AQLQ[S] treatment comparisons, overall scores, end of treatment	167
Table 97. SD-039-0717, Adjusted means for budesonide PK parameters (PK analysis set)	168
Table 98. SD-039-0717, Adjusted means for formoterol PK parameters (PK analysis set)	169
Table 99. SD-039-0717, Exposure ITT/SAS	170
Table 100. SD-039-0717, Adverse event overview (ITT/SAS)	172
Table 101. SD-039-0717, Listing of SAEs and DAEs during all study phases* (SAS)	172
Table 102. SD-039-0717, Summary of system organ class (SOC) categories with at least 1 AE reported during the treatment period, sorted by decreasing order of frequency across all treatment groups (ITT/SAS)	173
Table 103. SD-039-0717, Adverse events reported by at least 3% of patients in any treatment group during the treatment period (ITT/SAS)	174
Table 104. SD-039-0726, Treatment Means, Evening & Morning PEF, Evening & Morning FEV ₁ (EAS)	181
Table 105. SD-039-0726, Number and percentage of patients with a CRF pre-defined asthma event (EAS)	182
Table 106. SD-039-0681, Treatment Means	185
Table 107. SD-039-0682, Treatment Means	188
Table 108. SD-039-0715, Study Plan	192
Table 109. SD-039-0715, Treatment Means and Ranges, FEV ₁ and FVC	193
Table 110. SD-039-0715, FEV ₁ by subgroup, Symbicort MDI treatment group	194
Table 111. SD-039-0715, AEs by preferred term	195
Table 112. SD-039-0715, Number of patients with severe asthma exacerbations, total and by sub-criterion	196
Table 113. SD-039-0715, SAEs	198
Table 114. SD-039-0715, DAEs	199
Table 115. SD-039-0715, Mean cortisol results (Mean, range)	201
Table 116. SD-039-0715, Shift table for Plasma spot AM cortisol	201
Table 117. SD-039-0715, ECG findings	202
Table 118. SD-039-0715, Shift table for QT, QTcB, and QTcF, Visit 1 to highest on-treatment result (msec)	203
Table 119. SD-039-0715, Summary of QT, QTcB, and QTcF positive and negative changes (msec)	203
Table 120. SD-039-0719, Pre-dose FEV ₁ (Mean, SD)	207
Table 121. SD-039-0719, Adverse event overview	208
Table 122. SD-039-0719, Listing of SAEs and DAEs during all study phases (SAS)	209
Table 123. SD-039-0719, AEs by preferred term	209
Table 124. SD-039-0719, Mean 24-hour cortisol results (nmol/24 hours)*	210
Table 125. SD-039-0719, Shift table for 24-hour urinary cortisol at end of treatment	211
Table 126. SD-039-0719, Patients with clinically notable 24-hour urinary cortisol findings at any time during treatment	211
Table 127. SD-039-0719, ECG findings	213
Table 128. SD-039-0719, Patients with QTc ≥450 and QTcB change ≥60 msec (all on Symbicort)	213

Table of Figures

Figure 1. Studies 716 and 717, Comparisons for co-primary efficacy variables (morning pre-dose FEV ₁ and baseline-adjusted average 12-hour FEV ₁)	15
Figure 2. Symbicort MDI device	25
Figure 3. Study SD-039-0716, Treatment comparisons, Average 12-hour FEV ₁ (L) at Week 2	49
Figure 4. Study SD-039-0717, Treatment comparisons, Average 12-hour FEV ₁ (L) at Week 2	49
Figure 5. Study SD-039-0716, Treatment comparisons, Pre dose FEV ₁	50

Figure 6. Study SD-039-0717, Treatment comparisons, Pre dose FEV ₁	51
Figure 7. SD-039-0716, Percent CRF predefined asthma events	52
Figure 8. SD-039-0717, Percent CRF predefined asthma events	52
Figure 9. Studies 716 and 717, Odds ratio comparisons for predefined CRF asthma worsening criteria.....	53
Figure 10. Study 717, Mean percent change from baseline in FEV ₁ over 12 hours on day of randomization and at end of treatment	54
Figure 11. SD-039-0729, Adjusted mean FEV ₁ over time, by treatment (LOCF).....	101
Figure 12. SD-039-0729, Mean percent change in FEV ₁ over time from pre-dose value, by treatment (LOCF).....	101
Figure 13. SD-039-0729, Adjusted mean FEV ₁ over first 60 minutes after administration (LOCF)	102
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).....	103
Figure 15. SD-039-0729, Twelve-hour excretion of unchanged formoterol by treatment and dose	103
Figure 16. SD-039-0716, Flow chart of study treatments.....	106
Figure 17. SD-039-0716, LS mean FEV ₁ values at Week 2 LOCF, (EAS ≥12)	120
Figure 18. SD-039-0716, Mean percent change from baseline in FEV ₁ on Day of Randomization, (EAS ≥12)	121
Figure 19. SD-039-0716, Mean percent change from baseline in FEV ₁ at Week 2 LOCF, (EAS ≥12).....	121
Figure 20. SD-039-0716, Mean percent change from baseline in FEV ₁ at End of treatment LOCF, (EAS ≥12).....	122
Figure 21. SD-039-0716, Mean percent change from baseline in pre-dose FEV ₁ by visit (EAS ≥12 yr).....	125
Figure 22. SD-039-0716, Kaplan-Meier curves of time (days) to first CRF pre-defined asthma event (EAS ≥12)*	129
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)	131
Figure 24. SD-039-0717, LS mean FEV ₁ values at Week 2 LOCF (EAS).....	153
Figure 25. SD-039-0717, Mean percent change from baseline in FEV ₁ on Day of Randomization (EAS)	153
Figure 26. SD-039-0717, Mean percent change from baseline in FEV ₁ at Week 2 LOCF (EAS)	154
Figure 27. SD-039-0717, Mean percent change from baseline in FEV ₁ at End of treatment LOCF (EAS).....	154
Figure 28. SD-039-0717, Mean percent change from baseline in pre-dose FEV ₁ by visit (EAS)	158
Figure 29. SD-039-0717, Kaplan-Meier curves of time (days) to first CRF pre-defined asthma event (EAS), All dose strata.....	162
Figure 30. SD-039-0717, Kaplan-Meier plot of time to 15% improvement in FEV ₁ during the first 60 minutes after first dose, Day 1 (EAS)	163
Figure 31. SD-039-0717, Mean budesonide plasma concentrations (PK analysis set).....	168
Figure 32. SD-039-0717, Mean formoterol plasma concentrations (PK analysis set).....	169
Figure 33. SD-039-0726, Evening PEF, Mean change from baseline by study day (EAS, LOCF).....	182
Figure 34. SD-039-0726, Mean % change from baseline in FEV ₁ 0-12 hours at Week 2	183
Figure 35. SD-039-0681, Daily mean PEF, Top: Absolute values; Bottom: Change from mean	186
Figure 36. SD-039-0682, Daily mean PEF, Top: Absolute values; Bottom: Change from mean	189
Figure 37. SD-039-0715, Mean FEV ₁ ; Absolute values (left) and change from baseline (right)	194
Figure 38. SD-039-0715, Severe asthma exacerbations by patient	196
Figure 39. SD-039-0715, Kaplan-Meier plot of time to first severe asthma exacerbation	197
Figure 40. SD-039-0715, Mean 24-hour cortisol results	201
Figure 41. SD-039-0715, Shift graph for QTcB (msec)	202
Figure 42. SD-039-0719, Mean percent change from baseline in pre-dose FEV ₁	207

1 EXECUTIVE SUMMARY

NDA 21-929 is a 505(b)(1) application for Symbicort® 80/4.5 and 160/4.5 (budesonide and formoterol fumarate dehydrate) inhalation aerosol, a new product from AstraZeneca LP (AZ). The stamp date for the application is September 23, 2005; the filing date is November 22, 2005; and the PDUFA date is July 23, 2006. Symbicort is a fixed-dose combination product of budesonide (corticosteroid) and formoterol fumarate dehydrate (long-acting beta-agonist) intended for the maintenance treatment of asthma in patients ≥ 12 years of age. The drug product is a pressurized metered dose inhaler (MDI or pMDI) using HFA 227 as the propellant. Two dosage strengths are proposed for different asthma severities, 80/4.5 and 160/4.5 mcg, containing 80 or 160 mcg of budesonide and 4.5 mcg of formoterol fumarate, respectively.

1.1 Recommendation on Regulatory Action

I recommend approval of this application.

1.2 Recommendation on Postmarketing Actions

1.2.1 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.

1.2.2 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.

1.2.3 Other Phase 4 Requests

I have no recommendations for other Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The clinical program for Symbicort was ambitious, but was gradually pared due to CMC and efficacy issues. Originally, approval of — dosage strengths (— 80/4.5, and 160/4.5 mcg) was to be sought in populations of asthmatics — years of age and above, for — twice-daily dosing.

— thereby limiting the program to asthmatics ≥ 12 years of age.

— The clinical program was a full program of PK, PD, efficacy and safety, and long-term safety studies, briefly summarized below. The table of Phase 3 studies (Table 5) will be found in Section 4.2 of this document.

Several PK studies were performed that showed equal or less systemic exposure from Symbicort when compared to “similar” doses of the monoproducts. PK was also performed in one of the pivotal clinical trials, 717.

Study SD-039-0729 was the pivotal pharmacodynamic study linking the formoterol in the Symbicort and Oxis Turbuhaler devices, and helping to resolve the pharmacologic differences presented by use of different devices in the pivotal studies. Three different doses of Symbicort MDI and Oxis TBH were used: 0, 1, 2, and 4 inhalations. There was evidence of a dose-response relationship for both drug products. As measured by average 12-hour FEV₁, the bronchodilating effects of formoterol from Symbicort MDI and Oxis TBH were comparable dose for dose in the range of 4.5 to 18 mg (i.e. 1 to 4 inhalations). A similar pattern of results was seen for the secondary endpoints of maximum FEV₁ and FEV₁ at 12 hours.

Studies SD-039-0716 and SD-039-0717 were the pivotal 12-week safety and efficacy studies. The protocols for these studies were almost identical, differing primarily in the dosage strength and asthma population studied.

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 480 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: FEV₁ on ICS therapy 60% to 90% predicted; for < 12 years: $\geq 75\%$ predicted). Randomization was stratified by age group (< 12 years 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 FEV₁ was 2.5 L and mean percent reversibility was 18.9% (range 10.3% to 62.6%). At baseline, the mean percent predicted FEV₁ 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.

Study SD-039-0717 was a randomized, double-blind, double-dummy, placebo-controlled 12-week study comparing the efficacy and safety of Symbicort MDI (160/4.5 mcg dosage strength) with its pharmacologic monoproducts, budesonide MDI (160 mcg) and formoterol (Oxis) Turbuhaler, the free combination of monoproducts, and placebo, each administered as 2 inhalations BID, in 596 adolescents and adults ≥ 12 years of age with moderate-to-severe asthma (FEV₁ on moderate to high dose ICS therapy 45% to 80% predicted). Randomization was stratified by previous ICS treatment. The study comprised a screening visit, a 14 (± 7) day single-blind budesonide (80 mcg, 2 inhalations BID) run-in period, and a 12-week double-blind treatment period. The study population was approximately 78% Caucasian, 16% Black, 38% male, and 62% female. The mean age was 41 years (range 12 to 87 years), with 37 patients ≥ 65 years of age and 37 below 16 years of age. The average length of asthma history was 23 years. At screening, 427 (71.6%) were on moderate doses of ICS and 169 (28.4%) were on high doses; the mean pre-dose FEV₁ was 2.2 L, mean percent predicted FEV₁ was 66.9%, and mean percent reversibility was 22.2% (range -0.4% to 97.7%) while being treated with an average ICS dose of 590 mcg daily (range 160 to 1600 mcg a day). At baseline, the mean percent predicted FEV₁ for most patients was in the moderate range (68.1 % predicted). 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. Treatment groups were well balanced at randomization.

For both studies, 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 studies 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 FEV₁ of $\geq 20\%$ from the pre-dose FEV₁ 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 $\geq 20\%$ 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 FEV₁ and pre-dose FEV₁. **Baseline-adjusted average 12-hour FEV₁ 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 FEV₁ at 2 weeks** was used to demonstrate the stabilizing, anti-inflammatory effect of the corticosteroid (budesonide) component (comparison: Symbicort minus formoterol). In study 716, efficacy was assessed only in patients ≥ 12 years of age. These variables and endpoints are typical of those used to evaluate controlled and bronchodilators, and are acceptable.

Originally, both studies 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 studies, this variable was demoted to a secondary efficacy variable and pre-dose FEV₁ 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.

Secondary efficacy variables included: pre-defined asthma events and withdrawals due to pre-defined asthma events; other spirometry-related variables (2-hour post-dose FEV₁, maximum FEV₁, onset of effect [15% improvement in FEV₁ 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.

Study SD-039-0715 was the pivotal long-term safety study for this application. This 52-week safety study provides open-label, non-placebo-controlled (the study had an active control, but the active control was a different formulation of Symbicort, i.e. Symbicort TBH) safety data for the Symbicort MDI 160/4.5 drug product in 673 adults, of whom 446 were randomized to Symbicort MDI and 392 completed one year of treatment with Symbicort MDI. The Symbicort MDI group comprised 446 patients: 273 (61.2%) women, 173 (38.8%) men, 370 (83.0%) Caucasian, 8 (1.8%) Black, 61 (13.7%) Oriental, 7 (1.6%) Other, with a mean age of 40 years (range 12-85, 58 12-17 and 36 (8.1%) ≥65 years), and a history of asthma for approximately 10 years. The average ICS dose was 686 mcg (range 200-1600 mcg) per day. The mean FEV₁ was 2.47 L, 80.3% predicted, with 24% reversibility.

Several other studies supported various aspects of the clinical program, lending weight to the findings. All studies using either the 80/4.5 or 160/4.5 dosage strengths administered BID were reviewed. All reviewed studies may be found in the Appendix of this document. Specifically, Study SD-039-0726 included a comparison of the 80/4.5 mcg to placebo, administered BID in patients ≥16 years, using evening PEF as the primary endpoint. In addition, Study SD-039-0681 included the 160/4.5 mcg dosage strength BID in patients ≥12 years using morning PEF, but did not include placebo, the same budesonide as used in the pivotal clinical studies, or formoterol. Finally, Study SD-039-0682 included the 80/4.5 mcg dosage strength BID in patients 6-11 years using morning PEF, but did not include placebo, the same budesonide as used in the pivotal clinical studies, or formoterol.

1.3.2 Efficacy

In both pivotal studies, Symbicort showed statistical superiority over its monoproducts for each of the co-primary efficacy endpoints, FEV₁ 0-12 hours for the formoterol component and pre-dose FEV₁ 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. For each endpoint, the size of the treatment effect (comparison of Symbicort to placebo) was considered

clinically meaningful. Treatment comparisons for the co-primary endpoints in the two studies are shown in Figure 1.

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; the results thereby provided support for the primary efficacy outcome analyses. In both studies 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 FEV₁ 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 FEV₁ etc. In both studies, AQLQ[S] results of change from baseline to end of treatment for the comparison of Symbicort to placebo were both statistically significant and clinically relevant (MID = 0.5 to total score).

In both studies, 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, for other secondary endpoints the results of the two studies differed. In study 716 in mild to moderate asthmatics, except for AM and PM PEF and the prevention [or delay] of tachyphylaxis, in the milder study population there was little if any additive effect for the combination in comparison to the monoproducts for their respective expected endpoint results. In this population, the addition of a LABA did not substantively affect frequency or time to onset of pre-defined asthma exacerbation events. In study 717 in moderate to severe asthmatics, the addition of formoterol to budesonide did appear to have an effect beyond either of the two monoproduct arms with regard to multiple secondary endpoints including key factors in asthma control such as frequency and severity of exacerbations, time to exacerbations, rescue medication use, etc.

In summary, the submitted studies support the efficacy of Symbicort.

**Appears This Way
On Original**

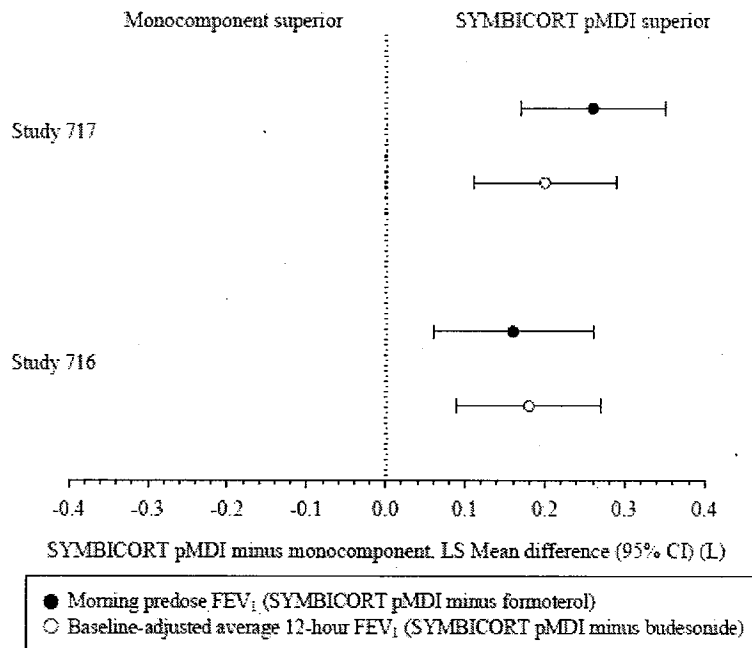


Figure 1. Studies 716 and 717, Comparisons for co-primary efficacy variables (morning pre-dose FEV₁ and baseline-adjusted average 12-hour FEV₁)

Source: F1, p29; clinover.pdf

1.3.3 Safety

The safety review of this application did not reveal any new or unusual safety trends. The two drugs in Symbicort represent a convenience packaging of the individual drugs, both of which are marketed (but not as an HFA formulation) in the United States. The clinical experience with budesonide extends for the last decade, and with formoterol for the last half-decade. For the most part, safety issues with these two drugs are well-known. The clinical community is quite comfortable with use of ICS, and specifically with use of budesonide. The safety findings in this application did not reveal any new or unexpected safety trends with regard to budesonide. On the other hand, the safety of formoterol is still of concern, as witnessed by the Advisory Committee meeting regarding safety of LABAs within the last year. The safety review of this application therefore focused on those aspects of both drugs that might be of clinical concern based on the current state of knowledge of these two drug classes. The major review issue encountered was the relative paucity of safety data on patient populations other than Caucasians. No safety trends were noted.

1.3.4 Dosing Regimen and Administration

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, as recommended in the proposed Dosing and Administration section. The maximum proposed daily dose is appropriate, at 640/18 mcg/day, administered as 160/4.5, 2 inhalations BID.

1.3.5 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. The applicant performed analyses of AE's by use of concomitant medications, and no clinically meaningful safety trends were noted.

1.3.6 Special Populations

No special population studies [other than the pediatric studies discussed below] 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 or 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. Analyses included evaluations for effects of gender, race, and age on the frequency of adverse events, and none were found.

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. AstraZeneca has evaluated Symbicort MDI in asthma populations down to 6 years of age.

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). Under PREA, AstraZeneca is requesting a deferral of submission of pediatric studies in patients 6 to <12 years of age until some time (unspecified) in 2007, and this 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.

**Appears This Way
On Original**

Referential Notation

References to source material are bracketed [] and follow a standard format: [the section, table, or figure; the page number(s); the pdf file name]; for example, [S5.3.5.1, T 51, p499-501; name_me.pdf]. References assume the original submission, otherwise they show the submission and date. References to hard copy material outside the submission (e.g., FDA reviews, correspondence, meeting minutes) are descriptive; for example, [NDA XX-XXX, Medical Officer's Review, December 12, 1998].

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

NDA 21-929 is a 505(b)(1) application for Symbicort® 80/4.5 and 160/4.5 (budesonide and formoterol fumarate dehydrate) inhalation aerosol, a new product from AstraZeneca LP (AZ). The stamp date for the application is September 23, 2005; the filing date is November 22, 2005; and the PDUFA date is July 23, 2006. The application is in CTD format and was filed electronically, but it is not an eCTD application.

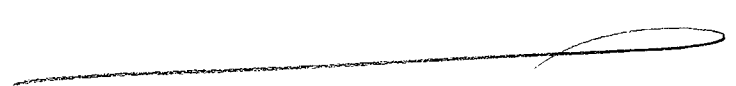
Symbicort is a fixed-dose combination product of budesonide (corticosteroid) and formoterol fumarate dehydrate (long-acting beta-agonist) intended for the maintenance treatment of asthma in patients ≥ 12 years of age. The drug product is a pressurized metered dose inhaler (MDI or pMDI) using HFA 227 propellant. ***Note: This would be the first inhalational drug product to use HFA 227; all currently approved inhalation aerosol drug products use HFA 134.*** Two dosage strengths are proposed for different asthma severities, 80/4.5 and 160/4.5 mcg, containing 80 or 160 mcg of budesonide and 4.5 mcg of formoterol, respectively. Each is proposed for two actuations twice daily as shown in Table 1. Throughout this review, references to dose forms of the product will be abbreviated by showing the nominal (ex-actuator) doses of the two components, budesonide followed by formoterol; for example, 80 mcg budesonide + 4.5 mcg formoterol will be indicated by "80/4.5" mcg.

Table 1. Symbicort MDI Dosage Strengths

Dosage Strength	Dosage	Total Daily Dose
80 mcg budesonide + 4.5 mcg formoterol/actuation	2 actuations (160/9) BID	320/18
160 mcg budesonide + 4.5 mcg formoterol/actuation	2 actuations (320/9) BID	640/18

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

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

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

2.2 Currently Available Treatment for Indications

Currently available treatment includes various formulations of both budesonide and formoterol single-ingredient products. The combination of budesonide and formoterol are also available in a dry powder inhaler (Symbicort Turbuhaler) outside the US. Please see the next section for complete details.

Also available are multiple approved HFA or DPI formulations of other orally inhaled corticosteroids, and several approved formulations of other long-acting beta agonists, either as single ingredient or together with other corticosteroids (e.g. Advair).

2.3 Availability of Proposed Active Ingredient in the United States

Each active ingredient is available in the United States, but the combination is not.

Budesonide is available in several formulations for intranasal, orally inhaled, and oral use. The following budesonide-containing products have been approved in the United States: Rhinocort Nasal Inhaler (NDA 20-333, 2/14/1994), Pulmicort Turbuhaler® (NDA 20-441, 6/24/1997), Rhinocort Aqua® Nasal Spray (NDA 20-746, 10/1/1999), Pulmicort Respules® (NDA 20-929, 8/8/2000), and Entocort™ EC (NDA 21-324, 10/2/2001). Pulmicort Respules is approved for maintenance treatment of asthma in patients 12 months to 8 years of age. All are marketed by AstraZeneca.

Formoterol is approved in the United States as Foradil® Aerolizer® (formoterol fumarate inhalation powder) (NDA 20-831, 2/16/2001, Novartis) for maintenance treatment of asthma in patients 5 years of age and older.

Several products played key roles in the Symbicort MDI clinical development program. They are listed and described in the Table below.

Table 2. NDA 21-929 Clinical Products

Product	Description
• Symbicort pMDI	MDI – The NDA drug.
• Symbicort Turbuhaler (TBH)	DPI – Marketed for asthma and COPD outside US.
• Budesonide pMDI	MDI – Used as the NDA comparator monoproduct. <u>Not</u> a marketed product.
• Pulmicort Turbuhaler (budesonide)	DPI approved for asthma in US (NDA 20-441).
• Oxis Turbuhaler (formoterol)	DPI – Used as the NDA comparator monoproduct. Marketed for asthma outside US.

Reviewer's Note: The reader will note that there are two presentations of Symbicort, although only one is the subject of this NDA (the MDI form). For clarity, Symbicort HFA MDI (referred to by the applicant as Symbicort pMDI) will hereafter in this review be referred to as

Symbicort or Symbicort MDI, whereas the Symbicort Turbuhaler (TBH) will always be specified as such (i.e. Symbicort TBH).

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

1. Symbicort Turbuhaler (TBH) is a dry powder inhaler (DPI) presentation of Symbicort marketed widely around the world, as noted in Section 2.2, 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. There were more than 60 clinical studies with Symbicort TBH. The applicant grouped the studies according to their designs and applicability to Symbicort MDI. For the most part these studies provide background safety data for the combination of the two ingredients, but do not provide direct support for the safety or efficacy of the Symbicort MDI drug product. Therefore, these studies were not considered except as a part of the safety assessment of both budesonide and formoterol in [a different] combination. To distinguish it from Symbicort MDI, Symbicort TBH always appears as a separate column within the tables of this review.

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. For Oxis, 27 studies were considered to be core studies. 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 or efficacy of Symbicort MDI. Therefore, these studies were not considered except as a part of the safety assessment of formoterol in the combination drug product.

Nevertheless, Oxis has a critical role for this NDA. It is a DPI presentation, unlike Symbicort and the budesonide comparator (both MDI presentations), and this difference generates concern about distinguishing pharmacologic from pharmacological effects in evaluating the contribution of the formoterol component to the combination product. After ongoing discussions on this issue with the Division, the Sponsor agreed to conduct a separate study to address this issue. That study was SD-039-0729. Its review was pivotal in the determination of whether the application meets criteria for approvability. Please refer to the Clinical Pharmacology section of this review for further details (as well as the Appendix for a more complete review of the study). A second link was provided by the PK data in one of the two pivotal studies, SD-039-0717. The final link was provided by CMC data for the various products. The sum of this information provided support for the use of this DPI product as a mono-comparator in the pivotal clinical studies. Nevertheless, in combination with the primary and other efficacy data, the Oxis efficacy data had to be sufficient by itself to support its use as a comparator monoproduct. This is addressed in the various appropriate sections of the review.

3. Finally, the budesonide HFA MDI monoproduct comparator used in the program is not the same as the marketed Pulmicort Turbuhaler DPI product. This is important because Pulmicort was also included in some studies as a comparator and the distinction is important because of pharmaceutical differences between the (unapproved) MDI and the (approved) DPI budesonide products. Because Pulmicort TBH 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.

Nevertheless, the budesonide MDI had several issues that also required addressing in the development program. Unlike the Oxis TBH there were two dosage strengths, 80 and 160 mcg. Like Oxis TBH, it is an unapproved drug product. Therefore, the program had to provide CMC data for the products and at the same time, in combination with the primary and other efficacy data, had to be sufficient by itself to support its use as a comparator monoproduct. This is addressed in the various appropriate sections of the review.

Because of the multiple products and the ambition of the Symbicort MDI clinical program, the appropriate sections of the NDA review discuss these various points and distinctions about the products, and present data to support each aspect.

2.4 Important Issues With Pharmacologically Related Products

Several long-acting beta-agonists (LABAs) are approved in the United States, salmeterol and formoterol. Both are selective beta₂-adrenergic receptor agonists. Whereas salmeterol is considered to be a partial receptor binding agent, formoterol is considered to be completely bind the beta₂ adrenergic receptor.

Salmeterol is approved as Serevent (single-ingredient salmeterol xinafoate) and Advair (salmeterol plus the corticosteroid fluticasone propionate). Serevent is approved as both a Diskus (dry powder) formulation (NDA 020-692, 9/19/1997, GSK) and as an inhalation aerosol (NDA 020-236, 2/4/1994, GSK). Advair is approved as a Diskus formulation (NDA 021-077, 8/24/2000, GSK), and is available in 100/50, 250/50, and 500/50 mcg dosage strengths. Both Serevent and Advair carry two indications: 1) as a long-term, twice-daily maintenance treatment of asthma in patients 4 years of age and older, and 2) as maintenance treatment of airflow obstruction in patients with COPD associated with chronic bronchitis. Serevent is also indicated as a long-term, twice-daily maintenance treatment of patients with nocturnal asthma and for prevention of bronchospasm in patients 4 years of age and older.

Formoterol is approved as Foradil Aerolizer (formoterol fumarate inhalation powder) (NDA 20-831, 2/16/2001, Novartis). The indications for Foradil are similar to those for Serevent, as a long-term, twice-daily maintenance treatment of asthma in patients 5 years of age and older, including patients with nocturnal asthma. Somewhat similar to Serevent, Foradil is also indicated as a long-term, twice-daily maintenance treatment of bronchoconstriction in patients with COPD including chronic bronchitis and emphysema. In addition, Foradil carries an indication for acute prevention of exercise-induced bronchospasm (EIB) in patients 5 years of age when administered on an occasional, as needed basis. The approved dose is 12 mcg BID.

A Pulmonary-Allergy Drug Advisory Committee Meeting was held on July 13, 2005, to discuss the safety findings associated with use of long-acting beta-agonists in patients with asthma. 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 (see below), and is being currently negotiated for the formoterol drug products.

Serevent Diskus boxed warning [Label approved 3/2/2006]:

WARNING

Long-acting beta₂-adrenergic agonists, such as salmeterol, the active ingredient in SEREVENT DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, SEREVENT DISKUS should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, including SEREVENT DISKUS. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo) (see warnings and CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*).

Advair Diskus boxed warning [Label approved 3/2/2006]:

WARNING

Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo) (see WARNINGS).

2.5 Presubmission Regulatory Activity

IND 63,394 was filed in October, 2001, to study Symbicort in the U.S. The development program was ambitious, involving: a combination product, intended around the world registration, and intended for approval for adults and children in _____ once-daily dosing regimens. _____ Many clinical studies were planned and ultimately conducted, and much of the regulatory history of the product involved discussions between the Sponsor and the Division about clinical study design issues. The several studies involved disparate populations, dosages, endpoints, and comparators. Early in development, it was questionable whether the program could satisfy the combination policy because the intended formoterol monoproduct comparator was a dry powder inhaler (DPI) formulation, unlike Symbicort and the budesonide monoproduct which are HFA propellant-driven MDI presentations. The Division was concerned that it would be difficult to differentiate pharmacological effects from pharmaceutical effects in evaluating the contribution of formoterol to the product. Eventually, the Sponsor agreed to conduct a clinical study (SD-039-0729) to sort out this issue. That study was performed and is included in the NDA.

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

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

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

2.6 Other Relevant Background Information

Symbicort MDI was approved in Switzerland in July, 2005. As of December 1, 2005, applications are pending in Australia, New Zealand, South Africa, UK, and Venezuela. Symbicort MDI has not been withdrawn from any market nor has regulatory approval been denied because of safety or effectiveness reasons. [Submission of 1/19/2006, p3; foreignm.pdf]

A dry powder inhaler form of Symbicort known as Symbicort Turbuhaler is approved in 91 countries as of December, 2004. The monoproduct components are each also available commercially in the US or in other countries, but not necessarily in the same formulation. Budesonide is available in the US and internationally as a DPI formulation as Pulmicort® Turbuhaler® and as a nebulization formulation as Pulmicort Respules®. However, the HFA MDI formulation of budesonide used as the mono-component comparator in the pivotal clinical studies is not marketed in any country. The AZ formoterol product is available as a DPI formulation as Oxis® Turbuhaler in 82 countries, but is not approved nor the subject of an NDA in the US.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Alan Schroeder, Ph.D., performed the product quality review of this application. Please refer to his review(s) for details beyond this brief summary. CMC issues that impacted on clinical issues were discussed during the course of both the CMC and clinical reviews, and are reflected below. As of the time of finalization of this review, there were still a number of DMF deficiencies, and a recommendation from the Office of Compliance with regard to the site inspections is still pending.

Microbiology review of the drug substance specifications was performed Anastasia Lolas. The microbial limit specifications and testing procedures were considered adequate.

3.1.1 Drug Product / Device Overview

Symbicort is a pressurized metered dose inhaler (MDI or pMDI), which has been developed in two dosage strengths containing either 80 mcg or 160 mcg of micronized budesonide plus 4.5 mcg micronized formoterol fumarate dehydrate per actuation, ex-actuator, suspended in HFA 227 as the propellant. ***Note: This would be the first inhalational drug product to use HFA 227; all currently approved inhalation aerosol drug products use HFA 134.***

Each formulation includes povidone K 25 as a suspending agent, PEG 1000 as a lubricant, and HFA 227 as the propellant. The aluminum canister with a metering valve, and fitted with a standard press-and-breathe actuator. Each device is individually wrapped in a foil pouch containing a sachet of desiccant. Each product is manufactured to deliver a minimum of 120 actuations, although AstraZeneca has also developed 60-actuation physician sample packs.

The formoterol fumarate used in this drug product is manufactured, tested, and released by AstraZeneca AB, Södertälje, Sweden.

It is micronized at the same AstraZeneca AB site. Testing and release may also be performed at AstraZeneca Dunkerque Production, Dunkerque, France. The micronized budesonide used in this drug product is the same as that used for NDA 21-441, Pulmicort Turbuhaler. The drug product is manufactured, packaged, stability tested and released under the control of AstraZeneca Dunkerque Production, Dunkerque, France.

There are several differences between the commercial product and the clinical trial product. These include:

- changes to the fill weight,
- additions of propellant
- change in the site of manufacture
- change in the valve,
- new source for the canister,
- change in the manufacture for the actuator,
- addition of a red pigment to the actuator body,
- use of small manufacturing (both drugs),
- change in the valve during manufacture,
- use of stress testing during manufacture,
- use of tightened valve dimensional controls,
- a change of actuator manufacturer (not yet validated in the NDA), and
- addition of a gray shield to the top of the device.

The shield component is a gray plastic piece attached to the opposite end of the canister from the valve

AstraZeneca designates the name _____ Symbicort MDI for the device without the shield and using a standard actuator; AstraZeneca designates the name _____ for the device with the shield (Figure 2), which also requires that the actuator be flared or widened. The Symbicort MDI device (i.e. without the shield) was used in the clinical trials and primary stability studies. However, AstraZeneca appears intent to market the _____ device with the shield as the commercial product. During the course of the review, the Agency had to determine whether the _____ and Symbicort MDI device substantively differed in any manner that could materially affect the interpretation and applicability of the efficacy and safety studies. The major concern was that the addition of the Shield might alter the flow resistance of the device in a negative manner, impeding inspiratory flow and changing delivery of the respirable fraction of the drug product to the patient. A comparison of flow resistance between the two drug products was requested. AstraZeneca responded that at an airflow of _____ the clinical product and the product intended for marketing _____ have flow resistances of _____ respectively. These flow resistances are considered to be very low, particularly compared to various DPI devices. It was also noted that the mouthpiece (including the orifice through which the aerosol passes) has not changed throughout the development process. In addition, comparative drug product performance data provided for both products do not appear to differ substantially (there may be small shifts in aerodynamic particle size distribution). Based on this information, the Agency made the determination that the addition of the Shield component would not negatively alter the inspiratory characteristics of the to-be-marketed _____ device. [M3; description-and-composition.pdf and pharmaceutical-development.pdf; Submission of 3/16/2006, Comment 4.1(xi), p6; clarification.pdf]

Source: M3.2.P.1; description-and-composition.pdf

Of note, both budesonide and formoterol are micronized in order to obtain particle size distributions suitable for topical delivery to the lung. Both have very similar densities, both being less dense than HFA 227;

AstraZeneca states that the formulation is a physically stable suspension that is immediately and homogeneously dispersed upon shaking. Since for MDI drug products the metering valve meters the next dose immediately after release of the canister with the prior actuation, shaking

_____ is an important step in use of the device with every actuation. This needs to be addressed by labeling requiring shaking prior to each actuation.

In addition to the standard CMC review of an MDI drug product, one of the goals of the CMC review was to evaluate both of the unapproved budesonide MDI monoproducts (80 and 160 mcg presentations) as well as the Oxis Turbuhaler used as comparators in the clinical trials. The goal was to determine whether the dose content (DCU) and aerosolized particle size distribution (APSD) of budesonide were dose proportional, and whether the results were substantially similar to that for the Symbicort MDI drug products (80/4.5 and 160/4.5 mcg dosage strengths), with the intent to assess whether the nominally delivered doses were similar enough to allow clinical comparison of the budesonide component in the clinical program. In the end, it was judged that any differences seen between the different drug products and different dosage strengths were not clinically significant. The information below summarizes the products, any comparisons to Symbicort MDI, and the corresponding information about the Symbicort MDI drug product.

3.1.2 Formoterol fumarate

The mono-product formoterol comparator for this NDA was Oxis Turbuhaler. Oxis Turbuhaler is a dry powder inhaler formulation of formoterol. Like many dry powder inhalers, is subject to decreases in the respirable dose as flow rates drop below 60 L/min. For example, comparing the aerodynamic particle size distribution (APSD) results at the two flow rates _____ there is a significant increase in particle sizes at the low relative to the high flow rate. The applicant attributes this to lower deaggregation efficiency of the formulation at the lower flow rate. As an example, for 6 batches, the mean "fine particle dose" (% of label claim, LC) was _____; this is a loss of _____ at the lower flow rate. At low flow rates, delivered dose is also reduced and the variability of dose delivery is increased relative to higher flow rates (e.g., at _____ average delivered dose was _____ LC and at _____ LC; tests were for dose numbers 1 to 5, 28 to 32 and 56 to 60, i.e., through the life of the product). It is hard to judge the effect of this phenomenon on the application. Patients enrolled in study SD-039-0729 were likely well trained, and there should have been no effect on this pivotal pharmacodynamic study. For patients enrolled in the two pivotal (716 and 717) clinical [as well as other] studies, this may or may not have been an issue. More patients in the placebo and formoterol arms withdrew from the pivotal studies due to lack of asthma control, but this is more likely to have been a function of LABAs [formoterol] not being controller medications than any decrease in effect due lack of good inspiratory effort.

Regarding Symbicort MDI, each dosage strength has the same labeled strength of formoterol fumarate. There is, however, a slight decrease (_____) in the amount of formoterol fumarate fine particle dose delivered in going from the 80/4.5 strength to the 160/4.5 strength. This is not considered clinically significant.

3.1.3 Budesonide

The CMC reviewer reports that Symbicort appears to be dose proportional for budesonide in terms of delivered dose; however, it is not quite dose proportional for fine particle dose _____. This is shown in Table 3 below. Means for fine particle dose of budesonide as % of label claim for each dosage strength of Symbicort, along with the number of observations (batches) and % RSDs are shown. If the product were fully dose proportional, the fine particle dose (since it is expressed as % of the label claim) would be the same for all _____ strengths. The

difference is not large, and was judged not to be clinically relevant. There is also some shift within the fine particle size range of the drug product as the strength is increased, as well as a decrease in the fine particle dose itself. These data imply that the higher strength product has a budesonide suspension that is shifted somewhat to larger particle sizes within the fine particle dose, relative to the lower strength product. The differences were noted to be small and not clinically relevant.

The mono-product budesonide comparator for this NDA was an unapproved budesonide HFA MDI. To allow use of the unapproved budesonide HFA MDI as a comparator, the NDA included information for this drug product to demonstrate dose proportionality and provide a comparison of the Symbicort and budesonide MDIs. The graphical data shows that they are similar (but not identical) for delivered dose and for fine particle dose, with trends similar to that for Symbicort.

Table 3. Means for fine particle dose of budesonide as % of label claim for each dosage strength of Symbicort

Strength	Fine Particle Dose % LC	N	RSD
Beginning of canister			
80/4.5			
160/4.5			
End of canister			
80/4.5			
160/4.5			
Source: Communication from CMC reviewer, Dr. Schroeder. The data are obtained from the CMC pharmaceutical development section for the drug product (Attachment 5).			

3.1.4 Other CMC issues

Stability data show that there are occasional outliers in delivered doses (for both active ingredients). The highest outliers reported are — of label claim for budesonide and — of label claim for formoterol fumarate dihydrate. Outliers (when they occur) are more likely to be between — of label claim. The vast bulk of the data are between — of label claim. An occasional dose at this level was not considered to be of clinical concern.

One other issue noted was that the first dose after storage of the product (in a valve-up position) for 9 months causes an increase of drug delivered in the first dose (actuations #1 & 2), for both drug substances (e.g., up to — of label claim). The applicant claims that the amount of delivered drug returns to approximately the label claim value by the second dose (actuations #3 & 4). Such high doses are said not to be observed for valve down storage, and the drug product used for clinical studies was stored valve down “in the supply chain.” In patient hands, this may be dealt with by labeling that reinforces the need for “test sprays” before first use and if not used for a period of time.

3.1.5 Device performance and reliability

The Symbicort MDI clinical program does not appear to have included a full program of device performance and reliability evaluation. For inhalational drug products, the knowledge base in this area, and corresponding FDA requests for applicants to obtain this information at all phases of clinical development, has changed substantially in the last few years. Typically, applicants now are encouraged to develop a plan to be incorporated into the Phase 3 studies. In such a plan, patients are asked to report devices they perceive to be broken or malfunctioning, and any device so reported returned and evaluated to identify the problem. Device use and performance is also evaluated through directed questions defined in the protocols. In this way, information is generated regarding the types and frequencies of device malfunction based on data from a large number of devices, and an analysis of the cause may lead to potential improvements to the device itself. In addition, a small number (e.g. 100) of devices that are apparently functioning normally in patients' hands should be collected near the end of the life of the device and evaluated by *in vitro* performance testing to assure ruggedness throughout the product's intended span of use.

A limited amount of data with regard to *in vitro* testing at the end of the life-of-device was found in the NDA, summarized by Dr. Schroeder below. A comment was sent to the Applicant in the 74-day letter noting the absence of device performance evaluations. This is a deficiency in the clinical program, but not a fatal flaw. Unfortunately, data obtained post-approval would be of no value in the approval process, so a decision must be made on the available data, such as it is. The information below addresses the issue of *in vitro* testing of dose content at the end of the life-of-the-device, but does not fully address device reliability, since only visual inspections were performed. Nevertheless, it is judged sufficient to allow approval.

"Drug product was used in clinical studies according to the protocol and then returned to the applicant, partially used. These canisters were not heat stressed during manufacturing and environmental storage was not under the control of the applicant during the clinical study."

"Due to time taken to have product returned to AstraZeneca R&D Charnwood and processed, it was common for product to be out of the protective foil wrap for at least 3 months prior to analysis. When product was received at AstraZeneca R&D Charnwood, it was randomly sampled for analysis (by visual evaluation, delivered dose and actuation weight performance, and APSD by Andersen cascade impaction). Results on samples chosen for analysis: "there was some evidence of a small amount of stem deposition consistent with product usage, but no evidence of heavy drug deposition on the ferrule of the canister or on the stem and hence no visual evidence of leakage." There were 477 samples assessed for visual appearance.

Delivered dose results (25 MDIs per clinical study; 75 MDIs total) are summarized below:

Table 4. Summary data for clinical returns dose analysis

Parameter	Budesonide	Formoterol fumarate dihydrate
Delivered dose (% label claim)		
Relative standard deviation (%)	6.9	6.8
Percent of doses within $\pm 20\%$ of label claim	98.7	98.0
Percent of doses within $\pm 25\%$ of label claim	99.0	99.3
Percent of doses within $\pm 35\%$ of label claim	100.0	100.0

Uniformity of actuation weight: individual actuation weights were determined in the study of delivered dose (above). For n=600 individual weights, the mean weight is 72.0 mg, with RSD=2.0%.

APSD: "All individual determinations complied with the Phase 3 specification for fine particle dose. Ninety six percent of individual fine particle doses and all can mean fine particle doses comply with the proposed commercial specification. Refer to 'P.5.1 Specifications for Drug Product'."

3.2 Animal Pharmacology/Toxicology

Tim Robison, Ph.D., performed the pharmacology/toxicology review of this application. Please refer to his review(s) for details beyond this brief summary.

Because the preclinical profile of each of the monoproducts is well characterized, AstraZeneca conducted limited bridging preclinical studies to support the Symbicort MDI clinical program. The program included a few pharmacology studies, 3-month bridging inhalational toxicology/toxicokinetic studies in rats and dogs, and an embryofetal toxicity study in rats. Also included were a 6-month toxicity and 24-month carcinogenicity studies in rats and 6-month and 12-month toxicity studies in dogs to support the excipients.

During the review, the Pharmacology/ toxicology team focused on the sponsor's nonclinical program for bridging the excipients, PVP K-25 and PEG-1000. These excipients (PVP K-25 and PEG-1000) have never been used in any inhalation drug products, although they are found in many oral drug products. The 3-month inhalation toxicology study in rats with Formoterol HFA pMDI contained PVP K-25, PEG-1000, and HFA-227. In this study, the incidence and severity of alveolar histiocytosis, pneumonitis, and congestion in the lungs were increased for the vehicle-control group as compared to the air-control group in the initial reading. It was determined that these findings are suggestive of local toxicity induced by the vehicle. The dog study was considered clean.

The Division communicated these concerns to AstraZeneca. A reanalysis of lung slides was performed. Examination was done in a blinded fashion, with particular emphasis for histiocytosis, pneumonitis, and congestion. The results were completely different than the original reading. The original findings either disappeared or were observed in all animals (air-control and vehicle-treated). P.J. Kerry, Ph.D., FRCPath of AstraZeneca R&D Charnwood did the original analysis as well as the reanalysis. To reconcile the differences between the first and second analyses, the Division asked for an independent re-analysis, either by a single individual or a workgroup. AstraZeneca had the slides reanalyzed by an independent toxicologist, with clean findings similar to the reanalysis performed by AstraZeneca. The Division accepted this reanalysis, and the preclinical concerns were considered fully addressed.

**Appears This Way
On Original**

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

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

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

Phase 2 was intended to evaluate the bronchodilating properties of Symbicort MDI. The "pivotal" study in this evaluation was SD-039-0729, which addressed the pharmaceutical aspects of the pharmacodynamic behavior of formoterol, providing a PK/PD link between formoterol when administered via TBH and MDI formulations.

The Phase 3 program was originally intended to support and satisfy multiple objectives, including the combination policy, adult — indications, — dosage strengths, and twice-daily — dosing regimens. Nine Phase 3 studies provide the bulk of evidence for clinical effectiveness and safety, as shown in Table 5. The Table illustrates the complexity of the program, with the several different doses and comparators. The review strategy for this complex program is outlined in the section following the table.

4.2 Tables of Clinical Studies

Table 5. Symbicort MDI Phase 3 Studies

Study Duration	Ages/N	Comparators ^a	Symbicort Daily Doses and Formulation ^b					Primary Endpoints
			BID Program			QD Program		
			160/18	320/18	640/18	160/9	320/9	
Placebo-controlled								
716 12 wks	≥12 yrs/480 6-11 yrs/31	Bud MDI 80 Form DPI Placebo		80/4.5				Pre-dose FEV ₁ Avg 12h FEV ₁
717 12 wks	≥12 yrs/560	Bud MDI 160 Form DPI Bud MDI+Form TBH Placebo			160/4.5			Pre-dose FEV ₁ Avg 12h FEV ₁
726 12 wks	≥16 yrs/750	Bud MDI 160 (admin as 320 QD) Placebo		80/4.5		80/4.5	160/4.5	Evening PEF
Active-controlled								
718 12 wks	6-15 yrs/411	Bud MDI Form TBH	40/4.5					Morning PEF
681 12 wks	≥12 yrs/680	Bud MDI CFC Sym TBH			160/4.5			Morning PEF

Study Duration	Ages/N	Comparators ^a	Symbicort Daily Doses and Formulation ^b					Primary Endpoints
			BID Program			QD Program		
			160/18	320/18	640/18	160/9	320/9	
682 12 wks	6-11 yrs/622	Bud MDI CFC Sym TBH		80/4.5				Morning PEF
725 12 wks	6-15 yrs/540	Bud MDI 80	40/4.5			80/4.5		Evening PEF
Safety studies								
719 26 wks	6-11 yrs/187	Pulmicort TBH			160/4.5			Safety
715 52 wks	≥12 yrs/673	Symbicort TBH			160/4.5			Safety
a Comparators: Comparator's dosage strength is shown. All active doses were given at comparable dose to the corresponding Symbicort MDI dose in the study. In study 726, in which multiple doses of Symbicort were used, the budesonide comparator dose was 320 mcg QD. Budesonide MDI HFA 80 mcg was used in studies 716 and 725; Budesonide MDI HFA 160 mcg was used in study 717. Bud = Budesonide mono-component comparator. Budesonide MDI HFA was used in studies 716, 717, 718, 725, 726. Budesonide MDI CFC was used in studies 681, 682. Budesonide Turbuhaler (Pulmicort TBH) was used in study 719. Budesonide MDI HFA 80 mcg was used in study 716, whereas Budesonide MDI HFA 160 mcg was used in study 717. Form = formoterol DPI (Oxis Turbuhaler), all doses at 4.5 mcg/inhalation Bud+Form = Bud administered concurrently with Form Pulm TBH = Pulmicort Turbuhaler (budesonide DPI) Symb TBH = Symbicort Turbuhaler (DPI) b Table shows both Symbicort MDI total daily doses and formulation (40/4.5, 80/4.5, 160/4.5) studied.								
Source: p 2997, clinsum.pdf; T2, p11, clinover.pdf								

4.3 Review Strategy

Despite the apparent complexity of the clinical program, the review strategy for this application was simplified somewhat by the fact that several of the clinical program objectives were dropped and not included with this application.

Therefore, the clinical program is now based on satisfying the combination policy for adults and adolescents, with two dosage strengths and the twice-daily dosage regimen.

Efficacy: To meet the combination policy requirement, the strategy for US regulatory development program was to study Symbicort in comparison to the individual monoproduct comparators. However, the program included monoproducts that are not approved in the US, one of which is pharmaceutically different (Turbuhaler vs MDI for formoterol component). Therefore, it was necessary for the program to establish that each comparator monoproduct delivers the same nominal dose of active and that there were no pharmaceutical differences between products that would confound interpretation of the efficacy results. One link for the formoterol pharmaceutical differences is in study SD-039-0729. Other links included the free-standing mono-components administered together in one arm of one of the pivotal studies, SD-039-0717, and *in vitro* links. Part of establishing that each mono-component has active was the comparison of each to placebo for the desired efficacy variable. However, there were only three placebo-controlled studies in the Phase 3 program, one of which did not include mono-

component BID arms. Therefore, SD-039-0716 and SD-039-0717, which encompass both monoprodut comparators as well as placebo arms within a single study, were considered pivotal for review. They are also the two studies featured in the proposed package insert (see Section 5 below). For this reason, the efficacy review strategy focused primarily on these two studies and study 729.

Several other studies supported various aspects of the clinical program, lending weight to the efficacy findings. All studies using either the 80/4.5 or 160/4.5 dosage strengths administered BID were reviewed. Specifically, Study SD-039-0726 included a comparison of the 80/4.5 mcg to placebo, administered BID in patients ≥ 16 years, using evening PEF as the primary endpoint. In addition, Study SD-039-0681 included the 160/4.5 mcg dosage strength BID in patients ≥ 12 years using morning PEF, but did not include placebo, the same budesonide as used in the pivotal clinical studies, or formoterol. Finally, Study SD-039-0682 included the 80/4.5 mcg dosage strength BID in patients 6-11 years using morning PEF, but did not include placebo, the same budesonide as used in the pivotal clinical studies, or formoterol.

Safety: In addition to the two pivotal safety and efficacy studies, there were two open-label long-term safety studies performed: one in adults and adolescents, SD-039-0715, and one in children 6-11 years of age, SD-039-0719. Since the current indication being sought is limited to patients ≥ 12 years of age, study SD-039-0715 was considered as a pivotal safety study, and study SD-039-0719 considered supportive. Both were reviewed. Study SD-039-0715 used the high-dose formulation of Symbicort, 160/4.5, which is reasonable. It compared the Symbicort MDI and Turbuhaler formulations but did not include either monoprodut or placebo controls. Therefore, the long-term safety program lacks any placebo-comparator. Just as for the efficacy program, the safety review strategy focused on the two 12-week pivotal efficacy and safety studies, along with the 2 safety studies outlined above.

The 4-Month Safety Update (4MSU) [January 19, 2006] contained data from 4 Phase 2/3 clinical studies completed since the preparation of the original submission document.

The cutoff date for this submission was September 30, 2005. Studies submitted with this safety update are shown 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, 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.

Clinical Issues: The clinical program has several minor [*deficiencies*] and one more significant deficiency that should be noted at the outset. None are considered significant enough to prevent approval.

- Within in the entire program there is no within-study comparison of different doses, so conclusions about dose responses must be inferred from the results of separate studies with similar designs but enrolling patients with different levels of asthma severity. This is not considered a major review issue.
- Strictly speaking, there was no within-dose replication of results within the program. This was true for both the Symbicort in comparison to its mono-components and for the budesonide MDI mono-component against placebo (Budesonide 80 mcg was used in study 716, whereas Budesonide 160 mcg was used in study 717). The only replication was for the formoterol mono-component against placebo. On the other hand, the free mono-components were included in study 717, and do help support the efficacy of the 160/4.5 dosage strength. Secondary studies used different protocols, populations, dosing regimens, and endpoints, making cross-study comparison difficult if not impossible. Replication of results for a given dosage strength is not a requirement for a clinical program, and replication may be accepted based on the two different dosage strengths studied, the inclusion of placebo in the two pivotal studies, and the linking *in vitro* data.
- The Symbicort MDI clinical program included no clinical device reliability evaluation, although *in vitro* testing was performed of 477 returned canisters. A comment was sent to the Applicant in the 74-day letter noting its absence. This was a deficiency, but not a fatal flaw in the clinical program. Please see the CMC section for a more complete discussion.
- The Symbicort MDI clinical program included a relative paucity of safety data on patient populations other than Caucasians in the pivotal clinical trials. 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. Nevertheless, the 4 month safety update contained safety data from one long-term safety study using BID dosing and doses at or above the proposed dose. [*Note: The study report was not submitted to the NDA; only the safety data was submitted.*] The combined safety data was felt to be sufficient to support approval.

4.4 Data Quality and Integrity

The clinical program for Symbicort was comprised of 27 studies; of which nine were Phase 3. Of the nine Phase 3 studies, two are considered pivotal by the Division and were the focus of the Division of Scientific Investigations (DSI) audit. They are studies SD-039-0716 and SD-039-0717. In addition, one of the Phase 2 studies, SD-039-0729, was included in the audit because it was critical to the overall program. As a combination product, Symbicort had to be compared to each of its monoproduct components, but the formoterol component was only available in a dry

powder inhaler (DPI) formulation, not an MDI like Symbicort. This difference in the pharmaceutical properties of the combination and monoproduct was potentially problematic for the program. To help address the issue, at the Division's prompting, the Applicant conducted study SD-039-0729. This gives the study a more vital role in the overall program than might otherwise be expected of a Phase 2 study. In addition, one of the investigators in that study disclosed financial interest.

Within the three studies identified for auditing, centers for audit were selected based on several criteria: the number of patients enrolled at the center; whether results in the primary endpoints were discrepant from other centers; and whether investigators declared financial interests. Regarding the last criterion, no investigators in SD-039-0716 disclosed financial interests. One investigator who participated _____ disclosed financial interest. He was _____ disclosed a significant equity interest as defined in 21 CFR 54.2(b). Dr. _____ center is among those recommended for audit _____. No other investigators in any of the studies disclosed financial interest.

Based on the stated criteria, five study sites were recommended for audit, although because Dr. _____ participated in two studies, there are only four geographic sites. The recommended sites are shown in Table 6. The Division recommended that all study patients at each site be audited since there were relatively few patients at each site; spreadsheets of key submitted FEV₁ measurements, corresponding to the primary efficacy parameter, were included in the audit consult to allow for verification of primary data by the auditors.

Table 6. DSI Audit Sites and Results

Study & Center Number	Principal Investigator and Address	N at Center	Endpoints Evaluated	Results of Audit
SD-039-0716: 6027	Edward E. Lisberg, M.D. 7420 Central Avenue, Suite 2020 River Forest, IL 60305	18	FEV ₁ measurements at study visits 3 and 5 (weeks 2 and 12)	No significant deviations or data discrepancies noted.
SD-039-0716: 6050	Sanchayita Tripathy, M.D. Clinical Research of the Ozarks 509 East 10 th Street Rolla, MO 65401	21		No significant deviations or data discrepancies noted.
SD-039-0717: 7026	Edward M. Kerwin, M.D. Clinical Research Institute of Southern Oregon, PC 3860 Crater Lake Ave, Suite B Medford, OR 97504	15	FEV ₁ measurements at study visits 3 and 5 (weeks 2 and 12)	No significant deviations or data discrepancies noted. Two patients with ↓ FEV ₁ ≥20% were not D/C'd per protocol.
SD-039-0717: 7014	Mark H. Ellis, M.D. Children's Hospital of Orange County 725 West LaVeta Orange, CA 92868	12		No significant deviations or data discrepancies noted.
SD-039-0729: 2904	Mark H. Ellis, M.D. Children's Hospital of Orange County 725 West LaVeta Orange, CA 92868	3	All study FEV ₁ measurements	No significant deviations or data discrepancies noted.

_____. For Study SD-039-0717, _____ patients were screened, _____ randomized, _____ completed. For study SD-039-0729, _____ patients were enrolled. The patient record data listings were compared with source documents on site; no significant discrepancies were noted. A Form 483, Inspections Observations, was not issued.

At Dr. Lisberg's site, 29 patients were screened, 20 randomized, 13 completed. The patient record data listings were compared with source documents on site; no significant discrepancies were noted. The data from the site was acceptable. However, a Form 483, Inspections Observations, was issued due to one protocol violation because the investigator did not document a pregnancy test for one female patient prior to randomization, as required by the protocol.

At Dr. Kerwins's site, 23 patients were screened, 16 randomized, 8 completed. The patient record data listings were compared with source documents on site; no significant discrepancies were noted. A Form 483, Inspections Observations, was not issued. However, the inspection documented that 2 patients (6011 and 6008) had a decrease in FEV₁ of $\geq 20\%$ from baseline at Visits 3 and 4 (respectively), and the investigator did not provide adequate follow-up in accordance with the protocol. A voluntary action letter was sent.

At Dr. Tripathy's site, 40 patients were screened, 23 randomized, 17 completed. The patient record data listings were compared with source documents on site; no significant discrepancies were noted. A Form 483, Inspections Observations, was not issued.

4.5 Compliance with Good Clinical Practices

Each study report stated that the study was conducted 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. All protocols received IRB approval.

4.6 Financial Disclosures

The applicant submitted Form 3454 for the following studies: SD-039-0681, SD-039-0682, SD-039-0715, SD-039-0716, SD-039-0717, SD-039-0718, SD-039-0719, SD-039-0725, SD-039-0726, SD-039-0729, SD-039-0732, and SD-039-0733. Where applicable, form 4355 was also submitted. Among these are the three pivotal studies to this application: SD-039-0716, SD-039-0717, and SD-039-0729. This is considered adequate disclosure of the financial arrangements with clinical investigators, as recommended in the FDA guidance for industry on Financial Disclosure by Clinical Investigators.

In the following 6 studies investigators reported no financial interest: SD-039-0715, SD-039-0716, SD-039-0725, SD-039-0726, SD-039-0732, and SD-039-0733.

In the following 6 studies investigators reported a financial interest: _____

_____. The studies and the information disclosed are presented in Table 7. As noted in Section 4.4 above, _____ site was referred for routine audit by DSI.

Table 7. Listing of studies with financial interest disclosed

Study *	Investigator	Investigator Type/ Center No.	Comments
			Equity interest
			Significant payments
			Equity interest
			Significant payments
			Equity interest
			Equity interest
			Significant payments
			Equity interest

* Studies in **bold** are considered by the Division to be pivotal studies.

Source: M1, finandis.pdf

5 CLINICAL PHARMACOLOGY

The pharmacological properties of the two active drugs, budesonide and formoterol, are well known. Several Pharmacokinetic studies were performed. Please refer to the Clinical Pharmacology and Biopharmaceutics review for details.

A 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 [monoprotect] (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. Other pharmaceutical links included CMC data and an arm in study **SD-039-0717** containing the free combination of the two monoprotects, budesonide MDI and Oxis TBH. While a brief description of the two studies follow, a more complete summary of each may be found in the Appendix of this review.

5.1 Pharmacokinetics

There were no specific pharmacokinetic issues in this NDA. Several PK studies were performed that showed equal or less systemic exposure from Symbicort when compared to "similar" doses of the monoprotects. PK was also performed in one of the pivotal clinical trials, **717**.

Study **SD-039-0723** was a PK study designed to examine the pharmacokinetic dose proportionality of budesonide across the different Symbicort formulation strengths. It demonstrated that systemic exposure to budesonide increases approximately two-fold when dosing with Symbicort pMDI 160/4.5 mcg compared with Symbicort pMDI 80/4.5 mcg.

Study **SD-039-0717** was a one of the pivotal, 12-week efficacy and safety studies. It compared Symbicort MDI (160/4.5 mcg) with its pharmacologic monoprotects, budesonide MDI (160 mcg) and formoterol (Oxis) Turbuhaler, each administered as 2 inhalations BID, in adolescents and adults (≥12 years of age) with moderate-severe asthma (patients who had been on medium to

high dose ICS and had FEV₁ of 45-85% percent predicted). Treatment arms also included the free combination of the monoproducts and placebo. PK was performed in consenting patients after 2 weeks of treatment. The PK of budesonide was comparable between Symbicort, the budesonide MDI monoproduct and the budesonide monoproduct when administered in free combination with the formoterol monoproduct. Full results are shown in the Appendix of this review.

5.2 Pharmacodynamics

Study SD-039-0729 was the pivotal pharmacodynamic study linking the formoterol in the Symbicort and Oxis Turbuhaler devices, and helping to resolve the pharmaceutical differences presented by use of different devices in the pivotal studies. Three different doses of Symbicort MDI and Oxis TBH were used. Please see the Appendix of this review for more detailed review of this study. However, a brief description follows.

Study 729 was a randomized, multicenter, open-label, active-controlled, 5-period, incomplete-block, 21 treatment sequence, single-dose crossover study in adults with stable asthma. The study population included men and women ≥ 18 years of age with stable asthma and FEV₁ values between 45-90% predicted, and reversibility of FEV₁ 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. Patients were randomized to receive 5 of 7 possible single-day treatments with a 3- to 14-day washout. Patients were maintained on budesonide MDI such that all patients received budesonide 320 mcg BID throughout the study regardless of the dose of formoterol. Doses of formoterol included 1, 2 or 4 inhalations of Oxis TBH or Symbicort MDI. 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 FEV₁. 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 FEV₁, FEV₁ at 12 hours after dosing, and onset of effect.

As measured by average 12-hour FEV₁, the bronchodilating effects of formoterol from Symbicort MDI and Oxis TBH were comparable dose for dose in the range of 4.5 to 18 mg (i.e. 1 to 4 inhalations). 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. Relative dose potency was estimated using adjusted LS means for average 12-hour FEV₁ at each dose provided. 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).

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 35% greater systemic PK exposure with Symbicort than Oxis did not quite match with the estimated slightly lower relative potency of the Symbicort than Oxis, which was based on the PD effect. This difference was not explained.

5.3 Exposure-Response Relationships

There were no exposure-response issues raised during the course of this review.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

There is only one indication sought for this drug product, for the long-term maintenance treatment of asthma in patients 12 years of age and older. As noted earlier in this review, the clinical program for Symbicort was quite extensive.

Thus, the clinical program was limited to the twice-daily program for the 80/4.5 and 160/4.5 mcg dosage strengths. The entire twice-daily program with all dosage strengths was designed to satisfy the combination policy and provide evidence to support the safety and efficacy as maintenance therapy of persistent asthma in patient years of age and older.

The new indication is as follows:

“SYMBICORT is indicated for the long-term maintenance treatment of asthma in patients 12 years of age and older.”

6.1.1 Methods

To meet the combination policy requirement, the strategy for US regulatory development program was to study Symbicort in comparison to the individual monoproduct comparators. However, the program included monoproducts that are not approved in the US, one of which is pharmaceutically different (Turbuhaler vs MDI for formoterol component). Therefore, it was necessary for the program to establish that each comparator monoproduct delivers the same nominal dose of active and that there were no pharmaceutical differences between products that would confound interpretation of the efficacy results. This was further complicated by the multiple dosage strengths of Symbicort. The link for the formoterol pharmaceutical differences is in study SD-039-0729, a well-designed pharmacodynamic study that showed dose ordering and device overlaying at the three doses studied. Part of establishing that each mono-component has active drug was the comparison of each to placebo for the desired efficacy variable. However, there were only three placebo-controlled studies in the Phase 3 program, one of which

did not include mono-component BID arms. Therefore, SD-039-0716 and SD-039-0717, which encompass both monoproduct comparators and also placebo within a single study, were considered pivotal for review. While study 716 included a placebo arm, study 717 included both a placebo and free monoproduct combination arms. By inclusion of the free monoproducts in combination, 717 also addressed pharmaceutical issues presented by the different TBH/MDI device formulations. These two studies are featured in the Clinical Studies section of the proposed package insert. For this reason, the efficacy review strategy focused primarily on these two studies and study 729.

As discussed above, several pharmaceutical issues complicate the comparison of Symbicort to its mono-components. The issues were different for the budesonide and formoterol components. For the budesonide component, the budesonide mono-component MDIs (80 and 160 mcg dosage strengths) are not US-approved drug products. It was therefore necessary to assure that a comparison of each dosage strength of Symbicort MDI to the respective dosage strength budesonide MDI comparator was reliable, and superiority of the combination is not due a pharmaceutical issue with the respective non-approved budesonide mono-component. Several bridges were provided in the development package and submission, including *in vitro* evaluations of the dose content and particle size distribution of the two budesonide MDIs, and provision of placebo arms in the two pivotal studies. PK evaluations were also performed, but are not specifically reliable for an inhalational drug product intended for delivery to the lungs and not to the systemic circulation. PK was therefore helpful to establish safety rather than efficacy. In combination, the *in vitro* and clinical links provide a path to establish that the dose comparison was reasonable for each budesonide dosage strength. In fact, inclusion of a placebo arm in one study and both a placebo and the free monoproducts in combination in the second study, allow a reasonable stand-alone assessment of the safety and efficacy on the individual budesonide monoproducts.

A slightly different pharmaceutical issue is present for the formoterol comparator. The comparator for the program was Oxis Turbuhaler, a dry powder inhaler not approved in the US. Since Symbicort is an MDI, a pharmaceutical link was needed to bridge the different formulations. Unlike budesonide, there is only one dosage strength of the Oxis TBH (4.5 mcg), but there were still two dosage strengths of Symbicort MDI to evaluate. Study SD-039-0729 was negotiated to provide this pharmaceutical bridge (see the Clinical Pharmacology and the Review of Individual Study Reports sections of this review for details of the study). However, this study represents only a partial link between the products because the study incorporated only one of the two dosage strengths of Symbicort (the 80/4.5 mcg dosage strength). The rest of the links are provided by *in vitro* (CMC) data, PK data from study SD-039-0717 (for the 160/4.5mcg Symbicort dosage strength), and safety and efficacy data in the two clinical studies, including placebo in both studies and free monoproduct combination comparator arms study 717. Just as for the budesonide mono-component, the use of placebo and free mono-components allows a reasonable stand-alone assessment of the safety and efficacy on the individual formoterol monoproduct. Taken together, these data do support the pharmaceutical bridging for this program.

Efficacy was supported by several secondary studies: SD-039-0726, SD-039-0681, and SD-039-0682, which studied various dosage strengths of Symbicort MDI with various clinical endpoints

and comparators, as shown in Table 5. Finally efficacy was supported by two long-term open-label safety studies, in which efficacy was also assessed.

6.1.2 General Discussion of Endpoints

The endpoints for evaluation asthma are generally well established. Typically, endpoints include various spirometric measurements, such as FEV₁ and PEF, among others. Timing may be pre-dose or over the length of the dosing interval post-dose, depending upon the intent of the evaluation. Other endpoints may include various aspects of asthma stability and management, which may include episodes of asthma, hospitalizations, rescue medication use, care utilization, symptom scores, global assessments, and quality of life measures. While the various secondary clinical studies used various endpoints, the pivotal clinical studies in the Symbicort development program chose separate endpoints each of which the Division felt was reasonable and likely to define the efficacy of each component, budesonide and formoterol. Those endpoints are discussed below.

Because Symbicort contains two asthma medications, **co-primary efficacy variables** in the two pivotal studies were used to demonstrate the contribution of each of the individual components, budesonide or formoterol, to the efficacy of the combination drug product. For the **formoterol** component, AstraZeneca proposed that the primary variable be the **baseline-adjusted average 12-hour FEV₁** (AUC of FEV₁ over the dosing interval) to demonstrate the bronchodilator effect of the formoterol component. For the budesonide component, the comparison was therefore Symbicort minus formoterol. The Division agreed. The primary time point chosen for this measurement was at the 2 week visit (after 2 weeks of treatment). Of course, in light of the known issue of tachyphylaxis with continuous beta-agonist use other time points (including after the first dose, and at the end of treatment) are of interest, but the 2-week time point is a reasonable approach based on the mechanism of action of the drug. As part of the overall program, AstraZeneca also evaluated the onset of effect with the first dose, and is seeking to describe these findings in the Clinical Trials section.

For evaluation the **budesonide** component, two different methodologies were used to demonstrate the stabilizing, anti-inflammatory effect of the budesonide component, with the comparison being Symbicort minus formoterol. The applicant started by choosing the endpoint of **withdrawals due to asthma exacerbations**, as specifically defined by a series of criteria in the protocols and captured in the CRFs. The Division was in agreement with this approach. The studies 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 FEV₁ of ≥20% from the pre-dose FEV₁ 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.

However, during the course of the two studies, withdrawals due to asthma exacerbation was demoted from a co-primary to a secondary efficacy variable, and pre-dose FEV₁ was elevated from a secondary to a co-primary efficacy variable for evaluation of the contribution of the budesonide component. At the pre-NDA meeting, the applicant called attention to this change 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. This created a situation where the declared primary endpoint would not capture the entire scope of patients qualifying for withdrawal based on the pre-specified withdrawal criteria. Although the applicant could have switched to using all patients who qualified for withdrawal (as listed in the CRFs) instead of the patients who actually were withdrawn, they chose not to follow this approach. They state that since pre-dose FEV₁ had been collected on all patients, **average pre-dose FEV₁** over the course of the study was chosen as the second co-primary variable and endpoint. Because the primary variable was changed, the Division chose to look at both the original and the replacement variable as a means of assessing efficacy of the budesonide component. Since some patients who qualified for withdrawal were withdrawn and others were not, we chose to consider all patients who qualified for withdrawal (as listed in the CRFs) as more relevant. We also examined very closely the effect of withdrawals on the outcomes of the study.

Although patients 6-12 years of age were randomized in a subset of centers in study 716, the primary efficacy evaluations were performed in patients ≥ 12 years of age.

6.1.3 Study Design

6.1.3.1 Trial Design

The two pivotal studies, SD-039-0716 and SD-039-0717 were similar in design, with the major differences (highlighted below) being the severity of asthma at baseline and the dosage strengths of Symbicort studied. Both were randomized, double-blind, double-dummy, placebo-controlled 12-week safety and efficacy studies comparing Symbicort HFA MDI with its pharmacologic monoproducts, budesonide HFA MDI and formoterol (Oxis) Turbuhaler 4.5 mcg, and placebo, each administered as 2 inhalations BID, in adolescents and adults with asthma. The studies comprised a screening visit, a 2-week run-in period, and a 12-week double-blind treatment period, with on-treatment visits at 2, 6 and 12 weeks. The study was performed contemporaneously.

Study 716 evaluated the Symbicort 80/4.5 mcg dosage strength and the corresponding 80 mcg budesonide product in patients ≥ 12 years of age. The study included a subset of children 6 to 11 years of age, and stratified randomization by age group (< 12 years and ≥ 12 years). However, efficacy was assessed only in patients ≥ 12 years of age (EAS ≥ 12). Entry criteria included mild-moderate asthmatics (FEV₁ for ≥ 12 years: 60% to 90% predicted; FEV₁ for < 12 years: $\geq 75\%$

predicted) on ICS therapy with at least 12% reversibility (but no volume requirement). The study included a 2-week single-blind placebo run-in period.

Study 717 evaluated the Symbicort 160/4.5 mcg dosage strength and the corresponding 160 mcg budesonide product in patients ≥ 12 years of age. Treatment arms also included the free combination of the monoproducts and placebo. The entry criteria for this study included moderate to severe asthma patients who had been on medium to high dose ICS and had FEV₁ of 45-85% percent predicted with at least 12% and ≥ 200 mL reversibility. Randomization was stratified by asthma severity, based on consistent use of moderate vs high dose ICS use prior to screening. The study included a 2 (± 1) week single-blind run-in period of budesonide 160 mcg BID (budesonide 80 mcg, 2 actuations BID).

6.1.3.2 Endpoints

Co-primary endpoints for both studies, as discussed in the preceding section, were changed during the course of the studies. They included baseline-adjusted average 12-hour FEV₁ (to assess the contribution of the formoterol component) and morning pre-dose FEV₁ (to assess the budesonide component), although (withdrawals due to) predefined asthma events based on the CRF, having been demoted from co-primary to a secondary endpoint, was still of significant interest as a secondary endpoint. These endpoints are typical for beta-agonist and corticosteroid endpoints, respectively.

Revised secondary endpoints included: pre-defined asthma events and withdrawals due to pre-defined asthma events; other spirometry-related variables (2-hour post-dose FEV₁, maximum FEV₁, onset of effect [15% improvement in FEV₁ 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 perception of onset of effect using an Onset of Effect Questionnaire); various patient reported outcomes including the Asthma Quality of Life Questionnaire (AQLQ[S]), Pediatric Asthma Quality of Life Questionnaire, Patient Satisfaction with Asthma Medication Questionnaire, Medical Outcomes Study Sleep Scale; and Global Assessments.

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 (study 716: ≥ 12 years of age only), vital signs, and physical examinations.

6.1.3.3 Populations and Conduct

Study 716: Randomized 511 patients, 480 ≥ 12 years (EAS ≥ 12). The treatment groups appeared balanced for demographics and baseline characteristics including disease severity (daily ICS dose, mean pre-dose FEV₁, and percent reversibility). The study population was approximately 90% Caucasian, 40% males, and 60% females. The mean age was 35 years (range: 6 to 78 years), with 31/511 < 12 years of age and 480/511 ≥ 12 years of age. All except 1 were being treated with ICS prior to entry. The average length of asthma history was 19 years. At screening, the mean pre-dose FEV₁ was 2.5 L and mean percent reversibility was 18.9% (range 10.3% to 62.6%). At baseline, the mean percent predicted FEV₁ 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). Compliance with treatment appeared to be similar across treatment groups.

The rate of withdrawals was a significant issue evaluated as part of the review of this study. 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 higher withdrawal rate in the placebo group appeared to be 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). 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.

The impact of asthma adverse events that either qualified patients for withdrawal or lead to withdrawal were evaluated. Not surprisingly, the predominance of withdrawals in the placebo group were in patients who had poorer asthma control and lower baseline mean FEV₁ 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) (Table 61). 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 FEV₁ rose only slightly for patients still enrolled at Week 12 compared to those enrolled at Week 2.

We considered what effect the withdrawal pattern might have on various endpoints. The co-primary efficacy endpoint for the formoterol component (Symbicort minus budesonide) of baseline-adjusted average 12-hour FEV₁ (AUC of FEV₁ over the dosing interval) at 2 weeks would not be expected to have been affected by the withdrawal pattern, which occurred predominantly beyond 2 weeks of treatment. The co-primary efficacy endpoint for the budesonide component (Symbicort minus formoterol) of pre-dose FEV₁ over the entire study would be expected to have been affected by the withdrawal pattern, but the stability of baseline FEV₁ for the formoterol group and increase in baseline FEV₁ for the placebo group would likely not have been in favor of efficacy for the primary comparison or secondary comparisons to placebo. The observed pre-dose FEV₁ 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.

Study 717: Randomized 596 patients. The treatment groups appeared balanced for demographics and baseline characteristics including disease severity (daily ICS dose, mean pre-dose FEV₁, and percent reversibility). 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 FEV₁ was 2.2 L, and mean percent reversibility was 22.2% (range -0.4% to 97.7%). At baseline, the mean percent predicted FEV₁ for most patients was in the moderate range (66.9 % 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. Compliance with treatment appeared to be similar across treatment groups.

Just as for study 716, the rate of withdrawals was a significant issue evaluated as part of the review of this study. The overall withdrawal rate was 38%. 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). 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 evenly distributed across treatment groups in study 717. 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.

The effect of withdrawals in numbers of enrolled patients throughout the study and the corresponding drift in baseline FEV₁ from Week 2 to Week 12 may be seen in Table 87. 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 FEV₁ 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 FEV₁ for patients remaining at Week 12 were similar among treatment groups except that the formoterol group, which started slightly lower than the rest, drifted up slightly (Symbicort 2.25 L, budesonide 2.33 L, formoterol 2.26 L, bud + form 2.24 L, placebo 2.28 L). As a result, the withdrawal pattern did not appear to affect the treatment group differences at various timepoints throughout the study, as shown in Table 86, which shows the treatment comparisons at Week 2, Week 12 and End of Treatment.

In summary, the design of the studies appears to have been sufficiently rigorous and the study arms sufficiently balanced (see pooled data in Table 8 below and demographic tables with each study) to allow evaluation of all comparisons needed to support efficacy, including the primary comparisons of the combination to the respective mono-components as well as secondary comparisons of the combination and each mono-component to placebo. Use of the free-standing combination of mono-components in study 717 allowed assessment of pharmacologic issues within the study. The major issues that were considered as part of the efficacy assessment were

the effect of the change in one of the co-primary endpoints and the effect of withdrawals on the results of the study. Neither of these was judged of a nature that would invalidate the results.

Table 8. Demographic and Other characteristics, Pivotal Phase 3 studies 716 and 717 (Pool 3*)

Characteristic	Treatment group, n (%)				
	Symbicort MDI	Bud MDI	Form TBH	Bud + Form	Placebo
N	254	236	246	115	256
Sex (n, %)					
Male	94 (37.0)	88 (37.3)	89 (36.2)	50 (43.5)	108 (42.2)
Female	160 (63.0)	148 (62.7)	157 (63.8)	65 (56.5)	148 (57.8)
Race (n, %)					
Caucasian	211 (83.1)	191 (80.9)	198 (80.5)	89 (77.4)	220 (85.9)
Black	29 (11.4)	29 (12.3)	34 (13.8)	20 (17.4)	28 (10.9)
Oriental	0	4 (1.7)	4 (1.6)	2 (1.7)	3 (1)
Other	14 (5.5)	12 (5.1)	10 (4.1)	4 (3.5)	5 (2.0)
Age (years)					
Mean	38.6 (16.33)	38.1 (15.74)	36.7 (16.92)	40.3 (14.65)	38.0 (15.89)
Min, max	6, 77	7, 80	7, 87	13, 75	6, 75
Age group (n, %)					
12 to <16 years	18 (7.1)	17 (7.2)	27 (11.0)	5 (4.3)	17 (6.6)
16 to <65 years	215 (84.6)	205 (86.9)	194 (78.9)	104 (90.4)	222 (86.7)
≥65 years	14 (5.5)	8 (3.4)	16 (6.5)	6 (5.2)	8 (3.1)
≥75 years	1 (0.4)	2 (0.8)	1 (0.4)	1 (0.9)	1 (0.4)
Baseline ICS (n, %)					
None	0	1	0	0	0
Low	100 (39.4)	97 (41.1)	98 (39.8)	18 (15.7)	104 (40.6)
Medium	132 (52.0)	117 (49.6)	117 (47.6)	71 (61.7)	123 (48.0)
High	22 (8.7)	21 (8.9)	32 (12.6)	26 (22.6)	29 (11.3)
Percent predicted FEV ₁ (mean, SD)					
Screening	72.2 (10.8)	72.4 (10.0)	70.8 (10.9)	65.4 (10.2)	71.0 (10.3)
Baseline	69.6 (11.6)	70.4 (10.6)	69.5 (11.1)	66.9 (10.9)	70.0 (11.1)
*Pool 3 refers to safety pooling of studies. Please see Section 7.2.1 for details.					
Source: T23, p3036; clinsum.pdf					

6.1.4 Efficacy Findings

6.1.4.1 Results

Symbicort showed statistical superiority over its monoproducts for each of the co-primary efficacy endpoints, FEV₁ 0-12 hours for the formoterol component and pre-dose FEV₁ for the corticosteroid component. The key secondary endpoint of pre-specified asthma events supported the co-primary efficacy conclusions. In both pivotal studies, Symbicort and each of the mono-component products showed statistical superiority over placebo. This provided internal validity to the studies, and supported 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; the results thereby provided support for the primary efficacy outcome analyses. In both studies 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 FEV₁ 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 FEV₁ etc. In both studies, AQLQ[S] results of change from baseline to end of treatment for the comparison of Symbicort to placebo were both statistically significant and clinically relevant (MID = 0.5 for total score).

In both studies, 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, for other secondary endpoints the results of the two studies differed. In study 716 in mild to moderate asthmatics, except for AM and PM PEFR and the prevention [or delay] of tachyphylaxis, in the milder study population there was little if any additive effect for the combination in comparison to the monoproducts for their respective expected endpoint results. In this population, the addition of a LABA did not substantively affect frequency or time to onset of pre-defined asthma exacerbation events. In study 717 in moderate to severe asthmatics, the addition of formoterol to budesonide did appear to have an effect beyond either of the two monoproduct arms with regard to multiple secondary endpoints including key factors in asthma control such as frequency and severity of exacerbations, time to exacerbations, rescue medication use, etc.

Results of the pivotal studies are supported by the open-label findings in the two long-term safety studies and the non-placebo-controlled secondary studies. Efficacy results from the pivotal and the long-term safety studies are shown in the tables and graphs that follow.

Primary and key secondary efficacy findings were replicated by the FDA statistician. Analyses based on sex, race, age, and baseline ICS use (study 717) did not show any evidence of clinically relevant differences. Two things should be noted, however. First, the numbers of patients other than Caucasian studied in the development program were small. While this is not considered an issue from an efficacy perspective, it is addressed in the safety section of this review. Second, although intuitively obvious, it should be stated that the efficacy findings for the Symbicort MDI drug product combination of budesonide and formoterol apply only to patients 12 years of age and older, despite the fact that the individual mono-components may (as other drug products) be approved for use in younger age groups for the same maintenance-of-asthma indication. This, of course, will be reflected in the Indication as well as Dosing and Administration sections, and will also need to be addressed in the Precautions, Pediatric Use subsection.

6.1.4.2 Result Tables and Graphs

Results for the final declared primary efficacy co-variables (baseline-adjusted average 12-hour FEV₁ at Week 2 and average morning pre-dose FEV₁) are shown in Table 9 and Table 11, with the corresponding treatment comparisons shown in Table 10 and Table 12, respectively. For

completeness, these tables contain all treatments and most treatment comparisons, although the primary comparisons are **bolded**. Figure 3 and Figure 4 summarize the results of the co-primary comparison of baseline-adjusted average 12-hour FEV₁ at Week 2 in studies 716 and 717, respectively. Figure 5 and Figure 6 summarize the results of the co-primary comparison of average morning pre-dose FEV₁ in studies 716 and 717, respectively.

Results for the key secondary endpoints of predefined asthma worsening criteria and withdrawals due to predefined asthma worsening criteria (demoted primary endpoint) are shown in Table 13, with the corresponding comparisons for the odds ratios shown in Table 14. Results for CRF predefined asthma events are shown graphically in Figure 7 and Figure 8. All odds ratio treatment comparisons are graphically represented in Figure 9. While withdrawals due to predefined events had been a primary endpoint, the unevenness that these withdrawal criteria were applied made the CRF notation of having satisfied one of the criteria more accurate than the withdrawals themselves. Figure 10 shows the mean percent change from baseline in FEV₁ over 12 hours on day of randomization and at end of treatment for one of the two studies, study 717. These results are considered representative of the results found in both studies. Table 15 shows the AQLQ[S] treatment comparison for Symbicort minus placebo for overall scores at the end of treatment in both studies. Table 16 shows the results of mean AM Pre-dose FEV₁ (L) found in the open-label Safety Studies 715 and 719.

**Appears This Way
On Original**

Table 9. Studies 716 and 717, Baseline-adjusted average 12-hour FEV₁ (L), Treatment Means*, Week 2

Treatment / Dose	Study	N	Baseline FEV ₁	Week 2 LOCF*		
			Observed value	From ANCOVA		
			Mean (SD)	Mean (SD)	LS Mean (SEM)	95% CI
Symbicort						
160/9 BID	716	123	2.40 (0.62)	0.47 (0.37)	0.45 (0.04)	(0.38, 0.52)
320/9 BID	717	124	2.24 (0.72)	0.34 (0.33)	0.32 (0.03)	(0.26, 0.38)
Budesonide						
160 BID	716	121	2.33 (0.62)	0.30 (0.35)	0.26 (0.04)	(0.19, 0.34)
320 BID	717	109	2.30 (0.63)	0.15 (0.26)	0.13 (0.03)	(0.06, 0.19)
Formoterol						
9 BID	716	114	2.38 (0.64)	0.40 (0.39)	0.38 (0.04)	(0.31, 0.45)
9 BID	717	123	2.18 (0.60)	0.19 (0.28)	0.17 (0.03)	(0.11, 0.23)
Bud + Form						
320 + 9 BID	717	115	2.24 (0.61)	0.32 (0.29)	0.31 (0.03)	(0.24, 0.37)
Placebo						
	716	122	2.39 (0.65)	0.12 (0.33)	0.10 (0.04)	(0.03, 0.17)
	717	125	2.28 (0.68)	-0.03 (0.34)	-0.05 (0.03)	(-0.11, 0.02)
*Treatment means at Week 2 LOCF using the WV Pre-CF imputation method (716: EAS ≥12 yr)						
Source: T35, p9960-1; clinsum.pdf						

Table 10. Studies 716 & 717, Treatment Comparisons*, Baseline-adjusted average 12-hour FEV₁ (L), Week 2

Treatment Comparisons*	716			717		
	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	0.37 (0.04)	(0.29, 0.45)	<0.001
Symbicort minus Budesonide	0.18 (0.04)	(0.09, 0.27)	<0.001	0.20 (0.04)	(0.11, 0.28)	<0.001
Symbicort minus Formoterol	0.07 (0.05)	(-0.02, 0.16)	0.148	0.15 (0.04)	(0.07, 0.23)	<0.001
Symbicort minus Bud + Form				0.01 (0.04)	(-0.07, 0.09)	0.739
Budesonide minus Placebo	0.17 (0.04)	(0.08, 0.25)	<0.001	0.17 (0.04)	(0.09, 0.25)	<0.001
Formoterol minus Placebo	0.28 (0.05)	(0.19, 0.37)	<0.001	0.22 (0.04)	(0.14, 0.30)	<0.001
*Treatment comparisons at Week 2 LOCF (primary endpoint) using the WV Pre-CF imputation method (716: EAS ≥12 yr). Primary comparison bolded .						
Source: T36, p997; clinsum.pdf						

Appears This Way
On Original

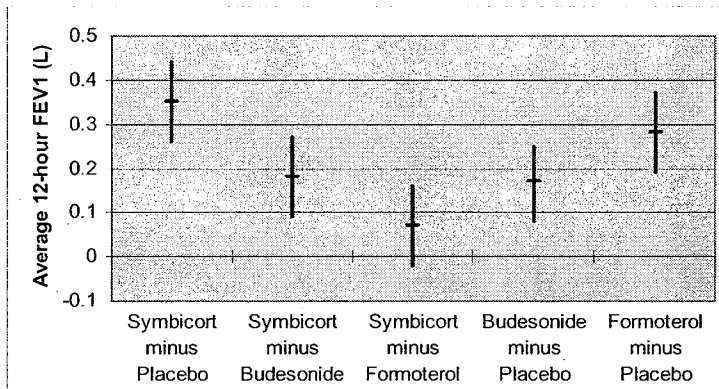


Figure 3. Study SD-039-0716, Treatment comparisons and 95% confidence intervals, Average 12-hour FEV₁ (L) at Week 2

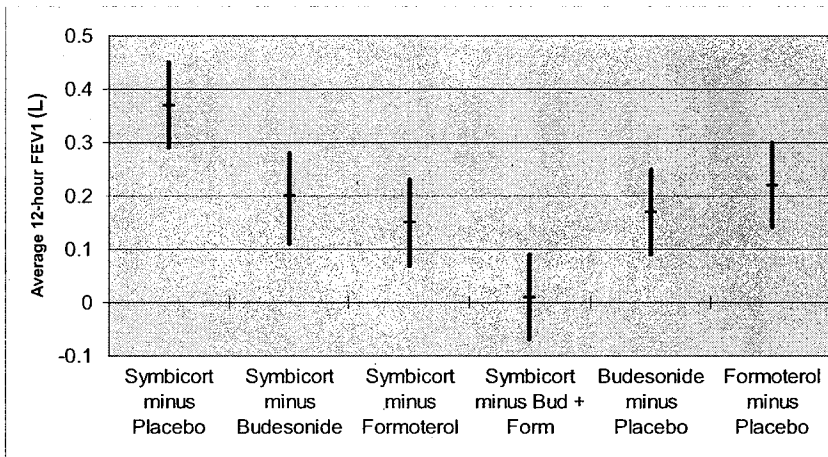


Figure 4. Study SD-039-0717, Treatment comparisons and 95% confidence intervals, Average 12-hour FEV₁ (L) at Week 2

Note: In each of the above figures, the primary comparison for the endpoint of average 12-hour FEV₁ at 2 Weeks was Symbicort minus budesonide represented in the second comparison from the left.

Table 11. Studies 716 and 717, AM Pre-dose FEV₁ (L), Treatment Means*

Treatment / Dose	Study	N	Baseline FEV ₁	Randomized Treatment Period*			
				Observed value	Change from baseline		
			Mean (SD)		Observed	(From ANCOVA)	
				Mean (SD)	Mean (SD)	LS Mean (SEM)	95% CI
Symbicort							
160/9 BID	716	123	2.40 (0.62)	2.74 (0.67)	0.34 (0.34)	0.32 (0.04)	(0.24, 0.40)
320/9 BID	717	117	2.23 (0.72)	2.41 (0.77)	0.18 (0.28)	0.17 (0.03)	(0.10, 0.23)
Budesonide							
160 BID	716	116	2.32 (0.60)	2.55 (0.65)	0.23 (0.37)	0.18 (0.04)	(0.11, 0.26)
320 BID	717	108	2.30 (0.64)	2.37 (0.69)	0.07 (0.33)	0.05 (0.03)	(-0.02, 0.12)
Formoterol							
9 BID	716	105	2.41 (0.63)	2.59 (0.73)	0.18 (0.39)	0.16 (0.04)	(0.08, 0.24)
9 BID	717	114	2.19 (0.59)	2.12 (0.65)	-0.07 (0.31)	-0.09 (0.03)	(-0.16, -0.03)

Treatment / Dose	Study	N	Baseline FEV ₁	Randomized Treatment Period*			
				Observed value	Change from baseline		
					Observed	(From ANCOVA)	
			Mean (SD)	Mean (SD)	Mean (SD)	LS Mean (SEM)	95% CI
Bud + Form							
320 + 9 BID	717	111	2.23 (0.62)	2.39 (0.66)	0.15 (0.26)	0.13 (0.03)	(0.07, 0.20)
Placebo							
	716	111	2.43 (0.64)	2.47 (0.76)	0.04 (0.38)	0.01 (0.04)	(-0.07, 0.09)
	717	116	2.29 (0.69)	2.11 (0.69)	-0.18 (0.39)	-0.20 (0.03)	(-0.26, -0.13)
*Means of all AM pre-dose FEV ₁ values from scheduled visits during the treatment period (716: EAS ≥12 yr)							
Source: T37, p1003; clinsum.pdf							

Table 12. Studies 716 and 717, Treatment comparisons*, AM Pre-dose FEV₁ (L), Average over study

Treatment Comparisons*	716			717		
	LS Mean (SEM)	95% CI	p-value	LS Mean (SEM)	95% CI	p-value
Symbicort minus Placebo	0.31 (0.05)	(0.21, 0.40)	<0.001	0.37 (0.04)	(0.28, 0.45)	<0.001
Symbicort minus Budesonide	0.14 (0.05)	(0.04, 0.23)	0.005	0.12 (0.04)	(0.04, 0.21)	0.006
Symbicort minus Formoterol	0.16 (0.05)	(0.06, 0.26)	0.001	0.26 (0.04)	(0.17, 0.35)	<0.001
Symbicort minus Bud + Form				0.04 (0.04)	(-0.05, 0.12)	0.399
Budesonide minus Placebo	0.17 (0.05)	(0.08, 0.27)	<0.001	0.25 (0.04)	(0.16, 0.33)	<0.001
Formoterol minus Placebo	0.15 (0.05)	(0.05, 0.25)	0.004	0.11 (0.04)	(0.02, 0.19)	0.012
*Treatment comparisons for means of all AM pre-dose FEV ₁ values from scheduled visits during the treatment period (716: EAS ≥12 yr). Primary comparison bolded .						
Source: T38, p1004; clinsum.pdf						

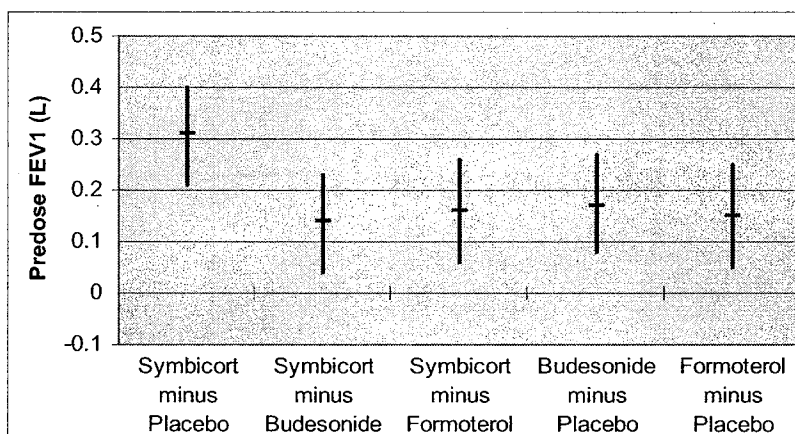


Figure 5. Study SD-039-0716, Treatment comparisons and 95% confidence intervals, Pre dose FEV₁
Note: The primary comparison for the endpoint of average pre dose FEV₁ was Symbicort minus formoterol.

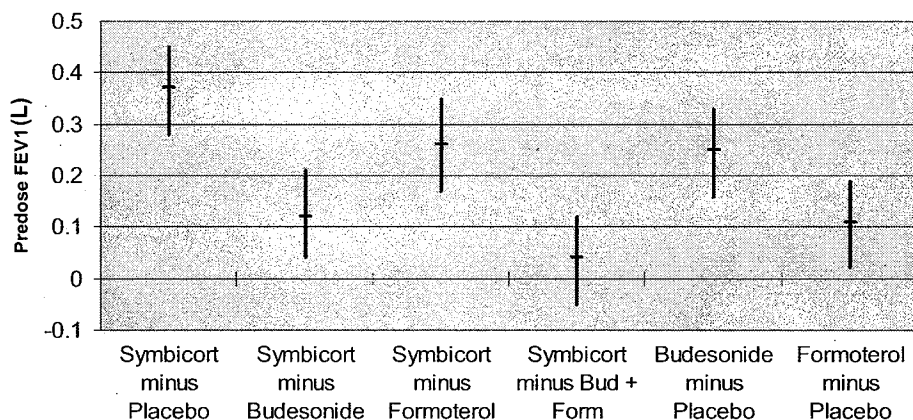


Figure 6. Study SD-039-0717, Treatment comparisons and 95% confidence intervals, Pre dose FEV₁

Note: The primary comparison for the endpoint of average pre dose FEV₁ was Symbicort minus formoterol.

Table 13. Studies 716 and 717, Pre-defined asthma events, Number and percentage of patients meeting predefined withdrawal criteria (CRF data)

Criteria	Treatment group, n (%)				
	Symbicort	Bud + Form	Budesonide	Formoterol	Placebo
716 (EAS ≥12)	123		121	114	122
Number of patients withdrawn due to pre-defined asthma event	9 (7.3)		8 (6.6)	21 (18.4)	40 (32.8)
Number of patients with pre-defined asthma event in CRF	23 (18.7)		26 (21.5)	48 (42.1)	69 (56.6)
Time to Event (Mean days)	24.2		22.6	23.8	21.0
Criterion 1: Decrease in FEV ₁	3 (2.4)		3 (2.5)	11 (9.6)	9 (7.4)
Criterion 2: Rescue medication	1 (0.8)		3 (2.5)	1 (0.9)	3 (2.5)
Criterion 3: Decrease in AM PEF	3 (2.4)		1 (0.8)	8 (7.0)	14 (11.5)
Criterion 4: Nighttime awakening	17 (13.8)		20 (16.5)	31 (27.2)	52 (42.6)
Criterion 5: Clinical exacerbation	1 (0.8)		3 (2.5)	5 (4.4)	20 (16.4)
717 (EAS)	124	115	109	123	115
Number of patients withdrawn due to pre-defined asthma event	13 (10.5)	13 (11.3)	22 (20.2)	44 (35.8)	62 (49.6)
Number of patients with pre-defined asthma event in CRF	37 (29.8)	24 (20.9)	48 (44.0)	68 (55.3)	84 (67.2)
Time to event (Mean days)	33.6	30.5	22.2	29.2	18.6
Criterion 1: Decrease in FEV ₁	4 (3.2)	8 (7.0)	7 (6.4)	15 (12.2)	14 (11.2)
Criterion 2: Rescue medication	2 (1.6)	0	3 (2.8)	3 (2.4)	7 (5.6)
Criterion 3: Decrease in AM PEF	2 (1.6)	5 (4.3)	5 (4.6)	17 (13.8)	15 (12.0)
Criterion 4: Nighttime awakening	24 (19.4)	11 (9.6)	29 (26.6)	32 (26.0)	49 (39.2)
Criterion 5: Clinical exacerbation	7 (5.6)	6 (5.2)	5 (4.6)	17 (13.8)	16 (12.8)
Number and percentage of patients who met at least 1 predefined asthma criterion (based on CRF entry) or were withdrawn due to having met a predefined asthma worsening criterion					

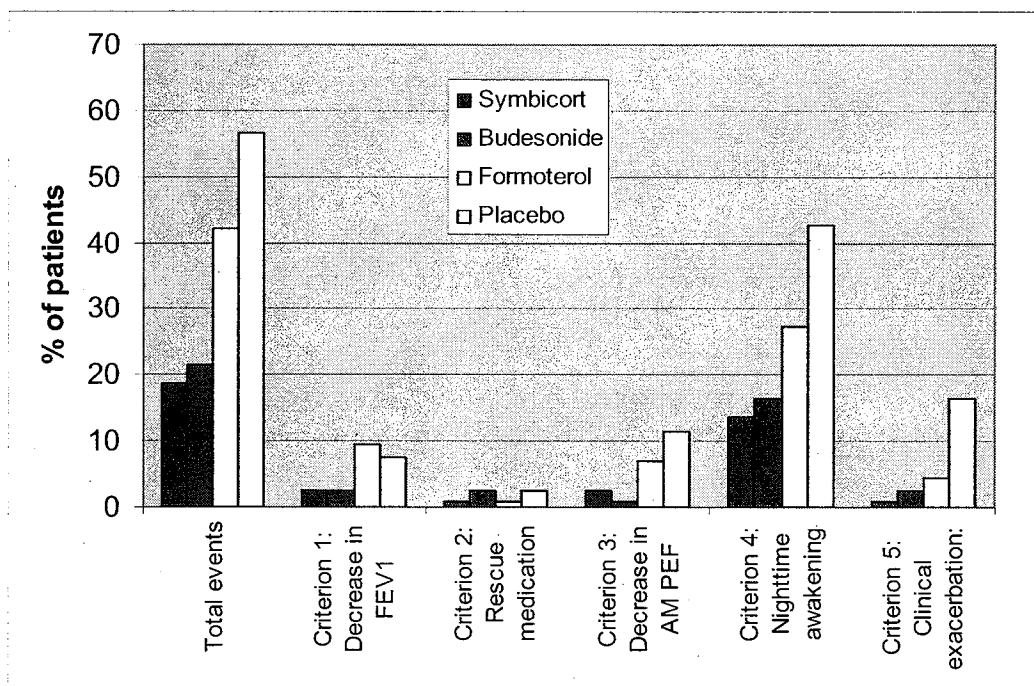


Figure 7. SD-039-0716, Percent CRF predefined asthma events

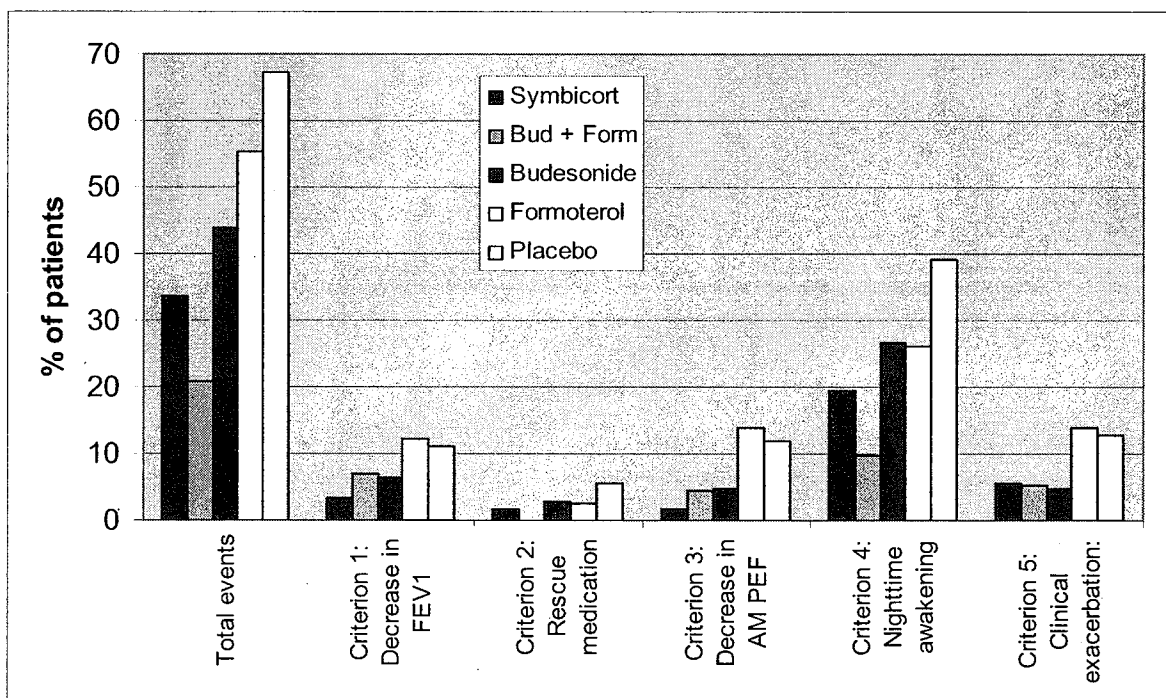


Figure 8. SD-039-0717, Percent CRF predefined asthma events

Table 14. Studies 716 and 717, Treatment comparison odds ratios, Pre-defined asthma events

Treatment Comparisons	Study	CRF events			Withdrawals		
		Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
Symbicort minus Placebo	716	0.18	(0.10, 0.31)	<0.001	0.16	(0.07, 0.35)	<0.001
	717	0.21	(0.12, 0.35)	<0.001	0.12	(0.06, 0.23)	<0.001
Symbicort minus Budesonide	716	0.84	(0.45, 1.57)	0.587	1.12	(0.42, 2.99)	0.829
	717	0.54	(0.32, 0.93)	0.025	0.46	(0.22, 0.97)	0.040
Symbicort minus Formoterol	716	0.32	(0.18, 0.57)	<0.001	0.35	(0.15, 0.80)	0.010
	717	0.34	(0.20, 0.58)	<0.001	0.21	(0.11, 0.42)	<0.001
Symbicort minus Bud + Form	717	1.62	(0.90, 2.94)	0.107	0.93	(0.41, 2.12)	0.871
Budesonide minus Placebo	716	0.21	(0.12, 0.37)	<0.001	0.15	(0.06, 0.33)	<0.001
	717	0.39	(0.23, 0.66)	<0.001	0.26	(0.15, 0.47)	<0.001
Formoterol minus Placebo	716	0.56	(0.33, 0.94)	0.027	0.46	(0.25, 0.85)	0.012
	717	0.60	(0.36, 1.01)	0.053	0.56	(0.33, 0.93)	0.027

Source: T48, p1024; clinsum.pdf

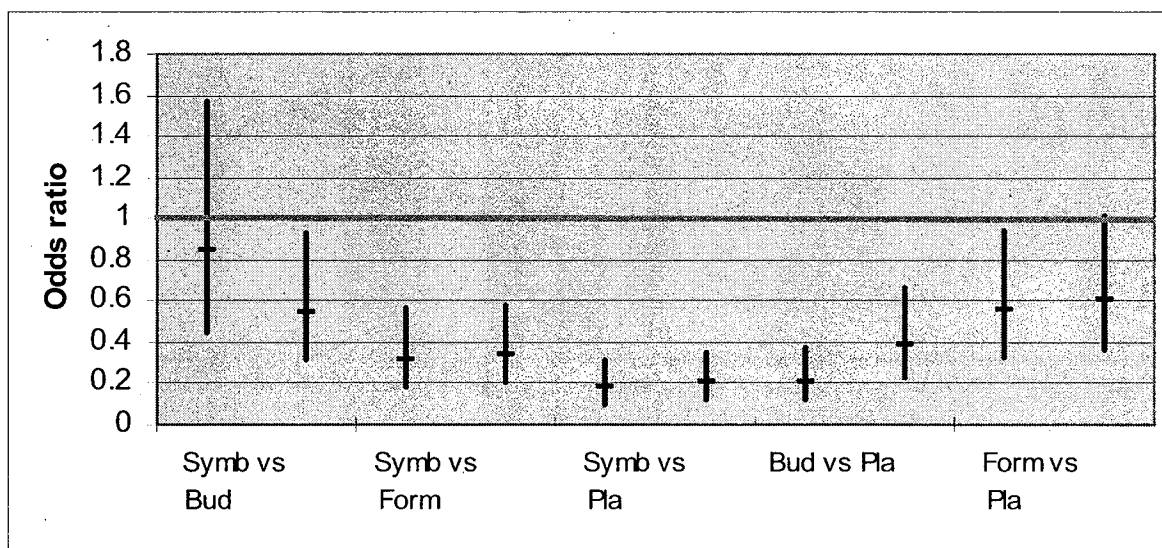


Figure 9. Studies 716 and 717, Odds ratio comparisons and 95% confidence intervals for predefined CRF asthma worsening criteria

Reviewer's Note: In the figure above, for each comparison, study 716 is on the left and study 717 is on the right. While the comparison of Symbicort minus formoterol was the primary comparison for the added benefit of the corticosteroid component, it should be noted that for study 716 in mild-to-moderate asthmatics Symbicort and budesonide gave roughly comparable results with little added benefit from the addition of formoterol to budesonide.

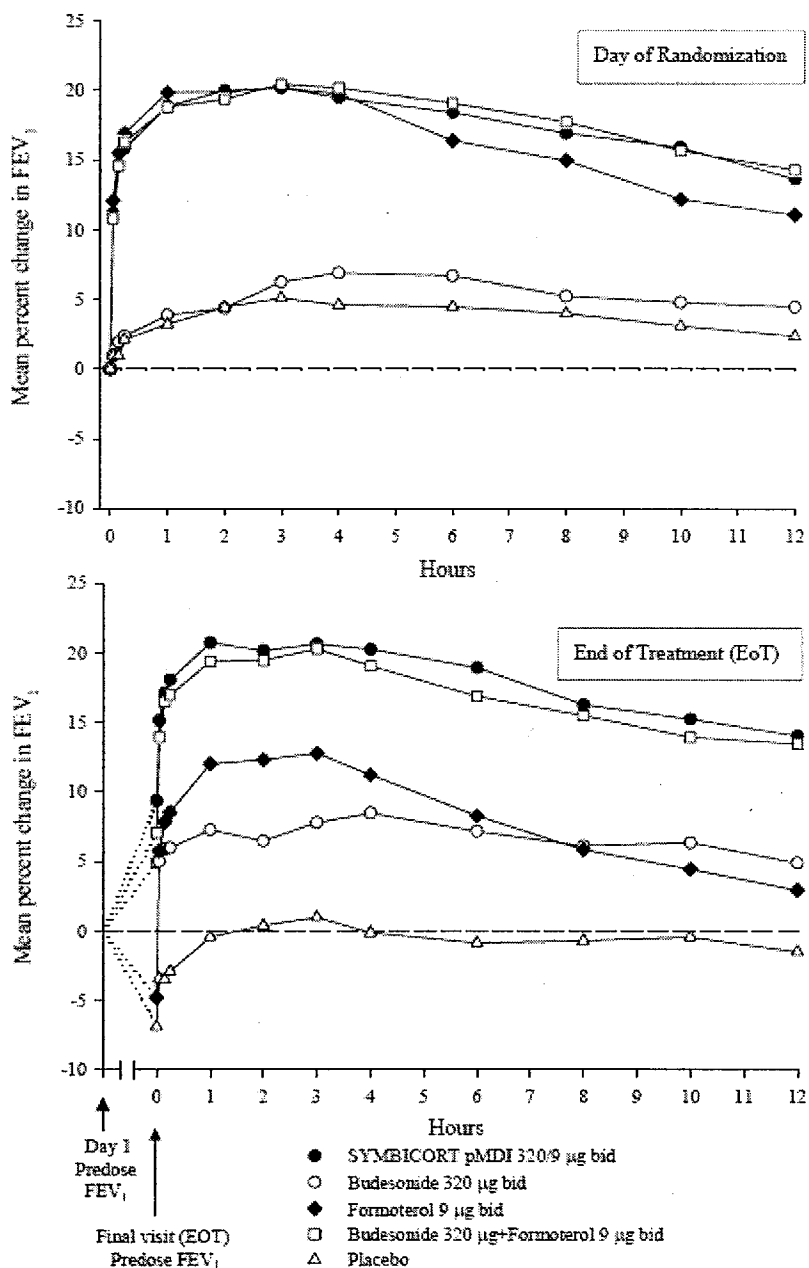


Figure 10. Study 717, Mean percent change from baseline in FEV₁ over 12 hours on day of randomization and at end of treatment

Source: F3, p34; clinover.pdf

Reviewer's Note: The above figure does not take into account patients who qualified for withdrawal due to having met a predefined asthma criterion. AstraZeneca was asked to supply this figure, but it was not available prior to finalizing this review.

Table 15. AQLQ[S] treatment comparisons for Symbicort minus placebo, overall scores, end of treatment

Study	LS mean	95% CI	p-value
AQLQ (S) Overall score, Symbicort minus Placebo			
SD-039-0716	0.84	0.58, 1.09	<0.001
SD-039-0717	0.70	0.47, 0.93	<0.001

Table 16. Open-label Safety Studies 715 and 719, FEV₁ (L) *, Treatment Means

Treatment / Dose	Study	N	Baseline FEV ₁	Randomized Treatment Period*			
				Observed value	Change from baseline		
			Observed		(From ANCOVA)		
					Mean (SD)	Mean (SD)	Mean (SD)
Symbicort							
320/9 BID	715	440	2.48 (0.84)	2.79 (0.90)	0.31 (0.43)	0.27 (0.02)	(0.22, 0.31)
320/9 BID	719	119	1.74 (0.45)	1.88 (0.44)	0.14 (0.16)	0.15 (0.02)	(0.11, 0.19)
* In study 715, FEV ₁ at treatment visits was performed post-dose in the AM. In study 719, FEV on treatment was performed pre-dose.							
Source: T45, p1020; clinover.pdf							

6.1.5 Clinical Microbiology

There were no clinical microbiology issues in this application. As an inhaled drug product, it is required to be manufactured sterile. In addition, as a non-aqueous based HFA drug product, it would not easily support bacterial growth. Please see the CMC section for results of the Microbiology review.

6.1.6 Efficacy Conclusions

The results of the pivotal studies SD-039-0716 and SD-039-0717, supported by the bridging pharmaceutical study SD-039-0729 and the open-label safety study SD-039-0715, provide support to satisfy both the combination policy of superiority of the combination to the respective mono-components, as well as the need to show that the unapproved mono-components contain active at therapeutically meaningful levels.

7 INTEGRATED REVIEW OF SAFETY

Reviewer's Note: This review follows the format of the Good Review Management Practices MAPP. The reader is advised that the Safety section presents information in a bottoms-up approach. The typical approach of presenting methodology for the review, the extent of exposure and description of the safety database prior to presentation of findings, is not followed. Please refer to the appropriate sections that follow for this information. In addition, several sections do not contain the information that otherwise might be expected. For example, the Methods and Findings section that immediately follows is in fact a misnomer. Rather, this section presents the Findings of the safety review. Methodology is presented in Section 7.2 under the Descriptions of the Primary and Secondary Data Sources, not in the

Methodology section, Section 7.4. This approach was taken to simplify and merge the description of the data sources with that for how the data were handled and evaluated.

7.1 Methods and Findings

The safety review of this application did not reveal any new or unusual safety trends. The two drugs in Symbicort represent a convenience packaging of the individual drugs, both of which are marketed (but not as an HFA formulation) in the United States. The clinical experience with budesonide extends for the last decade, and with formoterol for the last half-decade. For the most part, safety issues with these two drugs are well-known. The clinical community is quite comfortable with use of ICS, and specifically with use of budesonide. The safety findings in this application did not reveal any new or unexpected safety trends with regard to budesonide. On the other hand, the safety of formoterol is still of concern, as witnessed by the Advisory Committee meeting regarding safety of LABAs within the last year. The safety review of this application therefore focused on those aspects of both drugs that might be of clinical concern based on the current state of knowledge of these two drug classes. No safety trends were noted with this application.

That said, the following tables (Table 17 and Table 18) present an overview of the adverse events, including serious adverse events, deaths, AEs causing discontinuation, etc, from the two pivotal and from all Phase 3 studies, respectively. The Phase 1 and 2 safety data were also reviewed, but are not presented as no safety issues were raised by the mostly single-dose studies. Review of the data supports the applicant's contention that Symbicort does not present a safety profile different from its monoproducts when administered in free combination. Differences in exposure must be taken into account when reviewing the tables, with lower exposure in the formoterol and placebo arms. In the two pivotal studies, Symbicort MDI and the free combination arms had higher frequency of SAEs and AEs leading to discontinuation. However, overall AEs leading to discontinuation were higher in the formoterol and placebo arms, due primarily to higher numbers of episodes of asthma exacerbations leading to withdrawal.

Table 17. Adverse events during randomized treatment, Pivotal Phase 3 studies (Pool 3*)

Overview of AEs, Pool 3	Treatment group, n (%)				
	Symbicort MDI n=254	Budesonide MDI N=236	Formoterol TBH n=246	Bud + Form n=115	Placebo n=256
Mean exposure (days)	76.0	74.3	62.3	74.5	52.3
Number of patients with an AE					
Any AE	160 (63.0)	141 (59.7)	144 (58.5)	73 (63.5)	131 (51.2)
SAEs	6 (2.4)	0	2 (0.8)	3 (2.6)	2 (0.8)
Deaths	0	0	0	0	0
Non-fatal SAEs	6 (2.4)	0	2 (0.8)	3 (2.6)	2 (0.8)
SAEs leading to discontinuation	5 (2.0)	0	0	2 (1.7)	2 (0.8)
DAEs	12 (4.7)	7 (3.0)	8 (3.3)	9 (7.8)	16 (6.3)
OAEs	0	0	0	0	0
Any study drug-related AE	24 (9.4)	10 (2.4)	21 (8.5)	10 (8.7)	13 (5.1)
*Pool 3 = Pivotal Phase 3 studies 716 and 717. See Table 35 for description of study pooling.					
DAE = Adverse event leading to discontinuation; OAE = Other significant adverse event					
Source: T29, p3051; clinsum.pdf					

Table 18. Overview of adverse events during randomized treatment, All Phase 3 studies (Pool 5*)

Overview of AEs, Pool 5	Treatment group, n (%)				
	Symbicort MDI n=2193	Budesonide MDI N=1182	Formoterol TBH n=384	Symbicort TBH n=668	Placebo n=409
Mean exposure (days)	135.2	80.9	65.1	170.1	55.8
Number of patients with an AE					
Any AE	1310 (59.7)	617 (52.2)	241 (62.8)	335 (50.1)	206 (50.4)
SAEs	51 (2.3)	8 (0.7)	3 (0.8)	17 (2.5)	2 (0.5)
Deaths	0	0	0	0	0
Non-fatal SAEs	51 (2.3)	8 (0.7)	3 (0.8)	17 (2.5)	2 (0.5)
SAEs leading to discontinuation	15 (0.7)	4 (0.3)	1 (0.3)	2 (0.3)	2 (0.5)
DAEs	62 (2.8)	44 (3.7)	19 (4.9)	7 (1.0)	19 (4.6)
OAEs	1 (<0.01)	0	0	0	0
Any study drug-related AE					
US	74 (5.6)	35 (4.6)	30 (7.8)	NA	26 (6.4)
Non-US	3 (0.3)	0	NA	1 (0.1)	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: T3, p41; clinover.pdf and T35, p3062-3; clinsum.pdf					

7.1.1 Deaths

There were no deaths in any of the Phase 1, 2 or 3 studies. However there was one death due to a fatal asthma attack 7 weeks after completion of safety study SD-039-0715, the one-year open-label safety study in adults and adolescents. For further details, please refer to Section 10.1.7.2.3.3 of this review.

7.1.2 Other Serious Adverse Events

There were no serious adverse events in the Phase 1 studies, and 1 in the Phase 2 studies (endometritis, placebo). SAEs by MedDRA system organ class (SOC) and preferred term (PT) for the 2 pivotal studies are shown in Table 19, and by SOC for all Phase 3 studies in Table 20. Pool 6 is not shown, but the results did not change significantly from Pools 3 and 5. Both the Symbicort MDI and Symbicort TBH had slightly increased frequencies of SAEs, although exposure was also higher in these two groups.

In study 717, 2 patients had an SAE of asthma and one had an SAE of upper respiratory tract associated with asthma, all in the Symbicort arm (640/18 mcg total daily dose). In the same study, 1 patient on In other studies, an additional 2 Symbicort MDI patients (supraventricular tachycardia, ventricular tachycardia), and two Symbicort TBH patients (tachycardia, ventricular bigeminy) had cardiac SAEs in other studies. Evaluation of SAEs by Symbicort dose was not specifically revealing. While asthma SAEs occurred in the highest dose, these were also the patients with more moderate to severe asthma at baseline.

In ongoing studies, there were an additional 3 SAEs reported, one of which was a case of atrial fibrillation in a patient on Pulmicort and Foradil.

Table 19. SAEs during randomized treatment, Pivotal Phase 3 studies (Pool 3*)

SAEs, Pool 3	Treatment group, n (%)				
	Symbicort MDI n=254	Budesonide MDI N=236	Formoterol TBH n=246	Bud + Form n=115	Placebo n=256
Mean exposure (days)	76.0	74.3	62.3	74.5	52.3
Number of patients with an SAE	6 (2.4)	0	2 (0.8)	3 (2.6)	2 (0.8)
MedDRA SOC/PT					
GI disorders	0	0	0	1 (0.9)	2 (0.8)
Abdominal pain	0	0	0	0	1 (0.4)
Intestinal obstruction	0	0	0	0	1 (0.4)
Small intestinal obstruction	0	0	0	1 (0.9)	0
Infections and infestations	2 (0.8)	0	0	1 (0.9)	0
Lobar pneumonia	1 (0.4)	0	0	0	0
Pneumonia		0	0	1 (0.9)	0
URTI	1 (0.4)	0	0	0	0
Injury, poisoning, procedural comp.	1 (0.4)	0	1 (0.4)	1 (0.9)	0
Abdominal injury	0	0	0	1 (0.9)	0
Facial bones fracture	1 (0.4)	0	0	0	0
Muscle rupture	0	0	1 (0.4)	0	0
Respiratory, thoracic, mediastinal	2 (0.8)	0	0	0	0
Asthma	2 (0.8)	0	0	0	0
Cardiac disorders	0	0	1 (0.4)	0	0
Angina pectoris	0	0	1 (0.4)	0	0
Investigations	1 (0.4)	0	0	0	0
ECG T-wave inversion	1 (0.4)	0	0	0	0
*Pool 3 = Pivotal Phase 3 studies 716 and 717. See Table 35 for description of study pooling.					
Source: T47, p3090; clinsum.pdf					

Table 20. SAEs during randomized treatment, All Phase 3 studies (Pool 5*)

SAEs, Pool 5	Treatment group, n (%)				
	Symbicort MDI n=2193	Budesonide MDI N=1182	Formoterol TBH n=384	Symbicort TBH n=668	Placebo n=409
Mean exposure (days)	135.2	80.9	65.1	170.1	55.8
Number of patients with an SAE	51 (2.3)	8 (0.7)	3 (0.8)	17 (2.5)	2 (0.5)
MedDRA SOC					
Respiratory, thoracic, mediastinal	14 (0.6)	4 (0.3)	1 (0.3)	6 (0.9)	0
Infections and infestations	14 (0.6)	0	0	5 (0.7)	0
GI disorders	6 (0.3)	0	0	4 (0.6)	2 (0.5)
Injury, poisoning, procedural comp.	5 (0.2)	1 (0.1)	1 (0.3)	1 (0.1)	0
Cardiac disorders	2 (0.1)	0	1 (0.3)	2 (0.3)	0
Reproductive, breast	5 (0.2)	0	0	0	0
Nervous system	0	1 (0.1)	0	1 (0.1)	0
Ear and labyrinth	2 (0.1)	0	0	1 (0.1)	0
Musculoskeletal, connective tissue	1 (0.1)	0	0	2 (0.3)	0
Neoplasms	2 (0.1)	0	0	1 (0.1)	0
Renal and urinary	2 (0.1)	0	0	1 (0.1)	0
Investigations	2 (0.1)	0	0	0	0
Congenital, familial, genetic	0	1 (0.1)	0	0	0

SAEs, Pool 5	Treatment group, n (%)				
	Symbicort MDI n=2193	Budesonide MDI N=1182	Formoterol TBH n=384	Symbicort TBH n=668	Placebo n=409
Hepatobiliary	1 (<0.1)	0	0	0	0
Psychiatric	0	1 (0.1)	0	0	0
Skin, subcutaneous tissue	1 (<0.1)	0	0	0	0
Vascular	1 (<0.1)	0	0	0	0
*Pool 5 = All Phase 3 studies. See Table 35 for description of study pooling.					
Source: T49, p3094; clinsum.pdf					

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Since pre-defined asthma events qualified patients for withdrawal in both of the pivotal studies, the rate of withdrawals was a major issue in the review of the studies, but primarily because of the potential effect on efficacy rather than on safety; this is discussed elsewhere in this review, and will not be discussed here. Safety issues related to dropouts are discussed below.

The incidence of dropouts due to adverse events was relatively low, with no safety pattern emerging.

7.1.3.2 Adverse events associated with dropouts

AEs that lead to dropout (DAEs), by MedDRA SOC and PT for the 2 pivotal studies are shown in Table 21, and by SOC for all Phase 3 studies in Table 22. Pool 6 is not shown, but the results did not change significantly from Pools 3 and 5. As with other AEs, interpretation of results must consider differences in mean exposure among treatment arms.

In the pivotal studies, the frequency of dropouts was lowest in the budesonide and formoterol arms, highest in the placebo and free combination arms, with Symbicort MDI in the middle. In all studies, the most common reason for dropout was respiratory, with asthma leading the list and highest in the placebo arms. This is not unexpected, given the fact that the patients enrolled in the studies needed controller therapy. The rest of the DAEs were scattered as to cause, with no clear pattern.

There was no pattern of DAEs by subgroup of dose, or baseline characteristics including ICS dose. There were too few DAEs in Blacks, Orientals, and Others to meaningfully evaluate DAEs by race. However, the percent of asthma DAEs in Blacks (16/420, 3.6%) in all treatment groups was higher than in the other groups (Caucasian: 40/3741, 1.1%; Oriental: 2/317, 0.6%; Other: 2/473, 0.6%).

Appears This Way
On Original

Table 21. DAEs, Most commonly reported SOC/PTs, Pivotal Phase 3 studies (Pool 3*)

DAEs, Pool 3	Treatment group, n (%)				
	Symbicort MDI n=254	Budesonide MDI N=236	Formoterol TBH n=246	Bud + Form n=115	Placebo n=256
Mean exposure (days)	76.0	74.3	62.3	74.5	52.3
Number of patients with a DAE	12 (4.7)	7 (3.0)	8 (3.3)	9 (7.8)	16 (6.3)
MedDRA SOC/PT					
Respiratory, thoracic, mediastinal	4 (1.6)	3 (1.3)	4 (1.6)	1 (0.9)	7 (2.7)
Asthma	3 (1.2)	3 (1.3)	3 (1.2)	0	7 (2.7)
Cough	0	0	0	1 (0.9)	1 (0.4)
Hoarseness	1 (0.4)	0	0	0	0
Pharyngolaryngeal pain	0	0	0	0	1 (0.4)
Wheezing	0	0	1 (0.4)	0	0
Infections and infestations	3 (1.2)	0	2 (0.8)	2 (1.7)	4 (1.6)
Bronchitis	1 (0.4)	0	1 (0.4)	0	3 (1.2)
Sinusitis	0	0	1 (0.4)	0	1 (0.4)
URTI	1 (0.4)	0	0	0	1 (0.4)
Lobar pneumonia	1 (0.4)	0	0	0	0
Pharyngitis	0	0	0	1 (0.9)	0
Pneumonia	0	0	0	1 (0.9)	0
Cardiac disorders	4 (1.6)	1 (0.4)	2 (0.8)	1 (0.9)	2 (0.8)
Atrial fibrillation	1 (0.4)	0	2 (0.8)	0	0
Ventricular tachycardia	1 (0.4)	1 (0.4)	0	0	1 (0.4)
Ventricular extrasystoles	1 (0.4)	0	0	0	1 (0.4)
AV block second degree	1 (0.4)	0	0	0	0
Supraventricular tachycardia	0	0	0	1 (0.9)	0
GI disorders	0	1 (0.4)	0	1 (0.9)	3 (1.2)
Abdominal distention	0	1 (0.4)	0	0	0
Abdominal pain	0	0	0	0	1 (0.4)
Abdominal pain upper	0	0	0	0	1 (0.4)
Dyspepsia	0	0	0	1 (0.9)	0
Intestinal obstruction	0	0	0	0	1 (0.4)
Small intestinal obstruction	0	0	0	1 (0.9)	0
Investigations	1 (0.4)	0	0	2 (1.7)	1 (0.4)
ECG T-wave inversion	1 (0.4)	0	0	1 (0.9)	0
ECG signs of myocardial ischemia	0	0	0	1 (0.9)	0
FEV ₁ decreased	0	0	0	0	1 (0.4)
Musculoskeletal, connective tissue	1 (0.4)	0	0	1 (0.9)	0
Arthralgia	1 (0.4)	0	0	1 (0.9)	0
Skin, subcutaneous tissue	0	1 (0.4)	0	1 (0.9)	0
Dermatitis contact	0	1 (0.4)	0	0	0
Eczema	0	0	0	1 (0.9)	0
General, administration site	0	0	0	0	1 (0.4)
Chest pain	0	0	0	0	1 (0.4)
Immune system	0	0	0	0	0
Seasonal allergy	0	1 (0.4)	0	0	0
Metabolism, nutritional	0	1 (0.4)	0	0	0
Increased appetite	0	1 (0.4)	0	0	0

DAEs, Pool 3	Treatment group, n (%)				
	Symbicort MDI n=254	Budesonide MDI N=236	Formoterol TBH n=246	Bud + Form n=115	Placebo n=256
Psychiatric	0	0	0	1 (0.9)	0
Insomnia	0	0	0	1 (0.9)	0
*Pool 3 = Pivotal Phase 3 studies 716 and 717. See Table 35 for description of study pooling.					
Source: T50, p3099-3100; clinsum.pdf					

Table 22. DAEs, Most commonly reported SOC/PTs, All Phase 3 studies (Pool 5*)

DAEs, Pool 5	Treatment group, n (%)				
	Symbicort MDI n=2193	Budesonide MDI N=1182	Formoterol TBH n=384	Symbicort TBH n=668	Placebo n=409
Mean exposure (days)	135.2	80.9	65.1	170.1	55.8
Number of patients with a DAE	62 (2.83)	44 (3.7)	19 (4.9)	7 (1.0)	19 (4.6)
MedDRA SOC/PT					
Respiratory, thoracic, mediastinal	26 (1.2)	31 (2.6)	8 (2.1)	2 (0.3)	9 (2.2)
Asthma	16 (0.7)	26 (2.2)	7 (1.8)	2 (0.3)	8 (2.0)
Dyspnea	1 (<0.1)	0	0	0	1 (0.2)
Dyspnea exacerbated	0	1 (0.1)	0	0	0
Wheezing	0	0	1 (0.3)	0	1 (0.2)
Cough	4 (0.2)	0	0	0	2 (0.5)
Increased upper airway secretion	0	0	0	0	1 (0.2)
Hoarseness	5 (0.2)	1 (0.1)	0	0	0
Pharyngolaryngeal pain	0	1 (0.1)	0	0	1 (0.2)
Rhinitis allergic	0	2 (0.2)	0	0	0
Rhinitis seasonal	0	1 (0.1)	0	0	0
Infections and infestations	10 (0.5)	6 (0.5)	5 (1.3)	0	4 (1.0)
URTI	2 (0.1)	2 (0.2)	2 (0.5)	0	1 (0.2)
Bronchitis	1 (<0.1)	1 (0.1)	1 (0.3)	0	3 (0.7)
Bronchitis acute	1 (<0.1)	0	1 (0.3)	0	0
Sinusitis	0	1 (0.1)	1 (0.3)	0	1 (0.2)
Acute sinusitis	0	1 (0.1)	0	0	0
Influenza	2 (0.1)	0	0	0	0
Lower respiratory tract infection	1 (<0.1)	1 (0.1)	0	0	0
Lobar pneumonia	1 (<0.1)	0	0	0	0
Ear infection	0	1 (0.1)	0	0	0
Impetigo	1 (<0.1)	0	0	0	0
Nasopharyngitis	1 (<0.1)	0	0	0	0
Rash pustular	1 (<0.1)	0	0	0	0
Cardiac	15 (0.7)	1 (0.1)	3 (0.8)	2 (0.7)	3 (0.7)
Ventricular extrasystoles	4 (0.2)	0	0	0	1 (0.2)
Ventricular tachycardia	2 (0.1)	1 (0.1)	0	0	2 (0.5)
Palpitations	3 (0.1)	0	0	1 (0.1)	0
Atrial fibrillation	1 (0.0)	0	2 (0.5)	0	0
AV block second degree	3 (0.1)	0	0	0	0
Supraventricular tachycardia	2 (0.1)	0	0	0	0
Ventricular bigeminy	0	0	0	1 (0.1)	0
WPW syndrome	0	0	1 (0.3)	0	0

DAEs, Pool 5	Treatment group, n (%)				
	Symbicort MDI n=2193	Budesonide MDI N=1182	Formoterol TBH n=384	Symbicort TBH n=668	Placebo n=409
*Pool 5 = All Phase 3 studies. See Table 35 for description of study pooling. For ease of review, the MedDRA PTs in the table above have been grouped by similar terms. Source: T52, p3103; clinsum.pdf and T2.7.4.7, p11814; summary_appendices_2_7_4a.pdf					

7.1.3.3 Other significant adverse events

All significant AEs are discussed in the sections above.

7.1.4 Other Search Strategies

Search strategies included groupings of adverse events, both serious and non-serious, by SOC and PT for cardiac, asthma, and corticosteroid effects. These are discussed in the sections below.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Occurrence of adverse events was routinely elicited as part of the safety evaluation of the Phase 3 clinical studies.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were classified using MedDRA terminology for SOC and PT. no issues with regard to event categorization were noted.

7.1.5.3 Incidence of common adverse events

The labeling seeks to incorporate an AE table showing adverse events (regardless of causality) occurring at an incidence $\geq 3\%$ in any Symbicort MDI group and more commonly than placebo. The AE table comes from the three placebo-controlled studies (i.e. Pool 4), studies **716**, **717**, and **726**. While study 726 included BID Symbicort (160/9 BID) and placebo arms, it also included a once-daily (QD) budesonide (320 mcg QD) active comparator arm. The PI seeks to include this information in the Budesonide 230 total daily dose column. However, efficacy and safety may not be the same with once-daily vs twice-daily dosing. Therefore, the AEs with QD dosing should not be included in the labeling, and are not represented in the AE table (Table 23) below.

Also of note, MedDRA terminology was used for the adverse event tables. MedDRA tends to split preferred terms, making AE trends more difficult to find, evaluate, and express meaningfully. For example, separate terms for both upper respiratory tract infection and viral upper respiratory tract infection are available. Because of the complexities that might ensue from trying to combine terms in multiple studies, no attempt was made to do so. However, the reader should be aware of this phenomenon.

7.1.5.4 Common adverse event tables

Table 23. PI AE table. AEs $\geq 3\%$ in any Symbicort MDI group and higher than placebo, Pool 4*, BID treatment only, Patients ≥ 12 years

PI AE table	Treatment group, n (%)					
	Symbicort MDI	Symbicort MDI	Budesonide	Budesonide	Formoterol	Placebo
Total daily dose (mcg)	320/18	640/18	320	640	18	0
Dosage	160/9 BID	320/9 BID	160 BID	320 BID	9 BID	0
N	277	124	127	109	237	400
Studies from which AEs were derived	716, 726	717	716	717	716, 717	716, 717, 726
Mean exposure (days)	77.7	73.8	76.7	71.4	62.4	55.9
Adverse Event						
Nasopharyngitis	29 (10.5)	12 (9.7)	17 (13.4)	12 (11.0)	24 (10.1)	36 (9.0)
Headache	18 (6.5)	14 (11.3)	14 (11.0)	14 (12.8)	21 (8.9)	26 (6.5)
Upper respiratory tract infection	21 (7.6)	13 (10.5)	10 (7.9)	10 (9.2)	18 (7.6)	31 (7.8)
Pharyngolaryngeal pain	17 (6.1)	11 (8.8)	6 (4.7)	8 (7.3)	7 (3.0)	19 (4.8)
Sinusitis	16 (5.8)	6 (4.8)	7 (5.5)	3 (2.8)	15 (6.3)	19 (4.8)
Influenza	9 (3.2)	3 (2.4)	9 (7.1)	1 (0.9)	7 (3.0)	5 (1.3)
Back pain	9 (3.2)	2 (1.6)	3 (2.4)	6 (5.5)	5 (2.1)	3 (0.8)
Nasal congestion	7 (2.5)	4 (3.2)	4 (3.1)	4 (3.7)	3 (1.3)	4 (1.0)
Stomach discomfort	3 (1.1)	8 (6.5)	0	5 (4.6)	3 (1.3)	7 (1.8)
Vomiting	4 (1.4)	4 (3.2)	2 (1.6)	3 (2.8)	4 (1.7)	4 (1.0)
Oral candidiasis	4 (1.4)	4 (3.2)	0	0	0	3 (0.8)
*Pool 4 = All placebo-controlled Phase 3 studies: 716, 717, and 726. See Table 35 for description of study pooling.						
Source: T46, p3087; clinsum.pdf; T11.3.2.4.3.2, p3969; SD-039-0716.pdf						

7.1.5.5 Identifying common and drug-related adverse events

Search strategies employed by the applicant included groupings of adverse events, both serious and non-serious, by SOC and PT and classified by events of potential interest including cardiac, asthma, and corticosteroid effects, subcategorized by local and systemic effects. Lists of terms were created based on the applicant's assessment of PTs that might qualify [p12181-12196; summary_appendices_2_7_4a.pdf]. For beta-agonist and cardiac effects, the listing of PTs was fairly complete, whereas for asthma events the listing included the PTs of asthma, bronchospasm, and status asthmaticus, but did not include wheezing, dyspnea, cough, or chest tightness, which were listed separately as part of an event class termed 'disease under study' (DUS). Local steroid events included various PTs to identify events of candidiasis and voice effects, but did not include oropharyngeal discomfort or pain. Events were tabulated using Pool 4 (all placebo-controlled studies) for comparison to placebo and Pool 5 (all Phase 3 studies) to provide the largest number of exposures to Symbicort. [p3107; clinsum.pdf]

7.1.5.5.1 Potential corticosteroid effects

Results of the tabulations of events of interest representing potential local or systemic corticosteroid effects are shown in Table 24 and Table 25 for Pools 4 and 5, respectively. Symbicort in both the MDI and TBH formulations appeared to be associated with more local

effects such as candidiasis and hoarseness than placebo, formoterol, or even budesonide alone. However, the tabulation did not reveal any evidence of association with systemic effects. The one patient who had evidence of adrenal suppression (laboratory event: urinary free cortisol decreased in study 719) was on budesonide only.

Table 24. ICS events of interest, All placebo-controlled Phase 3 studies (Pool 4*)

ICS events of interest, Pool 4	Treatment group, n (%)			
	Symbicort MDI n=707	Budesonide MDI N=381	Formoterol TBH n=246	Placebo n=409
Patients with 1 or more AEs representing local effects of ICS	19 (2.7)	4 (1.0)	1 (0.4)	4 (1.0)
Candidiasis	12 (1.7)	1 (0.3)	0	3 (0.7)
Voice Effects	7 (1.0)	3 (0.8)	1 (0.4)	1 (0.2)
Patients with 1 or more AEs representing systemic effects of ICS	6 (0.8)	6 (1.6)	5 (2.0)	4 (1.0)
Fractures	4 (0.6)	2 (0.5)	2 (0.8)	3 (0.7)
Skin effects	0	2 (0.5)	1 (0.4)	1 (0.2)
Diabetes control	1 (0.1)	0	1 (0.4)	0
Taste effects	1 (0.1)	0	0	0
Ocular effects	0	1 (0.3)	0	0
Weight gain	0	1 (0.3)	1 (0.4)	0
Adrenal suppression	0	0	0	0
Metabolic bone effects	0	0	0	0
Growth retardation	0	0	0	0
Psychiatric effects	0	0	0	0
*Pool 4 = All placebo-controlled Phase 3 studies. See Table 35 for description of study pooling.				
Source: T53, p3108; T 54, p3109; clinsum.pdf				

Table 25. ICS events of interest, All Phase 3 studies (Pool 5*)

ICS events of interest, Pool 5	Treatment group, n (%)				
	Symbicort MDI n=2193	Budesonide MDI N=1182	Formoterol TBH n=384	Symbicort TBH n=668	Placebo n=409
Patients with 1 or more AEs representing local effects of ICS	68 (3.1)	16 (1.4)	2 (0.5)	20 (3.0)	4 (1.0)
Candidiasis	39 (1.8)	9 (0.8)	0	9 (1.3)	3 (0.7)
Voice Effects	31 (1.4)	7 (0.6)	2 (0.5)	11 (1.6)	1 (0.2)
Patients with 1 or more AEs representing systemic effects of ICS	26 (1.2)	12 (1.0)	6 (1.6)	11 (1.6)	4 (1.0)
Fractures	15 (0.7)	2 (0.5)	2 (0.8)	6 (0.9)	3 (0.7)
Skin effects	5 (0.2)	2 (0.5)	1 (0.4)	1 (0.1)	1 (0.2)
Diabetes control	1 (0.1)	0	1 (0.4)	1 (0.1)	0
Taste effects	2 (0.1)	0	0	2 (0.3)	0
Ocular effects	1 (<0.1)	1 (0.1)	0	1 (0.1)	0
Weight gain	1 (<0.1)	1 (0.1)	1 (0.3)		0
Adrenal suppression	0	1 (0.1)	0	0	0
Metabolic bone effects	1 (<0.1)	0	0	0	0
Growth retardation	0	0	0	0	0
Psychiatric effects	0	0	0	0	0
*Pool 5 = All Phase 3 studies. See Table 35 for description of study pooling.					

ICS events of interest, Pool 5	Treatment group, n (%)				
	Symbicort MDI n=2193	Budesonide MDI N=1182	Formoterol TBH n=384	Symbicort TBH n=668	Placebo n=409
Source: T55, p3110; T 56, p3111; clinsum.pdf					

7.1.5.5.2 Beta-adrenergic effects

Results of the tabulations of events of interest representing beta-adrenergic effects are shown in Table 26 and Table 27 for Pools 4 and 5, respectively. Not unexpectedly, Symbicort exhibited some beta-adrenergic side effects, although overall the formoterol group showed the highest frequency of beta-adrenergic effects. This is not a specific safety concern. The most common side effect, headache, tended to be reported more frequently in the first month of treatment. The only effect more common in Symbicort than the formoterol groups was palpitations.

Table 26. Beta-adrenergic events of interest, All placebo-controlled Phase 3 studies (Pool 4*)

Beta-adrenergic events of interest, Pool 4	Treatment group, n (%)			
	Symbicort MDI n=707	Budesonide MDI N=381	Formoterol TBH n=246	Placebo n=409
Patients with 1 or more AEs representing Beta-adrenergic events	64 (9.1)	48 (12.6)	37 (15.0)	28 (6.8)
Headache	49 (6.9)	39 (10.2)	22 (8.9)	27 (6.6)
Sleep effects	6 (0.8)	1 (0.3)	4 (1.6)	0
Tremor	3 (0.4)	2 (0.5)	6 (2.4)	0
Anxiety	4 (0.6)	2 (0.5)	5 (2.0)	0
Muscle cramp	3 (0.4)	3 (0.8)	2 (0.8)	0
Palpitation	3 (0.4)	0	1 (0.4)	1 (0.2)
Tachycardia	2 (0.3)	1 (0.3)	0	0
Potassium	0	1 (0.3)	0	0
Agitation	0	0	0	0
Glucose	0	0	0	0
*Pool 4 = All placebo-controlled Phase 3 studies. See Table 35 for description of study pooling.				
Source: T58, p3117; clinsum.pdf				

Appears This Way
On Original

Table 27. Beta-adrenergic events of interest, All Phase 3 studies (Pool 5*)

Beta-adrenergic events of interest, Pool 5	Treatment group, n (%)				
	Symbicort MDI n=2193	Budesonide MDI N=1182	Formoterol TBH n=384	Symbicort TBH n=668	Placebo n=409
Patients with 1 or more AEs representing Beta-adrenergic events	247 (11.3)	112 (9.5)	64 (16.7)	53 (7.9)	28 (6.8)
Headache	195 (8.9)	98 (8.3)	46 (12.0)	35 (5.2)	27 (6.6)
Palpitation	26 (1.2)	0	1 (0.3)	12 (1.8)	1 (0.2)
Sleep effects	14 (0.6)	6 (0.5)	5 (1.3)	2 (0.3)	0
Muscle cramp	8 (0.4)	4 (0.3)	5 (1.3)	6 (0.9)	0
Tremor	8 (0.4)	3 (0.3)	6 (1.6)	7 (1.0)	0
Anxiety	9 (0.4)	3 (0.3)	7 (1.8)	1 (0.1)	0
Tachycardia	5 (0.2)	1 (0.1)	0	2 (0.3)	0
Glucose	1 (<0.1)	0	0	1 (0.1)	0
Potassium	0	1 (0.1)	0	0	0
Agitation	0	0	0	0	0
*Pool 5 = All Phase 3 studies. See Table 35 for description of study pooling.					
Source: T60, p3120; clinsum.pdf					

7.1.5.5.3 Cardiac effects

Results of the tabulations of events of interest representing cardiac effects are shown in Table 28 and Table 29 for Pools 4 and 5, respectively. Not unexpectedly, both the Symbicort and formoterol groups exhibited some cardiac side effects, likely due to the beta-adrenergic component, but the overall frequency was low. This is not a specific safety concern. Cardiac SAEs and DAEs are considered within each of those respective sections above.

Table 28. Cardiac events of interest, All placebo-controlled Phase 3 studies (Pool 4*)

Cardiac events of interest, Pool 4	Treatment group, n (%)			
	Symbicort MDI n=707	Budesonide MDI N=381	Formoterol TBH n=246	Placebo n=409
Patients with 1 or more AEs representing Cardiac events ¹	19 (2.7)	4 (1.0)	6 (2.4)	6 (1.5)
Ventricular extrasystoles	5 (0.7)	1 (0.3)	0	1 (0.2)
Ventricular tachycardia	2 (0.3)	1 (0.3)	0	2 (0.5)
Atrial fibrillation	2 (0.3)	0	2 (0.8)	0
Chest pain	2 (0.3)	0	1 (0.4)	1 (0.2)
AV block 2 nd degree	3 (0.4)	0	0	0
Hypertension	1 (0.1)	1 (0.3)	0	0
Blood pressure increased	1 (0.1)	0	0	1 (0.2)
ECG T wave inversion	1 (0.1)	0	0	0
Heart rate increased	0	1 (0.3)	1 (0.4)	0
Supraventricular tachycardia	1 (0.1)	0	0	0
Angina pectoris	0	0	1 (0.4)	0
Bundle branch block right	1 (0.1)	0	0	0
Cardiac flutter	0	0	0	1 (0.2)
ECG ST-T change	0	0	1 (0.4)	0
Sinus tachycardia	1 (0.1)	0	0	0

Cardiac events of interest, Pool 4	Treatment group, n (%)			
	Symbicort MDI n=707	Budesonide MDI N=381	Formoterol TBH n=246	Placebo n=409
¹ Since the listing is extremely long, not all the potential cardiac events are listed, and only those reported are represented in the table.				
*Pool 4 = All placebo-controlled Phase 3 studies. See Table 35 for description of study pooling.				
Source: T59, p3118; clinsum.pdf				

Table 29. Cardiac events of interest, All Phase 3 studies (Pool 5*)

Cardiac events of interest, Pool 5	Treatment group, n (%)				
	Symbicort MDI n=2193	Budesonide MDI N=1182	Formoterol TBH n=384	Symbicort TBH n=668	Placebo n=409
Patients with 1 or more AEs representing Cardiac events ¹	43 (2.0)	8 (0.7)	7 (1.8)	17 (2.5)	6 (1.5)
Chest pain	12 (0.5)	2 (0.2)	1 (0.3)	5 (0.7)	1 (0.2)
Hypertension	8 (0.4)	3 (0.3)	0	5 (0.7)	0
Ventricular extrasystoles	6 (0.3)	1 (0.1)	0	0	1 (0.2)
Ventricular tachycardia	3 (0.1)	1 (0.1)	0	0	2 (0.5)
Blood pressure increased	1 (<0.1)	0	0	3 (0.4)	1 (0.2)
Atrial fibrillation	2 (0.1)	0	2 (0.5)	0	0
Heart rate increased	1 (<0.1)	1 (0.1)	1 (0.3)	1 (0.1)	0
AV block 2 nd degree	3 (0.1)	0	0	0	0
Supraventricular tachycardia	2 (0.1)	0	0	0	0
Angina pectoris	1 (<0.1)	0	1 (0.3)	0	0
Bradycardia	1 (<0.1)	0	0	0	0
Bundle branch block right	1 (<0.1)	0	0	1 (0.1)	0
ECG T wave inversion	1 (<0.1)	0	0	0	0
Sinus tachycardia	1 (<0.1)	1 (0.1)	0	0	0
Arrhythmia	0	0	0	1 (0.1)	0
Arrhythmia supraventricular	1 (<0.1)	0	0	0	0
Arteriospasm coronary	1 (<0.1)	0	0	0	0
Bundle branch block	1 (<0.1)	0	0	0	0
Cardiac flutter		0	0	0	1 (0.2)
ECG ST-T change		0	1 (0.3)	0	0
Extrasystoles		0	0	1 (0.1)	0
Hypotension	1 (<0.1)	0	0	0	0
Ventricular bigeminy	0	0	0	1 (0.1)	0
WPW syndrome	0	0	1 (0.3)	0	0

¹ Since the listing is extremely long, not all the potential cardiac events are listed, and only those reported are represented in the table.

*Pool 5 = All Phase 3 studies. See Table 35 for description of study pooling.

Source: T62, p3123; clinsum.pdf

7.1.5.5.4 Asthma effects

Results of the tabulations of events of interest representing asthma and asthma-related events of interest are shown in Table 30 and Table 31 for Pools 4 and 5, respectively. Not unexpectedly, both the Symbicort and budesonide were the lowest in frequency of these events, corresponding to the ICS component and underscoring efficacy of use as a controller agent. Of concern,

formoterol alone fared worse than placebo, clarifying what is seen in the review of the clinical studies, i.e. that formoterol alone may help FEV₁ but does not prevent asthma type of AEs and therefore should not be considered an effective controller medication.

Table 30. All placebo-controlled Phase 3 studies (Pool 4*)

Asthma and potentially asthma-related events of interest	Treatment group, n (%)			
	Symbicort MDI n=707	Budesonide MDI N=381	Formoterol TBH n=246	Placebo n=409
Patients with 1 or more AEs representing Asthma or potentially Asthma-related events	29 (4.1)	21 (5.5)	28 (11.4)	34 (8.3)
Asthma	7 (1.0)	7 (1.8)	8 (3.3)	12 (2.9)
Potentially asthma related (DUS)	22 (3.1)	14 (3.7)	22 (8.9)	24 (5.9)
Cough	10 (1.4)	7 (1.8)	13 (5.3)	11 (2.7)
Breathlessness	4 (0.6)	0	4 (1.6)	8 (2.0)
Wheezing	4 (0.6)	3 (0.8)	4 (1.6)	5 (1.2)
Chest tightness	2 (0.3)	3 (0.8)	6 (2.4)	4 (1.0)
Phlegm	2 (0.3)	1 (0.3)	1 (0.4)	2 (0.5)
*Pool 4 = All placebo-controlled Phase 3 studies. See Table 35 for description of study pooling.				
Source: T64, p3130; clinsum.pdf				

Table 31. Asthma and potentially asthma-related events of interest, All Phase 3 studies (Pool 5*)

	Treatment group, n (%)				
	Symbicort MDI n=2193	Budesonide MDI N=1182	Formoterol TBH n=384	Symbicort TBH n=668	Placebo n=409
Patients with 1 or more AEs representing Asthma or potentially Asthma-related events	148 (6.7)	90 (7.6)	45 (11.7)	33 (4.9)	34 (8.3)
Asthma	63 (2.9)	41 (3.5)	15 (3.9)	24 (3.6)	12 (2.9)
Potentially asthma related (DUS)	87 (4.0)	51 (4.3)	32 (8.3)	10 (1.5)	24 (5.9)
Cough	62 (2.8)	33 (2.8)	21 (5.5)	4 (0.6)	11 (2.7)
Wheezing	10 (0.5)	12 (1.0)	7 (1.8)	3 (0.4)	5 (1.2)
Breathlessness	7 (0.3)	2 (0.2)	4 (1.0)	2 (0.3)	8 (2.0)
Chest tightness	7 (0.3)	4 (0.3)	6 (1.6)	1 (0.1)	4 (1.0)
Phlegm	3 (0.1)	1 (0.1)	1 (0.4)	0	2 (0.5)
*Pool 5 = All Phase 3 studies. See Table 35 for description of study pooling.					
Source: T65, p3131; clinsum.pdf					

7.1.5.6 Additional analyses and explorations

No additional analyses or explorations were performed.

7.1.6 Less Common Adverse Events

Please see the AE event discussions for a discussion of all relevant AEs.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Clinical laboratory measures were performed throughout the development program, including hematology, clinical chemistry, glucose, potassium, urinalysis, and effects on HPA axis. 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. In particular, effects on glucose, potassium and HPA axis were examined. 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.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

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.

7.1.7.3 Standard analyses and explorations of laboratory data

Please see the review of the individual studies in the Appendix of this document; the results will not be duplicated here. The expected minor effects related to increase [from baseline] in glucose and decrease [from baseline] in potassium were seen in the clinical studies. As expected, some dose ordering was noted. In Pools 3-5, percentages of patients with potentially significant abnormalities in these two parameters were similar across active treatment groups and placebo. This was also true for subsets of patients evaluated in the pivotal studies (Pool 3). There were no significant effects on urinalysis, other clinical chemistry, or hematology parameters.

7.1.7.3.1 HPA axis

HPA axis was evaluated as part of the development program by AM plasma and 24-hour urine cortisol levels. While HPA axis was not evaluated in the two pivotal Phase 3 studies, AM plasma and 24-hour urine cortisol were performed in studies 682 and 715, and 24-hour urine cortisol was performed in studies 719, 725 and 726. Cortisol (24-hour plasma) was also in Phase 1 study, 626, a single-dose 2-way crossover study evaluating Symbicort MDI vs Symbicort TBH. The only placebo-controlled study evaluating HPA axis was study 726. Brief summaries of the studies follow, with results mean urinary cortisol levels shown in Table 32. For all results, the variability of results exceeded any mean differences, making interpretation difficult. In study 726, no mean difference from placebo was noted. While in several studies there were trends noted for individual changes from normal baseline to low at the end of treatment, these results were not unexpected, and appeared somewhat dose related, but did not correlate to clinical adverse events. Only one Adverse Event corresponding to an alteration in HPA axis function was noted in the clinical program (decreased urinary cortisol level, see the Adverse Event subsection of this review for details).