CLINICAL REVIEW

Application	NDA 21-929, S-013
Letter Date	July 28, 2016
Stamp Date	July 28, 2016
PDUFA Goal Date	January 27, 2017
Reviewer Name	Peter Starke, MD
Review Completion Date	December 21, 2016
Established Name	Budesonide / formoterol fumarate dihydrate inhalation aerosol
Trade Name	Symbicort® Inhalation Aerosol
Therapeutic Class	Corticosteroid / long-acting beta-agonist fixed combination
Applicant	AstraZeneca LP
Priority Designation	Priority
Formulation	HFA-propelled pressurized metered dose inhaler
Dosage Strength	80 mcg budesonide / 4.5 mcg formoterol fumarate
Dosing Regimen	Two inhalations twice daily
Indication	Treatment of asthma
Intended Population	Pediatric patients 6 through 11 years of age

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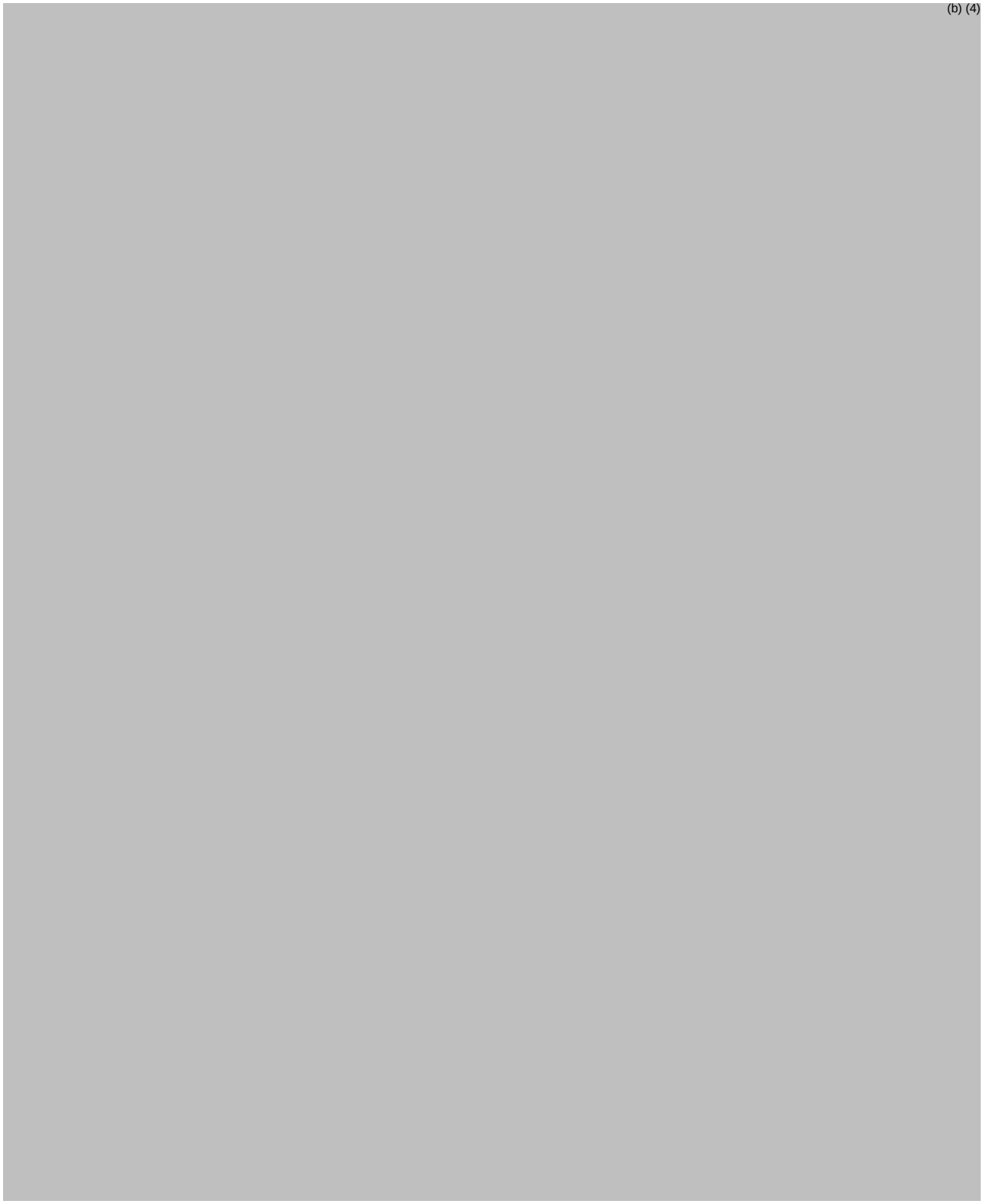

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Submissions Reviewed in this Document

Document Date	Submission #	Comments
June 3, 2008	SD-103	Pediatric supplement SE5-013
April 3, 2009		*CR Action to original supplement submission*
October 1, 2009	SD-155	Pediatric Study Plan
July 28, 2016	SD-1959	Response to CR action of April 3, 2009
October 25, 2016	SD-2024	Periodic Benefit-Risk Evaluation Report (PBRER)
October 31, 2016	SD-2029	Response to Clinical IR of October 26, 2016
December 2, 2016	SD-2053	Response to Clinical IR of November 28, 2016

Referential Notation

References to source material are bracketed [ ] and follow a standard format: [submission: table, or figure; page number(s)]; for example, [ISE, T51, p499-501]. 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].

Naming Conventions

The reader should be aware of the following naming conventions used throughout this document.

The product under discussion, Symbicort Inhalation Aerosol [Symbicort], is an HFA-propelled metered dose inhaler [MDI]. However, some products and formulations used prior to 2007 used CFC, which is no longer marketed, as the propellant. As a result, the designations 'HFA' and 'CFC' are used as needed to distinguished between HFA- and CFC-propelled MDI products. Throughout the review the US-approved Symbicort is referred to as Symbicort without a specific designation after the trade name. Since a second Symbicort product, Symbicort Turbuhaler [TBH] dry powder inhaler [DPI], is marketed ex-US, the non-US-approved Symbicort Turbuhaler product is **always** referred to with the 'TBH' or 'Turbuhaler' designation. When appropriate, the nominal (ex-actuator) dosage strength follows the trade name, e.g., 'Symbicort 40/4.5', with the budesonide strength followed by the formoterol strength, i.e., '40/4.5' = budesonide 40 mcg and formoterol 4.5 mcg. Further, in the text, tables, and notations, the nominal dosage strength is generally used rather than the administered dose (2 inhalations), or the total daily dose (TDD) of 2 inhalations twice daily. This is to avoid confusion, since 2 inhalations is the approved/recommended dose, and both once daily and twice daily dosing was used in at least one of the studies. When the total daily dose is used, such use is clearly demarcated.

Age ranges in the review may be referred to in several different ways. The term of '6-11' years, which may be read as 6 to 11 years, is often used to mean 6 through 11 years, or alternately, as 6 to less than 12 years of age. All of these terms are used in various locations throughout this review, but they all mean the same thing.

A common terminology is used to label/number the studies submitted to the supplement. All of the original Symbicort Inhalation Aerosol studies used the terminology 'SD-039-0xxx' where **xxx** is the number designated for the study, whereas all of the subsequent Complete Response / Written Request studies used the terminology 'D589GC00xxx' where **xxx** is the number designated for the study. This review refers to the studies by their last three digits. Note also AstraZeneca also uses the term CHASE to designate the new three studies performed for the Complete Response, namely 'CHASE 1' for study '001', 'CHASE 2' for study '002', and 'CHASE 3' for study '003'.

Glossary

AC	advisory committee
AE	adverse event
API	active pharmaceutical ingredient
BA	bioavailability
BAN	British approved name
BE	bioequivalence
BID	twice-daily
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	benefit risk framework
CBER	Center for Biologics Evaluation and Research
CCABA	Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic monograph (21 CFR 341.16)
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader

CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
DMPP	Division of Medical Policy Programs
DPARP	Division of Pulmonary, Allergy, and Rheumatology Products
ECG	electrocardiogram
EP	European Pharmacopoeia
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IFU	instructions for use
IM	intramuscular
IND	Investigational New Drug
INN	international nonproprietary name
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NDC	National Drug Code
NME	new molecular entity
NSAIDs	nonsteroidal anti-inflammatory agents
OCS	Office of Computational Science
OPDP	Office of Prescription Drug Promotion
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OTC	over-the-counter
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PLR	Physician Labeling Rule
PLLR	Pregnancy and Lactation Labeling Rule
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol

PPI	patient package insert
PREA	Pediatric Research Equity Act (21 U.S.C. 355c)
PRO	patient reported outcome
PSP	Pediatric Study Plan
PSUR	Periodic Safety Update report
RA	rheumatoid arthritis
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
USAN	United States approved name

1 RECOMMENDATIONS/RISK-BENEFIT ASSESSMENT

1.1 Recommendation on Regulatory Action

I recommend Approval of this supplement.

1.2 Risk Benefit Summary

This is a pediatric efficacy supplement (NDA 21-929, SE5-013) submitted by AstraZeneca LP, for Symbicort® (budesonide / formoterol fumarate dihydrate) Inhalation Aerosol [hereafter called Symbicort] to extend the current indication of treatment of asthma from patients 12 years and older to patients 6-11 [i.e., 6 to 11, or 6 through 11] years of age for the Symbicort 80/4.5 mcg dosage strength. Symbicort is a fixed-dose combination product of budesonide, a corticosteroid, and formoterol fumarate dehydrate [formoterol], a long-acting beta-agonist (LABA). The drug product is a pressurized metered dose inhaler (MDI or pMDI) using HFA 227 as the propellant. Two dosage strengths are approved, 80/4.5 and 160/4.5 mcg, containing (b) (4) doses of 80 or 160 mcg of budesonide and 4.5 mcg of formoterol per inhalation, respectively.

At the time of approval in 2006, a deferral under PREA was granted for patients 6-11 years of age, and a waiver of pediatric study requirements was granted for patients less than 6 years of age. The supplement (S-013) for the 6-11 year asthma population was submitted on June 3, 2008, and received a Complete Response (CR) action on April 3, 2009, because (b) (4) there was not sufficient support for extrapolation of the currently approved dosage strengths to a younger population (for further details, see section 2.2). After discussions with the Agency, the applicant then performed three new trials, which included two initial trials to find / support the dosages of the individual components (a study to support the 80 mcg dose of budesonide in this age range, and a single-dose dose-ranging study to support the choice of the formoterol dose) and a pivotal trial to support extension of the currently approved 80/4.5 dosage strength to patients 6-11 years of age. All three trials were performed under a pediatric Written Request, for which pediatric exclusivity is now being sought.

The new pediatric program provides support for the efficacy and safety of each component and the combination, and therefore supports approval of the Symbicort 80/4.5 dosage strength for treatment of asthma in patients 6-11 years of age. No new safety findings were noted during the course of this review.

There have been longstanding safety concerns regarding an increase in asthma-related death as well as respiratory-related deaths or life-threatening experiences in adults, and an increased risk of asthma-related hospitalization in children, exposed to LABAs. It is unknown whether use of a corticosteroid with a LABA changes these risks. As a result, in 2010 the FDA required large safety trials to evaluate the risk associated with a LABA on a background of ICS. Early results from the postmarketing LABA safety studies do not appear to substantiate that there is a significant increase in risk in serious asthma outcomes with use of an ICS/LABA in adults, adolescents and pediatric patients. The size and scope of the Symbicort clinical development

program for pediatric patients 6-11 years of age was not sufficient to add new information regarding this risk (nor was it intended that the studies do so).

In sum, the new trials demonstrate that the currently approved dosage strength of 80/4.5 is appropriate for use in asthma patients 6-11 years of age. Namely, the trials show both a reasonable efficacy profile in this population as well as a safety profile that is consistent with that seen in older populations. Therefore, the risk-benefit supports approval of the Symbicort 80/4.5 dosage strength for the treatment of asthma in patients 6-11 years of age.

1.3 Recommendation on Postmarketing Actions

1.3.1 Risk Management Activity

None recommended at this time.

1.3.2 Required Phase 4 Commitments

None recommended at this time. The submitted pediatric studies fulfill the outstanding pediatric study requirement for Symbicort.

1.3.3 Other Phase 4 Requests

None recommended at this time.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

NDA 21-929, S-013, is an efficacy supplement submitted by AstraZeneca LP, for Symbicort® (budesonide / formoterol fumarate dihydrate) Inhalation Aerosol [hereafter called Symbicort] to extend the current indication of maintenance treatment of asthma from patients ≥12 years to patients 6-11 years of age. Symbicort is a fixed-dose combination product containing budesonide (corticosteroid) and formoterol fumarate dihydrate (long-acting beta-agonist or LABA). The drug product is a pressurized metered dose inhaler (MDI or pMDI) using HFA 227 as the propellant. Two dosage strengths are approved, 80/4.5 and 160/4.5, containing 80 mcg or 160 mcg of budesonide and 4.5 mcg of formoterol per inhalation, respectively.[1]

This submission constitutes a complete response to an efficacy supplement (S-013) for treatment of asthma in patients 6-11 [i.e., 6 through 11] years, which was submitted on June 3, 2008, and received a Complete Response (CR) action on April 3, 2009. This submission also includes clinical trials performed under a Pediatric Written Request, for which pediatric exclusivity is now being sought.

The application is in CTD format and was filed electronically on July 28, 2016.

2.2 Presubmission Regulatory Activity

The NDA for Symbicort was approved on July 21, 2006, for the indication of long-term maintenance treatment of asthma [the indication was subsequently shortened to 'treatment of asthma' in 2010] in patients 12 years of age and older. An actuation counter was added to the product in 2007, and an efficacy supplement for a second indication of maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema, was approved on February 27, 2009.

At the time of initial approval for treatment of asthma, a deferral under PREA was granted for patients 6-11 years of age, and a waiver of pediatric study requirements was granted for patients <6 years of age. Although the pediatric studies had been completed at the time that the NDA was initially submitted, the delay in submission of the pediatric studies related to (b) (4) . However, after the pediatric supplement was submitted in 2008, the Division considered that there was not sufficient support for any the proposed dosages or dosage strengths in patients 6-11 years of age and gave a Complete Response action to the initial efficacy supplement (April 3, 2009). Deficiencies in the initial submission that resulted in a CR action were as follows:

> "You have not provided adequate data to support approval of (b) (4) strengths of Symbicort Inhalation Aerosol for maintenance treatment of asthma in patients 6 to 11 years

1 ***Note***: Throughout this review, references to the various dosage strengths of the product are 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 is indicated by the designation '80/4.5'. Note that this designation is *not* the same as a given dose, which is twice this amount, considering that the dosing instructions call for 2 inhalations per dose, nor is it equal to the total daily dosage, which is 4 times this amount, considering that the dosing instructions call for 2 inhalations twice daily.

of age. [redacted] You have not provided rationale and supporting data to justify the use of [redacted] strengths of Symbicort Inhalation Aerosol products in patients 6 to 11 years of age. Furthermore, the selection of dose of inhaled formoterol is not supported by any data specific to the age group of 6 to 11 years."

To resolve these deficiencies, the applicant was asked to provide the following:

"1. Data to establish efficacy and safety of appropriate dose or doses of budesonide inhalation aerosol and dose of formoterol inhalation aerosol as single ingredient products for patients 6 to 11 years of age, and provide convincing evidence of the contribution of the selected dose or doses of the individual components to Symbicort Inhalation Aerosol.

2. [redacted]"

Following the CR action, there were a number of interactions between AstraZeneca and the Agency. A Type C meeting was held on July 28, 2009, to discuss the Complete Response action, following which AstraZeneca submitted a Pediatric Plan in response to the CR action letter on October 1, 2009, followed by protocols for the first two studies, and a Proposed Pediatric Study Request (PPSR) on October 1, 2010.

3 PEDIATRIC PROGRAM, DATA SOURCES, AND DATA INTEGRITY

3.1 Summary of the Pediatric Development Program

*Reviewer's Note: A common terminology is used to label/number a study in this review. All of the original Symbicort Inhalation Aerosol studies used the terminology 'SD-039-0**xxx**' where **xxx** is the number designated for the study, whereas all of the Written Request studies used the terminology 'D589GC00**xxx**' where **xxx** is the number designated for the study. The pivotal adult and pediatric efficacy and safety studies were studies **716** [redacted], safety studies were **715** and **719**, and pharmacodynamic/pharmaceutic study linking the formoterol in Symbicort MDI with that in Oxis TBH was **729**. The new studies were **001**, **002** and **003** (note that AstraZeneca also uses the terms **CHASE 1** for study **001**, **CHASE 2** for **002**, and **CHASE 3** for **003**). This review refers to the studies by their last three digits as well as CHASE 1, 2, and 3.*

The initial Symbicort asthma development program for patients 6-11 years of age consisted of 7 studies: 1 Phase 1 and 6 Phase 3 trials (presented in two ways, in Table 1 by study type, and in Table 2 by dosage strength). These trials were intended to extend the adult and adolescent asthma clinical program to the 6-11 year age range. The nature of the studies comprising the original 6-11 year old development program were not discussed with the Agency except in the context of the initial discussion of the entire Symbicort development program, which comprised summaries of studies **716** through **719**. Like the adult and adolescent clinical development program, the program relied on trials that provided pharmaceutic and pharmacologic links to support the mono-component comparators, Budesonide HFA MDI, and Oxis Turbuhaler (TBH), neither of which are approved in the United States (see my review of the original Symbicort

NDA). As a result, the adult/adolescent development program was, of necessity, very complex. Adding to the complexity, both once-daily and twice-daily dosing was evaluated, although only twice-daily dosing was proposed. (b) (4)

(b) (4)

(b) (4)

Finally, the support that was provided for the Symbicort 80/4.5 and 160/4.5 dosage strengths was not considered sufficient to allow extrapolation of efficacy for these dosage strengths to a younger population without additional data.

As a result, the Division considered that there was not sufficient evidence to support approval (b) (4) in patients 6-11 years of age, and a Complete Response action to the initial efficacy supplement was given, requesting additional data to support each component (b) (4)

Based on interactions with the Agency, AstraZeneca proposed a new development program, summarized in Table 3, which was also incorporated into a pediatric Written Request. Three trials were proposed and conducted, a placebo-controlled trial to support an 80 mcg dosage strength of budesonide (D589GC00**001** or **CHASE 1**); a single-dose, dose-ranging bronchodilation trial to provide support for the proposed dosage strength of formoterol (D589GC00**002** or **CHASE 2**); and a 12-week efficacy and safety trial that evaluated two doses

of formoterol in the Symbicort combination against budesonide alone (D589GC00**003** or **CHASE 3**). Since LABAs should not be used as a single-ingredient product in patients with asthma, CHASE 3 was of necessity an incomplete factorial design. Including the previously submitted studies, the final grouping of studies that support the 80.4.5 dosage strength administered as 2 inhalations twice daily are shown in Table 4. Note that, of the previous studies, only study **719**, the higher dose safety study, is still relevant.

(b) (4)

[redacted]

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Three additional supportive studies that were performed and submitted with the previous development program were studies **719**, D5896C00**013**, and **743**. Study **719** was a 6-month, open label study that evaluated the safety and systemic exposure of Symbicort 160/4/5 in pediatric patients 6-11 years of age. Unfortunately, the study did not use a factorial design with either of the mono-components or with placebo. The active comparator used was Pulmicort Turbuhaler. Pulmicort Turbuhaler (now replaced by Pulmicort Flexhaler) was approved for use in children 6 years of age and older at starting doses of 200 mcg [metered dose; 160 mcg delivered dose] twice daily and highest doses of 400 mcg [metered dose; 320 mcg delivered dose] twice daily. As such, study **719** is supportive of safety of use of Symbicort in this age range, since it provided open label safety as well as systemic exposure of Symbicort compared with Pulmicort TBH at the highest approved dosage of budesonide in this age range. It had been reviewed with the original NDA submission, was reassessed as part of the review of the original pediatric supplement, and is therefore included in the Appendix of this review.

Study D5896C00**013** provided PK information with high single doses (4 inhalations) of Symbicort 160/4.5 and Pulmicort TBH 160 mcg; thereby providing another link between systemic exposures of budesonide delivered by Symbicort and by Pulmicort TBH. Since AstraZeneca had previously studied multiple dosages of budesonide in the form of Pulmicort Turbuhaler in this age group and the micronized budesonide used in both products is said to be the same, studies D5896 C00**013** and **719**, which demonstrated comparable or lower systemic exposure to budesonide from Symbicort than a comparable dose from Pulmicort Turbuhaler, allows use of the prior known safety information obtained with budesonide in these other products to support use of Symbicort 80/4.5 in this age group.

Study **743** was an open label device functionality study that was previously reviewed to support the Symbicort application.

Table 1. Original Symbicort pediatric development 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								
SD-039-0716 12 wks	≥12 yrs/480 6-11 yrs/31	Bud MDI 80 Oxis TBH 4.5 Placebo		80/4.5				Pre-dose FEV_1 Avg 12h FEV_1
Active-controlled								
[redacted] (b) (4)								
SD-039-0725 12 wks	6-15 yrs/522 (6-11y: 351)	Bud HFA MDI 80 QD	40/4.5			80/4.5		Evening PEF
Safety studies								
SD-039-0719 26 wks	6-11 yrs/187	Pulmicort TBH 160			160/4.5			Safety
Other studies								
D5896 C00013	6-11y/24	Oxis 4x4.5 + Pulm TBH 4x160			4x 160/4.5			SD Systemic bioavailability
SD-039-0743 6 wks	6-84y/283 6-11y/52	NA – OL device functionality study		80/4.5				# of devices collected

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. 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 (b) (4) and 725. [redacted] (b) (4) Pulmicort Turbuhaler (TBH) was used in study 719.

Oxis TBH = Oxis Turbuhaler (formoterol DPI), delivers 4.5 mcg per inhalation

Pulm TBH = Pulmicort Turbuhaler (budesonide DPI), provides 200 mcg per metered dose, delivers 160 mcg from mouthpiece per inhalation

Symb TBH = Symbicort Turbuhaler (DPI).

b Table shows both Symbicort MDI total daily dose in heading row and formulation studied ((b) (4), 80/4.5, 160/4.5) in table cell.

Source: Original submission, table-of-all-clinical-studies.pdf; T1, clinical-overview.pdf

Table 2. Summary of original pediatric studies to support each proposed dose

Study	Design	Arms	Population	Endpoints
40/4.5, 2 inhalations BID				
(b) (4)				
725 128/US	R, DB, DD, AC 12-week maintenance-of-stability study in 522 pts 6-15y (6-11y: 351)	Symb 40/4.5, 2 BID x4-5w, then: Symb 40/4.5, 2 BID Symb 80/4.5, 2 QD PM Bud HFA MDI 80, 2 QD PM	6-15y: 522 184 168 170	Stability (Evening PEF) in children previously on Symb 40/4.5, 2 BID for 4-5 weeks
80/4.5, 2 inhalations BID				
(b) (4)				
716 US	R, DB, DD, factorial monoproduct AC, PC, 12-week study in pts ≥6y Subset of 31 6-11y in pivotal adult 80/4.5 study	Symb 80/4.5, 2 BID Bud HFA MDI 80, 2 BID Oxis TBH 4.5, 2 BID Placebos, 2 BID	Total: 480 6-11y: 31 pts	Pre-dose FEV_1 Avg 12h FEV_1
160/4.5, 2 inhalations BID				
719 29/US	R, OL, AC, 6-month safety study in 187 pts 6-11y with ICS-dependent asthma (FEV_1 ≥50% predicted on daily ICS + ≥12% reversibility)	Symb 160/4.5, 2 BID Pulm TBH 160, 2 BID	124 63	Safety
Note: Study designations are shortened to the last 3 digits: i.e., study SD-039-0716 is shown as 716, etc.				

Table 3. Studies submitted with the Complete Response (Written Request studies)

Study	Design	Arms	Number of Patients*	Key Endpoints
80/4.5, 2 inhalations BID				
D589G C00001 CHASE 1	R, DB, PC, 6-week study in 6-11y with asthma (PEF ≥50% predicted on daily ICS 375-1000 mcg/d)	Bud HFA MDI 80, 2 BID Placebo, 2 BID	R 304 T 304 C 213	1º: Pre-dose morning PEF Key 2º: Pre-dose morning FEV_1
D589G C00002 CHASE 2	R, blinded, 5-period crossover, PC and AC dose-finding bronchodilation study in 6-11y with asthma receiving background budesonide 160 mcg BID	Symb 80/2.25 Symb 80/4.5 Symb 80/9 Foradil Aerolizer 12 mcg plus Bud 160 mcg Placebo plus Bud 160 mcg	R 54 T 54 C 50	1º: Avg 12h (AUC_{0-12h}) FEV_1 Secondary: Maximum FEV_1 over 12 hours FEV_1 at 12 hours FEV_1 at each time point
D589G C00003 CHASE 3	R, DB, 12-week study in 6-11y with asthma (on med- to high-dose ICS or ICS-LABA who were not controlled on low-dose ICS during run-in)	Symb 80/4.5, 2 BID Symb 80/2.25, 2 BID Bud HFA MDI 80, 2 BID	R 279 T 273 C 253	1-hour post-dose FEV_1 Secondary: Other clinic lung function variables, PAQLQ(S) (overall and each

Study	Design	Arms	Number of Patients*	Key Endpoints
				domain), eDiary variables, time to discontinuation of IP, and time to occurrence of first asthma exacerbation
R = Randomized, T = Treated, C = Completed				

Source: Submission of 7/28/2016, table-of-all-clinical-studies.pdf, p4; CSRs for the 3 studies

Table 4. Studies with the 80/4.5 dosage strength administered as 2 inhalations BID in pediatric patients 6 through 11 years of age

Study	Design	Arms	Number of Patients	Primary Endpoint
Budesonide 80 component				
001* **CHASE 1**	R, DB, PC, 6-week study in 6-11y with asthma (PEF ≥50% predicted on daily ICS 375-1000 mcg/d + ≥12% reversibility)	Bud HFA MDI 80, 2 BID Placebo, 2 BID	R 304 (C 213)	1º: Pre-dose morning PEF Key 2º: Pre-dose morning FEV_1
Formoterol 4.5 component				
002* **CHASE 2**	R, blinded, 5-period crossover, PC and AC dose-finding bronchodilation study in 6-11y with asthma, all receiving background budesonide 160 mcg BID	Symb 80/2.25 Symb 80/4.5 Symb 80/9 Foradil Aerolizer 12 mcg plus Bud 160 mcg Placebo plus Bud 160 mcg	R 54 (C50)	1º: Avg 12h (AUC_{0-12h}) FEV_1
Symbicort 80/4.5				
003* **CHASE 3**	R, DB, 12-week study in 6-11y with asthma (on med- to high-dose ICS or ICS-LABA who were not controlled on low-dose ICS during run-in, FEV_1 60-100% off LABA + ≥12% reversibility)	Symb 80/4.5, 2 BID Symb 80/2.25, 2 BID Bud HFA MDI 80, 2 BID	R 279 (C253)	1-hour post-dose FEV_1
[redacted] (b) (4)				
716 US	R, DB, DD, factorial monoproduct AC, PC, 12-week study in pts ≥6y Subset of 31 6-11y in pivotal adult 80/4.5 study	Symb 80/4.5, 2 BID Bud HFA MDI 80, 2 BID Oxis TBH 4.5, 2 BID Placebos, 2 BID	Total: 480 6-11y: 31 pts	Pre-dose FEV_1 Avg 12h FEV_1
Other studies to support Symbicort 80/4.5 in children 6-11 years of age				
719 29/US	R, OL, AC, 6-month safety study in 6-11y with ICS-dependent asthma (FEV_1 ≥50% predicted on daily ICS + ≥12% reversibility)	Symb 160/4.5, 2 BID Pulm TBH 160, 2 BID	124 63	Safety
D5896 C00013	SD systemic bioavailability	Symbicort 4x160/4.5 Oxis 4x4.5 + Pulm TBH 4x160	6-11y/24	PK
743	6-week, OL device functionality study		6-84y/283 6-11y/52	# of devices collected

Study	Design	Arms	Number of Patients	Primary Endpoint
* Study numbers in **bold** font are considered pivotal to this supplement. *Note*: Study designations are shortened to the last 3 digits: i.e., study D589GC00001 is shown as 001, etc.				

3.2 Data Quality and Integrity

A DSI audit was not conducted for this supplement, as an audit had already been performed during the review of the pivotal adult studies and no irregularities were noted during this review. Specifically, the pivotal pediatric studies that will contribute to support extension of the asthma indication to pediatric patients (b) (4)-11 years of age for treatment of asthma were all noted to be balanced with respect to support across centers, with no specific centers unduly contributing to the results. Further, no data integrity issues were noted during the review.

3.3 Compliance with Good Clinical Practices

AstraZeneca states that the studies were performed in compliance with good clinical practices.

3.4 Financial Disclosures

Financial disclosures were submitted as part of the original NDA application, the original supplement submission, and with submission of the Complete Response. There were no issues with financial disclosures of the investigators in any of the studies.

4 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

4.1 CMC

Two dosage strengths of Symbicort are currently approved, 80/4.5 and 160/4.5, for the maintenance treatment of asthma in patients 12 years of age and older. The 80/4.5 dosage strength contains 80 mcg of micronized budesonide and 4.5 mcg of micronized formoterol fumarate per actuation, ex-actuator. The 160/4.5 dosage strength contains 160 mcg of micronized budesonide and 4.5 mcg of micronized formoterol fumarate per actuation, ex-actuator. Differences between dosage strengths lie in the (b) (4) , the canisters and valves otherwise being identical. Each dosage strength also contains povidone K25, PEG 1000, the propellant HFA 227, and the same dose of formoterol fumarate.

(b) (4)

Several investigational product formulations were used in the clinical trials, as shown in Table 5. These include Symbicort 80/2.25, budesonide 80, (b) (4) . All of these products are MDIs that use HFA 227 as the propellant. They were identical in formulation to the approved Symbicort products, but with the (b) (4)

(b) (4)
. Likewise, the actuator used for these products was the same as that used in the approved Symbicort products.

Table 5. Investigational Formulations Used in the Clinical Programs

Product*	Type	Propellant	Budesonide	Formoterol fumarate	Program / Trials
(b) (4)					
Symbicort 80/2.25	MDI	HFA 227	80 mcg	2.25	D589GC00002 D589GC00003
Budesonide 80	MDI	HFA 227	80 mcg	--	Previous 6-11y and adult/adolescent clinical programs D589GC00001 D589GC00002 D589GC00003
Budesonide 40	MDI	HFA 227	40 mcg	--	D589GC00002
Placebo	MDI	HFA 227	--	--	Previous 6-11y and adult/adolescent clinical programs D589GC00001 D589GC00002
*All of these products are identical in formulation to the approved Symbicort products, but with the (b) (4) Likewise, the actuator used for these products was the same as that used in the approved Symbicort products.					

4.2 Animal Pharmacology/Toxicology

No new animal pharmacology or toxicology information is provided with this supplement.

4.3 Pharmacokinetics

Pharmacokinetic evaluations of budesonide were performed in two of the clinical studies, **719** and **D5896C00013**. These two studies provide multiple- and single-dose links [respectively] for systemic exposure to budesonide between Symbicort and Pulmicort Turbuhaler. In these studies, systemic exposure to budesonide from the highest approved dosages of Symbicort and Pulmicort was comparable, thereby allowing use of prior safety information from Pulmicort Turbuhaler, which was approved for use in children 6 years of age and older, to support use of Symbicort in children 6-11 years of age. A summary of the results is presented below.

Pharmacokinetic evaluation of urinary formoterol levels was performed in the single-dose, formoterol dose-ranging study, Study D589GC00**002** (CHASE 2) (b) (4)
. For further information, please see the review of this study in the Appendix of this review.

4.3.1 Study SD-039-0719

Study **719** was an 6-month, open-label, active-controlled study that compared the safety and systemic exposure of Symbicort 160/4.5 with Pulmicort TBH 200, each administered as 2 inhalations twice daily, in 186 children (2:1 randomization: 123 randomized to Symbicort and 63 to Pulmicort TBH). Along with PK from the single-dose PK study D5896C00013, this study provides systemic exposure safety data that supports use of Symbicort 80/4.5 in children 6-11 years of age. The reader will find a complete review of this study in the Appendix of this review.

A 1-week baseline period was followed by a 26-week open-label treatment period with study visits at 2, 12, and 26 weeks of treatment. No efficacy data were assessed, although spirometry data were collected at each study visit. PK for budesonide and formoterol were obtained, as appropriate, in consenting patients after 2 weeks of treatment. Safety assessments included AEs, clinical labs, 24-hour urinary cortisol, 12-lead ECGs, physical examinations, and vital signs. Limitations included the small number of pediatric patients who agreed to PK evaluations (n=11), and the considerable variability in budesonide levels.

As shown in Table 6, there was comparable exposure to budesonide from the two drug products. Lack of higher systemic exposure to budesonide from Symbicort than a comparable dose from the approved Pulmicort Turbuhaler supports use of this dosage in children 6-11 years of age should patients need higher doses of budesonide for adequate disease control.

Overall results for mean 24-hour urinary cortisol levels are show in Table 7. While mean values remained within the normal reference range, both treatment groups exhibited a trend for a decrease from baseline in mean urinary cortisol levels over the course of the treatment period, with the decrease for Pulmicort numerically slightly larger. Review of shift tables did not show any differences of note. AstraZeneca wishes to include this information in the Clinical Pharmacology section (12.2, under HPA axis effects) of the labeling.

Table 6. Study SD-039-0719. Multiple-dose budesonide PK (n=11)

	Symbicort 320/9 BID n=6	Pulmicort 400 BID n=5	Ratio (90%CI)
Budesonide			
AUC0-6	4.63	4.29	1.08 (0.44, 2.64)
Cmax	1.92	2.01	0.96 (0.37-2.48)

Source: Submission of 6/3/2008. T29, p104, SD-039-0719 Legacy Clinical Study Report.pdf

Table 7. Study SD-039-0719. HPA axis: 24-hour urinary cortisol

	Symbicort 320/9 BID n=113	Pulmicort 400 BID n=56	Ratio (90%CI)
Baseline (while on entry ICS treatment)	22.86	26.45	
End of treatment (Week 12)			
Observed geometric mean	17.83	15.73	
Adjusted geometric mean (ANCOVA)	19.82	17.04	1.16 (0.88, 1.55)

Source: Submission of 6/3/2008. T98, T99, p 191-2, Integrated Summary of Safety.pdf

4.3.2 Study D589C00013

Study **D5896C00013** was an open-label, randomized, 2-way, single-dose crossover study that evaluated the pharmacokinetics of budesonide and formoterol from 4 inhalations of Symbicort 160/4.5 (total dose 640/18) versus 4 inhalations of Pulmicort Turbuhaler 200 mcg (total dose 800/18, corresponding to a delivered dose of 640/18) plus 4 inhalations of Oxis Turbuhaler 4.5 mcg in 24 children 6-11 years of age. This study helps to link the systemic exposure to budesonide from single, high doses of Symbicort to that of a predecessor budesonide product, Pulmicort TBH, which was approved for use in children 6 years of age and older. Systemic exposure (AUC and Cmax) to budesonide was less with Symbicort 160/4.5 (total budesonide dose 720) than corresponding dose from Pulmicort TBH (total budesonide dose 800/720). With regard to formoterol exposure, there was slightly higher systemic exposure to formoterol fumarate from Symbicort than from the non-US-approved Oxis TBH.

Table 8. Study D5896C00013. Single dose budesonide and formoterol PK (n=24)

	Symbicort 720/18	Pulmicort 800 + Oxis TBH 18	Ratio (90%CI)
Budesonide			
AUC (nmol/L*h)	4.22	5.75	73% (52-103)
Cmax (nmol/L)	1.36	2.31	51% (38-92)
Formoterol			
Fe0-24h (%)	3.48	3.09	113% (80-158)

Source: T11, p58; d5896c00013-legacy-clinical-study-report.pdf

4.4 Pharmacodynamic and Pharmaceutic Issues

There were no specific pharmacodynamic issues for this supplement, although there were interrelated pharmaceutic issues, addressed in this section and in Section 4.1.

4.4.1 Budesonide

A currently unapproved product, budesonide 80 HFA MDI product (containing 80 mcg of micronized budesonide per actuation, ex-actuator) was used in trials D589GC00**001** (CHASE 1), D589GC00**002** (CHASE 2), and D589GC00**003** (CHASE 3), as well as in the adult and adolescent clinical development program. Additionally, an unapproved, investigational budesonide 40 HFA MDI product (containing 40 mcg of micronized budesonide per actuation, ex-actuator) was used in one study, D589GC00**002** (CHASE 2). All of these products are pressurized MDIs that use HFA 227 as the propellant. Further, they are identical in formulation to the approved Symbicort products, but with the (b) (4) . AstraZeneca provided *in vitro* data regarding the dose content and particle size distribution for all of the products used in the clinical trials, including the investigational formulations, to assure that any differences in the results were not due to pharmaceutic issues. See Section 4.1 for additional data.

4.4.2 Formoterol Fumarate

A currently unapproved product, Symbicort 80/2.25 (containing 80 mcg of micronized budesonide and 2.25 mcg of micronized formoterol fumarate per actuation, ex-actuator), was used in two trials, D589GC00**002** (CHASE 2) and D589GC00**003** (CHASE 3). Just as for the budesonide component in the budesonide HFA MDI product (see above and Section 4.1), the Symbicort 80/2.25 product was the same as the other Symbicort products with the (b) (4) (b) (4). AstraZeneca submitted *in vitro* data to support use of the product used in the trials.

5 INTEGRATED REVIEW OF EFFICACY

5.1 Indication

Only one indication is sought in this supplement, to extend the age range for treatment of asthma from patients 12 years of age and older to patients 6-11 years of age.

5.2 General Discussion of Endpoints

The endpoints for evaluation of asthma are generally well established. Typically, endpoints include spirometric measurements such as FEV_1 and peak expiratory flow rate (PEFR). Timing may be pre-dose, at a specified timepoint post-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. Efficacy evaluations and endpoints in the Symbicort development program for children 6-11 years of age differed from that in the adult program. Endpoints in the adult/adolescent program are discussed, followed by the endpoints used in the pediatric program.

In the two pivotal adult/adolescent studies, 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. For the formoterol component, the primary variable was the **baseline-adjusted average 12-hour FEV_1** (AUC of FEV_1 over the dosing interval) to demonstrate the bronchodilator effect of the formoterol component. For the formoterol component, the comparison was therefore Symbicort minus budesonide. The primary time point chosen for this measurement was at the 2 week visit (i.e., after 2 weeks of treatment). For evaluation of the budesonide component, two different methodologies were used to demonstrate the stabilizing, anti-inflammatory effect of budesonide, with the comparison being Symbicort minus formoterol. The endpoint originally chosen was **withdrawals due to asthma exacerbations**, as specifically defined by a series of criteria in the protocols and captured in the CRFs. The studies included a set of pre-defined criteria for withdrawal of patients due to an asthma event. 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 FEV_1** (assessed as the change from baseline over the entire treatment period) was elevated from a secondary to a co-primary efficacy variable for evaluation of the contribution of the budesonide component because 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; 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. Since pre-dose FEV_1 had been collected on all patients, it was elevated to co-primary variable for assessment of the contribution of budesonide. Please see the original review for details. That said, pre-defined asthma events, as captured in the CRFs, are more inclusive than withdrawals due to these events. [*Note*: AZ could have chosen to use pre-defined asthma events as captured in CRFs as a primary variable, but they chose not to do so.] Despite the fact that withdrawals were demoted to a secondary endpoint, pre-defined asthma events were considered a key secondary endpoint (b) (4) .

For the pediatric program, AstraZeneca deviated from the adult program and elected to rely on spirometric measurements (FEV_1 or PEF) as a single primary efficacy variable to evaluate each component in the combination, **pre-dose** spirometric endpoints (**PEF and FEV_1**) in the preliminary trial (D589GC00**001**) to support the choice of the budesonide 80 mcg dosage strength, **AUC of FEV_1** in the preliminary formoterol dose-finding trial (D589GC00**002**) to support the choice of the formoterol 4.5 and 2.25 mcg dosage strengths for the final trial (D589GC00**003**), and **1-hour post-dose FEV_1** in the final study to support the final choice of Symbicort 80/4.5 as the dosage strength for this age group. These are supported by all of the traditional secondary endpoints, including protocol pre-defined asthma events in the chronic dosing studies. Use of these endpoints is acceptable, and was discussed with the Agency prior to initiation of the studies.

5.3 Support for the Dose of Budesonide

Dose selection for the budesonide component was somewhat atypical for an inhaled corticosteroid. Namely, prior to evaluation of the 80 mcg dosage strength, (b) (4)

[redacted]

[2] (b) (4)

[redacted]

(b) (4)

Further, patients for whom it would be appropriate to use Symbicort should be those who warrant use of a LABA in addition to an ICS. In the interim years since the original studies to (b) (4) were performed, the understanding of where an ICS-LABA combination fits appropriately into the asthma treatment paradigm shifted from addition of a LABA to lower dosages of an ICS to addition of a LABA only after other treatments, including higher dosages of an ICS, were not sufficient. This shift came about because of the safety issues with LABAs (see Section 6.2 for a discussion of LABA safety issues). (b) (4) The guidelines for treatment of asthma, and their gradual changes, are discussed in Appendix 8.2 of this review.

After receiving a Complete Response action to their first submission, AstraZeneca decided to pursue development of the Symbicort 80/4.5 dosage strength, which is the lower of the two dosage strengths approved for adults and adolescents, for use in this lower age range. Use of this dosage strength results in a dose of 160 mcg (2 inhalations of 80 mcg) of budesonide, thereby providing a total daily dosage of 320 mcg of budesonide when administered twice daily. This is the same daily dosage of budesonide that was evaluated and shown to be effective as one of the two budesonide dosages in the Symbicort adult and adolescent development program, and there was prior experience using this dosage of budesonide in other clinical trials in this age group as well (Table 2). Choice of the lower ICS dosage strength approved for adults and adolescents is also consistent with the development programs for other ICS/LABA combination products for asthma. Therefore, there was / is ample evidence to expect that this dosage of budesonide, i.e., 160 mcg twice daily, would be efficacious in this population just as it has been shown to be in adolescent and adult asthma populations. Further, there is experience with a similar dosage of budesonide for treatment of asthma in this age group in the form of dry powder inhaler products, namely in Pulmicort Turbuhaler and Pulmicort Flexhaler, both of which are manufactured by AstraZeneca. AstraZeneca has shown that systemic exposure after high single doses of Symbicort and Pulmicort Turbuhaler are reasonably comparable (Study D589C00013, see Section 4.3.2 for details). Therefore, unlike the previous development program for the 40 mcg dosage strength, there was ample reason to suggest that this dose might also be efficacious in this age group. As such, the Division accepted that a single study would provide sufficient evidence to support use of this proposed dosage strength of budesonide in the combination.

As part of the revised clinical development program, AstraZeneca performed a new placebo-controlled trail (D589GC00**001**) in pediatric patients 6-11 years of age. The results provide support for the choice of budesonide 80 mcg as the dosage strength in Symbicort for use in this population. Please see the review of the study in Appendix 8.3.3, and a summary below for further details. A second trial, (D589GC00**003**) also provides some support for the chosen dose of budesonide, but somewhat more indirectly because it did not include a full factorial design. The study compared Symbicort with two different dosages of formoterol and the same product (budesonide HFA 80) without formoterol. This study supports the proposed dosage of

budesonide in the combination via the stability achieved by increasing the dosage of budesonide from an intentionally low dosage during the run-in period, during which patients were required to exhibit symptoms, to 160 mcg twice daily. As would be expected, improvements from baseline were noted in all three treatment arms, including for secondary endpoints such as symptom scores, rescue medication use, nighttime awakenings due to asthma, and PAQLQ. In fact, there were few differences between the three treatment arms for these secondary endpoints, indicating that the changes from baseline were likely due to the step-up in budesonide dose rather than to the addition of formoterol.

5.4 Support for the Dose of Formoterol

Initially, the dose selection strategy for the formoterol component was to continue with the same dosage selected and studied in adults, i.e., no dose finding or dose ranging was performed for formoterol fumarate in patients 6-11 (i.e., 6 through 11) years of age. As noted earlier, dose selection for the adult/adolescent program, had relied on information from Oxis TBH which was used as the mono-comparator in the Symbicort development program. Lack of dose exploration for formoterol in this age range is historically consistent with pediatric drug development for the LABA drugs, including both formoterol and salmeterol, as pediatric studies in this age range were conceived and performed without evaluation of lower LABA dosages. In the US, both Foradil Aerolizer (12 mcg) and Certihaler (10 mcg) are approved for the maintenance treatment of asthma in patients 5 years of age and above, with no difference in dosage between children 5 through 11 years of age and those 12 years of age and older. The same is true for salmeterol, both in the single-ingredient Serevent and the combination Advair, where there is no difference in the dose used in patients 4-11 years of age and in patients 12 years of age and older.

Discussions regarding dose selection for the pediatric program date back to the End-of-Phase 2 meeting held in 2002. Although a specific discussion of dose finding for formoterol for the pediatric age range does not appear to have occurred, the Division is on record as having stated that the path chosen is risky, and would be a review issue.

That said, upon review of the initial 6-11 year old development program, the path chosen by the applicant (which had followed the example set in previous LABA development programs), no longer appeared to be consistent with such development within the context of the current understanding of the risk/benefit of LABAs, which suggested an increase in asthma-related death as well as respiratory-related deaths or life-threatening experiences in adults, and an increased risk of asthma-related hospitalization in children, exposed to LABAs (see Section 6.2). There is insufficient data at this time to determine whether use of a corticosteroid with a LABA changes these risks. Therefore, with further elucidation of the risks of LABAs over time, the original assumptions regarding formoterol dose selection needed to be reexamined, despite the fact there is no evidence to determine whether lower LABA doses may provide similar efficacy but reduce the risk. However, we are aware that higher doses may be associated with an increased safety risk, since the Foradil 24 mcg dosage strength was not approved in adults because of safety concerns in the adult clinical trial data. As a result, it seemed reasonable to suggest that the applicant provide justification for the choice of the formoterol dose in children 6-11 years of age.

As a result, AstraZeneca conducted two new trials: a single-dose, dose-ranging, bronchodilatory trial (D589GC00**002**) to explore the appropriate formoterol dosages to be evaluated in a second chronic dosing, dose-ranging trial (D589GC00**003**). The first trial evaluated single formoterol doses of 2.25 through 9 mcg compared with placebo and the approved Foradil 12 mcg. The

second trial evaluated two of these doses in a chronic dosing setting, comparing Symbicort 80/2.25 and Symbicort 80/4.5 with budesonide HFA 80 alone. The result is that the applicant has provided a development program appropriate to support an appropriate dosage and dosage strength for this population.

5.5 Study Design and Enrollment

The revised clinical development program for treatment of asthma in the 6-11 year old population included 3 trials. The trial designs, including study size, durations, endpoints, and populations, were discussed with the Agency in advance, with agreement reached prior to initiation of the trials.

The preliminary study supporting the proposed budesonide dose, D589GC00**001** (CHASE 1), was 6 weeks in duration, and the final study, D589GC00**003** (CHASE 3), was 12 weeks in duration. In study **001**, milder asthmatics who required additional controller therapy were enrolled, and the test drug (budesonide 80 HFA MDI) was compared with placebo. Use of a placebo is acceptable in this setting as long as the study duration is kept to the shortest time that will allow for an adequate assessment of the endpoints and there is adequate provision for identifying patients who require additional or rescue treatment. And as may be seen by the Kaplan-Meier plot of time to withdrawal due to pre-defined asthma events (Figure 24), this was the case. In study **003**, moderate to severe asthmatics who were stable on moderate- to high-dose ICS controller (or ICS/LABA) therapy, but were symptomatic on low-dose ICS therapy, were enrolled. This study appropriately did not include placebo or LABA monotherapy arms for ethical and safety reasons.

Study **002**, which assessed dose-ranging of the formoterol fumarate component, was a single-dose study. It was performed in a study population that was receiving a background dose of 160 mcg of budesonide, the same dose that is proposed in the Symbicort combination for this age group and which is approved in the Symbicort 80/4.5 product. It assessed the AUC of FEV_1 over 12 hours post dose, thereby providing a reasonable assessment of doses of formoterol that could be carried into study **003** for a final assessment with the combination product.

Review of the study enrollment and conduct revealed no issues or concerns. The representation of age, sex, and racial and ethnic groups enrolled in the studies appeared adequate to assess the pediatric asthma population in the United States. Compliance with study drug appeared reasonable.

5.6 Summary of the Efficacy Findings

5.6.1 Study D589GC00001 (CHASE 1)

This was a 6-week, randomized, double-blind, parallel-group, placebo-controlled, multicenter, efficacy and safety trial conducted to support the choice of a dosage of 160 mcg (b) (4) as the budesonide component in the Symbicort combination. The two study arms included budesonide HFA 80 mcg MDI (Symbicort 80 without the LABA component), and matched placebo. The study population included 304 pediatric patients (152 budesonide, 152 placebo) 6 to <12 years with asthma who required either low-dose ICS therapy or daily leukotriene receptor antagonist treatment, had a morning pre-bronchodilator FEV_1 between 70 and 95% of predicted, and demonstrated reversibility of FEV_1 of ≥12% after a SABA. This is consistent with a

population of asthmatics who would be classified in the milder range of patients who require daily controller therapy. After a 7- to 21-day placebo run-in/qualification period, patients were randomized to 6 weeks of treatment with budesonide HFA 80 (n=152) or placebo (n=152), administered as 2 inhalations twice daily. Consistent with placebo controlled studies in children with asthma, the study included an asthma safety plan with mandated withdrawal if any of the pre-defined asthma event criteria were met. The primary endpoint was change from baseline to the treatment period average in pre-dose morning peak expiratory flow (PEF), with the key secondary endpoint being change in pre-dose morning FEV_1.

Review showed that the two study arms appeared well balanced, and that the patient population appeared to be representative of the target study population of pediatric patients with asthma who need ICS controller therapy. The majority of the 304 randomized patients were white (88.8%) and 6.6 % were black/African American, and the mean age was 9.0 (range 6 to 11) years, with 66 patients (21.7 %) <8 years of age. Of these, 213 (92 in the placebo group and 121 in the budesonide group) completed the study. Of the 91 patients who discontinued the study, the vast majority (n=73, 25 in budesonide 80, 48 in placebo) withdrew due to pre-defined asthma withdrawal criteria. This is not unexpected in a placebo-controlled asthma study, providing evidence that the patients enrolled were in fact representative of the intended population of asthmatic patients who require controller therapy. There was also an imbalance in withdrawals due to pre-defined asthma events that favored the budesonide treatment group.

Treatment differences between the budesonide and placebo arms were significant for the primary endpoint of change from baseline in morning PEF (Table 79 and Figure 25) and the key secondary endpoint of change from baseline in morning FEV_1 (Table 79 and Figure 26). Secondary endpoints were numerically supportive, including evening PEF, daytime and nighttime asthma symptom scores, nighttime awakenings (both total and awakenings when a rescue medication was used), daily rescue medication use, and withdrawals due to pre-defined asthma events.

Taken with the known data about the moiety and data from other age groups that support this dosage of budesonide, this study adequately supports use of budesonide 160 mcg (delivered as 2 inhalations of Symbicort) twice daily as the dosage for children 6-11 years of age.

5.6.2 Study D589GC00002 (CHASE 2)

This was a single-dose, randomized, active- and placebo-controlled, 5-way cross-over study that compared the bronchodilatory effect of formoterol over 12 hours. Study subjects were pediatric patients 6-11 years of age with a documented history of asthma requiring ICS, pre-bronchodilator FEV_1 60-85% predicted, and reversibility of FEV_1 of ≥15% after 180-360 mcg of albuterol. Doses studied included single formoterol doses of 2.25, 4.5, and 9 mcg administered via Symbicort, compared with Foradil Aerolizer 12 mcg and placebo MDI given in combination with budesonide MDI 160 mcg. All doses except Foradil were blinded. The primary efficacy variable was the FEV_1 averaged over 12 hours post-dosing.

A total of 54 patients were randomized, and 50 completed all treatments. Mean change from baseline in FEV_1 over time curves (ACU0-12h) demonstrated incremental benefits of successively higher doses of formoterol delivered via Symbicort, with the 9 mcg dosage strength being relatively similar in AUC0-12h to that obtained by Foradil 12 mcg. A clear benefit for the 4.5 mcg over the 2.25 mcg dose was seen across all time points, whereas the additional benefit of the 9 mcg over the 4.5 mcg dose was more modest. Nevertheless, there were differences

between the 9 mcg and the 4.5 mcg doses in both peak FEV_1 and the length of time that bronchodilation was maintained over the 12 hour dosing interval. On the basis of this study, AstraZeneca proposed to study the 4.5 and 9.0 mcg doses, administered as two inhalations of Symbicort 80/2.25 and 80/4.5 dosage strengths, in the chronic dosing study D589GC00003. The Division agreed with this proposal.

5.6.3 Study D589GC00003 (CHASE 3)

This was a 12-week, randomized, double-blind, parallel-group, multicenter trial conducted to evaluate which of the two dosage strengths of Symbicort should be proposed for this age range. The dosages of budesonide and formoterol studied in this trial were based on the results of studies D589GC00001 and D589GC00002. The study compared the approved Symbicort 80/4.5, an investigational Symbicort 80/2.25, and budesonide HFA 80, each administered as 2 inhalations twice daily, in children 6-11 years with asthma who required medium- to high-dose ICS therapy, had a morning pre-bronchodilator FEV_1 60-100% of predicted, reversibility of FEV_1 of ≥12% after a SABA, and were symptomatic on low-dose ICS during the run-in period.

The primary efficacy endpoint was change from baseline to Week 12 in 1-hour post-dose FEV_1 (L). The primary analysis first compared Symbicort 80/4.5 vs budesonide 80, followed by Symbicort 80/2.25 vs budesonide 80, with adjustment for multiplicity. Both comparisons had to win to meet the study objectives, and the study was sized accordingly. A secondary objective was to compare the two doses of Symbicort.

Review showed that the three study arms were relatively well balanced and that the patient population was representative of the target study population of pediatric patients with asthma who need ICS controller therapy. The mean age of the study population was 9.0 years, with 65% ≥9 years of age, 59.5% female, 62.4% white, 27.2% black, and 38% Hispanic. A total of 279 patients were randomized (92 to Symbicort 80/4.5, 95 to Symbicort 80/2.25, 92 to budesonide HFA 80). Of these, 273 patients received study treatment (6 patients were randomized in error and did not receive treatment), 249 (89.2%) completed treatment, and 253 (90.7%) completed the study (85 [92.4%] Symbicort 80/4.5, 84 [88.4%] Symbicort 80/2.25, 84 [91.3%] budesonide HFA 80).

The primary analysis comparing Symbicort 80/4.5 with budesonide HFA 80 was statistically significant (estimated difference 0.12 L [95% CI 0.03, 0.20; p=0.006]), whereas the comparison of Symbicort 80/2.25 with budesonide HFA 80 was numerically greater but not statistically significant (estimated difference 0.08 L [95% CI 0.00, 0.16; p=0.063]). The secondary endpoint comparison of Symbicort 80/4.5 with Symbicort 80/2.25 was numerically greater but not statistically significant (estimated difference 0.04 L [95% CI -0.05, 0.12], p=0.373). The Division considered that the initial declaration that both comparisons of Symbicort vs budesonide had to win for the study to be successful was not relevant if the higher dosage strength won and was chosen as the dosage strength for marketing (it would only have been relevant if AstraZeneca wished to choose the lower dosage strength studied).

Secondary endpoints that improve with LABA use, such as spirometric measurements, supported the primary results. While at visit pre-dose FEV_1 was not different for the three treatments, all other spirometric evaluations, including at home pre-dose AM and PM FEV_1 and PEF measurements, favored the Symbicort 80/4.5 dosage strength over both Symbicort 80/2.25 and Budesonide 80.

All treatment groups showed improvements in symptom scores, nighttime awakenings, and reliever use. Except for less frequent nighttime awakenings that required reliever medication use, there were no differences in daytime or nighttime asthma symptom scores, nighttime awakenings due to asthma symptoms (regardless of reliever use), or total daily reliever medication use between the three treatment groups.

While the Kaplan Meier plot to time to first asthma exacerbation event showed some separation between Symbicort 80/4.5 and the other two treatment groups, there were no differences between treatment groups in the number and percent of patients or the number of events of asthma exacerbations except for the subgroup of patients who were on Symbicort 80/4.5 and who required an increase in asthma medications (fewer patients and events in the Symbicort 80/4.5 treatment group).

Taken as a whole, the study adequately confirmed that the approved dosage strength of Symbicort 80/4.5 is appropriate for use in children 6 through 11 years of age.

5.7 Efficacy Conclusions

The three studies provided in the new submission adequately support use of the approved dosage strength of Symbicort 80/4.5, administered as 2 inhalations twice daily, in children with asthma 6-11 years of age (b) (4). In addition, a large body of independent data supports the choice of the dosage of each component for this age group, including clinical experience with both budesonide and formoterol at the same or similar dosages from this and other products, (b) (4) As a result, AstraZeneca's choice to carry the lower dosage strength of Symbicort (i.e., Symbicort 80/4.5) that has been shown to be efficacious and is approved for use in adults and adolescents 12 years of age and older to this younger age group makes good clinical sense.

6 INTEGRATED REVIEW OF SAFETY

6.1 Overview of Safety

The safety review of this application did not reveal any new or unusual safety trends. Safety trends, either expected or seen with use in children, are similar those seen in adults, excepting AEs more typical in children and in children with asthma. The two active ingredients 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 and formoterol extend for well over a decade and the commonly encountered 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 several Advisory Committee meetings regarding safety of LABAs within the last several years, the changes to the guidelines as well as labeling for use of LABAs in the last few years, and the concern with safety of LABA use in children, and in particular, asthma-related hospitalization, (but not asthma-related death or

life-threatening events). The safety review of this application therefore focused on aspects of both drugs that might be of clinical concern based on the current state of knowledge of these two drug classes, and none were found.

Long-term safety in patients 6-11 years of age comes from a single 6-month safety study (study **719**), in which 123 patients were treated with Symbicort 160/4.5 and 63 patients were treated with budesonide HFA MDI 160 mcg, each administered as 2 inhalations twice daily for 6 months. Note that this study used a higher daily dosage of budesonide but the same daily dosage of formoterol as proposed for use in this age range. Results did not reveal new trends or types of AEs other than those expected in children of this age group, and no significant or unexpected patterns of abnormalities in safety measures including clinical chemistry, hematology, ECG, and HPA axis assessments.

6.2 Safety Issues with LABA Products

There is a long history of concern for the safety of use of LABAs in patients with asthma, namely the concern that LABAs may increase the risk of serious asthma exacerbations, including asthma-related death. More recently, the concern has also been raised regarding an increased incidence of asthma-related hospitalization in children treated with LABAs. Whether these two issues represent different parts of a clinical spectrum of serious adverse reactions associated with use of these drugs remains uncertain. These safety concerns have led to a number of regulatory actions, including multiple advisory committee meetings, a Boxed Warning on all LABA products, and more recently a post-marketing requirement (PMR) for large safety trials to determine the safety of LABAs added to inhaled corticosteroids (ICS) compared to ICS alone for the treatment of asthma. This section summarizes the safety issues with LABA products.

A number of long-acting beta-agonists (LABAs) are approved in the United States, including salmeterol (Serevent and Advair), vilanterol (Breo), and formoterol (Foradil, Symbicort, and Dulera), which are selective $beta_2$-adrenergic receptor agonists. Whereas salmeterol and vilanterol are partial receptor binding agents, formoterol completely binds to the $beta_2$-adrenergic receptor. There are currently two LABAs (salmeterol and formoterol), which are approved as single ingredients or in combination with ICS in inhalation products for the treatment of asthma. All of the other products are approved as combinations with an inhaled corticosteroid (ICS).

Five Advisory Committees (AC) have discussed the safety of LABAs for asthma, in whole or in part. These include: a Pulmonary-Allergy Drug Advisory Committee (PADAC) for the Serevent NDA on February 26, 1993, a PADAC for the Advair Diskus NDA on November 23, 1999, a PADAC to present safety from the SMART and SNS trials on July 13, 2005, a PAC November 28, 2007, to discuss 1-year post-exclusivity [BPCA] safety of Serevent in children, and a joint Pulmonary-Allergy, Pediatric (PAC), and Drug Safety and Risk Management (DSaRM) Advisory Committee meeting was held on December 10-11, 2008. These meetings are discussed in more detail below.

The first discussion was at a PADAC Meeting held prior to the approval of the first LABA, Serevent Inhalation Aerosol, in February 1994 (no longer marketed due to the phase out of the CFC propellant). Around the time of approval of Serevent Inhalation Aerosol, the findings from the Salmeterol Nationwide Surveillance (SNS) study were available. The SNS study was conducted in the United Kingdom in the mid-1990s and it compared salmeterol twice daily with salbutamol (albuterol in the U.S.) administered four times daily for 16 weeks in approximately 25,000 patients who were considered to need regular beta2-agonist therapy. The SNS study

showed a non-significant (p=0.105) 3-fold increase in respiratory and asthma-related death in patients taking salmeterol (0.07%) vs. scheduled salbutamol (0.02%).[3]

Following the approval of salmeterol, and because of the concerns regarding detrimental effects of chronic dosing with beta$_2$-agonists, GSK initiated a large randomized, placebo-controlled study, the Salmeterol Multicenter Research Trial ('SMART', Study #SLGA5011), in 1996. SMART was a randomized, double-blind study that enrolled patients 12 years of age and older with asthma not currently using a LABA and randomized them to salmeterol (Serevent Inhalation Aerosol) or placebo twice daily added to usual asthma therapy.[4] There was one baseline study visit, and inhaled corticosteroid as baseline asthma therapy was not mandated. The proposed treatment duration was 28 weeks with a revised target sample size from 30,000 to 60,000 patients.

The SMART trial was halted prematurely in January 2003, after a planned interim analysis suggested that salmeterol may be associated with an increased risk of serious asthma exacerbations including asthma-related death. GSK submitted preliminary summary results of the SMART to the Agency in February 2003, which lead to labeling changes including a Boxed Warning was placed on all salmeterol containing products in August 2003, warning of a small increase in risk of asthma related deaths with salmeterol use in the SMART study. A second PADAC meeting was held on November 23, 1999, prior to approval of Advair Diskus.

Once all the data from the SMART study were available, a PADAC meeting was held on July 13-14, 2005, to discuss the safety associated with chronic use of LABAs in patients with asthma.[5] The results of SMART for the 28-week treatment period showed a 4-fold increase in asthma related deaths in patients treated with salmeterol compared to placebo (Table 9).

Table 9. SMART. Primary Endpoint and asthma related death for the 28 week treatment period

	Serevent n=13,176	Placebo n=13,179	Relative Risk (95% CI)
Primary Endpoint: Respiratory-related deaths or life-threatening experiences			
Total	50 (0.3%)	36 (0.3%)	1.4 (0.9, 2.1)
Caucasians [salm n=9281, pbo n=9361]	29 (0.3%)	28 (0.2%)	1.1 (0.6, 1.8)
African American [salm n=2366, pbo n=2319]	20 (0.8%)	5 (0.2%)	4.1 (1.5, 10.9)
Secondary Endpoint: Asthma-related death			
Total	13 (0.1%)	3 (0.02%)	4.4 (1.3, 15.3)
Caucasians [salm n=9281, pbo n=9361]	6 (0.06%)	1 (0.01%)	5.8 (0.7, 48.4)
African Americans [salm n=2366, pbo n=2319]	7 (0.3%)	1 (0.04%)	7.3 (0.9, 58.9)

Safety data from smaller studies with formoterol were also considered at the meeting. During the Foradil Aerolizer clinical development program, studies had shown a numerical increase in serious asthma exacerbations in patients on higher doses (24 mcg) of formoterol compared with patients treated with lower formoterol doses (12 mcg) or placebo (Table 10).[6] Based upon these

3 Castle W, Fuller R, et al. BMJ 1993: 306: 1034-7.

4 Nelson HS, Weiss ST, et al. Chest 2006; 129: 15-26.

5 Information regarding the July 13-14, 2005, FDA PADAC meeting may be found at: http://www fda.gov/ohrms/dockets/ac/cder05 html#PulmonaryAllergy.

6 Mann M, Chowdhury B, et al. Chest 2003; 124:70-74.

safety findings, [redacted] (b) (4) Novartis was asked to perform a phase 4 clinical study to further investigate the relative safety of the two different doses of formoterol. The study was started in 2002 and completed in 2004.

Table 10. Serious asthma exacerbations* in Foradil Aerolizer clinical development program

	Placebo	Albuterol 180 mcg BID	Formoterol 12 mcg BID	Formoterol 24 mcg BID
12-wk study in adults and adolescents (study 040)	0/136 (0%)	2/134 (1.5%)	0/136 (0%)	4/135† (3%)
12-wk study in adults and adolescents (study 041)	2/141 (1.4%)	0/138 (0%)	1/139 (0.7%)	4/136‡ (3.7%)
1-yr study in 5-12 year old children (study 049)	0/176 (0%)	NA	8/171 (4.7%)	11/171 (6.4%)

* Life-threatening experience, hospitalization, prolongation of hospitalization, persistent disability, or death
† 1 patient required intubation
‡ 2 patients had respiratory arrest, 1of the patients died

The formoterol phase 4 study was a randomized, blinded, placebo-controlled study of 16 weeks duration in 2,307 patients 12 years of age and older with mild-to-moderate persistent asthma. The study consisted of one baseline visit and subsequent visits in weeks 1, 4, 8, 12, and 16. This study allowed liberal use of anti-inflammatory medications. More patients enrolled in this phase 4 study received ICS during the study than those in the phase 3 studies (58% vs. 47%). Patients were randomized approximately equally to receive Foradil Aerolizer 12 mcg BID, Foradil Aerolizer 24 mcg BID, Foradil 12 mcg BID with up to two additional on-demand 12 mcg doses per day, and placebo. The Foradil fixed-dose groups and placebo group were treated in double-blind fashion, and the Foradil on-demand group was open-label. There were no deaths in this study. The overall rates of events of interest in this study were too low to draw any firm conclusion, although the trends showed a numerical increase in serious asthma exacerbations compared to placebo (Table 11).

Table 11. Asthma exacerbations in Foradil Aerolizer Phase 4 safety study

	Formoterol 12 mcg BID (n=527)	Formoterol 24 mcg BID (n=527)	Placebo (n=514)	Formoterol Open-label (n=517)
Serious asthma-related adverse events	5 (0.9%)	2 (0.4%)	1 (0.2%)	1 (0.2%)
Serious asthma exacerbations *	3 (0.6%)	2 (0.4%) †	1 (0.2%)	1 (0.2%)

* Life-threatening experience, hospitalization, prolongation of hospitalization, persistent disability, or death
† 1 patient required intubation

The results from all of these studies were presented to the PADAC in 2005, and the committee was asked whether salmeterol or formoterol should be withdrawn from the market. The committee unanimously recommended keeping both on the market, but recommended that both drug products contain a Boxed Warning and Medication Guide. Subsequently, the Boxed Warning was updated for all the salmeterol drug products, a new Boxed Warning was placed on all the formoterol drug products, including those only approved for COPD indications, and all LABA products were required to have a Medication Guide.

The risk/benefit of LABAs was also discussed at a Pediatric Advisory Committee (PAC) meeting held November 28, 2007. The issue was raised because Serevent Inhalation Aerosol had received pediatric exclusivity for studies performed under the Best Pharmaceuticals for Children

Act (BPCA). The Act requires the safety of every product receiving pediatric exclusivity to be discussed 1 year after exclusivity is received. Dr. Mosholder from the Office of Surveillance and Epidemiology (OSE) presented safety data for pediatric populations, including pediatric data from the SMART study (Table 12). Although there was no difference between treatment groups for the most serious outcomes of combined respiratory-related deaths or life-threatening experiences (primary) or respiratory-related deaths (secondary), there was a difference between treatment groups for all cause hospitalization and for the combined endpoint of respiratory death or asthma hospitalization (from hands-on review of case report forms). Since the outcomes for the primary and secondary endpoints were similar, the results were driven by the data for asthma hospitalizations in the pediatric patients. Based on these results and the results of meta-analyses, Dr. Mosholder expressed the concern that the risk/benefit of LABAs for treatment of asthma, both in children and in adults, needed to be re-examined. Since the scope of the PAC was limited, a new AC meeting was recommended.

Table 12. SMART study. Pediatric results

Outcome	Number of pediatric patients, 12-18y		Relative Risk (95% CI)
	Salmeterol N=1648	Placebo N=1619	
Primary: Combined respiratory-related death or life-threatening experience	2	2	1.0 (0.1-7.0)
Secondary: Respiratory-related death	1	0	Undefined
All cause hospitalization	37	16	2.3 (1.3-4.1)
Respiratory death or asthma hospitalization (from hands-on review of case report forms)	15	9	1.6 (0.7-3.7)

Source: PAC meeting, November 28, 2008, Slides presented by Dr. Andrew Mosholder

Prompted by a recommendation from a PAC meeting in November 2007, a joint PADAC, Pediatric, and DSaRM AC meeting was held on December 10-11, 2008, to re-address the risk/benefit ratio of LABAs for the treatment of asthma in the adult and pediatric populations. During the AC meeting, the FDA presented the results of a meta-analysis of available patient level data from randomized parallel controlled clinical trials submitted by the sponsors of LABA products. The objective of the meta-analysis was to evaluate if LABAs were associated with increased risk of serious asthma outcomes (death, intubation, hospitalization). One hundred and ten trials, with almost 61,000 patients were included. The analysis showed a risk difference (per 1000 patients) of 2.8 [95% CI 1.1, 4.5] for serious asthma outcomes in patients treated with LABA vs. No LABA. One of the subgroup analyses based upon age suggested an increase in risk for lower age groups (Figure 1). For details of the meta-analysis, refer to the FDA briefing package available at http://www.fda.gov/ohrms/dockets/ac/cder08.html#PulmonaryAllergy.

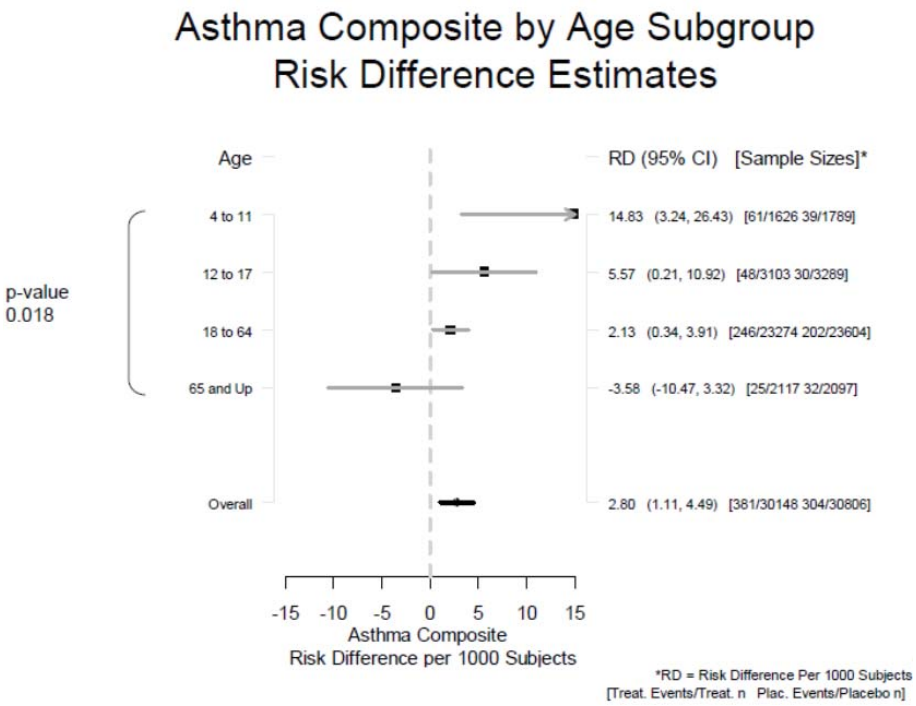

Figure 1. Risk difference estimates – age subgroup analysis

The committee stressed the appropriate use of LABAs (e.g. not as monotherapy), and the need for more safety data, especially in the adolescent and pediatric population where the data were very limited. They also made the general recommendation that larger safety databases be collected for these drugs in pediatric populations. Although they expressed some reservations with regard to use of these products in children up through 17 years of age, they did not recommend removal of the ICS/LABA combination products from use in pediatric patients. They did make that recommendation for the single-ingredient LABAs despite stating their belief that the use of ICS does not mitigate the risk of LABA use.

Following this 2008 AC meeting, on February 18, 2010, the Agency required further labeling changes including the following: contraindication of use of LABA without an asthma control medication; recommendation to use fixed dose ICS+LABA combination in pediatric and adolescent patients; and to assess asthma control and consider step down therapy (e.g. discontinue LABA).[7,8]

To evaluate the safety of LABAs when used in combination with ICS, the Agency issued post-marketing requirements (PMR) for safety trials to all of the sponsors of LABA products marketed in the US for asthma. The design of the trials was discussed at a March 10-11, 2010, PADAC meeting, and was finalized in 2011. A total of five trials were required, one each for Advair Diskus (fluticasone and salmeterol), Dulera (mometasone and formoterol), Symbicort (budesonide and formoterol), and Foradil Aerolizer (formoterol) in patients 12 years of age and older, and one for Advair Diskus in patients 4-11 years of age (because it is the only ICS+LABA combination product currently approved in this age range). The trials are multi-national,

7 Chowdhury BA, DalPan G. New Eng J Med 2010; 362:1169-1171.

8 Chowdhury BA, Seymour SM, Levenson MS. New Eng J Med 2011;364:2473-5.

randomized, double-blind, parallel group, active-controlled design in which asthma patients are randomized to an ICS+LABA or an ICS for 26 weeks. Three trials (Advair, Dulera, and Symbicort) compare the combination to corresponding doses of their respective ICS monotherapy products. Given that Foradil Aerolizer is a LABA single ingredient product, the Foradil Aerolizer trial includes treatment with fluticasone provided in a separate inhaler. In each of the 4 adult and adolescent trials, 11,700 patients 12 years and older will be enrolled, and in the single pediatric trial 6200 children 4 to 11 years of age will be enrolled. Because the strategy is to mimic a real-world scenario, patients may be eligible regardless of their current asthma therapy if their asthma severity warrants treatment with an ICS and LABA. The final study report submissions are due in June 2017. [9]

The primary endpoint for each trial is the number of patients experiencing the composite endpoint of serious asthma outcomes (asthma related hospitalization, asthma-related intubation, or asthma-related death). The pediatric trial also assesses other relevant quality of life endpoints such as days of school missed and emergency room visits because of asthma related illness. The trials are non-inferiority in design. Based upon an estimated background rate of 1.5% per year, the adult and adolescent trials have 90% power to rule out a 2.0 fold increase in event rate (87 composite events) and the pediatric trial has 90% power to rule out a 2.7 fold increase in event rate (43 composite events). Given the rarity of asthma intubations and death, it is expected that the primary endpoint will be driven by hospitalizations.

While each of the sponsors is conducting a separate trial, the trial designs are harmonized and there is a shared Joint Oversight Steering Committee and a shared Data Monitoring Committee, such that the results of the trials can be reviewed independently as well as jointly in order to evaluate the results for the rare events of intubations and death within the total enrolled population of 46,800 patients.

As of August 2016, the results of the two Advair Diskus trials have been made public by GSK, one in patients 12 years of age and older (AUSTRI, NCT01444430), and one in patients 4-11 years of age (VESTRI, NCT01462344). The results for AUSTRI were published in the New England Journal of Medicine (NEJM) on May 12, 2016 [10], the top-line results for VESTRI were announced in the GSK website in March 2016 [11] and published in the NEJM in September 2016[12], the results of both trials may be found at ClinicalTrials.gov. AstraZeneca submitted the results of their Symbicort safety study (D5896C00027, NCT01444430) on May 10, 2016, and the results were published in the NEJM on September 1, 2016[13]. Of note, while the study results have been submitted to the Agency, review of these studies has not been completed as of the time of completion of this review. Therefore, the results described below reflect the publications

9 http://www.fda.gov/Drugs/DrugSafety/ucm251512 htm.

10 Stempel, et al. Serious Asthma Events with Fluticasone plus Salmeterol versus Fluticasone Alone. N Engl J Med 2016; 374:1822-1830; http://www.nejm.org/doi/full/10.1056/NEJMoa1511049.

11 https://us.gsk.com/en-us/media/press-releases/2016/gsk-s-advair-diskus-achieves-primary-endpoint-in-laba-safety-study-of-children-aged-4-11-years-with-asthma/, referenced August 16, 2016.

12 Stempel, et al. Safety of Adding Salmeterol to Fluticasone Propionate in Children with Asthma. N Engl J Med 2016; 375(9):840-9; http://www nejm.org/doi/full/10.1056/NEJMoa1606356.

13 Peters SP, Bleecker ER, Canonica GW, et al. Serious Asthma Events with Budesonide plus Formoterol vs. Budesonide Alone. N Engl J Med 2016; 375:850-60; http://www.nejm.org/doi/full/10.1056/NEJMoa1511190.

and/or the submission summaries provided by the sponsors rather than the Agency's review findings.

AUSTRI was a multicenter (694 centers), randomized, stratified, double-blind, 6-month safety trial conducted in 11,679 adolescent and adult patients ≥12 years of age with persistent asthma, that compared Advair 100/50mcg or 250/50mcg twice-daily with corresponding doses of FP (100mcg or 250mcg) twice-daily. In the group that received Advair (ICS plus LABA), 34 patients experienced a serious asthma-related event compared with 33 patients in the steroid-only group, yielding a hazard ratio (HR) of 1.03; 95% confidence interval [CI], 0.64, 1.66) (p = 0.003) for the primary non-inferiority analysis of Advair compared with corresponding doses of FP for serious asthma-related events. There were no asthma-related deaths. While an equal number of patients in each group experienced an asthma-related hospitalization, 2 patients in the fluticasone-only group underwent asthma-related intubation. Severe asthma exacerbations occurred slightly less often in the Advair group than in the steroid-only group (480 of 5834 patients [8%] vs 597 of 5845 patients [10%], respectively (HR 0.79; 95% CI, 0.70 to 0.89).

VESTRI was a multicenter (31 countries), randomized, stratified, double-blind, parallel-group, 6-month safety trial in 6,250 patients 4-11 years of age with persistent asthma, that compared Advair 100/50mcg or 250/50mcg twice-daily with corresponding doses of FP (100mcg or 250mcg) twice-daily. The results showed a hazard ratio of 1.285, (95% CI 0.726, 2.272) p=0.006 for the primary non-inferiority analysis of Advair compared with corresponding doses of FP. All serious asthma-related events were hospitalizations (n=48); there were no asthma-related deaths or intubations. There was a non-statistically significant reduction of 14% in the risk of time-to-first asthma exacerbation for Advair compared to FP (HR 0.859; 95% CI 0.729, 1.012).

6.3 Specific Safety Issues

No specific safety issues were noted during the review of this supplement.

6.3.1 Serious Adverse Events (SAEs) and Significant AEs

There were no deaths or SAEs of note in any of the pediatric studies conducted with Symbicort. Nor were there any significant adverse events associated with dropouts in the Symbicort arms of the trials.

6.3.2 Common Adverse Events

Two trials provided adverse events with use of the Symbicort 80/4.5 dosage strength in patients 6 to11 years of age (D589GC00003 and SD-039-0716), i.e., with Symbicort 80/4.5 in comparison with one or more monoproducts. All other studies either used monoproducts or did not use the to-be-approve dosage strength of the combination. However, of these two trials, study SD-039-0716 only contributed a very small number of patients treated with Symbicort. Therefore, only study D589GC00003 was used to evaluate adverse events to include in labeling. Overall, the safety results in this population were consistent with those seen in older populations. Adverse events with a frequency of ≥3% and more common in the Symbicort 80/4.5 arm than the budesonide arm in study D589GC00003 are shown in Table 13, and adverse events with a frequency of ≥3% and more common in the Symbicort 80/4.5 arm than the budesonide arm in two combined studies is shown in Table 14.

Table 13. D589GC00003. Adverse events with a frequency of ≥3% and more common in the Symbicort 80/4.5 arm than the budesonide arm, by PT (Safety analysis set)

Preferred Term* n (%)	Symbicort 80/4.5 2BID (N=90)	Budesonide 80 2BID (N=90)
Upper respiratory tract infection	9 (10.0)	4 (4.4)
Pharyngitis	5 (5.6)	1 (1.1)
Headache	4 (4.4)	0
Rhinitis	3 (3.3)	2 (2.2)
*Based on MedDRA v18.1		

Source: CSR, T29, p123.

Table 14. Pooled data D589GC00003 and SD-039-0716. Adverse events with a frequency of ≥3% and more common in the Symbicort 80/4.5 arm than the budesonide arm, by PT (Safety analysis set, patients 6-11 years)

Preferred Term* n (%)	Symbicort 80/4.5 2BID (N=97)	Budesonide 80 2BID (N=96)
Upper respiratory tract infection	9 (9.3)	4 (4.2)
Nasopharyngitis	6 (6.2)	5 (5.2)
Headache	6 (6.2)	0
Pharyngitis	5 (5.2)	1 (1.0)
Rhinitis	3 (3.1)	2 (2.1)
Sinusitis	3 (3.1)	1 (1.0)
Oropharyngeal pain	3 (3.1)	1 (1.0)
*Based on MedDRA v18.1		

Source: Response to IR of 11/26/2016.

6.3.3 Less Common Adverse Events

No other relevant AEs were noted.

6.3.4 Laboratory Findings

No clinical laboratory measures were obtained in the two dose-finding studies, D589GC00001 or D589GC00002. In study D589GC00003 (Chase 3), serum potassium and non-fasting glucose levels were obtained at baseline (Visit 2), end of treatment (Visit 7), and at unscheduled visits. No safety concerns were identified. The limited laboratory program for this age group is acceptable based on clinical experience with the individual mono-components at the proposed dosages and the expectation that the combination will not adversely affect these findings.

6.3.5 Vital Signs and Physical Examinations

Vital signs and physical examinations were performed throughout the three studies. Vital signs (including systolic and diastolic blood pressures, pulse rate, height, and weight) and physical examinations were also performed throughout safety study SD-039-019. Assessment of vital signs in these studies revealed no clinically relevant treatment group differences.

6.3.6 Electrocardiograms (ECGs)

ECGs were performed in study D589GC00003 (Chase 3) at baseline and at the end of the study. Heart rate and QTcF assessments did not find any unexpected trends. Three patients had notable ECGs during the study as described within the summary of the study report in Section 8.3.

Study SD-039-0719 also included 12-lead ECG (pre-dose Visit 1 as baseline and 1hour post-dose at treatment visits, and read by an independent central cardiologist). ECG assessments included HR, PR interval, RR interval, QRS duration, T wave morphology (normal vs abnormal), QT interval (uncorrected), QTcB (Bazett), QTcF (Fridericia). No unusual findings were noted for these parameters.

6.3.7 Assessment of Effect on Growth

No formal growth studies were conducted with Symbicort, and growth data from the 6-month safety study (719) with Symbicort in children were inconclusive. The Symbicort labeling already contains the results of a study conducted with Pulmicort TBH that was also published in the literature (Szefler et al 2000). This was a 5-year NIH-sponsored longitudinal study (CAMP study) of asthmatic children 5 to 12 years of age, evaluating Pulmicort TBH in doses of 200 mcg administered BID. The results showed a 1.1 centimeter mean reduction in growth compared to those receiving placebo (n=418) at the end of 1 year. The difference between these 2 treatment groups did not increase further during the study; by the end of the 5-year study period, children treated with budesonide and children treated with placebo had similar growth velocities and the projected final height was comparable in both groups.

6.4 Safety Update

Since there are no ongoing pediatric studies, requirement for submission of a 4-Month Safety Update was waived at the pre-NDA meeting. Review of the annual periodic benefit-risk evaluation report (PBRER) submitted on October 25, 2016, for the period of August 25, 2015 through August 24, 2016, did not show any new safety signals for Symbicort. Please see Section 6.2 for a discussion of safety signals with LABAs.

7 ADDITIONAL CLINICAL ISSUES

7.1 Pediatric Exclusivity

As noted in Sections 2.1 and 2.2, Pediatric Exclusivity is being sought with this submission. In response to the PPSR submitted on October 1, 2010, a Pediatric Written Request was issued on January 28, 2011. The PPSR contained the three trials outlined in the Pediatric Plan that are were conducted and are now submitted to address the deficiencies cited in the 2009 CR action for this pediatric supplement. The Written Request was subsequently amended four times, on May 5, 2011, April 6, 2012, March 9, 2015, and October 19, 2015, each time based on interactions between AstraZeneca and the Agency, to align the WR with minor changes to the conduct of the studies as they were being performed. As with the Pediatric Plan and the initial WR, on each occasion the Division discussed the changes with, and got advice and acceptance from, the Pediatric Review Committee (PeRC).

AstraZeneca complied with all provisions of the Written Request except one. For Study 3 (D589GC00003), the Written Request required that the company randomize and treat at least 93 patients per treatment group to the three treatment groups (giving a total of 279 patients). The WR goes on to specify that if the company was not able to do so, they must provide a description of their efforts to do so and an explanation for why they were unsuccessful. AstraZeneca states that while they randomized 279 patients, only 273 treated patients were treated (Table 15). With regard to justification for why this requirement was not met, AstraZeneca stated that enrollment was stopped when it was known that 4 patients who had been randomized were not treated because they were incorrectly randomized; therefore, the randomized/treated goal had been raised to 283 patients. At that time, 277 patients had been randomized and 16 patients were in the run-in period. AstraZeneca states that their expectation was that this would result in an adequate number of patients randomized and treated. However, several things interfered with this. First, unexpectedly, only 3 of these final 16 patients were subsequently randomized. Second, after the close of enrollment it was discovered that one patient had been randomized twice at two different sites and times, and two patients had been incorrectly randomized and therefore did not receive treatment. This combination of events reduced the total number of randomized and treated patients to below the goal set in the WR. The resultant effect on powering of the study is shown in Table 15; the power to detect the difference specified in the primary endpoint of the study was reduced from 90% to 89%. This difference is felt to be clinically insignificant.

Additionally, the WR requested that randomization be stratified, and that if the company was not able to enroll an adequate number of patients into each age group to provide a description of their efforts along with an explanation for why they were unsuccessful. The summary results of study enrollment by age group are shown in Table 16, with more detailed information for each treatment group provided in Table 89. A description of the attempts to randomize a good balance of patients in each age group was provided.

As is typical of other WRs, the Written Request required that the studies take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities, and that if the company was not able to enroll an adequate number of these patients, they would need to provide a description of their efforts and an explanation for why they were unsuccessful. The summary results of study enrollment by age group are shown in Table 16,

with more detailed information for each treatment group provided in Table 89. A description of the attempts to randomize a good balance of patients in each age group was provided.

The matter of pediatric exclusivity was discussed at the Exclusivity Board meeting on November 14, 2016. At the time of finalization of this review, the Exclusivity Board has not yet published their decision; the FDA website will be updated once the paperwork is completed:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049997.htm

Table 15. D589GC00003. Randomized and treated enrollment summary

	Symbicort 80/4.5	Symbicort 80/2.25	Budesonide 80	Total	Power (%)[2]
Written Request requirement: Randomized and treated	93	93	93	279	90%
Randomized	92[1]	95	92	279	
Not treated	2	2	2	6	
Received treatment	90[1]	93	90	273	89%

1 Does not include one occurrence of a patient who was randomized twice (E7866008 and E7809017), once at each of two study sites, both times to Symbicort 80/4.5. Only data for the patient's first occurrence in the study is included in the tables and figures.

2 Powering is based on the assumptions of equal numbers of patients in each treatment group, a difference in means of 0.12L to be detected, a common standard deviation of 0.25L, and a 2-sided test on a 5% significance level.

Source: Submission of 7/28/2016, Attachment 1 – Justification of Efforts.pdf, T1, p4; T2, p6

Table 16. Sex, Age, and Racial / Ethnic enrollment summary

	WR Target	D589GC00001	D589GC00002	D589GC00003
Sex				
Males	50%	63.2%	57.4%	59.5%
Females	50%	36.8%	42.6%	40.5%
Age range				
6-8y	50%	39.5%	31.5%	35.1%
9-11y	50%	60.5%	68.5%	64.9%
Racial and Ethnic group				
Caucasian		88.8%	57.4%	62.4%
African American	10-15%	6.6%	40.7%	27.2%
Asian	3%	0.3%	0	0.7%
Other		4.3%	0	9.8%
Hispanic	20%	6.9%	16.7%	38.0%

Source: NDA 21929, Submission of 7/28/2016; Attachment 1 – Justification of Efforts.pdf; CSRs; Response to IR of 10/28/2016.

7.2 Advisory Committee Meeting

An Advisory Committee meeting was neither requested nor carried out as part of the assessment of this application. However, there have been a number of Advisory Committee meetings regarding use of LABAs in patients with asthma in the past, and an Advisory Committee did meet to discuss the risk/benefit of LABAs on December 10-11, 2008. Please refer to Section 7.2 of this review for a discussion of LABA risks and Advisory Committee Meetings.

7.3 Literature Review

A literature review was not performed during the review of this application. That said, a literature was reviewed as part of the preparation for the joint AC meeting held on December 10-11, 2008. The major analyses and findings in the literature consist of meta-analyses regarding the safety of LABAs. Since the literature was reviewed for the AC meeting, and is summarized in FDA documents and in the transcripts of the AC meeting, it will not be summarized here. However, it should be noted that some of the meta-analyses, such as that of Salpeter, elected to only include studies in which a patient experienced an AE of interest, i.e., an asthma related hospitalization, intubation, or death. As a result, there are significant limitations to this approach.

7.4 Labeling Review

The labeling submitted with this supplement will but be finalized until after finalization of this review. That stated, several things are notable regarding the proposed labeling.

(b) (4)

Regarding PI Section 6, the Division has concluded that common adverse events from study D589GC00003 should be described,

(b) (4)

(b) (4)

(b) (4)

8 APPENDICES

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8.3.2 Study SD-039-0719

This was a 6-month open-label study compared the safety of Symbicort 160/4.5 mcg with Pulmicort Turbuhaler (TBH) 200 mcg in children 6-11 years with asthma. This safety study provides an open-label comparison of the high-dose Symbicort 160/4.5 MDI product, (b) (4) not (b) (4) for this age group, with a similar budesonide dose delivered from Pulmicort TBH (each administered as 2 actuations BID). The study included systemic exposure through multiple-dose PK and HPA axis data. This study was reviewed during the original NDA review cycle. My original review is reproduced below, with minor modifications due to reassessment of the results as part of the current application.

Protocol #:	SD-039-0719
ClinicalTrials.gov Identifier	NCT00646529
Title:	A six-month, randomized, open-label safety study of Symbicort® (160/4.5 µg) compared to Pulmicort Turbuhaler® in asthmatic children 6 to 11 years.
Study Dates:	July 22, 2002 to October 6, 2003
Sites:	29 centers in the US
IRB:	A listing of Institutional Review Boards (IRB) was provided. Each study site had a separate IRB, although the larger majority of study sites (all except 5) used a central (b) (4) .
Ethics:	The study report states that the study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements and the AstraZeneca policy on Bioethics.
Source references:	Unless otherwise indicated, all source references are to: SD-039-0719-legacy-clinical-study-report.pdf, submitted June 3, 2008, and SD-039-0719.pdf in the original NDA submission [the two files appear to be identical except for their names].

8.3.2.1 Protocol

This was a 26-week, multicenter, open-label, randomized, active-controlled, safety study to investigate the safety of Symbicort MDI 160/4.5 mcg compared with Pulmicort TBH 200 mcg, each administered as 2 actuations BID, in 187 asthmatic children 6 to <12 years of age. After a 1-week baseline period, randomization was 2:1 to Symbicort 160/4.5 mcg [Batches: P6040; P6502A] or Pulmicort Turbuhaler® 200 mcg [Batches: P6478; P6583; X1447; DE1682]. On-treatment study visits were at 2, 12, and 26 weeks. There were no specific efficacy objectives, although study assessments included pre-dose FEV_1, FVC, FEF_{25-75}, PEFR, and physician and caregiver global assessments of asthma control. The primary objective was to compare the long-term safety profile of Symbicort MDI with that of Pulmicort TBH by means of safety assessments, as assessed by: Adverse Events (AEs), physical examinations, vital signs

(temperature, pulse, blood pressure), laboratory parameters (hematology, clinical chemistry, urinalysis, 24-hour urinary-cortisol [at baseline, 12, 26 weeks]), PK for consenting patients [budesonide and formoterol Tmax, Cmax, and AUC_{0-6} at 2 weeks: 5 specimens drawn pre-dose and at 10, 40, 120 and 360 minutes]), and electrocardiograms (12-lead ECG 30 minutes post-dosing). The secondary objective was to compare the measurements of health economics and health-related quality of life (HRQOL) using the Pediatric Asthma Quality of Life Questionnaire in patients ≥7 years between the two treatment groups (PAQLQ[S] for patients, and PACQLQ for caregivers). Medical resource utilization included: ER visits (all-cause and due to asthma or breathing problems); hospital admissions (all-cause and due to asthma or breathing problems); and urgent care visits, unscheduled visits, and unscheduled telephone calls due to asthma or breathing problems. Indirect asthma resource utilization included: days the child was unable to participate in normal daily activities, days the caregiver's daily routine was interrupted, and days the caregiver missed work due to asthma or breathing problems.

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

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

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

8.3.2.2 Results

8.3.2.2.1 Disposition, Demographics, Analysis Sets, and Baseline Characteristics

The study randomized 187 patients at 28 centers: 119 (36%) females, 67 (64%) males, 167 (89.8%) Caucasians, 14 (7.5%) Blacks, 2 (1.1%) Orientals, 3 (1.6%) Others, with a mean age of 9.0 years (range 6-11 years), and a history of asthma for approximately 6.0 years (Table 63). The average daily ICS use at entry was 307 mcg (range 44-1000 mcg) per day. The mean screening FEV_1 was 1.75 L, 84.2% predicted; the mean baseline FEV_1 was 1.74 L, 83.6% predicted. Treatment groups were relatively similar in baseline and demographic characteristics, including FEV_1, use of ICS, and other pulmonary function measurements. The Symbicort MDI group comprised 123 patients: 44 females, 79 males, 109 Caucasians, 11 Blacks, 1 Oriental, 2

Others, with a mean age of 9.0 years (range 6-11 years), and a history of asthma for approximately 6 years. The average ICS dose was 306 mcg (range 50-1000 mcg) per day. The mean baseline FEV_1 was 1.75 L, 84.0% predicted. [p77]

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

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

Table 63. SD-039-0719. Demographic and key baseline characteristics, ITT

Demographics / Baseline	Symbicort MDI 160/4.5 N=123	Pulmicort TBH 200 N=63	Total N=186
Sex (n, %)			
Male	79 (64.2)	40 (63.5)	119 (64.0)
Female	44 (37.5)	23 (36.5)	67 (36.0)
Race (n, %)			
Caucasian	109 (88.6)	58 (92.1)	167 (89.8)
Black	11 (8.9)	3 (4.8)	14 (7.5)
Oriental	1 (0.8)	1 (1.6)	2 (1.1)
Other	2 (1.6)	1 (1.6)	3 (1.6)
Mean Age (yr), (mean, range)	9.0 (6,11)	8.9 (6,11)	9.0
Age group (yr), (n, %)			
6-7y	27 (22.0)	14 (22.2)	
8-11y	96 (78.0)	49 (77.8)	
Years since diagnosis Mean (SD)	6.0 (3.0)	6.0 (2.9)	6.0 (3.0)
ICS use at entry (mcg/day)			
Mean (SD)	306 (214)	309 (213)	307 (213)
Min, Max	50, 1000	44, 1000	44, 1000
Screening (Visit 1, pre-bronchodilator) (mean, SD)			
FEV_1 (L)	1.75 (0.44)	1.75 (0.40)	1.75 (0.42)
FEV_1 % predicted	84.6 (13.2)	83.5 (12.1)	84.2 (12.9)
Baseline (Visit 2, pre-dose) (mean, SD)			
FEV_1 (L)	1.75 (0.45)	1.73 (0.40)	1.74 (0.43)
FEV_1 % predicted	84.0 (13.5)	82.9 (13.3)	83.6 (13.4)

Source: T13, p77; T11.1.4.2, p253-5. ISE; T25, p69

8.3.2.2.2 Efficacy and Pharmacokinetics

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

Spirometry, PAQLQ, and Health Resource Utilization measures

Treatment means, ranges, and treatment comparisons for FEV_1 over the treatment and at the end of treatment are shown in tabular format in Table 64 and graphically for FEV_1in Figure 22. Results favored Symbicort MDI over Pulmicort TBH, although treatment differences were numerically small. It will be seen that the results parallel each other. It is unclear why the results changed between 12 and 26 weeks' time frame into the study. It is also unclear whether the differences are due to pharmaceutic differences between the products with regard to delivery of the budesonide component, or whether they are due to the addition of the LABA in Symbicort.

PAQLQ(S) and PACQLQ instruments were used to evaluate PROs in patients and caregivers of patients 7 years of age and older, one of the secondary objectives in the study. PAQLQ(S) and PACQLQ overall and individual domain scores are shown in Table 65 and Table 66, respectively. Mean overall and individual domain PAQLQ(S) scores improved from baseline for the Symbicort group, with improvements exceeding the MID (the Minimally Important Difference was defined as an increase of ≥0.5 point from baseline to end of treatment) for the overall score and 2 of 3 individual domains. Pulmicort TBH mean scores improved as well, but change from baseline did not meet the MID. Although the 95% confidence intervals for treatment differences excluded zero, none reached the MID. For PACQLQ, the mean overall and individual domain scores improved from baseline for both treatment groups, but improvements did not reach the MID. While the 95% confidence intervals for treatment differences excluded zero for several of the scores, none of the differences reached the MID.

Global physician assessments also favored Symbicort. Differences between treatment groups in direct health resource utilization did not clearly favor one drug product, although the numbers of urgent care visits were less in the Symbicort treatment group. Differences between treatment groups in indirect health resource utilization numerically trended in favor of the Symbicort treatment group.

Table 64. SD-039-0719. Pre-dose FEV_1 (Mean, SD)

	N	Baseline	Observed	Change from baseline		LS mean Diff (95% CI)
				Change	ANCOVA LS mean (95% CI)	
FEV_1 (L) during treatment period						
Symbicort MDI	119	1.74 (0.45)	1.88 (0.44)	0.14 (0.16)	0.15 (0.11, 0.19)	0.08 (0.02, 0.13)
Pulmicort TBH	63	1.73 (0.40)	1.81 (0.40)	0.08 (0.19)	0.07 (0.02, 0.13)	
FEV_1 (L) at treatment end (LOCF)						
Symbicort MDI	119	1.74 (0.45)	1.95 (0.47)	0.21 (0.20)	0.20 (0.16, 0.25)	0.11 (0.05, 0.18)
Pulmicort TBH	63	1.73 (0.40)	1.85 (0.41)	0.13 (0.21)	0.09 (0.03, 0.15)	

Source: T19, T20, p86; T21, T22, p87

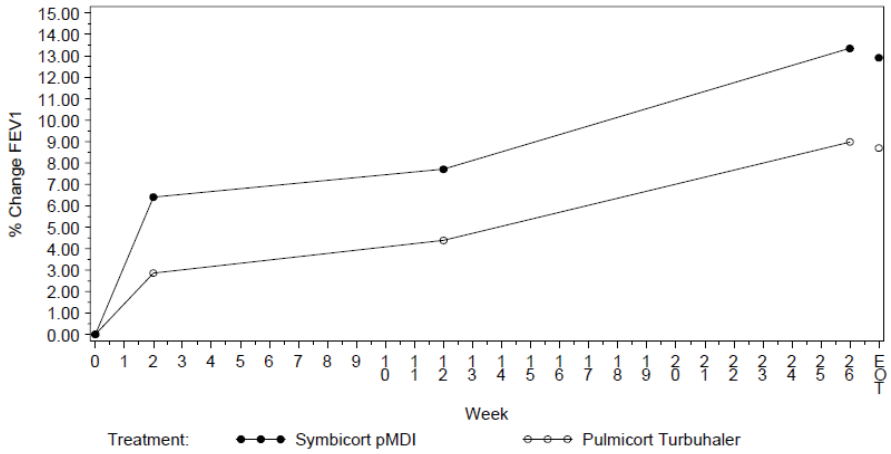

Figure 22. SD-039-0719. Mean percent change from baseline in pre-dose FEV_1 (Safety)
Source: F3, p88

Table 65. SD-039-0719. PAQLQ(S), Ages ≥7 years

Domain / Treatment	N	Baseline	End of Treatment			LS mean Diff (95% CI)
			Observed	Change	ANCOVA LS mean (95% CI)	
Overall						
Symbicort MDI	108	6.03	6.56	0.53	0.58 (0.44, 0.72)	0.35 (0.14, 0.57)
Pulmicort TBH	55	5.84	6.20	0.36	0.23 (0.02, 0.43)	
Symptom score						
Symbicort MDI	108	5.86	6.45	0.59	0.64 (0.48, 0.79)	0.32 (0.09, 0.55)
Pulmicort TBH	55	5.69	6.13	0.43	0.32 (0.10, 0.54)	
Activity score						
Symbicort MDI	108	6.07	6.47	0.41	0.49 (0.32, 0.65)	0.44 (0.18, 0.69)
Pulmicort TBH	55	5.67	5.95	0.29	0.05 (-0.19, 0.29)	
Emotional function score						
Symbicort MDI	108	6.24	6.74	0.50	0.51 (0.33, 0.68)	0.33 (0.08, 0.59)
Pulmicort TBH	55	6.14	6.43	0.30	0.17 (-0.07, 0.42)	

Source: T23, p95-6; T24, p96

Table 66. SD-039-0719. PACQLQ, Ages ≥7 years

Domain / Treatment	N	Baseline	End of Treatment			LS mean Diff (95% CI)
			Observed	Change	ANCOVA LS mean (95% CI)	
Overall						
Symbicort MDI	108	6.20	6.59	0.39	0.44 (0.31, 0.56)	0.26 (0.08, 0.45)
Pulmicort TBH	55	6.21	6.38	0.17	0.17 (-0.00, 0.35)	
Activity score						
Symbicort MDI	108	6.44	6.70	0.30	0.30 (0.15, 0.45)	0.14 (-0.08, 0.36)
Pulmicort TBH	55	6.44	6.60	0.16	0.16 (-0.05, 0.37)	
Emotional function score						
Symbicort MDI	108	6.10	9.56	0.50	0.50 (0.36, 0.64)	0.33 (0.13, 0.54)
Pulmicort TBH	55	6.12	6.29	0.17	0.17 (-0.03, 0.36)	

Source: T25, p97-8; T26, p98

Pharmacokinetics

Please see Section 5.1 of this review for the PK results. The numbers of pediatric patients who agreed to PK evaluations were quite small, limiting usefulness of the results. There was considerable variability in budesonide levels, with comparable or less exposure to budesonide from Symbicort but no clear differences in results between the two drug products. Lack of higher systemic exposure to budesonide from Symbicort than a comparable dose from the approved Pulmicort Turbuhaler supports use of this dosage in children 6-11 years of age should patients need higher doses of budesonide for adequate disease control.

8.3.2.2.3 Safety

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

Both treatment groups exhibited a trend for decrease from baseline in mean 24-hour urinary cortisol over the course of the treatment period (numerically the decrease for Pulmicort was larger). This is different from the results of study 715 in adults, where changes in mean 24-hour urine results trended up for the Symbicort MDI and down for the Symbicort TBH treatment groups. Cortisol/creatinine ratios also showed similar trends for both treatment groups including a numerically larger decrease for the Pulmicort than the Symbicort group. The HPA axis results follow the PK results for budesonide in this study, which show less systemic exposure to budesonide from Symbicort than a corresponding dose from Pulmicort Turbuhaler.

Three patients in the Symbicort group had a QTcB of ≥450 msec and also had a change from baseline in QTcB of ≥60 msec. This is likely an effect of the formoterol component, and the Symbicort label includes a WARNING with regard to effects on QT interval.

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

Adverse Events

Reviewer's Note: When viewing the tables, it is helpful to keep in mind the 2:1 randomization of Symbicort to Pulmicort.

There were no deaths, and no pregnancies were reported. During the treatment phase, there was one hospitalization for asthma in the Symbicort treatment group (patient not intubated) and none in the Pulmicort treatment group.

SAEs and DAEs are summarized in Table 67 and listings are shown in Table 68. There were 3 SAEs (2 Symbicort MDI [asthma, pneumonia], 1 Pulmicort TBH [sickle cell crisis]), all leading to temporary discontinuation of treatment but not permanent discontinuation. None were considered by the investigators to be drug related. One patient had an SAE of asthma during the screening period and was not randomized. One patient in the Symbicort group experienced an SAE of asthma in the post-treatment period. Four patients were discontinued due to an AE, 3 of which occurred during the first month of treatment. There were two asthma DAEs, one in each

treatment group. One patient experienced Wolff-Parkinson-White syndrome prior to randomization and was discontinued shortly after starting treatment. One patient had an asthma exacerbation during the screening period and was not randomized, but was re-screened and randomized at a later date.

The numbers and percent of patients with AEs by SOC were similar between treatment groups, although the percent of patients with respiratory event was higher in the Symbicort MDI (41.5%) than in the Pulmicort TBH (34.9%) group. The most commonly reported AEs by MedDRA preferred term are summarized in Table 69. No clear pattern is present.

Table 67. SD-039-0719. Adverse event overview

Number (%) of patients with an AE	Symbicort MDI n=123	Pulmicort TBH n=63
Mean duration of exposure (days)	171.2	166.3
Any AE (during treatment)*	104 (84.6)	54 (85.7)
SAE	2 (1.6)	1 (1.6)
SAE leading to death	0	0
SAE leading to discontinuation	0	0
Discontinuations due to an AE	2 (1.6)	2 (3.2)
Other significant AEs	0	0
Total number of AEs		
Any AE	431	244
SAE	2	1

Source: T32, p113; T33 p116

Table 68. SD-039-0719. Listing of SAEs and DAEs during all study phases (SAS)

Identifier	Term	Age	Sex	Race	AE Onset*	SAE	DAE	Comments
Symbicort								
E9008004	Asthma	10	F	C	98	Yes	No	Hospitalized. CXR WNL. Rx: Prednisone and albuterol.
E9010012	Pneumonia	6	M	C	17	Yes	No	Hospitalized for LUL pneumonia, lethargy and dehydration from gastroenteritis (vomiting and abd pain). Rx: IV fluids, antibiotics, O2, nebulized budesonide and albuterol.
E9015007	Asthma	11	F	C	190 (7 days post study)	Yes	No	Hospitalized. Rx'd: IV fluids, solumedrol, albuterol. DC meds: prednisone x3d, maintenance Foradil and Pulmicort.
E9006011	Abdominal pain, upper	9	M	C	17	No	Yes	
E9020011	Asthma	9	M	C	8	No	Yes	
E9018008	Wolff-Parkinson-White syndrome	10	M	O	Prior (-6)	No	Yes	
E9010007 (E9010010)	Asthma	9	F	C	Prior (-45)	No	Yes	
Pulmicort								
E9008011	Sickle cell crisis	8	F	B	45	Yes	No	Hospitalized. Rx: pain meds, antibiotics.
E9005002	Asthma	6	M	C	21	No	Yes	
E9026004	Disturbance in	8	M	C	34	No	Yes	

Identifier	Term	Age	Sex	Race	AE Onset*	SAE	DAE	Comments
	attention							
* Onset expressed as relative to day of randomization.								

Source: T36, p123; T37, p125; Narratives: p833-7.

Table 69. SD-039-0719. AEs by preferred term

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

Source: T35, p119-20

Laboratory parameters

Clinical lab results reviewed included those for hematology, clinical chemistry, glucose, potassium, and 24-hour urine cortisol. Within each set of laboratory parameters, results were considered by change in mean values over time, changes by individual patient (shift tables), and individual clinically important abnormalities. For clinical laboratory values, other than expected changes (e.g. glucose and potassium) based on pharmacologic effects of ICS and beta-agonists,

there were no significant or clinically meaningful findings. Effects on HPA axis were noted, as measured by 24-hour urinary cortisol. The results are discussed below.

Changes in mean 24-hour urine cortisol levels over the course of the study are shown in Table 70. For both sets of results, the range of results was quite large; the variability of results exceeded any mean differences, making interpretation somewhat difficult. It should also be noted that the mean values remained well within the normal reference range. Nevertheless, both treatment groups exhibited a trend for a decrease from baseline in mean 24-hour urinary cortisol over the course of the treatment period, with the decrease for Pulmicort numerically larger. This trend is different from the results of study 715 in adults, where changes in mean 24-hour urine results trended up for the Symbicort MDI and down for the Symbicort TBH treatment groups. Cortisol/creatinine ratios also showed similar trends for both treatment groups including a numerically larger decrease for the Pulmicort than the Symbicort group. Results of urinary cortisol and creatinine-corrected cortisol were similar across genders. The study report provided a shift table for urine cortisol (Table 71) based on the low and high reference ranges for urine cortisol (Quest Diagnostics), 1.4 to 18 mcg/24 hours [equivalent to 3.9 to 49.7 nmol/24 hours in SI units] for ages 6 to 7 years and 1.6 to 21 mcg/24 hours [equivalent to 4.4 to 57.9 nmol/24 hours in SI units] for ages 8 to 11 years. Six patients in each treatment group (4.9% of patients on Symbicort MDI, 9.5% of patients on Pulmicort TBH) shifted from normal or high at baseline to low at the end of treatment. The study report notes that no cortisol-related DAEs or SAEs were reported. In a brief review, I was not able to specifically identify any AEs due to the cortisol findings in the patients who experienced low levels on testing. A listing of patients who experienced a low urinary cortisol level at any time during treatment is shown in Table 72.

In sum, the urinary cortisol results follow those of the PK in this study, with slightly higher systemic exposure and numerically more HPA axis effect from the budesonide in Pulmicort than in Symbicort.

Table 70. SD-039-0719. Mean 24-hour cortisol results (nmol/24 hours)*

	N	Arithmetic mean (SD)	Geometric mean	Geometric mean %
Symbicort 160/4.5, 2BID (TDD = 640/18 mcg/day)				
Baseline	122	29.3 (19.3)	23.5	
12 weeks	107	29.8 (28.6)	20.9	89.9%
26 weeks	106	24.6 (21.0)	17.7	75.7%
End of treatment	114	24.9 (20.5)	18.2	78.0%
Treatment average	114	27.6 (19.0)	21.7	93.4%
Pulmicort 200, 2 BID (TDD = 800 mcg/day)				
Baseline	62	30.3 (17.0)	25.5	
12 weeks	56	24.6 (17.5)	18.3	68.3%
26 weeks	50	25.8 (29.7)	15.4	61.1%
End of treatment	57	24.9 (28.2)	15.4	59.5%
Treatment average	57	24.6 (17.6)	18.8	73.1%

*The reference range supplied by the testing laboratory for urinary cortisol (24h) was in different units of measurement (mcg/24hours) than the results presented in the study report. The reference range was: 1.4 to 18 mcg/24 hours [equivalent to 3.9 to 49.7 nmol/24 hours in SI units] for ages 6 to 7 years and 1.6 to 21 mcg/24 hours [equivalent to 4.4 to 57.9 nmol/24 hours in SI units] for ages 8 to 11 years.

Source: T46, p134

Table 71. SD-039-0719. Shift table for 24-hour urinary cortisol at end of treatment

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

Source: T50, p138

Table 72. SD-039-0719. Patients with clinically notable 24-hour urinary cortisol findings at any time during treatment

Identifier	Age	Sex	Race	Visit	Cortisol (nmol/24h)	Cortisol/Creatinine ratio (mcg/g)
Symbicort MDI						
E9002012	10	F	C	Screening	12.7	14.4
				Week 12	13.2	11.0
				Week 26	2.5	2.5
E9002015	9	M	C	Screening	12.7	9.7
				Week 12	1.4	1.0
				Week 26	6.6	4.7
E9006006	9	M	C	Screening	4.1	2.8
				Week 12	3.9	7.8
				Week 26	8.3	5.7
E9012001	8	M	C	Screening	16.3	8.3
				Week 12	4.7	2.9
				Week 26	3.0	1.8
E9015014	11	M	C	Screening	13.5	9.0
				Week 12	4.1	3.6
				Week 26	5.8	18.5
E9021012	11	M	C	Screening	22.9	9.1
				Week 12	39.7	11.9
				Week 26	3.9	8.4
E9026007	10	M	C	Screening	4.4	8.0
				Week 12	1.4	0.6
				Week 26	3.6	1.1
E9026010	10	M	C	Screening	86.6	19.9
				Week 12	2.2	1.4
				Week 26	2.5	1.4
E9029001	11	F	C	Screening	20.4	15.2
				Week 12	33.4	20.6
				Week 26	3.6	4.7

Identifier	Age	Sex	Race	Visit	Cortisol (nmol/24h)	Cortisol/Creatinine ratio (mcg/g)
Pulmicort TBH						
E9002013	7	F	C	Screening	13.5	11.3
				Week 12	3.0	2.2
				Week 26	3.9	3.5
E9005011	10	M	C	Screening	13.8	4.7
				Week 12	3.3	4.2
				Week 26	7.7	5.4
E9005013	9	F	C	Screening	Missing	Missing
				Week 12	Missing	Missing
				Week 26	2.2	1.9
E9006002	11	M	C	Screening	50.2	38.3
				Week 12	12.7	9.0
				Week 26	3.9	10.2
E9008011	8	F	B	Screening	48.3	39.0
				Week 12	3.9	5.9
				Week 26	7.2	8.4
E9013008	7	M	C	Screening	10.2	7.5
				Week 12	15.7	13.5
				Week 26	2.2	1.2
E9019005	11	M	C	Screening	41.7	14.8
				Week 12	40.6	10.1
				Week 26	3.0	0.6
E9021002	9	M	C	Screening	18.8	11.7
				Week 12	18.8	9.6
				Week 26	2.8	2.5
E9021009	11	F	C	Screening	26.5	10.8
				Week 12	49.9	27.3
				Week 26	3.3	1.5
E9026012	10	F	C	Screening	15.5	9.9
				Week 12	2.2	1.7
				Week 26	11.0	5.9

Source: T52, p140-1

Vital signs, ECGs, Physical examinations

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

The overwhelming majority of the patients had normal values for pulse, blood pressure, and ECG at baseline and normal values at end of treatment. No unusual findings were noted for these parameters. Mean heart rate, uncorrected, and corrected QTc results are shown in Table 73. No patients on Pulmicort experienced a QT, QTcB, or QTcF of ≥450 msec. One Symbicort patient had an uncorrected QT ≥450 msec and 5 Symbicort patients had a QTcB ≥450 msec, but none of these experienced a QT, QTcB, or QTcF of ≥500 msec. In the Pulmicort group, 1 patient had a change from baseline of ≥60 msec in QTcB. In the Symbicort group, 2, 5, and 4 patients had a change from baseline of ≥60 msec in QT, QTcB, or QTcF, respectively. Ten patients met any of the above criteria, and their information was reviewed. In the Symbicort

group, 3 patients had a QTcB of ≥450 msec and also had a change from baseline in QTcB of ≥60 msec (Table 74). [p144-56]

Table 73. SD-039-0719. ECG findings

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

Source: T53, p146

Table 74. SD-039-0719. Patients with QTc ≥450 and QTcB change ≥60 msec (all on Symbicort)

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

Source: T59, p154

8.3.2.3 Conclusions

Review of this 6-month open-label safety study in children 6-11 years of age did not pick up on any new or unexpected safety concerns. There were no deaths and no pregnancies, although there was one hospitalization due to asthma in the Symbicort group (not intubated).

Because of the small numbers of patients who were not Caucasian, the study could not be said to represent safety in other racial groups. HPA axis findings and QT effects in this age group were elucidated, although interpretation is hindered by lack of a placebo control. Both treatment

groups exhibited a trend for decrease from baseline in mean 24-hour urinary cortisol over the course of the treatment period. Numerically, the decrease for Pulmicort was larger than for Symbicort. Results are different from those in study **715** in adults/adolescents, where changes in mean 24-hour urine results trended up for the Symbicort MDI and down for the Symbicort TBH treatment groups. Cortisol/creatinine ratios also showed similar trends for both treatment groups including a numerically larger decrease for the Pulmicort than the Symbicort group. PK results for budesonide parallel the HPA axis results in this study, with less systemic exposure to budesonide from Symbicort than the corresponding dose from Pulmicort Turbuhaler. Three patients in the Symbicort group had a QTcB of ≥450 msec and also had a change from baseline in QTcB of ≥60 msec. This is likely an effect of the formoterol component. Such effects are already included as a WARNING in the Symbicort labeling.

8.3.3 Study D589GC00001 (CHASE 1)

This trial was the first of three studies performed to respond to the CR action of April 3, 2009. The trial was designed to support the proposed budesonide 80 mcg per actuation component in Symbicort.

Protocol #:	D589GC00001 (CHASE 1)
ClinicalTrials.gov Identifier	NCT01136382
Title:	A Phase 2, double-blind, randomized, parallel-group, placebo-controlled, multicenter study, comparing budesonide pMDI 160 µg bid with placebo: a 6-week efficacy and safety study in children aged 6 to <12 years with asthma
Study Dates:	First subject enrolled: August 7, 2011 Last subject last visit: April 5, 2013
Sites:	72 sites in Bulgaria, Hungary, Latvia, Poland, Slovakia, South Africa, and the United States (US)
CRO:	Quintiles
IRB:	Because this study was performed in multiple countries and sites, multiple IRBs were involved. A listing of Institutional Review Boards (IRB) was provided.
Ethics:	The study report states that the study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements and the AstraZeneca policy on Bioethics.
Source references:	D589GC00001 Clinical Study Report.pdf, submitted July 28, 2016 (plus, errata lists, protocol with amendments,

8.3.3.1 Protocol

This was a 6-week, randomized, double-blind, parallel-group, placebo-controlled, multicenter, efficacy and safety trial that compared inhaled budesonide 160 mcg (administered as 2 actuations

budesonide HFA MDI 80 mcg) twice daily (TDD = 320 mcg of budesonide) with matched placebo in pediatric patients 6 to <12 years with asthma who demonstrated the need for ICS controller therapy. The study was used to confirm the dosage of budesonide to be taken into study D589GC00003 (Written Request Study 3).

Note that an investigational version of budesonide HFA MDI that delivers a nominal ex-actuator dose of 80 mcg of budesonide was used in this study, and its use was supported by *in vitro* data submitted with the original Symbicort application. This product was developed to mimic the ex-actuator dose of budesonide delivered by Symbicort 80/4.5. See Section 4.1 for details.

Inclusion criteria included patients with a documented history of asthma (ATS criteria) for at least 6 months that required either low-dose ICS therapy or daily leukotriene receptor antagonist treatment for at least 30 days, morning pre-bronchodilator FEV_1 between 70 and 95% of predicted, and reversibility of FEV_1 of ≥12% after a SABA. Patients were excluded if they had been on systemic corticosteroids during the run-in, had a respiratory or other infection, or met any of the criteria for pre-defined asthma withdrawal events during the run-in.

The study consisted of a screening visit (Visit 1), an enrollment visit (Visit 2), a 7- to 21-day run-in/qualification period, a randomization visit (Visit 3), 6 weekly on-treatment visits, and telephone follow-up at approximately 2 weeks after the final study visit. During the run-in period, patients were treated with single-blinded placebo, with albuterol rescue treatment available as-needed.

The study included an asthma safety plan with criteria for pre-defined asthma events mandating withdrawal if any of the following conditions were met:

1. A decrease in morning pre-dose FEV_1 ≥20% from the Visit 3 (randomization visit) morning pre-dose FEV_1 or a decrease to <65% of predicted normal value,
2. The use of ≥8 actuations of albuterol/salbutamol per day on 3 or more days within any period of 7 consecutive days following randomization,
3. A decrease in morning PEF ≥20% from baseline (defined as the mean of all values from the 7-day period immediately preceding Visit 3 [randomization visit]) on 3 or more days within any period of 7 consecutive days after randomization,
4. Two or more nights with an awakening due to asthma, which required the use of reliever medication within any period of 7 consecutive days after randomization,
5. A clinical exacerbation requiring emergency treatment, hospitalization, or use of an asthma medication not allowed by the study protocol.

An electronic diary (eDiary) collected information from patients daily. If any of the criteria 2 through 4 were fulfilled, the eDiary provided a message to patients to call the study center and also sent an indicator to the study center that the patient met criteria for a pre-defined asthma event. All patients meeting criteria 1, 2, 3, or 5 were to be withdrawn. If the pre-defined event was based solely on criterion 4, the investigator had the discretion to decide whether the patient was clinically stable enough to continue in the study. Withdrawal criteria also included voluntary discontinuation, investigator discretion, clinically significant AEs, severe noncompliance, and loss to follow-up.

The primary outcome measure was change from baseline (mean of last 7 days of run-in) to treatment average in pre-dose morning peak expiratory flow (PEF). Change from baseline was analyzed with an ANCOVA model including terms for treatment, age group (<8 years and ≥8 years of age) and country, with baseline morning PEF as a covariate. In addition, analysis was

performed on the patient's change from baseline to their average value at the end of treatment (average of the last 7 available treatment days).

The key secondary endpoint was change from baseline (last available pre-dose value) to treatment average in pre-dose FEV_1, with multiplicity addressed by a step-down procedure provided that the treatment difference for the primary variable reached a statistical significance of 0.05 level.

Pharmacokinetic evaluations were not performed as part of this trial.

There were four protocol amendments, only one of which was instituted after enrollment began (Amendment 4 on November 30, 2011). This amendment was instituted because of slow enrollment into the trial. It clarified and streamlined the inclusion and randomization criteria to make it somewhat easier to enroll patients. Review shows that the changes to be acceptable.

Table 75. D589GC00001. Investigational products used in the trial

Investigational product	Dosage form and strength	Manufacturer	Batch number
Budesonide 80	HFA pMDI with AC, budesonide 80 mcg	AstraZeneca	10-002604AZ 2000164C00 2000122C00
Placebo	HFA pMDI with AC	AstraZeneca	10-002365AZ 3000447C00 3000319E00
AC=actuation counter; DPI=Dry powder inhaler; HFA=hydrofluoroalkane; pMDI=pressurized metered dose inhaler.			

Source: CSR, T2, p33

8.3.3.2 Results

8.3.3.2.1 Disposition and Analysis Sets

Patient disposition for the study is shown in Table 76. A total of 304 patients were randomized and treated (152 to each treatment group), 24 in Bulgaria, 112 in Hungary, 17 in Latvia, 25 in Poland, 5 in Slovakia, 11 in South Africa, and 110 in the United States. Since the numbers of patients randomized and treated were the same, the ITT and Safety populations (analysis sets) were the same.

Of the randomized patients, 213 (70.1%) patients completed the study and 91 (29.9%) withdrew from treatment, 31 (20.4%) and 60 (39.5%) in the budesonide and placebo treatment groups, respectively. This imbalance in withdrawals was primarily due to development of protocol-specified, pre-defined asthma event criteria that mandated withdrawal from treatment, which occurred in 73 (24%) patients overall, 25 (16.4%) and 48 (31.6%) in the budesonide and placebo treatment groups, respectively. The imbalance in withdrawals is shown graphically in Figure 23. Withdrawal due to a pre-defined asthma event was both a secondary efficacy outcome measure and a safety outcome, and is discussed the section below.

Table 76. D589GC00001. Patient Disposition

Disposition	Budesonide MDI 160 BID	Placebo	Total
Screened			1361
Received run-in			520
Randomized	152	152	304

Disposition	Budesonide MDI 160 BID	Placebo	Total
Received treatment	152 (100%)	152 (100%)	304 (100%)
Completed study	121 (79.6%)	92 (60.5%)	213 (70.1%)
Discontinued	31 (20.4%)	60 (39.5%)	91 (29.9%)
Subject decision	1 (0.7%)	4 (2.6%)	5 (1.6%)
Severe non-compliance	2 (1.3%)	0	2 (0.7%)
Asthma withdrawal criteria	25 (16.4%)	48 (31.6%)	73 (24.0%)
Other	3 (2.0%)	8 (5.3%)*	11 (3.6%)
*2 patients in the Placebo group (E1211003 and E1861011) had pre-defined asthma events, but their primary reason for withdrawal was given as Other. The study report notes that, in retrospect, neither of these patients should have been randomized as they did not meet the FEV_1 criteria at Visit 3.			

Source: CSR, T6, p52; T1.11.1, p 101

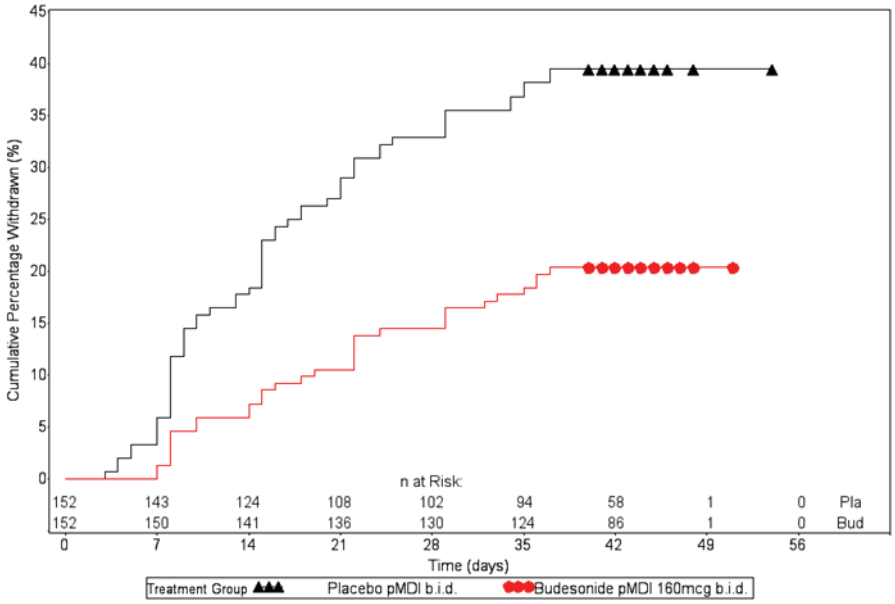

Figure 23. D589GC00001. Time to withdrawal (ITT)

Source: CSR, F2, p54

8.3.3.2.2 Demographic and baseline characteristics

Demographic and baseline characteristics of the treatment groups were similar (Table 77). The majority of patients were White (88.8%), with a mean age of 9.0 years of age (range 6 to 11 years), and 78.3% were ≥8 years of age. The two arms appeared well balanced, and the patient population appeared to be representative of the target study population of pediatric patients with asthma who need ICS controller therapy.

Table 77. D589GC00001. Demographic and key baseline characteristics (ITT)

Demographics / Baseline	Budesonide MDI 160 BID N=152	Placebo N=152	Total N=304
Sex (n, %)			
Male	98 (64.5)	94 (61.8)	191 (63.2)
Female	54 (35.5)	58 (38.2)	112 (36.8)

Demographics / Baseline	Budesonide MDI 160 BID N=152	Placebo N=152	Total N=304
Race (n, %)			
Caucasian	132 (86.8)	138 (90.8)	270 (88.8)
Black	13 (8.6)	7 (4.6)	20 (6.6)
Asian	1 (0.7)	0	1 (0.3)
Other	6 (3.9)	7 (4.6)	13 (4.3)
Ethnicity (n, %) (partial listing)			
Hispanic	11 (7.2%)	10 (6.6%)	21 (6.9%)
African American	9 (5.9%)	7 (4.6%)	16 (5.3%)
Native Hawaiian / Pacific Islander	0	1 (0.7%)	1 (0.3%)
Asian	2 (1.3%)	0	2 (0.7%)
Age group, Mean (yr)			9.0
6-8y (n, %)	57 (18.8)	63 (20.7)	120 (39.5)
9-11y (n, %)	95 (31.3)	89 (29.3)	184 (60.5)
Medication use at entry (n, %)			
ICS	140 (92.1)	130 (85.5)	270 (88.8)
LTRA	19 (12.5)	23 (15.1)	42 (13.8)
Baseline (Visit 3 [randomization], pre-bronchodilator) (mean, SD)			
FEV_1 (L)	1.69 (0.39)	1.70 (0.42)	1.70 (0.40)
FEV_1 % predicted	78.6 (7.4)	79.0 (6.4)	78.8 (6.9)

Source: CSR, T10, p58; T11.1.12, p138-9; T11.1.13, p140, Response to IR of 10/28/2016.

8.3.3.2.3 Concurrent Medications

Review of concurrent medications during treatment showed reasonably similar use patterns across the treatment groups, and review of the diary compliance data showed similar treatment compliance across the treatment groups.

8.3.3.2.4 Withdrawals due to pre-defined asthma events

As noted previously, to assure an ethical trial, the protocol pre-defined escape (i.e., mandated withdrawal) criteria should placebo (or budesonide) treated patients develop asthma symptoms over the course of 6 weeks of treatment in the trial. As it turned out, development of one or more of the pre-defined asthma withdrawal criteria was by far the most common reason for withdrawal from treatment, with an imbalance in these events between the two treatment groups that favored the budesonide arm (Table 78):73 (24%) patients overall, 25 (16.4%) in the budesonide treatment group, and 48 (31.6%) in the placebo treatment group. The Kaplan-Meier plot of the time to withdrawal due to a pre-defined asthma event visually depicts this imbalance over the course of the study (Figure 24). The number of withdrawals due to a pre-defined asthma event was both a secondary efficacy outcome measure and a safety outcome. To deal with withdrawals, the SAP specified LOCF methodology for the primary and key variables.

Table 78. D589GC00001. Withdrawals due to pre-defined asthma events (ITT)

	Budesonide MDI 160 BID N=152	Placebo N=152
Number of pre-defined asthma events [a]	35	63
Number of patients with at least one pre-defined asthma event [b]	33 (21.7%)	61 (40.1%)
Number with 1 event	32 (21.1%)	59 (38.8%
Number with 2 events	0	2
Number with 3 events	1	0
Maximum number of events/patient	3	2
Number of withdrawals due to a pre-defined asthma event	25 (16.4%)	50 (32.9%)
Number withdrawing with 1 event	25 (16.4%)	50 (32.9%)
Maximum Number of events/patient	1	1

a Patients may have multiple pre-defined asthma events.
b Patients may also have an asthma event and not be withdrawn from the study.

Source: CSR, T22, p78

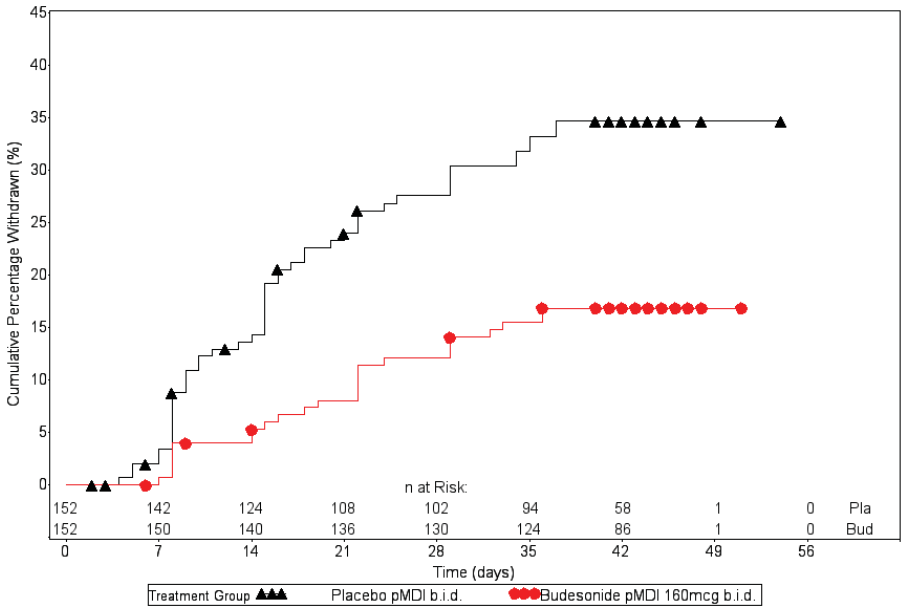

Figure 24. D589GC00001. Kaplan-Meier plot of the time to withdrawal due to a pre-defined asthma event (efficacy analysis set)

Source: CSR, F5, p80

8.3.3.2.5 Efficacy

This trial evaluated AstraZeneca's proposal to extend the approved dosage of budesonide in the Symbicort 80/4.5 dosage strength to children 6-11 years of age. Treatment differences between the budesonide and placebo arms were significant for the primary endpoint of change from baseline in morning PEF (Table 79 and Figure 25) and the key secondary endpoint of change from baseline in morning FEV_1 (Table 79 and Figure 26). Secondary endpoints were numerically supportive, including evening PEF, daytime and nighttime asthma symptom scores,

nighttime awakenings (both total and awakenings when a rescue medication was used), daily rescue medication use, and withdrawals due to pre-defined asthma events.

Table 79. D589GC00001. Primary and key secondary efficacy results (ITT)

Treatment Group	Baseline Mean (SD)	Change from Baseline LS Mean (SE)	Treatment Difference		
			LS Mean (SE)	95% CI	p-value
Primary: AM PEF(L/min)*					
Budesonide 160 BID (n=151)	205.2 (58.7)	17.8 (3.2)	13.6 (3.1)	7.5, 19.8	<0.0001
Placebo (n=151)	207.5 (67.5)	4.1 (3.2)			
Key Secondary: FEV_1 (L)*					
Budesonide 160 BID (n=152)	1.69 (0.39)	0.06 (0.023)	0.06 (0.022)	0.02, 0.11	0.0047
Placebo (n=149)	1.71 (0.42)	0.00 (0.023)			
Secondary endpoints					
Evening PEF (L/min)					
Budesonide 160 BID (n=151)	217.2 (61.2)	14.7 (3.1)	10.8 (3.0)	4.9, 16.7	
Placebo (n=150)	221.0 (66.8)	4.0 (3.1)			
Daytime asthma symptom scores					
Budesonide 160 BID (n=152)	1.3 (0.56)	-0.4 (0.06)	-0.2 (0.06)	-0.31, -0.09	
Placebo (n=151)	1.3 (0.57)	-0.2 (0.06)			
Nighttime asthma symptom scores					
Budesonide 160 BID (n=152)	1.1 (0.63)	-0.4 (0.06)	-0.01 (0.06)	-0.26, -0.04	
Placebo (n=152)	1.2 (0.64)	-0.3 (0.06)			
Nighttime awakenings (%)					
Budesonide 160 BID (n=151)	23.3 (30.5)	-14.5 (1.8)	-4.7 (1.8)	-8.2, -1.1	
Placebo (n=150)	20.7 (28.4)	-9.8 (1.8)			
Daily reliever use (inh/day)					
Budesonide 160 BID (n=152)	1.3 (1.7)	-0.7 (0.1)	-0.5 (0.1)	-0.7, -0.2	
Placebo (n=151)	1.4 (1.6)	-0.3 (0.1)			

* n=number of patients in the analysis set with data available for the analysis. Results are based on the treatment period average, which was defined as the mean value across all available on-treatment days (PEF) or visits (FEV1).
Change from baseline to endpoint was analyzed using an analysis of covariance (ANCOVA) model with terms for treatment, age group (<8 years and ≥8 years of age) and country with baseline as a covariate. Baseline was defined as the mean of the last 7 available days of the run-in period (PEF) or the latest non-missing assessment prior to the first randomized dose (FEV1).
Asthma symptom scores range from 0-3 (0=None, 1=Mild, 2=Moderate, 3=Severe).

E1002005 (Placebo) and E1870002 (Budesonide) had no morning and evening PEF or FEV1 captured in the eDiary.

Source: CSR, T12, p 64; T13, p65;T14, p68; T15, p69; T16, p 70; T11.2.1.1.1, p 198; T19, p73 ; T11.2.1.3.1, p374-5; T20, p75; T11.2.1.4.1, p; T21, p76; T11.2.1.5.1, p483

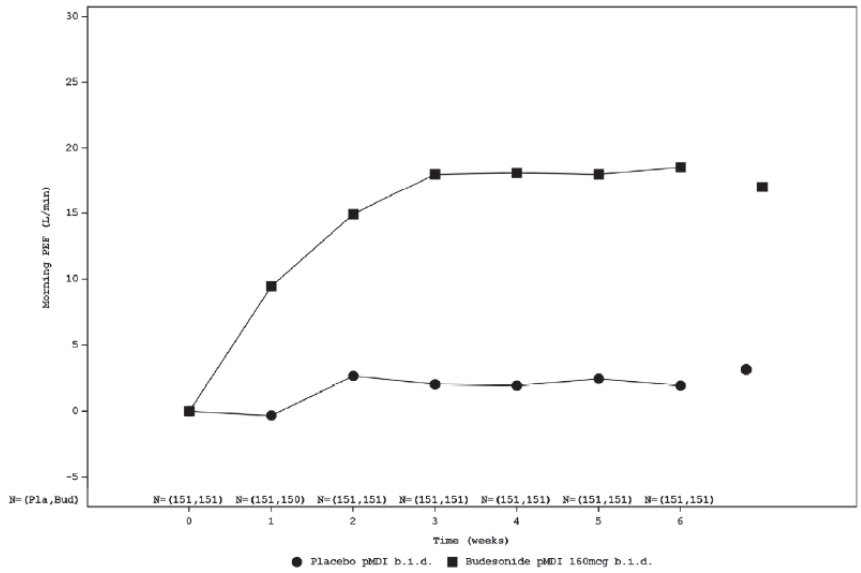

Figure 25. D589GC00001. Change from baseline in morning PEF weekly means (LOCF) (ITT)
Source: CSR, F3, p63

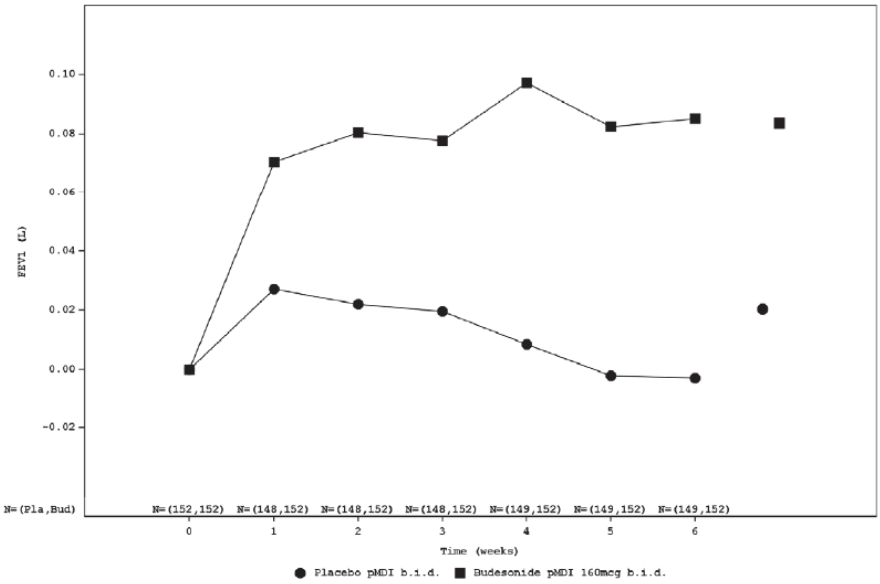

Figure 26. D589GC00001. Change from baseline in pre-dose FEV_1 at clinic visits (LOCF) (ITT)
Source: CSR, F4, p67

8.3.3.2.6 Safety

Consistent with differences in withdrawals between the two arms, the mean duration of exposure in the budesonide arm was slightly longer, 38 (SD 10.6, range 6 to 51) days for the budesonide treatment arm compared with 32 (SD 14.8, range 2 to52) days for the placebo treatment arm.

Adverse Events

There were no deaths or serious adverse events (SAEs). However, there were differences in the number of AEs (64 budesonide, 89 placebo), number of patients with an AE (44 [28.9%] budesonide, 62 [40.8%] placebo) (Table 80) as well as number of AEs leading to discontinuation

(3 budesonide, 13 placebo) (Table 81). Except for nasopharyngitis (more frequent in budesonide arm), the number and percent of patients with adverse events with a frequency of ≥2% were similar or numerically favored budesonide treatment (Table 80). As with discontinuations, these results are both consistent with events that typically occur in this age group as well as consistent with an enrolled population that needed maintenance controller therapy to maintain asthma control.

Table 80. D589GC00001. Adverse events by PT, frequency ≥2% (Safety)

Number and percent of patients with adverse events, by Preferred Term	Budesonide MDI 160 BID N=152	Placebo N=152
Patients with any AE (n, %)	44 (28.9%)	62 (40.8%)
Nasopharyngitis	12 (7.9%)	9 (5.9%)
Pharyngitis	5 (3.3%)	8 (5.3%)
Asthma	1 (0.7%)	11 (7.2%)
Viral upper respiratory tract infection	3 (2.0%)	8 (5.3%)
Influenza	4 (2.6%)	4 (2.6%)
Oropharyngeal pain	3 (2.0%)	4 (2.6%)
Epistaxis	1 (0.7%)	3 (2.0%)
Sinusitis	1 (0.7%)	3 (2.0%)
Cough	0	3 (2.0%)
Based on MedDRA version 15.1		

Source: CSR, T26, p86

Table 81. D589GC00001. Adverse events leading to discontinuation (Safety)

Adverse events leading to discontinuation, by SOC and PT	Budesonide MDI 160 BID N=152	Placebo N=152
Patients with at least 1 DAE (n, %)	3 (0.2%)	13 (8.6%)
Infections and infestations	2 (1.3%)	2 (1.3%)
Nasopharyngitis	1 (0.7%)	1 (0.7%)
Lower respiratory tract infection	1 (0.7%)	0
Viral upper respiratory tract infection	0	1 (0.7%)
Respiratory, thoracic, and mediastinal disorders	1 (0.7%)	11 (7.2%)
Asthma	1 (0.7%)	11 (7.2%)

Source: CSR, T27, p88

Laboratory parameters

Clinical laboratory evaluations were not performed as part this trial.

Vital signs, ECGs, Physical examinations

ECGs were not performed as part of this trial. Shifts in vital signs and physical examination parameters were reviewed, and except for abnormal in respiratory examinations (budesonide 5.4%, placebo 16.3%), no clinically relevant differences were noted.

8.3.3.3 Conclusions

This was a 6-week, randomized, double-blind, parallel-group, placebo-controlled, efficacy and safety trial that tested whether inhaled budesonide 160 mcg twice daily (administered as 2 inhalations from a HFA-propelled MDI that delivers an 80 mcg ex-actuator dose, which is similar to the ex-actuator dose of budesonide delivered by Symbicort 80/4.5) was safe and effective in asthma patients 6-11 years of age who demonstrated the need for ICS controller therapy. The results support AstraZeneca's proposal to use 80 mcg of budesonide, as delivered by the Symbicort 80/4.5 dosage strength, in children 6-11 years of age with asthma who are in need of combination ICS/LABA therapy.

8.3.4 Study D589GC00002 (CHASE 2)

Protocol #:	D589GC00002
ClinicalTrials.gov Identifier	NCT01136655
Title:	A Phase 2, randomized, blinded, 5-period cross-over, placebo and active-controlled, multicenter, dose-finding study of single doses of formoterol 2.25 µg, 4.5 µg, and 9 µg delivered via Symbicort pMDI and Foradil® Aerolizer® 12 µg evaluating the bronchodilating effects and safety in children, ages 6 to <12 years, with asthma who are receiving background treatment with budesonide pMDI 160 µg BID
Study Dates:	First patient enrolled: October 7, 2010 Last patient last visit: January 3, 2012
Sites:	19 centers in the United States
IRB:	A listing of Institutional Review Boards (IRB) was provided.
Ethics:	The study report states that the study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements and the AstraZeneca policy on Bioethics.
Source references:	D589GC00002 Clinical Study Report.pdf, submitted July 28, 2016

8.3.4.1 Protocol

This was a multicenter, randomized, active- and placebo-controlled, 5-way cross-over study that compared the bronchodilatory effect of single doses of 2.25, 4.5, and 9 mcg of inhaled formoterol given via Symbicort, Foradil Aerolizer 12 mcg, and placebo, given in combination with budesonide MDI 160 mcg, in pediatric patients with asthma. Inclusion criteria included patients with a documented history of asthma (ATS criteria) for at least 6 months requiring ICS, pre-bronchodilator FEV_1 between 60 and 85% of predicted, and reversibility of FEV_1 of ≥15% within 15-30 minutes after 180-360 mcg (2-4 inhalations) of albuterol. Patients were excluded if they had been on systemic corticosteroids during the run-in, had a respiratory or other infection, or had been hospitalized or received treatment in an emergency department for acute asthma during the run-in period.

Note that investigational versions of 1) Symbicort HFA 80/2.25 that delivers an ex-actuator dose of 80 mcg of budesonide and 2.25 mcg of formoterol fumarate, 2) Budesonide HFA 40 MDI that delivers an ex-actuator dose of 40 mcg of budesonide, and 3) Budesonide HFA 80 MDI that delivers an ex-actuator dose of 80 mcg of budesonide were used in this study. These products are identical to Symbicort, but with the amount of active changed to adjust the dose. Use of these products in the trial was supported by *in vitro* data submitted to the application. See Section 4.1 for details.

The study consisted of a screening visit (Visit 1), an enrollment visit (Visit 2), a 1- to 2-week run-in (standardization) period, a randomization visit (Visit 3), and 4 further visits separated by approximately 7-day (minimum 3 days; maximum 14 days) wash-out (stabilization) periods. For each patient, the total study duration was approximately 4 to 8 weeks, depending upon the length of the wash-out periods.

Withdrawal criteria included failure to meet the criterion to maintain less than 12% variation from the pre-dose, baseline FEV_1 measurement obtained at the reversibility visit, or failure to have met the inclusion or exclusion criteria for the study. Serial spirometry at a visit was terminated early if a patient's FEV_1 dropped to <50% of predicted, or if the investigator considered the patient to be at risk. However, early termination of spirometry did not mandate withdrawal, and patients remained at the clinic to complete a 12-hour urine sample.

All of the Symbicort, budesonide, and placebo treatments were blinded, whereas the Foradil treatment arm was partially blinded. Each of the devices was primed by study personnel, following which all treatments were delivered as 3 inhalations from a combination of devices such that all formoterol doses were administered on top of a background of 160 mcg of budesonide. To achieve this, the dosing schema shown in Table 82 below was used. To achieve the formoterol 2.25 and 4.5 doses, one or two inhalations of Symbicort HFA 80/2/25 were used. To achieve the formoterol 9 mcg dose, two inhalations of the approved Symbicort 80/4.5 were used. As a result, the only dose of formoterol that was not achieved by administering two inhalations of a test product was the lowest 2.25 mcg dose. Stated in another way, two inhalations of the unapproved Symbicort 80/2.25 product rather than one inhalation of the approved Symbicort 80/4.5 product was used to achieve the formoterol 4.5 dose. This is acceptable, since inter-dose variability is minimized by using two rather than one inhalation from a drug product, which is why the recommended dosage of Symbicort is always two inhalations of a particular dosage strength per given dose.

The primary efficacy endpoint was the average FEV_1 over the 12 hours of serial FEV_1 measurements (FEV_1 AUC0-12h). The primary endpoint was assessed using an ANCOVA model appropriate for a crossover design, adjusting for the fixed factors of patient, period, and treatment, and for the covariate of pre-dose FEV_1.

There were no protocol amendments for this trial. The SAP was amended once, but prior to unblinding.

Table 82. D589GC00002. Dosing schema

Formoterol Dose	Budesonide Dose	Product	Number of Inhalations
Formoterol 2.25	Budesonide 160	Symbicort 80/2.25 Budesonide HFA 40	1 inhalation 2 inhalations
Formoterol 4.5	Budesonide 160	Symbicort 80/2.25 Placebo	2 inhalations 1 inhalation
Formoterol 9	Budesonide 160	Symbicort 80/4.5 Placebo	2 inhalations 1 inhalation
Placebo	Budesonide 160	Placebo Budesonide HFA 80	1 inhalation 2 inhalations
Foradil 12	Budesonide 160	Foradil 12* Budesonide HFA 80	1 inhalation 2 inhalations
*Partially blinded			

Table 83. D589GC00002. Investigational products used in the trial

Investigational product	Dosage form and strength	Manufacturer	Batch number
Budesonide/formoterol 80/4.5	Approved Symbicort HFA pMDI with AC, budesonide 80 mcg / formoterol fumarate dihydrate 4.5 mcg	AstraZeneca	2000097D00 2000105D00 2000125D00 2000091G00
Budesonide/formoterol 80/2.25	HFA pMDI with AC, budesonide 80 mcg / formoterol fumarate dihydrate 2.25 mcg	AstraZeneca	10-002603AZ 10-002603AZ 5000002C00
Budesonide 80	HFA pMDI with AC, budesonide 80 mcg	AstraZeneca	10-002604AZ 10-002604AZ 2000122C00
Budesonide 40	HFA pMDI with AC, budesonide 40 mcg	AstraZeneca	10-002584AZ 10-002584AZ 1000014C00
Placebo	HFA pMDI with AC	AstraZeneca	10-002586AZ 10-002586AZ 3000319E00
Foradil Aerolizer	US-approved budesonide 90 mcg DPI	Merck	S0226, S0256AB, F8002, S0226
AC=actuation counter; DPI=Dry powder inhaler; HFA=hydrofluoroalkane; pMDI=pressurized metered dose inhaler.			

Source: CSR, T2, p23

8.3.4.2 Results

8.3.4.2.1 Disposition, Analysis Sets, Demographics and Baseline Characteristics

A total of 54 patients were randomized, and 50 completed all treatments. The 4 withdrawals were due to patient/caregiver decision (n=2), and adverse events (n=2) of sinusitis/asthma (n=1) and headache (N=1).

Seven (13%) of the randomized patients had protocol deviations, of whom 3 (5.6%) were excluded from the Per Protocol population (n=51) because the violations were judged to be important protocol deviations (failed to meet FEV_1 entry criteria of 60-85% predicted = 1, failed 15% reversibility criteria = 1, incorrect dose administered = 1).

Since all treatments were administered under supervision of study personnel, treatment compliance was not an issue.

Demographics of the study population are shown in Table 84. The study population was reasonably representative of pediatric patients with asthma and covered the entire age group.

Table 84. D589GC00002. Demographics

Demographics / Baseline	Randomized Patients N=54
Sex (n, %)	
Male	31 (57.4)
Female	23 (42.6)
Age, Mean (yr)	9.2 (1.8)
6-7y (n, %)	11 (20.4)
8-11y (n, %)	43 (79.6)
6-8y (n, %)	17 (31.5)
9-11y (n, %)	37 (68.5)
Race (n, %)	
White	31 (57.4)
Black	22 (40.7)
Other	1 (1.9)
Ethnicity (n, %)	
Hispanic	9 (16.7)
African American	21 (38.9)
Not Applicable	24 (44.4)

Source: CSR, T9, p37; T11.1.2; Response to IR of 10/28/16

8.3.4.2.2 Efficacy and Pharmacokinetics

The primary variable was the FEV_1 averaged over 12 hours post-dosing. Mean change from baseline in FEV_1 over time curves are shown in Figure 27, and results for the mean 12-hour FEV_1 along with treatment comparisons for average 12-hour FEV_1 and end of the 12^{th} hour FEV_1 for the formoterol 9, 4.5 and 2.25 mcg arms vs placebo, are shown in Table 85. The figure visually demonstrates the benefit of the 4.5 mcg dosage over the 2.25 mcg dosage across all time points, with an additional modest benefit of the 9 mcg compared with the 4.5 mcg dosage, both in peak FEV_1 and the length of time that bronchodilation is maintained. Treatment comparisons in the table confirm what is shown in the figure. Thus, the main benefit of the 9 mcg dosage over the 4.5 mcg dosage is bronchodilation that is maintained over a longer period such that the FEV_1 at the end of 12 hours is numerically higher after the 9 mcg dosage than the 4.5 mcg dosage. Note that, on the basis of this study, AstraZeneca is proposing a dosage of 9 mcg, to be achieved by two inhalations of the Symbicort 80/4.5 dosage strength. The FEV_1 results in this study support their proposal.

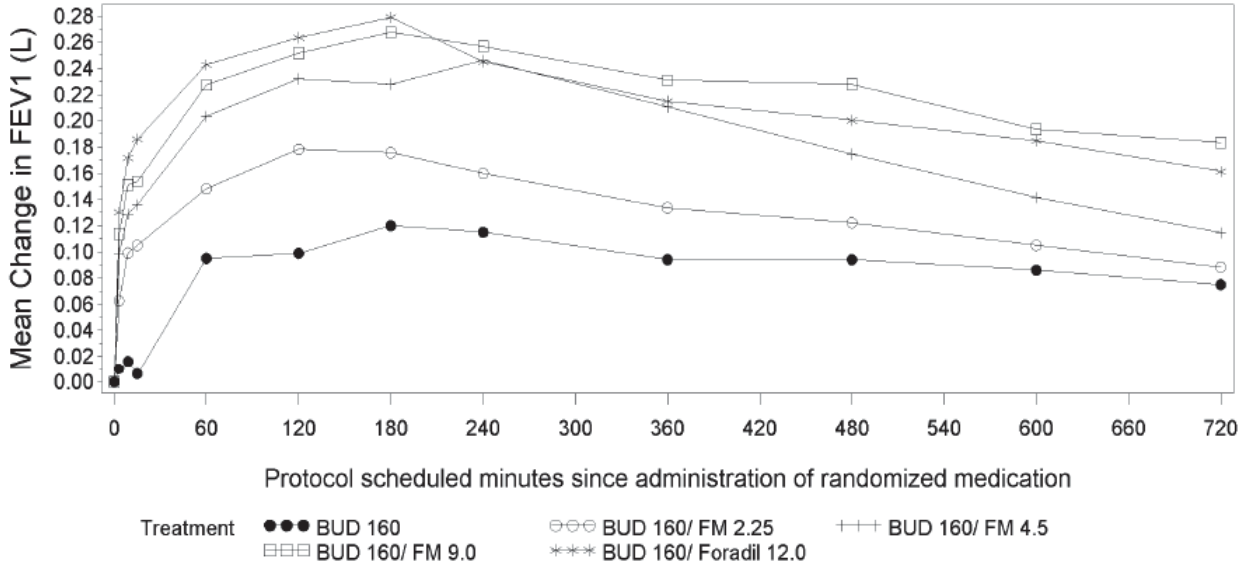

Figure 27. D589GC00002. Mean change from baseline in FEV_1 over time (ITT)

Source: CSR, Figure 3, p 44

Table 85. D589GC00002. Mean 12-hour FEV_1 and treatment comparisons for 12-hour and at 12th hour FEV_1

Treatment	12-hour FEV_1 (L)		Treatment Comparisons vs Bud 160	
	LS Mean (SE)	95% CI	12-hour FEV_1 (L)	FEV_1 at 12th hour
Bud 160	1.489 (0.0101)	1.469, 1.509		
Bud 160 / FM 2.25	1.546 (0.0097)	1.527, 1.566	0.058 (0.030, 0.085)	0.015 (-0.035, 0.065)
Bud 160 / FM 4.5	1.594 (0.0099)	1.575, 1.614	0.105 (0.078, 0.133)	0.066 (0.017, 0.116)
Bud 160 / FM 9.0	1.603 (0.0099)	1.584, 1.622	0.114 (0.087, 0.142)	0.105 (0.056, 0.155)
Bud 160 / Foradil 12.0	1.603 (0.0101)	1.583, 1.623	--	--
Bud = budesonide, FM = formoterol				

Source: CSR, T13, p45;T14, p46; T15, p48

During the study, systemic exposure to formoterol was evaluated by measurement of unchanged formoterol in post-dose 12-hour urines following each dose. Mean urinary formoterol excretion increased with increasing dose, except that urinary excretion of formoterol was higher after a 9 mcg dosage administered via Symbicort than after 12 mcg administered via Foradil: 2.25 mcg = 278 pmol; 4.5 mcg = 532 pmol; 9 mcg = 1091 pmol; 12 mcg = 860 pmol. The results suggest dose proportionality for the MDI treatments.

However, there were some expected findings in the study. Six (12%) patients in the Foradil 12 mcg treatment arm unexpectedly did not have measurable urinary formoterol levels after receiving Foradil, and repeat PK analyses confirmed these findings. The study report noted that the used inhalers were inspected and for all but one inhaler it was clearly evident that the inhalers had been used, i.e., empty capsules and/or powder residue inside the device. As a result, the

reason for why these patients did not have measurable formoterol levels is not known, although AstraZeneca postulates that it could have been the result of poor inhalation technique (e.g., failing to exhale prior to inhalation or exhaling through the device) or inadequate inspiratory flow. However, there are also reports in the literature that have noted several potential errors that can lead to failure to receive a dose via Aerolizer. These include failure of the capsule to rotate in the inhalation chamber, the piercing needle may get stuck in the capsule, the capsule may get stuck in the chamber during inhalation, or the capsule may be inadequately pierced or completely crushed by the needle.[v] Excluding these patients, the mean formoterol level for the 12 mcg treatment arm was 980 pmol, the mean average 12-hour FEV_1 increased from 1.603 L to 1.619 L, maximum FEV_1 increased from 1.892 L to 1.910 L, and FEV1 at 12 hours increased from 1.709 L to 1.710 L. Thus, exclusion of these 6 patients did not change the overall results. [CSR, p54, p74]

However, additional PK analyses also revealed that 3 patients had measurable urinary formoterol levels after placebo treatment, two of whom had very low levels and one had no measurable level on re-testing. These findings were not explained in the study report.

8.3.4.2.3 Safety

Adverse Events

There were no deaths or SAEs in this trial. Two patients had AEs that led to discontinuation on the day of treatment, one each in the formoterol 2.25 (acute sinusitis and asthma) and 9 mcg (headache) dosing arms. Review of the AE tables did not reveal any AEs of concern, although 5 patients in the formoterol 9 mcg arm experienced headaches (compared with 1, 1, 2, and 0 in the 4.5, 2.25, placebo, and Foradil 12 mcg treatment arms, respectively).

Laboratory parameters

Clinical laboratory evaluations were not performed as part this trial.

Vital signs, ECGs, Physical examinations

ECGs were not performed as part of this trial. Shifts in vital signs and physical examination parameters were reviewed, and except for abnormal in respiratory examinations (budesonide 5.4%, placebo 16.3%), no clinically relevant differences were noted. Since vital signs were only performed pre-dose in this trial, the information from these data are not particularly useful.

8.3.4.3 Conclusions

This was a single-dose, randomized, double-blind, placebo- and active-controlled, 5-arm crossover, pharmacodynamic trial that tested the bronchodilatory effect over 12 hours following formoterol doses of 2.25, 4.5, and 9 mcg vs placebo delivered from an investigational or approved Symbicort product, along with open-label Foradil 12 mcg, in asthma patients 6-11 years of age who demonstrated the need for ICS controller therapy, all of whom were being treated with budesonide 160 mcg. The results support AstraZeneca's proposal to use 4.5 mcg of formoterol, as delivered by the Symbicort 80/4.5 dosage strength, in children 6-11 years of age with asthma who are in need of combination ICS/LABA therapy.

8.3.5 Study D589GC00003 (CHASE 3)

Protocol #: D589GC00003

ClinicalTrials.gov Identifier	NCT02091986
Title:	A Phase 3, 12-Week, Double-Blind, Randomized, Parallel-Group, Multicenter Study Investigating the Efficacy and Safety of Symbicort pMDI 80/2.25 µg, 2 Actuations Twice Daily, and Symbicort pMDI 80/4.5 µg, 2 Actuations Twice Daily, Compared with Budesonide pMDI 80 µg, 2 Actuations Twice Daily, in Children Ages 6 to <12 Years with Asthma
Study Dates:	First patient enrolled: April 14, 2014 Last patient last visit: April 14, 2016
Sites:	The trial was conducted at 88 study centers in the USA (74 centers), Mexico (3 centers), Panama (4 centers) and Slovakia (7 centers), of which 62 centers randomized patients.
IRB:	The trial included Independent Ethics Committees (IEC)/Institutional Review Boards (IRB) in each participating country. A listing of Institutional Review Boards (IRB) was provided.
Ethics:	The study report states that the study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements and the AstraZeneca policy on Bioethics.
Source references:	D589GC00003 Clinical Study Report.pdf

8.3.5.1 Protocol

8.3.5.1.1 Study Details

This was a 12-week, randomized, double-blind, parallel-group, multicenter trial that compared the approved Symbicort 80/4.5, investigational version of Symbicort 80/2.25, and an investigational budesonide HFA 80, each administered as 2 inhalations twice daily, in children aged 6 <12 years with asthma who demonstrated the need for ICS controller therapy. The dosages of budesonide and formoterol studied in this trial were based on the results of studies D589GC00001 and D589GC00002.

Note that investigational versions of Symbicort HFA 80/2.25 that delivers an ex-actuator dose of 80 mcg of budesonide and 2.25 mcg of formoterol fumarate, and Budesonide HFA 80 MDI that delivers an ex-actuator dose of 80 mcg of budesonide were used in this study (Table 87). These products are identical to Symbicort, but with the amount of active changed to adjust the dose. Use of these products in the trial was supported by *in vitro* data submitted to the application. See Section 4.1 for details.

The study consisted of an enrollment visit (Visit 1), a run-in visit (Visit 2), a single-blind run-in period of up to 4 weeks (minimum 7 days), a randomization visit (Visit 3), a 12-week treatment period with clinic visits at Weeks 2, 4, 8 and 12 (Visits 4 to 7), and telephone follow-up to document adverse events (AEs) and concomitant medications approximately 2 weeks after the last visit to the clinic. Visits 1 and 2 could be combined for patients with no change in medications prior to the Visit 2 lung function assessments. Clinic visits were scheduled in the

morning (08:00 ±2 hours), at least 6 hours after the most recent use of a reliever medication and at least 2 hours after vigorous exercise, with all subsequent visits within ±1 hour of the initial visit, but no later than 10:00 AM. During the run-in period, asthma medications were restricted to low-dose Pulmicort Flexhaler® (AstraZeneca), a dry powder inhaler (DPI) that provides 90 mcg of budesonide per dose, administered as 1 inhalation twice daily, and albuterol/salbutamol MDI as needed.

Study inclusion criteria included patients with a documented history of asthma (ATS criteria) for at least 6 months that required medium- to high-dose ICS therapy for at least 4 weeks prior to screening, morning pre-bronchodilator FEV_1 between 60 and 100% of predicted, reversibility of FEV_1 of ≥12% after a SABA, and demonstrated ability to use the devices in the study. Patients were excluded if they had been hospitalized once or required emergency treatment more than once for an asthma-related condition within the previous 6 months; if they required systemic corticosteroids within 6 weeks; if they has a significant disease, disorder, or physical findings that could place them at risk; if they were on a beta-blocker; if they had taken omalizumab or any other monoclonal or polyclonal antibody within 6 months; if they had hypersensitivity to any of the drugs used in the study; if they had a planned hospitalization during the study; if they had a positive pregnancy test at any time during the study. Additional inclusion criteria at the randomization visit included either a combined asthma symptom score (combined nighttime and following daytime) of ≥1 or reliever medication use on at least 4 of the 7 previous consecutive days; pre-dose AM FEV_1 of at least 55% predicted at least 6 hours after a SABA and an absolute increase of ≤5% in absolute FEV_1 value during the run-in period. Additional exclusion criteria at the randomization visit included discontinuation of all asthma medications except the run-in medications, respiratory infections or other viral/bacterial illness that might interfere with ability to perform spirometry, interim treatment with systemic corticosteroids, or clinically significant ECG or laboratory screening findings.

The study included pre-defined asthma worsening criteria that mandated a clinic evaluation (but not necessarily withdrawal) if any of the following conditions were met:

- A morning eDiary PEF drop of 15% or more below baseline (for single-blind run-in period defined as morning PEF performed using the eDiary at Visit 2, and for randomization period defined as the mean of all values from the 7-day period immediately preceding Visit 3 [randomization visit]),

OR

- The patient experiences a nighttime awakening due to asthma that requires reliever medication use,

OR

- The patient takes ≥6 inhalations of albuterol/salbutamol per day for relief of asthma symptoms.

Patients were asked to withhold reliever medication use within 6 hours of a study visit, restrict vigorous exercise within 2 hours of a study visit, withhold study medication on study visit days, and perform morning and evening diary assessments prior to each dose of study drug. Patients could discontinue study drug treatment voluntarily at any time, if the patient experienced a significant or serious AE, at the investigator's discretion if the patient was seen for an unscheduled visit due to asthma, or for severe non-compliance. Patients could also voluntarily withdraw from the study at any time, after which they could not be re-enrolled or replaced.

Patients who withdrew had a final study visit similar to Visit 7, plus a follow-up telephone call 2 weeks later to ascertain AEs and concomitant medication use.

An electronic diary (eDiary) was used to capture morning and evening FEV_1 and PEF measurements, nighttime awakenings, daytime and nighttime asthma symptom scores, and daytime and nighttime reliever medication use throughout the trial.

The study flow chart is shown in Figure 28, and the overall study plan and assessments are summarized in Table 86. Eight-hour serial spirometry was performed at Week 12 (Visit 7) at pre-dose, 15 minutes, 1, 2, 4, 6, and 8 hours post-dose in a subset of patients who completed treatment (these patients were included in the exploratory analysis set), and the average post-dose FEV_1 (L) over 8 hours was calculated as the area under the curve (AUC) over the time interval.

The protocol was amended twice, once for all study centers and once for the Panama study center. Both amendments were instituted on December 19, 2014, after enrollment had begun. Review showed that most of the changes were minor and would not significantly affect the outcome of the trial. The most critical change was that the primary analysis was revised to include all clinic FEV_1 data from all subjects, regardless of discontinuation from study drug.

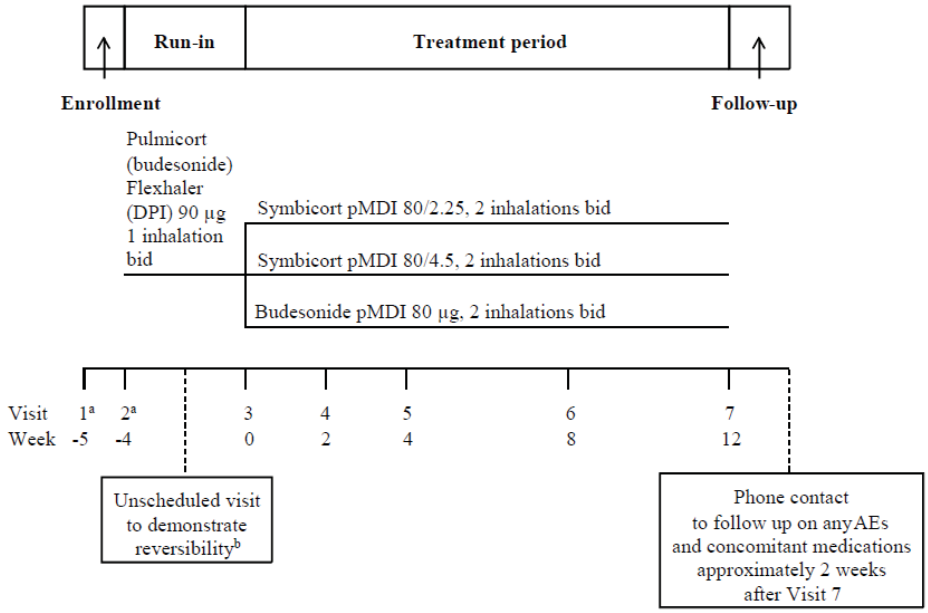

Figure 28. D589GC00003. Study flow chart
Source: CSR, F1, p17

Table 86. D589GC00003. Study plan

	Enrollment	Run-in	Treatment			Phone Follow-up	Unscheduled visits	Unscheduled reversibility test
Visit[a]	**1**[b]	**2**[b]	**3**	**4, 5, & 6**[c]	**7**[d]	**Visit 7 +2 weeks**		**2A**[e]
Week	**-5**	**-4**	**0**	**2, 4, & 8**	**12**			
Visit window (days)		**±5**	**0**	**±5**	**±5**	**±5**		
Informed consent	X							
Demography	X							
Medical history	X							
Surgical history	X							
Inclusion/exclusion criteria	X	X						
Review allowed/disallowed medication, including withholding medications prior to each visit	X	X	X	X				
Weight and height (for calculation of BMI)[f]		X			X			
Physical examination		X			X		X[g]	
Brief physical examination[h]			X	X				
Randomization criteria			X					
Randomization			X					
Study medication training[i]		X	X	X				
Run-in study medication (D=dispense, R=return)		D	R					
Randomized study medication (D=dispense, R=return)			D	D/R[j]	R			
Reliever study medication (D=dispense, R=return)		D	D/R	D/R	R[k]			
PAQLQ(S)[k]		X[l]	X[m]	X[m,j]	X[m]			
Vital signs (heart rate, blood pressure, and respiratory rate)[n]		X	X	X	X			
12-lead ECG (central)		X			X		X[o]	
Clinical chemistry (serum potassium and glucose)[p]		X			X		X[o]	
Pregnancy test (female patients who reached menarche)[q]		X	X	X	X			
Pre-bronchodilator lung function[r]		X						X
Reversibility testing		X[s]						X
Pre-dose lung function[r]			X	X	X		X[g]	
15-minute post-dose lung function[r]			X		X			
1-hour post-dose lung function[r]			X	X	X			
2-, 4-, 6-, and 8-hour post-dose lung function [r,t]					X			
Dispense home spirometry equipment		X						

	Enrollment	Run-in	Treatment			Phone Follow-up	Unscheduled visits	Unscheduled reversibility test
Visit[a]	**1[b]**	**2[b]**	**3**	**4, 5, & 6[c]**	**7[d]**	**Visit 7 +2 weeks**		**2A[e]**
Week	**-5**	**-4**	**0**	**2, 4, & 8**	**12**			
Visit window (days)		**±5**	**0**	**±5**	**±5**	**±5**		
Dispense diary and instruct on completion		X						
Diary review[u]			X	X	X		X[g]	
Adverse events		X	X	X	X	X	X[g]	X
Concomitant medications	X[v]	X	X	X	X	X	X[g]	

a Visits were held in the morning (8:00 ±2 hours).
b Visits 1 and 2 could have been combined for those patients who did not need to withhold/change medication prior to Visit 2 lung function assessments.
c If the patient discontinued randomized study medication since the previous study visit, refer to Section 5.8.1 of the CSP (Appendix 12.1.1) for instructions on the assessments that were performed.
d Patients who were withdrawn from the study had a study visit equivalent to the Visit 7 assessments.
e Was to be scheduled after Visit 2, but before Visit 3. The patient's morning dose of run-in medication was not be withheld on the day of the visit.
f Performed with indoor clothing and without shoes.
g These study procedures were performed when an unscheduled visit was done for pre-defined worsening of asthma or for parent/guardian concern about his/her child's asthma. The patient did not need to withhold his/her morning dose of asthma maintenance medication or SABA on the day of the visit. Lung function testing at the visit was not required to be pre-dose.
h Brief physical examination included lung and heart auscultation and ENT exam.
i Run-in study medication training (DPI) was performed at Visit 2 and randomized study medication training (pMDI) was performed at Visit 3. Patients demonstrated their ability to use the pMDI at Visits 4, 5, and 6, with additional pMDI training performed as needed. Parents/guardians also received training and instructions (see Section 5.5.2.6 of the CSP [Appendix 12.1.1]).
j Performed at Visits 5 and 6 only.
k PAQLQ(S) were not administered to patients who attended Visit 2 prior to their seventh birthday.
l PAQLQ(S) training session held at Visit 2.
m Completed prior to other study procedures (except information collection).
n Vital signs assessed before spirometry, ECG, and clinical chemistry blood draw.
o If an ECG recording or laboratory test needed to be repeated, the patient returned to the clinic for an unscheduled visit for the assessment.
p Clinical chemistry (potassium and glucose) blood drawn after vital signs, ECG, and spirometry. Total volume = 8 mL for two samples.
q All post-menarche female patients were to have a urine pregnancy test done starting at Visit 2 and every visit thereafter. If female patients achieved menarche during the study, a urine pregnancy test was performed at the next scheduled visit and every visit thereafter. A negative urine pregnancy test result was to be obtained before performing spirometry (including reversibility), ECG, and laboratory testing at Visit 2, and prior to administration of IP at all other visits. In Panama only, serum pregnancy tests were performed instead of urine pregnancy tests and the same process was followed as described for urine pregnancy tests.
r The lung function standard panel consisted of clinic FVC (L), clinic FEV1 (L), clinic FEF25-75 (L/s), and clinic PEF (L/min).
s The reversibility assessment could be repeated once, after Visit 2, but prior to Visit 3.
t Assessed only in a subset of patients (approximately 25 patients per treatment group) who did not discontinue randomized study medication. These assessments plus the 15-minute and 1-hour post-dose assessments performed at Week 12 comprised 8-hour post-dose serial spirometry.
u Morning and evening eDiary PEF, nighttime and daytime asthma symptom scores, nighttime awakenings due to asthma symptoms, daytime and nighttime reliever medication use.
v All medication taken within 3 months prior to enrollment was recorded

Source: CSR, T1, p18-9

Table 87. D589GC00003. Investigational products used in the trial

Investigational product	Dosage form and strength	Manufacturer	Batch number
Budesonide/formoterol 80/4.5	Approved Symbicort HFA pMDI with AC, budesonide 80 mcg / formoterol fumarate dihydrate 4.5 mcg	AstraZeneca	2000244D00 (14-000052AZ) 2000291D00 (14-002814AZ) 2000291D00 (15-000247AZ) 2000291D00 (L000016)
Budesonide/formoterol 80/2.25	HFA pMDI with AC, budesonide 80 mcg / formoterol fumarate dihydrate 2.25 mcg	AstraZeneca	5000004D00 (13-002527AZ) 5000007D00 (14-002879AZ) 5000008D00 (15-000230AZ) 5000009D00 (15-001453AZ) 5000009D00 (L000027)
Budesonide 80	HFA pMDI with AC, budesonide 80 mcg	AstraZeneca	2000238C00 (13-002550AZ) 2000294C00 (14-002875AZ) 2000294C00 (15-000242AZ) 2000346C00 (L002988)
Run-In: Pulmicort Flexhaler 90 [a]	US-approved budesonide 90 mcg DPI	AstraZeneca	13-002559AZ 14-002753AZ
a Flexhaler is the registered trademark in the US for the dry powder inhaler Turbuhaler®. The trademark Turbuhaler is used outside the US and is a registered trademark of the AstraZeneca group of companies. AC=actuation counter; DPI=Dry powder inhaler; HFA=hydrofluoroalkane; pMDI=pressurized metered dose inhaler.			

Source: CSR, T2, p28

8.3.5.1.2 Endpoints and Statistical Plan

The primary efficacy variable was change from baseline (Visit 3) to Week 12 (Visit 7) in 1-hour post-dose FEV_1 (L). The efficacy analysis set included all randomized patients who took at least 1 dose of study medication and contributed at least 1 post-baseline data point (i.e., regardless of whether they remained on treatment). The primary analysis was performed using a mixed model repeated measures (MMRM) analysis assuming data missing at random (MAR) and including all 1-hour post-dose clinic FEV_1 data prior to discontinuation, with terms for treatment, age group, and country/region as factors, and with baseline FEV_1 (pre-dose at Visit 3) as a covariate.

The primary analysis included comparisons of both Symbicort 80/4.5 vs budesonide 80 and Symbicort 80/2.25 vs budesonide 80. To address multiplicity, statistical testing was done in a hierarchical manner starting with the higher formoterol dose and proceeding to the lower dose only if the comparison was statistically significant at the 0.05 significance level. Both comparisons had to win to meet the study objectives, and the study was sized accordingly. A secondary objective was to compare the two doses of Symbicort.

The sample size of 93 patients per treatment group was based on a 2-sided 5% significance level and 90% power to detect a difference in means of 0.12 L for post-dose FEV_1 at Week 12, assuming a standard deviation of 0.25 L. The estimate of variability was obtained from an AstraZeneca study previously performed in similar age group of children with asthma.

In accordance with the Agency's recommendations, patients who discontinued treatment were encouraged to remain in the study and to attend the scheduled visits, with the primary analysis \ based on all available data regardless of whether patients had discontinued treatment.

Sensitivity analyses of the primary endpoint included:

- The effect of treatment for all on-treatment data only.
- The effect of treatment incorporating all data collected during the study period, except for data recorded after patients were switched to maintenance therapy with a bronchodilator containing product (e.g., Advair®) as defined following blinded medical review.

- The effect of treatment incorporating all data collected during the study period, except for spirometry data from patients with percent predicted normal FEV_1 ≥150% at any time point, besides run-in assessments, due to values beyond the expected intrinsic variability in lung function. For this analysis, 5 patients (E7882003, E7882013, E7888001, E4902009, and E7865008) were removed.
- "Jump to the reference" analysis. The missing not at random sensitivity analysis assumes that post-withdrawal FEV_1 in patients from the Symbicort groups will immediately change to have the mean of budesonide group at the relevant time point, conditional only on baseline values (O'Kelly and Ratitch, 2014), using multiple imputation techniques.
- The effect of region was also explored by adding treatment-by-region, visit-by-region, and treatment-by-visit-by-region as interaction factors.

Secondary efficacy endpoints included the following. No adjustments for multiplicity were made, and unadjusted (nominal) p-values were reported.

- Change from baseline to treatment period average and change from baseline to Week 12 for:
  - Pre-dose and 15-minute post-dose clinic FEV_1 (L)
  - Pre-dose, 15-minute post-dose and 1-hour post-dose clinic FVC (L)
  - Pre-dose, 15-minute post-dose and 1-hour post-dose clinic FEF25-75 (L/s)
  - Pre-dose, 15-minute post-dose and 1-hour post-dose clinic PEF (L/min)
  - Morning and evening FEV_1 (L) and PEF (L/min) recorded in the eDiary
  - Nighttime, daytime, and total daily asthma symptom scores recorded in the eDiary
  - Nighttime awakenings due to asthma symptoms requiring reliever use recorded in the eDiary
  - Nighttime, daytime, and total daily reliever medication use recorded in the eDiary
  - PAQLQ[S] scores (overall and each domain)
- Time to occurrence of first protocol defined asthma exacerbation
- Time to discontinuation of treatment

An exploratory objective was to evaluate maintenance of bronchodilation over 8 hours by serial spirometry in a subgroup of patients who did not discontinue treatment during the study.

8.3.5.2 Results

8.3.5.2.1 Disposition, Discontinuations, and Analysis Sets

Patient disposition in the trial is shown in Table 88. A total of 279 patients were randomized (92 to Symbicort 80/4.5, 95 to Symbicort 80/2.25, 92 to budesonide HFA 80). However, 6 of these patients were randomized in error and did not receive treatment, 2 in each treatment group, resulting in a modified ITT (efficacy analysis) population of 273 patients who received study treatment. Of these, 249 (89.2%) completed treatment and 253 (90.7%) completed the study (85 [92.4%] Symbicort 80/4.5, 84 [88.4%] Symbicort 80/2.25, 84 [91.3%] budesonide HFA 80). One patient (E7866008 and E7809017) enrolled and was randomized twice at two different sites and time points, both times to the Symbicort 80/4.5 arm. However, only the first occurrence (E7866008) was included in the efficacy (EAS) and safety analyses sets. During the second study enrollment, the patient (E7809017) experienced 1 non-serious asthma exacerbation that started on Day 49 and lasted for 5 days.

The effect of patient disposition on powering for the primary endpoint was assessed (see Table 15), since the powering calculation was based on the assumption of randomizing and treating at

least 93 patients to each treatment group and two of the treatment groups only randomized and treated 90 patients, the powering of the study was affected. However, lowering the number of randomized and treated patients per arm to 90 would only affect the powering very slightly, changing the power to 89% to detect differences in the primary endpoint. This is not considered a clinically meaningful difference in the powering of the study, especially considering that the powering calculation took into account that two Symbicort dosages would be compared with budesonide but only the highest dose has been chosen to pursue for marketing.

In total, 24 patients (8.6%) discontinued treatment, with the proportion being about the same for all three treatment arms. However, the time to discontinuation was longer in the Symbicort 80/4.5 treatment arm (Figure 29). Only 2 patients (both in the budesonide 80 arm) withdrew due to an adverse event, with the most common reason for withdrawal being patient decision (n=15). The number of patients with an important protocol deviation was similar across treatment groups (14 [15.6%] Symbicort 80/4.5, 15 [16.1%] Symbicort 80/2.25, 15 [16.7%] budesonide HFA 80).

Table 88. D589GC00003. Patient disposition

Disposition	Symbicort 80/4.5, 2 BID	Symbicort 80/2.2.5, 2 BID	Budesonide MDI 80, 2 BID	Total
Screened				881
Received run-in				644
Randomized	92*	95	92	279
Received treatment (MITT)	90* (97.8)	93 (97.9)	90 (97.8)	273 (97.8)
Completed study	85 (92.4)	84 (88.4)	84 (91.3)	253 (90.7)
Discontinued	7 (7.6)	11 (11.6)	8 (8.7)	26 (9.3)
Adverse event	0	0	2 (2.2)	2 (0.7)
Patient decision	4 (4.3)	8 (8.4)	3 (3.3)	15 (5.4)
Lost to follow-up	1 (1.1)	0	0	1 (0.4)
Other	2 (2.2)	3 (3.2)	3 (3.3)	8 (2.9)

* Does not include one occurrence of a patient who was randomized twice (E7866008 and E7809017), once at each of two study sites, both times to Symbicort 80/4.5. Only data for the patient's first occurrence in the study is included in the tables and figures.

Source: CSR, T7, p 54-5

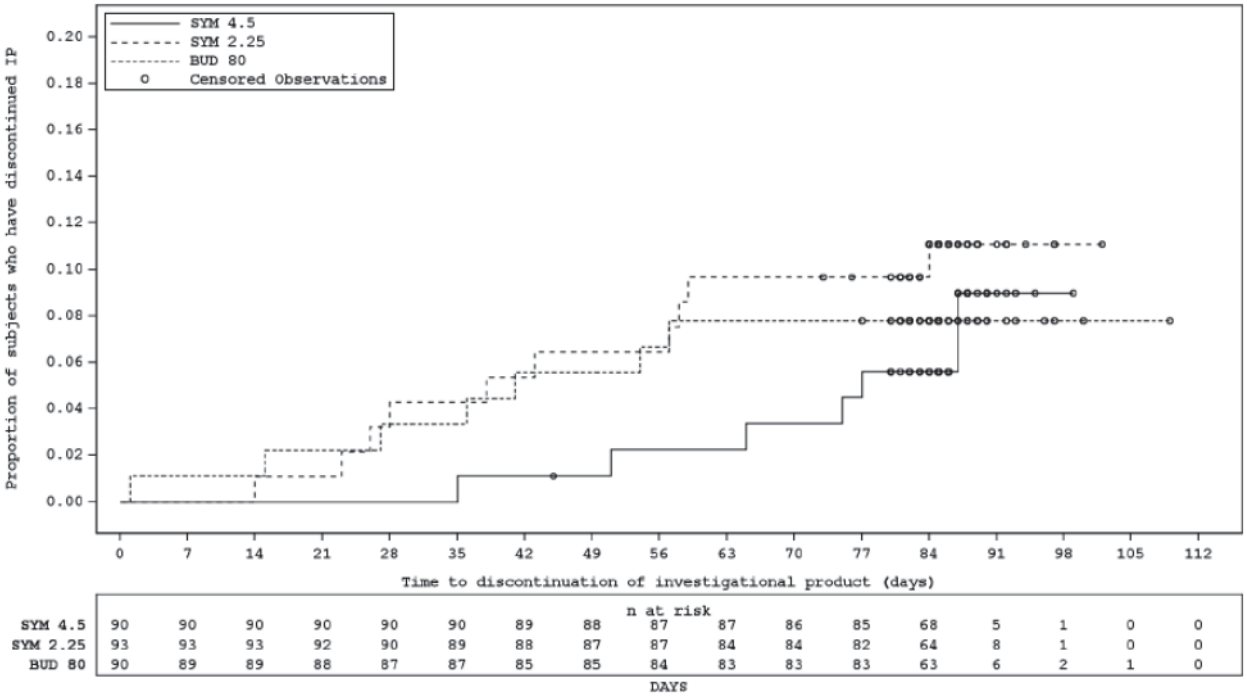

Figure 29. D589GC00003. Kaplan-Meier plot of time to discontinuation of study treatment (EAS)

Source: CSR, F20,p112

8.3.5.2.2 Demographics and Baseline Characteristics

Baseline and demographic characteristics of the treatment groups were relatively well balanced across treatment groups (Table 89), although there were small differences between the groups in the number of Whites, Hispanics, and males/females. The mean age of 9.0 years of age (range 6 to 11 years), and 65% were ≥9 years of age. The patient population appears to be representative of the target study population of pediatric patients with asthma who need ICS controller therapy.

Table 89. D589GC00003. Demographic and key baseline characteristics (ITT)

Demographics / Baseline	Symbicort 80/4.5, 2 BID N=92	Symbicort 80/2.2.5, 2 BID N=95	Budesonide MDI 80, 2 BID N=92	Total N=279	WR Target
Sex (n, %)					
Male	42 (45.7)	34 (35.8)	37 (40.2)	113 (40.5)	
Female	50 (54.3)	61 (64.2)	55 (59.8)	166 (59.5)	
Race (n, %)					
White	61 (66.3)	60 (63.2)	53 (57.6)	174 (62.4)	
Black	24 (26.1)	26 (27.4)	26 (28.3)	76 (27.2)	10-15%
American Indian or Alaska Native	2 (2.2)	3 (3.2)	3 (3.3)	8 (2.9)	
Native Hawaiian or Pacific Islander	1 (1.1)	0	0	1 (0.4)	
Asian	0	0	2 (2.2)	2 (0.7)	3%
Other	(4.3)	4 (4.2)	7 (7.6)	15 (5.4)	
Unknown	0	2 (2.1)	1 (1.1)	3 (1.1)	
Ethnic Group (n, %)					
Hispanic	38 (41.3)	36 (37.9)	32 (34.8)	106 (38.0)	20%

Demographics / Baseline	Symbicort 80/4.5, 2 BID N=92	Symbicort 80/2.2.5, 2 BID N=95	Budesonide MDI 80, 2 BID N=92	Total N=279	WR Target
Non-Hispanic	54 (58.7)	59 (62.1)	60 (65.2)	173 (62.0)	
Age group (yr),					
Mean (SD)	9 (1.6)	9 (1.6)	9 (1.4)	9 (1.5)	
6-8y (n, %)	30 (32.6)	36 (37.9)	32 (34.8)	98 (35.1)	50%
9-11y (n, %)	62 (67.4)	59 (62.1)	60 (65.2)	181 (64.9)	50%
Asthma medication use at entry (n, %)					
ICS	90 (100%)	90 (96.8%)	89 (98.9%)	269 (98.5%)	
ICS/LABA combination	27 (30.0%)	25 (26.9%)	19 (21.1%)	71 (26.0%)	
LTRA	35 (38.9%)	23 (24.7%)	24 (26.7%)	82 (30.0%)	
Baseline FEV_1 (Visit 3 [randomization], pre-bronchodilator) (mean, SD)					
FEV_1 (L)	1.58 (0.416)	1.57 (0.332)	1.62 (0.360)	1.59 (0.370)	
FEV_1 % predicted	74.5 (12.23)	75.5 (12.79)	73.8 (10.33)	74.6 (11.59)	
% Reversibility (Run-in)					
Mean (SD)	23.1 (18.5)	23.5 (14.9)	22.4 (13.1)	23.0 (15.6)	

Source: CSR, T10, p61; T11.1.8, p184-5; T11.1.9.1, p187; Attachment 1 – Justification of Efforts.pdf.

8.3.5.2.3 Concurrent Medications and Compliance

Review of concurrent medications during treatment showed reasonably similar use patterns across the treatment groups, and review of the diary compliance data showed similar treatment compliance across the treatment groups. Overall compliance rates were 82-85% and 71-76% for run-in and on-treatment medication use, respectively, and 83-86% and 79-85% for run-in and on-treatment diary use, respectively.

8.3.5.2.4 Efficacy Results

Primary Analyses

Results for the primary endpoint analysis of change from baseline (Visit 3) to Week 12 (Visit 7) in 1-hour post-dose FEV_1 (L) are shown in Table 90. The primary analysis comparing Symbicort 80/4.5 with budesonide HFA 80 was statistically significant (estimated difference 0.12 L [95% CI 0.03, 0.20; p=0.006]), whereas the comparison of Symbicort 80/2.25 with budesonide HFA 80 was numerically greater but not statistically significant (estimated difference 0.08 L [95% CI 0.00, 0.16; p=0.063]). The secondary endpoint comparison of Symbicort 80/4.5 with Symbicort 80/2.25 was numerically greater but not statistically significant (estimated difference 0.04 L [95% CI -0.05, 0.12], p=0.373). Clinic visit average change in 1-hour post-dose FEV_1 measurements over the course of the study are shown in Figure 30.

Table 90. D589GC00003. Primary efficacy results (EAS)

Treatment Group	Baseline[1] Mean (SD)	Change from Baseline[2] Mean (95%CI)	Comparison	Treatment Difference	
				Mean (95% CI)	p-value
Primary: 1-hour Post-Dose FEV_1 (L/min)					
Symbicort 80/4.5 2BID (n=90)	1.58 (0.41)	0.28 (0.22, 0.34)	Symbicort 80/4.5 vs Bud 80	0.12 (0.03, 0.20)	p=0.006
Symbicort 80/2.25 2BID (n=93)	1.58 (0.33)	0.24 (0.18, 0.31)	Symbicort 80/2.25 vs Bud 80	0.08 (0.00, 0.16)	p=0.063

Treatment Group	Baseline[1] Mean (SD)	Change from Baseline[2] Mean (95%CI)	Comparison	Treatment Difference	
				Mean (95% CI)	p-value
Budesonide 80 2BID (n=90)	1.61 (0.36)	0.17 (0.10, 0.23)	Symbicort 80/4.5 vs 80/2.25	0.04 (-0.05, 0.12)	p=0.373

1 Absolute values (descriptive statistics shown) for baseline and change from baseline. Baseline is the latest non-missing pre-dose assessment prior to first dose of investigational product (typically Visit 3, randomization)
2 Change from baseline to Week 12 (Visit7). For the primary analysis, estimates of the mean change from baseline and the comparisons between treatment groups were obtained using a repeated measures analysis, assuming data missing at random, with explanatory variables for treatment group, baseline FEV_1, region, age group, visit, and interaction term treatment-by-visit.

Source: CSR, T12, p 66-7; T13, p68; T19.

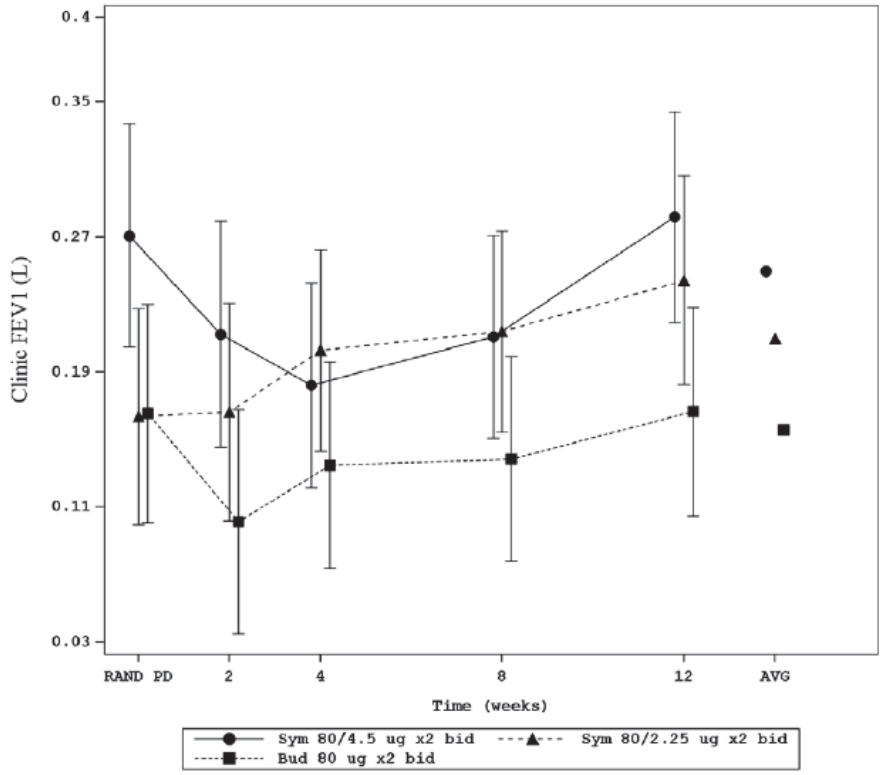

Figure 30. D589GC00003. Change in 1-hour post-dose FEV_1 (L) over time (EAS)

Source: Figure 3, p72

Secondary Analyses

Spirometric Measurements

Spirometric measurements were made at each clinic visit as well as at home twice daily and recorded in the eDiary. Results of at visit pre-dose FEV_1 and PEF measurements are shown in Table 91. Results of at home eDiary morning and evening pre-dose FEV_1 and PEF evaluations are shown in Table 92 and in Figure 31 (FEV_1) and Figure 32 (PEF).

While at visit pre-dose FEV_1 was not different for the three treatments, all other spirometric evaluations favored the Symbicort 80/4.5 dosage strength over both Symbicort 80/2.25 and Budesonide 80.

An exploratory analysis was performed in a subgroup of patients in whom FEV_1 measurements were obtained over 8 hours post-dosing at Week 12 (Figure 33). Interestingly, there were wide confidence intervals in this analysis, with significant overlap and no differences between treatment groups.

Table 91. D589GC00003. Pre-dose FEV_1 and PEF at visit evaluations (EAS)

Treatment Group	Baseline[1] Mean (SD)	Change from Baseline[2] Mean (SD)	Comparison[3]	Treatment Difference[3] Mean (95% CI)
Pre-dose FEV_1 (L/min) (at Visit)				
Symbicort 80/4.5 2BID (n=90)	1.58 (0.41)	0.11 (0.33)	Symbicort 80/4.5 vs Bud 80	0.02 (-0.07, 0.10)
Symbicort 80/2.25 2BID (n=93)	1.58 (0.33)	0.10 (0.21)	Symbicort 80/2.25 vs Bud 80	0.00 (-0.08, 0.09)
Budesonide 80 2BID (n=90)	1.61 (0.36)	0.09 (0.28)	Symbicort 80/4.5 vs 80/2.25	0.01 (-0.07, 0.09)
Pre-dose PEF (L/min) (at Visit)				
Symbicort 80/4.5 2BID (n=90)	233.94 (69.25)	29.67 (60.82)	Symbicort 80/4.5 vs Bud 80	11.72 (-3.63,27.06)
Symbicort 80/2.25 2BID (n=93)	222.25 (51.02)	19.33 (49.00)	Symbicort 80/2.25 vs Bud 80	-0.15 (-15.58,15.28)
Budesonide 80 2BID (n=90)	235.56 (53.88)	16.67 (44.53)	Symbicort 80/4.5 vs 80/2.25	11.87 (-3.43,27.16)

1 Baseline is the latest non-missing pre-dose assessment prior to first dose of investigational product (typically Visit 3, randomization)
2 Descriptive statistics for change from baseline to Week 12 (Visit7) for at Visit evaluations, and to Week 11-12 for eDiary evaluations.
3 Comparison is based on a repeated measures analysis, assuming missing at random, of mean change from baseline to Week 12 (Visit 7).
E1002005 (Placebo) and E1870002 (Budesonide) had no morning and evening PEF or FEV1 captured in the eDiary.

Source: CSR, T11.2.2.1.1, p285; T11.2.2.1.2, p286-7; T11.2.2.1.21, 311; T11.2.2.1.22, 312-3; T11.2.3.1.4, p322-7

Table 92. D589GC00003. eDiary FEV_1 and PEF evaluations (EAS)

Treatment Group	Baseline[1]		Week 11-12[2]		Change	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Morning FEV_1 (L/min)						
Symbicort 80/4.5 2BID	82	1.637 (0.5091)	72	1.766 (0.5035)	72	0.163 (0.3743)
Symbicort 80/2.25 2BID	87	1.593 (0.4566)	76	1.724 (0.5405)	75	0.139 (0.3770)
Budesonide 80 2BID	84	1.634 (0.4495)	72	1.713 (0.5229)	70	0.094 (0.3988)
Morning PEF (L/min)						
Symbicort 80/4.5 2BID	82	211 (65.7)	72	238 (61.1)	72	28 (49.8)
Symbicort 80/2.25 2BID	87	208 (63.2)	76	223 (68.7)	75	17 (58.4)
Budesonide 80 2BID	84	215 (64.2)	72	236 (66.3)	70	19 (46.9)

Treatment Group	Baseline[1]		Week 11-12[2]		Change	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Evening FEV_1 (L/min)						
Symbicort 80/4.5 2BID	80	1.708 (0.5150)	71	1.757 (0.5098)	71	0.083 (0.3555)
Symbicort 80/2.25 2BID	87	1.668 (0.4978)	73	1.721 (0.5175)	71	0.052 (0.3845)
Budesonide 80 2BID	85	1.729 (0.4316)	71	1.720 (0.5102)	69	0.018 (0.3839)
Evening PEF (L/min)						
Symbicort 80/4.5 2BID	80	229 (61.2)	71	244 (61.9)	71	16 (46.6)
Symbicort 80/2.25 2BID	87	219 (64.7)	73	230 (69.5)	71	7 (57.6)
Budesonide 80 2BID	85	225 (65.2)	71	240 (66.0)	69	9 (46.2)

1 For morning entries, baseline was the mean from the morning record of 6 days before up to and including the morning record at Visit 3. For evening entries, baseline was the mean from the evening record of 7 days before up to and including the day prior to Visit 3.

2 Week 11-12 included Days 71-89, the week immediately preceding the last study visit (Visit 7).

Source: CSR, T21, p87-90; T22, p93-6.

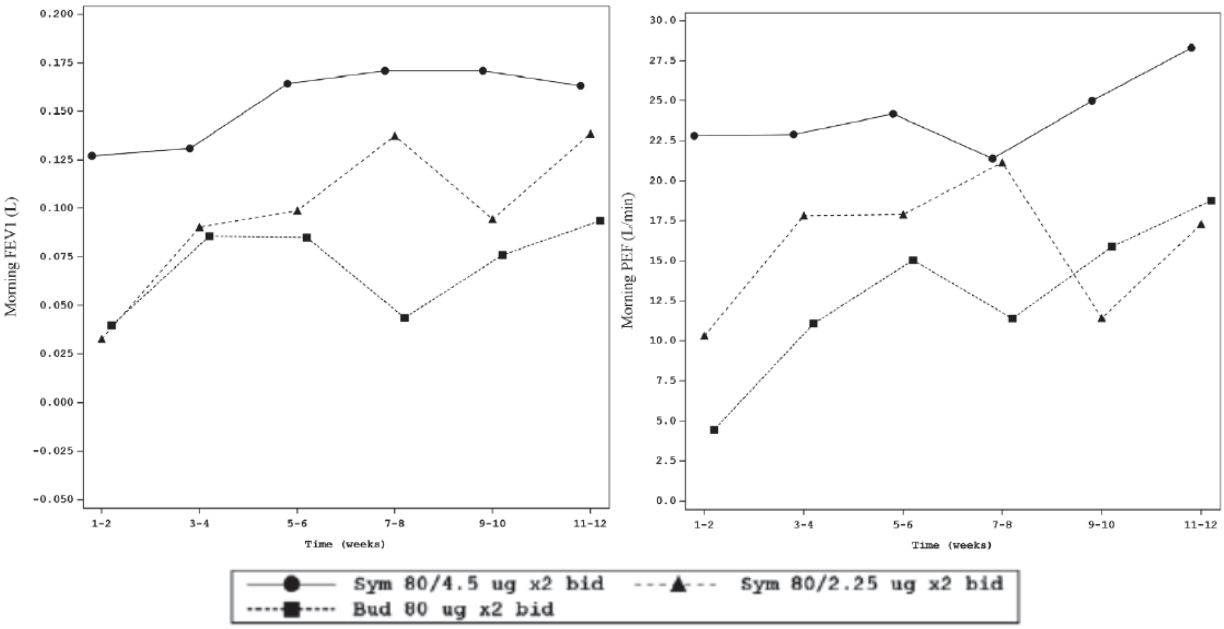

Figure 31. D589GC00003. Change from baseline in averaged weekly morning diary FEV_1 (L) (left) and PEF (L) (right) over time (EAS)

Source: CSR, F8, p91; F10, p97.

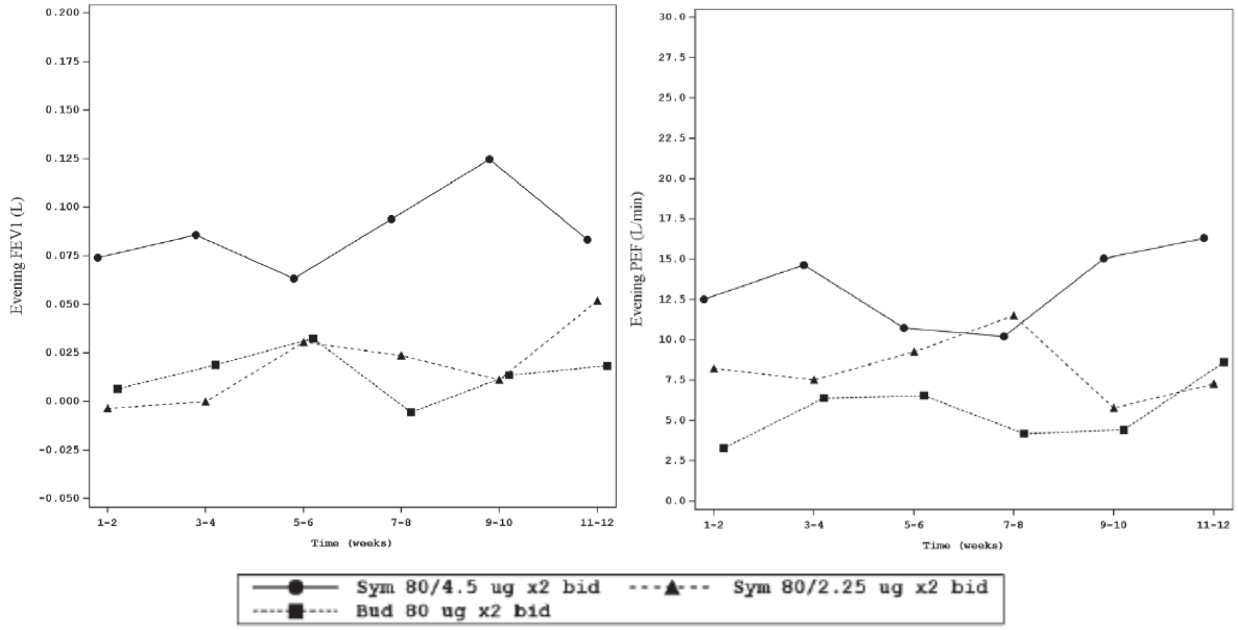

Figure 32. D589GC00003. Change from baseline in averaged weekly evening diary FEV_1 (L) (left) and PEF (L) (right) over time (EAS)

Source: CSR, F10, p97; F11, p98.

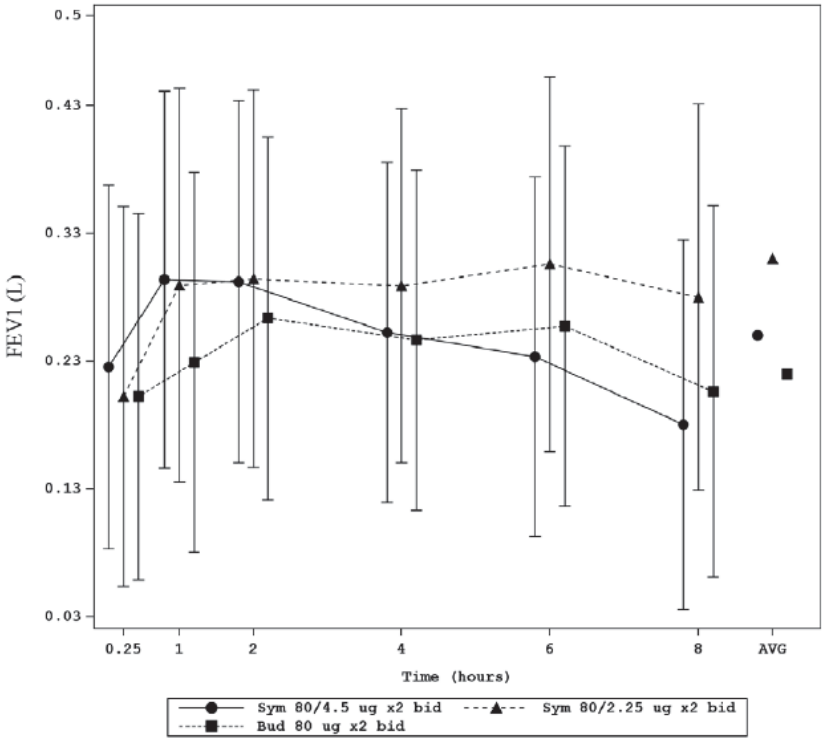

Figure 33. D589GC00003. FEV_1 (L) serial spirometry change over 8-hours at Week 12, repeated measures analysis (Exploratory analysis set)

Source: CSR, F21, p118.

Symptom Scores, Nighttime awakenings, and Rescue Medication Use

All treatment groups showed improvements from baseline in symptom scores, nighttime awakenings, and reliever use. Except for less frequent nighttime awakenings that required reliever medication use, there were no differences in daytime or nighttime asthma symptom scores, nighttime awakenings due to asthma symptoms (regardless of reliever use), or total daily reliever medication use between the three treatment groups (Table 93). Given the fact that all patients in the trial received a daily dosage of 320 mcg of budesonide and that LABAs are not anti-inflammatory agents, one would not necessarily expect to see much difference between the treatment groups for symptom scores, and this was the case. It is less clear why there were no differences in reliever use, as one could argue that this might have been expected to occur in the formoterol treatment arms.

Table 93. D589GC00003. eDiary evaluations of symptom and reliever use (EAS)

Treatment Group	Baseline[1]		Week 11-12[2]		Change	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Daytime asthma symptom scores[3]						
Symbicort 80/4.5 2BID	88	0.9 (0.42)	76	0.5 (0.53)	76	-0.4 (0.53)
Symbicort 80/2.25 2BID	93	0.8 (0.55)	79	0.4 (0.51)	79	-0.4 (0.56)
Budesonide 80 2BID	90	0.8 (0.50)	79	0.5 (0.54)	79	-0.3 (0.48)
Nighttime asthma symptom scores[3]						
Symbicort 80/4.5 2BID	89	0.2 (0.27)	78	0.0 (0.13)	78	-0.2 (0.27)
Symbicort 80/2.25 2BID	93	0.2 (0.28)	81	0.0 (0.10)	81	-0.2 (0.30)
Budesonide 80 2BID	90	0.2 (0.25)	80	0.0 (0.13)	80	-0.1 (0.22)
Nighttime awakenings due to asthma symptoms (%)						
Symbicort 80/4.5 2BID	89	18.9 (26.7)	78	3.8 (12.6)	78	-15.0 (26.6)
Symbicort 80/2.25 2BID	93	21.0 (28.4)	81	3.6 (9.8)	81	-19.3 (30.3)
Budesonide 80 2BID	90	16.5 (25.2)	80	3.0 (13.3)	80	-13.4 (21.6)
Nighttime awakenings requiring reliever use (%)						
Symbicort 80/4.5 2BID	89	12.2 (22.2)	78	2.3 (8.4)	78	-9.4 (21.3)
Symbicort 80/2.25 2BID	93	13.8 (23.6)	81	1.5 (7.8)	81	-13.5 (26.4)
Budesonide 80 2BID	90	12.0 (22.4)	80	2.1 (10.1)	80	-10.0 (19.6)
Total daily reliever use (inh/day)						
Symbicort 80/4.5 2BID	87	1.2 (1.4)	73	0.6 (1.4)	73	-0.7 (1.7)
Symbicort 80/2.25 2BID	92	1.8 (2.5)	75	0.7 (1.5)	75	-0.9 (2.4)
Budesonide 80 2BID	89	1.2 (1.5)	75	0.6 (1.4)	74	-0.6 (1.4)

1 For morning entries, baseline was the mean from the morning record of 6 days before up to and including the morning record at Visit 3. For evening entries, baseline was the mean from the evening record of 7 days before up to and including the day prior to Visit 3.

2 Week 11-12 included Days 71-89, the week immediately preceding the last study visit (Visit 7).

3 Asthma symptom scores range from 0-3 (0=None, 1=Mild, 2=Moderate, 3=Severe).

Source: CSR, T 11.2.3.1.7, p328-39; T11.2.3.1.11, p340-5; T11.2.3.1.13, p346-51; T11.2.3.1.15, p352-63.

Asthma Exacerbations

Results for study protocol defined asthma exacerbations are shown in Table 94, including the number and percent of patients, and the number of events in each group. Except for the subgroup of patients who were on Symbicort 80/4.5 and who required an increase in asthma medications (fewer patients and events in the Symbicort 80/4.5 treatment group), there were no differences between treatment groups. However, the Kaplan Meier plot to time to first asthma exacerbation event showed some separation between Symbicort 80/4.5 and the other two treatment groups (Figure 34).

Table 94. D589GC00003. Summary of patients who experienced a protocol defined asthma exacerbation during study (Safety analysis set)

	Number (%) of patients, number of events			
	Symbicort 80/4.5 2BID N=90	Symbicort 80/2.25 2BID N=93	Budesonide 80 2BID N=90	Total N=273
Patients who have a protocol defined asthma exacerbation[a,b]	9 (10.0), 9	12 (12.9), 12	12 (13.3), 13	33 (12.1), 34
Requiring emergency room treatment[a]	4 (4.4), 4	2 (2.2), 2	2 (2.2), 2	8 (2.9), 8
Requiring hospitalization[a]	0	0	1 (1.1), 1	1 (0.4), 1
Requiring systemic steroids[a]	7 (7.8), 7	7 (7.5), 7	9 (10.0), 9	23 (8.4), 23
Requiring an increase in, or additional asthma maintenance medication[a]	3 (3.3), 3	8 (8.6), 8	9 (10.0), 9	20 (7.3), 20
Classed as an adverse event[a]	7 (7.8), 7	12 (12.9), 12	10 (11.1), 11	29 (10.6), 30
Unclassified[c]	0	0	0	0

a Investigator determined asthma exacerbations are based on 'Were there any Asthma Exacerbations?' in the CRF. Includes asthma exacerbations between the date of randomization (Visit 3) and withdrawal from the study or completing Visit 7 (Week 12). Percentages calculated from the number of patients in the safety analysis set in each treatment group.
b Patients may have had multiple asthma exacerbations and are presented in all categories applicable.
c If the exacerbation was not defined as per protocol but still deemed an exacerbation by the investigator then it was counted as unclassified.

Source: CSR, T23, p107.

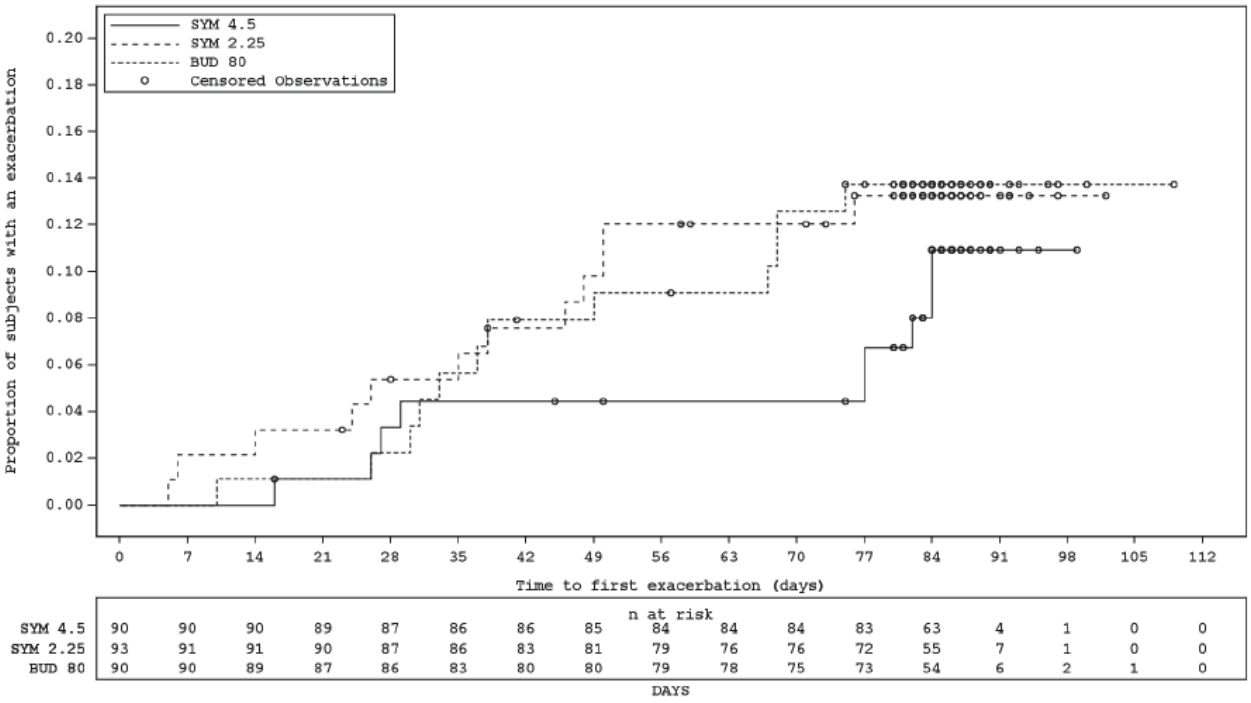

Figure 34. D589GC00003. Kaplan-Meier plot of time to occurrence of the first protocol defined asthma exacerbation (EAS)

Source: CSR, F19, p109.

PAQLQ(S)

As evaluated by overall and sub-domains scores on the PAQLQ(S), an improvement in health-related quality of life was observed in all treatment groups with a trend towards greater improvement noted in the budesonide HFA 80 treatment group (results not shown).

8.3.5.2.5 Safety

Extent of Exposure

The extent of exposure was similar between treatment groups (means of 84, 81, and 81 days for the Symbicort 80/4.5, Symbicort 80/2.25, and budesonide HFA 80 treatment groups, respectively.

Adverse Events

Review of adverse events (AEs), serious adverse events (SAEs), and adverse events leading to discontinuation DAEs revealed no clinically meaningful differences in the adverse event profiles among the three treatment groups (Table 95). Two SAEs were experienced by two patients on budesonide HFA 80, a case of acute lymphocytic leukemia and a case of asthma.

The overall adverse event profile experienced by patients in this trial was similar to what would be expected in this age group. The most commonly experienced adverse events with a frequency of ≥3% by MedDRA Preferred Term are shown in Table 96. Of note, since the Symbicort 80/2.25 will not be approved, the only arms of relevance are the Symbicort 80/4.5 and budesonide 80 arms; therefore, the Symbicort 80/2.25 arms are grayed in the two tables. Patients treated with budesonide experienced more frequent cough and asthma events, whereas patients

treated with Symbicort 80/4.5 experienced more frequent events (and with frequency higher than 3%) of upper respiratory tract infection, pharyngitis, and headache.

Table 95. D589GC00003. Overall summary of adverse events (Safety analysis set)

	Symbicort 80/4.5 2BID (N=90)	Symbicort 80/2.25 2BID (N=93)	Budesonide 80 2BID (N=90)
Number of adverse events (AE)	74	88	75
Patients with at least one AE n, (%)	42 (46.7)	41 (44.1)	40 (44.4)
Number of SAEs	0	0	2
Patients with at least one SAE n, (%)	0	0	2 (2.2)
Acute lymphocytic leukemia	0	0	1 (1.1)
Asthma	0	0	1 (1.1)
Number of DAEs*	1	1	3
Patients with at least 1 DAE n, (%)	1 (1.1)	1 (1.1)	3 (3.3)
Acute lymphocytic leukemia	0	0	1 (1.1)
Asthma	1 (1.1)	1 (1.1)	2 (2.2)
Deaths	0	0	0
* DAE = AE leading to discontinuation			

Source: CSR, T28, p122, T30, p125, T11.3.4.1.1, p508.

Table 96. D589GC00003. Adverse events with a frequency of ≥3%, by PT (Safety analysis set)

Preferred Term* n (%)	Symbicort 80/4.5 2BID (N=90)	Symbicort 80/2.25 2BID (N=93)	Budesonide 80 2BID (N=90)
Asthma	*7 (7.8)*	*11 (11.8)*	*10 (11.1)*
Upper respiratory tract infection	**9 (10.0)**	**12 (12.9)**	**4 (4.4)**
Pyrexia	4 (4.4)	4 (4.3)	4 (4.4)
Nasopharyngitis	4 (4.4)	2 (2.2)	5 (5.6)
Rhinitis allergic	3 (3.3)	3 (3.2)	4 (4.4)
Cough	*1 (1.1)*	*4 (4.3)*	*4 (4.4)*
Pharyngitis	**5 (5.6)**	**3 (3.2)**	**1 (1.1)**
Headache	**4 (4.4)**	**4 (4.3)**	**0**
Rhinitis	**3 (3.3)**	**2 (2.2)**	**2 (2.2)**
Vomiting	2 (2.2)	3 (3.2)	0
*Based on MedDRA v18.1. PTs in italics were more frequent in the budesonide than the Symbicort arms, whereas PTs that are bolded were more frequent in the Symbicort arms. (except that vomiting did not reach the 3% threshold in the Symbicort 80/.45 arm).			

Source: CSR, T29, p123.

Laboratory parameters

Blood samples for measurement of serum potassium and glucose (non-fasting) were taken at baseline (Visit 2), at the end of study (Visit 7), and at any unscheduled visits. Review of mean and maximum shifts from baseline in these parameters identified no safety concerns.

Vital signs, ECGs, Physical examinations

Vital signs were performed at baseline (Visit 2) and other clinic visits (Visits 3-7) throughout the study. No safety concerns were identified.

ECGs, and physical examinations were performed at baseline (Visit 2), at the end of study (Visit 7), and at any unscheduled visits. Review of mean shifts from baseline in ECG parameters identified no safety concerns.

Three patients had notable ECGs during the study as described below [CSR, p131]:

> "A 10-year old male patient (E7815005), who was receiving Symbicort pMDI 80/2.25, 2 inhalations bid, had a normal ECG at run-in, later followed by an abnormal ECG due to an AV block with dynamic PR-interval of 215, 245 and 236 msec on 3 recordings taken right after each other on the same day. An ECG at end of study showed a return of PR-interval to 215 msec. The investigator believed the AV block to be clinically significant, thus reported first degree AV block as an AE of mild intensity. However, first degree AV blocks are seen as a physiological variation in children and adolescents.
>
> A 10-year old male patient (E7834016), who was receiving Symbicort pMDI 80/4.5, 2 inhalations bid, had a normal ECG at run-in, then showed a change from baseline in QTcF of 43 msec, ending at a maximum value of 462 msec on the ECG. An ECG at the end of study showed a return of QTcF to 378 msec. This patient had a history of congenital heart disease (coarctation of aorta, arterial and ventricular septal defect corrected by surgery), which could explain the intermittent changes. The investigator considered the ECG changes as not clinically significant and no AE was reported.
>
> An 11-year old male patient (E7804009), who was receiving Symbicort pMDI 80/4.5, 2 inhalations bid, had a normal ECG at run-in, followed by an abnormal ECG due to long QT interval. The maximum QT interval in the ECG recordings was 436 msec. The investigator considered the ECG changes as not clinically significant and no AE was reported."

8.3.5.3 Conclusions

This was a 12-week, randomized, double-blind, parallel-group, multicenter trial that compared the approved Symbicort 80/4.5, investigational version of Symbicort 80/2.25, and an investigational budesonide HFA 80, each administered as 2 inhalations twice daily, in children aged 6 <12 years with asthma who demonstrated the need for ICS controller therapy. The results support AstraZeneca's proposal to extend the approved dosage of formoterol in the Symbicort 80/4.5 dosage strength to children 6-11 years of age.

8.3.6 Synopsis of Study SD-039-0716

Study **716** was one of the two pivotal efficacy and safety studies conducted to support the adolescent/adult Symbicort program. It evaluated efficacy and safety of the Symbicort 80/4.5 dosage strength. This was a randomized, double-blind, double-dummy, placebo-controlled 12-week study comparing the efficacy and safety of Symbicort MDI 80/4.5 with its pharmacologic monoproducts, budesonide MDI (80 mcg) and formoterol (Oxis) Turbuhaler, and placebo, each

administered as 2 inhalations BID. The study enrolled 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: FEV_1 on ICS therapy 60% to 90% predicted; for <12 years: ≥75% predicted). Randomization was stratified by age group (<12 years and ≥12 years), and efficacy was assessed only in patients ≥12 years of age (EAS ≥12). Entry criteria included mild-moderate asthmatics (FEV_1 for ≥12 years: 60% to 90% predicted; FEV_1 for <12 years: ≥75% predicted) on ICS therapy with at least 12% reversibility (but no volume requirement). The study comprised a screening visit, a 14 (±7) day single-blind placebo run-in period, and a 12-week double-blind treatment period.

Co-primary efficacy variables were used to demonstrate the contribution of each of the individual components, budesonide or formoterol, to the efficacy of the combination drug product. The co-primary efficacy variables were: baseline-adjusted average 12-hour FEV_1 and pre-dose FEV_1. **Baseline-adjusted average 12-hour FEV_1 averaged over the study** was used to demonstrate the bronchodilator effect of the long-acting beta-agonist (formoterol) component (comparison: Symbicort minus budesonide). **Pre-dose FEV_1 at 2 weeks** was used to demonstrate the stabilizing, anti-inflammatory effect of the corticosteroid (budesonide) component (comparison: Symbicort minus formoterol). Efficacy was only assessed in patients ≥12 years of age.

The study included a set of pre-defined criteria for withdrawal of patients due to an asthma event. Events that mandated withdrawal included [*only those for patients ≥12 years are shown; similar criteria were included for younger patients*]: a decrease in morning pre-dose FEV_1 of ≥20% from the pre-dose FEV_1 at randomization, or a decrease to <45% predicted; use of ≥12 actuations of albuterol/day on 3 or more days within 7 consecutive days; a decrease in morning PEF of ≥20% from baseline (mean of 7 days prior to randomization) on 3 or more days within 7 consecutive days; a clinical exacerbation requiring emergency treatment, hospitalization, or use of asthma medication not allowed by the protocol. Originally, withdrawals due to pre-defined asthma events had been defined as one of the co-primary endpoints to support efficacy of the budesonide component, but this was changed to a secondary endpoint when during the study it was realized that investigators were inconsistently withdrawing patients who qualified for withdrawal due to a pre-defined event. Secondary efficacy variables included: pre-defined asthma events and withdrawals due to pre-defined asthma events; other spirometry-related variables (2-hour post-dose FEV_1, maximum FEV_1, onset of effect [15% improvement in FEV_1 from baseline on Visit 2], time to onset of effect; diary variables (morning and evening PEF, nighttime and daytime asthma symptom scores, nighttime awakenings, rescue medication use; and patient reported outcomes including AQLQ and an Onset of Effect Questionnaire.

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 overall study population was approximately 90% Caucasian, 40% males and 60% females, with a mean age of 35 years (range 6 to 78 years). All except 1 patient had asthma controlled by a regimen of ICS prior to entry. The average length of asthma history was 19 years. At screening, the mean percent predicted FEV_1 for most patients was in the mild-to-moderate range (75.7 % predicted) while being treated with an average ICS dose of 341.5 mcg daily (range 80 to 1200 mcg a day). The screening mean pre-dose FEV_1 was 2.5 L and mean percent reversibility was 18.9% (range 10.3% to 62.6%). Baseline mean percent predicted FEV_1 was 71.3%.

The study enrolled 31/511 patients less than 12 years of age. Demographics for the 6-11 year subgroup are shown in Table 97, and the reasons for discontinuation are shown in Table 98.

For the EAS population, which included patients 12 years of age and older, Symbicort showed statistical superiority over its monoproducts for each of the co-primary efficacy endpoints, FEV_1 0-12 hours for the formoterol component and pre-dose 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. 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. 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, which combined many clinically meaningful endpoints such as drops in FEV_1 and PEF, asthma exacerbations, etc., as well as in most diary and PRO endpoints, including asthma symptom scores, rescue medication use, and PROs. Likewise, the expected beta-agonist effects of formoterol, namely as a bronchodilator that exerts effects for about 12 hours, were also seen. This was noted in spirometric endpoints, including onset of action, maximal FEV_1 etc. Formoterol did not add significantly to factors in key asthma control such as frequency and severity of exacerbations [as measured by the key secondary endpoint of pre-specified asthma events].

With regard to the subset of 31 patients 6 through 11 years of age randomized in this study, the study was not designed to evaluate efficacy in these patients (b) (4)

(b) (4)

The safety evaluation revealed no unexpected or unusual safety trends with regard to the subgroup of patients 6-11 years as compared to adolescent and adult patients. Only one patient in this subgroup experienced a serious adverse event; a 6 year old in the placebo treatment arm experienced severe abdominal pain and was discontinued from treatment. Just as for patients 12 years of age and older, the subgroup of patients 6-11 years of age treated with formoterol or placebo had more withdrawals due to prespecified events than those treated with Symbicort or budesonide (Table 98 and Table 100). Table 101 shows the odds ratios and nominal p-values for withdrawals due to these events. Numerically there were more withdrawals due to pre-defined asthma events in both the formoterol and placebo arms than in either arm containing budesonide, but the numbers and percentages of qualifying events was similar between the Symbicort and formoterol treatment groups. Again, the number of patients enrolled was too small to provide meaningful results.

Table 97. SD-039-0716. Demographic and key baseline characteristics, Subset of patients 6-11 years of age

Demographic / baseline characteristic, Ages 6-11 years		Symbicort N=7	Budesonide N=6	Formoterol N=9	Placebo N=9	Total N=31/511
Sex	Male	4	4	4	8	20
	Female	3	2	5	1	11
Age	Mean	8.3	8.8	9.3	8.1	8.6
	6-7	3	1	1	4	9
	8-11	4	5	8	5	22
Race	Caucasian	5	5	7	8	25
	Black	2	1	2	0	5
	Oriental	0	0	0	1	1
	Other	0	0	0	0	0
Baseline ICS dose category	Low	5	4	6	8	23
	Med	2	1	1	1	5
	High	0	0	2	0	2
	Missing	0	1	0	0	1
Screening	FEV_1 (L)	1.6	1.8	2.0	1.6	1.7
	FEV_1 % predicted	88.7	85.9	83.6	84.9	85.6
Baseline	FEV_1 (L)	1.6	1.9	2.0	1.7	1.8
	FEV_1 % predicted	90.3	87.8	83.3	91.7	88.2
	Reversibility (mL, %)	279 (17.9%)	293 (16.7%	299 (15.0%)	290 (20.1%)	290 (17.4%)

Source: S-013, submitted 6/1/2008, ISE T24 and T25, p 72-3; ISE Appendix, T1.1.4.1.2, p108-110

Table 98. SD-039-0716. Reasons for discontinuation, Subset of patients 6-11 years of age

Reasons for discontinuation, Ages 6-11y	Symbicort	Budesonide	Formoterol	Placebo	Total N=511
Randomized	7	6	9	9	31
Completed	5	5	5	4	19
Discontinued	2	1	4	5	12
Developed study specific discontinuation criteria*	1	0	4	4	9
Adverse event	1	0	0	1	2
Not willing to continue	0	1	0	0	1
*Same as secondary endpoint of withdrawals due to meeting pre-defined asthma worsening criteria					

Source: S-013, submitted 6/1/2008, ISE, T1.4.4.1.2, p246

(b) (4)

(b) (4)

Table 100. SD-039-0716, Number and percentage of patients meeting pre-defined asthma event withdrawal criteria (CRF data), Subgroup of patients 6-11 years

Criteria	Treatment group, n (%)			
	Symbicort	Budesonide	Formoterol	Placebo
Patients 6-11 years	7	6	9	9
Number of patients withdrawn due to pre-defined asthma event	1 (14.3)	0	4 (44.4)	4 (44.4)
Number of patients with pre-defined asthma event in CRF	3 (42.9)	1 (16.7)	4 (44.4)	5 (55.6)
Time to event (mean days)	55.3	41.0	28.5	29.0
Criterion 1: Decrease in FEV_1	1	0	1	0
Criterion 2: Rescue medication	0	0	1	0
Criterion 3: Decrease in AM PEF	1	0	0	2
Criterion 4: Nighttime awakening	3	1	1	1
Criterion 5: Clinical exacerbation	1	0	2	2

Source: S-013, submitted 6/1/2008, ISE Appendix, T2.1.2.1.1, p 480-5; T3.1.2.2.1, p496. Study 716: T11.2.3.1.1, p2260-1

Table 101. SD-039-0716, Odds ratios for pre-defined asthma events, Subgroup of patients 6-11 years

Treatment	N	Had Event (%)	Treatment Comparison*		
			Odds ratio	95% CI	Nominal p-value
Symbicort	7	3 (42.9)	--	--	--
Budesonide	6	1 (16.7)	3.75	0.27, 51.37	0.327
Formoterol	9	4 (44.4)	0.94	0.13, 6.87	0.951
Placebo	9	5 (55.6)	0.60	0.08, 4.40	0.626
* Comparisons for Symbicort minus component. Nominal p-value from general					

Treatment	N	Had Event (%)	Treatment Comparison*		
			Odds ratio	95% CI	Nominal p-value
association Chi-square test adjusted for treatment and age stratification.					

Source: S-013, submitted 6/1/2008,ISE Appendix, T3.1.2.1.1, p480. Study 716: T11.2.3.1.2.2, p2277.

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PETER R STARKE
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SALLY M SEYMOUR
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