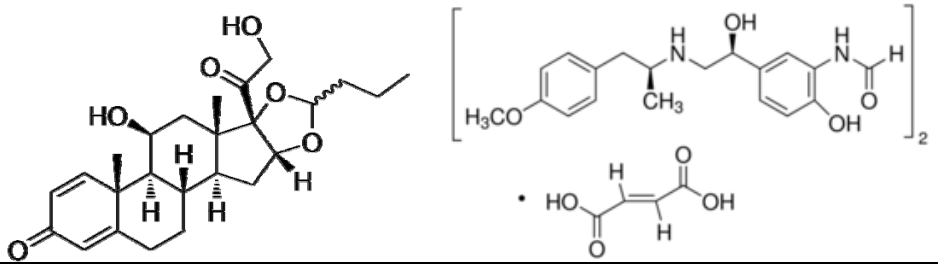
CLINICAL PHARMACOLOGY REVIEW	
sNDA Number:	021929 SDN1959 (S-013)
Submission Date:	07/28/2016
Submission Type:	Pediatric Supplement Resubmission
Proposed Brand Name:	Symbicort® Inhalation Aerosol
Generic Name:	Budesonide and formoterol fumarate dihydrate
Sponsor:	AstraZeneca
Route of Administration:	Inhalation
Dosage Form:	Inhalation aerosol delivered by pressurized metered-dose inhaler
Dosage Strength:	80/4.5 µg (budesonide/formoterol fumarate dihydrate) per inhalation
Proposed Dosing Regimen:	2 inhalations of 80/4.5 twice daily
Proposed Indication(s):	Treatment of asthma in patients aged 6 to <12 years
OND Divisions:	Division of Pulmonary, Allergy, and Rheumatology Products
OCP Division:	Clinical Pharmacology II
Reviewer:	Yunzhao Ren, M.D., Ph.D.
Team Leader (acting):	Bhawana Saluja, Ph.D.
Molecular Structure:	Budesonide (MW=430.5): Formoterol fumarate dihydrate (MW=840.9): 

Note –

In this review, for the purpose of convenient reading, wherever "formoterol X µg" is cited, it literally means formoterol fumarate dihydrate X µg.

TABLE OF CONTENTS

Item	Page number
1. EXECUTIVE SUMMARY	2
1.1 Recommendation	3
1.2 Phase 4 Commitments	3
1.3 Summary of Clinical Pharmacology Findings	3
2. QUESTION-BASED REVIEW	8
2.1 List of Clinical Pharmacology Studies	8
2.2 General Attributes of the Drug	8
2.3 General Clinical Pharmacology	10
2.4 PK characteristics of the drug	10
2.5 Intrinsic Factors	11
2.6 Drug-Drug Interactions	12
2.7 Analytical Section	12
2.8 Reference	14
3. Detailed Labeling Recommendations	15
4. APPENDIX	17
4.1 Individual Study Reviews	17

1. EXECUTIVE SUMMARY

Symbicort® 80/4.5 and 160/4.5 was originally approved on 07/21/2006 for the long-term maintenance treatment of asthma in patients 12 years of age and older. The pediatric supplement (to extend the asthma indication to patients 6-11 years of age) which included seven clinical studies was first submitted on 06/03/2008 under SDN 103 and received Complete Response (CR) on 04/03/2009. The cited deficiencies are listed as follows[1]:

(b) (4)

- You have not provided rationale and supporting data to justify the use of (b) (4) Symbicort Inhalation Aerosol products in patients 6 to 11 years of age.
- The selection of dose of inhaled formoterol is not supported by any data specific to the age group of 6 to 11 years.

In response to the CR, AstraZeneca resubmitted the pediatric supplement that included three new efficacy/safety clinical studies on 07/28/2016 under SDN 1959, to fulfil the PREA PMR #1749-2, and request Pediatric Exclusivity for Symbicort® pressurized metered dose inhaler (pMDI). The proposed indication extends the age of asthma patients from 12 to 6 years old. The proposed dose regimen in children aged 6 to <12 years is 2 inhalations of Symbicort 80/4.5 twice daily. Among the three newly submitted studies, only Study D589GC00002 has a pharmacokinetic (PK) component which provided

formoterol urine concentrations following single dose administration of formoterol (2.25µg, 4.5µg, and 9µg) in combination with budesonide pMDI 160 µg.

PK results from adults and initial pediatric submission (SDN103) showed that dose-normalized budesonide systemic exposure ($AUC_{0\text{-}inf}$ and C_{max}) in children (Study D5896C00010) was numerically lower than that of adults (Study D5896C00010) following single-dose inhalation delivered by Symbicort pMDI (Table 1.1). The formoterol systemic exposure ($AUC_{0\text{-}6}$ and C_{max}) at steady state were comparable between children (Study SD-039-0719) and adults (Study D5896C00011) following BID inhalations of the same dose (budesonide 320µg/formoterol 9µg) delivered via Symbicort pMDI (Table 1.2).

PK results from the newly submitted formoterol dose-ranging pediatric Study D589GC00002 showed that the mean formoterol $Ae_{0\text{-}12}$ (0-12 post-dose urine excretion amount) increased dose-proportionally from 2.25µg to 9µg following single dose inhalation as delivered via Symbicort pMDI (Table 1.3). Mean formoterol $fe_{0\text{-}12}$ (0-12h post-dose urine excretion fraction of dose) obtained from the same study was similar to that of Study D5896C00013 from the initial pediatric submission (SDN 103).

In conclusion, all these PK results support the safety profiles collected from pediatric studies.

1.1 Recommendation

The pediatric supplement SDN 1959 to NDA 021929 submitted on July 28, 2016 is acceptable from a clinical pharmacology perspective.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

1.3.1 Background

Symbicort® 80/4.5 and 160/4.5 was originally approved for the long-term maintenance treatment of asthma in patients 12 years of age and older on 07/21/2006. Symbicort® 80/4.5 was approved for chronic obstructive pulmonary disease (COPD) on 02/27/2009. The approved dosing regimen is 2 inhalations BID for both indications.

AstraZeneca first submitted pediatric supplement 06/03/2008 under SDN 103 and received a CR on 04/03/2009. The cited deficiency and the recommendations for addressing the deficiency are as follows[1]:

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 of age.* (b) (4) *You have not provided rationale and supporting data to justify the use 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 support approval of Symbicort Inhalation Aerosol for maintenance treatment of asthma in patients 6 to 11 years of age, provide:

a. *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.*
b. *A comparative assessment of various dosage strengths of Symbicort Inhalation Aerosol to justify approval of the various strengths*

The SDN 103 pediatric supplement was found acceptable from a clinical pharmacology standpoint. The results from a hypothalamic–pituitary–adrenal (HPA) axis Study SD-039-0719 showed that "*The SYMBICORT pMDI group generally manifested numerically smaller decreases in 24 hours urinary cortisol across visits compared with the PULMICORT TBH group.*" [2]

One pediatric Written Request (WR) dated 1/28/2011, and three amendments (dated 5/5/2011, 4/6/2012, and 3/9/2015) were issued by FDA since CR. Three studies were cited in the last amendment[3]:

The studies outlined in this Written Request are designed to provide evidence of efficacy and safety for use of this fixed dose combination in children 6 to <12 years of age. Studies in patients birth to <6 years of age were waived because the fixed-dose combination of an inhaled corticosteroid with a LABA is inappropriate for use in this age group. Studies 1 and 2 will evaluate the appropriate dose of budesonide in an HFA pMDI (Study 1) and of formoterol in an HFA pMDI (Study 2) to be carried into an efficacy and safety trial of the fixed-dose combination of budesonide and formoterol in an HFA pMDI (Study 3).

AstraZeneca resubmitted the pediatric supplement to include three new efficacy/safety clinical studies on 07/28/2016 under SDN 1959 in response to the CR of SDN 103. Only one of the studies, i.e., Study D589GC00002 has a PK component as a secondary objective where urine samples were collected to assess the formoterol concentrations.

1.3.2 Cross-study Comparison of systemic exposure of budesonide in adults and children

Study D5896C00010 was an open-label, randomized, single-dose, four-way crossover study in 29 adults with asthma. The four single-dose treatments were:

- Budesonide 1920 μg/formoterol 54μg delivered by 12 inhalations of Symbicort pMDI (160/4.5)
- Budesonide 1920 μg delivered by 12 inhalations of budesonide pMDI (160 μg)
- Budesonide 2400 μg delivered by 12 inhalations of Pulmicort Turbuhaler (200 μg)
- Formoterol 54 μg delivered by 12 inhalations of Oxis Turbuhaler (4.5 μg)

The dose-normalized budesonide geometric mean $AUC_{0\text{-}inf}$ and C_{max} following 12 inhalations of Symbicort pMDI (160/4.5) in adults were 9.68 pM·h/μg and 2.35 pM/μg, respectively (Table 1.1).

Study D5896C00013 was an open-label, randomized, single-dose, two-way crossover study in 24 children with asthma. The two single-dose treatments were:

- Budesonide 640μg/formoterol 18μg delivered by 4 inhalations of Symbicort pMDI (160/4.5)
- Budesonide 800μg/formoterol 18μg delivered by 4 inhalations of Pulmicort Turbuhaler (200 μg) and 4 inhalations of Oxis Turbuhaler (4.5 μg)

The dose-normalized budesonide geometric mean $AUC_{0\text{-}inf}$ and C_{max} following 4 inhalations of Symbicort pMDI (160/4.5) in children were 6.59 pM·h/µg and 2.13 pM/µg, respectively (Table 1.1).

Table 1.1 Comparison of Budesonide $AUC_{0\text{-}inf}$ and C_{max} following Single Dose Administration of Symbicort pMDI in Children and Adults

Population	Single Dose of Budesonide	Nominal[1]		Dose Normalized[1]	
		$AUC_{0\text{-}inf}$ (pM·h)	C_{max} (pM)	$AUC_{0\text{-}inf}$ (pM·h/µg)	C_{max} (pM/µg)
Adults (N=28)[2]	1920 µg	18594 (36%)	4512 (51%)	9.68 (36%)	2.35 (51%)
Children (N=24)[3]	640 µg	4221 (55%)	1361 (100%)	6.59 (55%)	2.13 (100%)

[1] geometric mean (CV%)
[2] from CSR d5896c00010, page 92, Table ST2
[3] from CSR d5896c00013, page 74, Table ST2

Therefore, the dose-normalized budesonide systemic exposure ($AUC_{0\text{-}inf}$ and C_{max}) in children was numerically lower than that of adults following single dose inhalation from the Symbicort pMDI device.

1.3.3 Cross-study Comparison of systemic exposure of formoterol in adults and children

Study D5896C00011 was an open-label, randomized, multiple-dose, parallel-group study assessing the steady state PK of budesonide and formoterol administered via Symbicort pMDI (budesonide 320µg/formoterol 9µg BID) for 6.5 days in adult patients with asthma compared to healthy subjects. In total, 26 asthma patients and 26 healthy subjects were randomized and completed the study. The formoterol geometric mean $AUC_{0\text{-}6}$ and C_{max} at steady state were 102 pM·h and 27.9 pM, respectively (Table 1.2).

Study SD-039-0719 was an open-label, randomized (2:1), 26-week study comparing the safety profile between Symbicort pMDI (budesonide 320µg/formoterol 9µg BID) and Pulmicort Turbuhaler [budesonide 400µg (approximately 320µg delivered)] in children (6-11 years of age) with asthma. In total, 187 children were randomized in the study. The formoterol PK samples at steady state were available from 6 children. The formoterol geometric mean $AUC_{0\text{-}6}$ and C_{max} at steady state following 2-week BID inhalations of Symbicort pMDI (320/9) in children with asthma were 110 pM·h and 27.0 pM, respectively (Table 1.2).

Table 1.2 Comparison of Formoterol Steady State $AUC_{0\text{-}6}$ and C_{max} via Symbicort pMDI (budesonide 320µg/formoterol 9µg BID) in Children and Adults with Asthma

Population	Dosing Regimen	$AUC_{0\text{-}6}$ (pM·h)[1]	C_{max} (pM)[1]
Adults (N=26)[2]	320/9, BID	102 (33%)	27.9 (49%)
Children (N=6)[3]	320/9, BID	110 (38%)	27.0 (45%)

[1] geometric mean (CV%)
[2] from CSR d5896c00011, page 94, Table ST3
[3] from CSR SD-039-0719, page 416, Table 11.2.7.2.1

Therefore, formoterol systemic exposure at steady state in children with asthma was comparable to that of adults with asthma following the same dose regimen (budesonide 320µg/formoterol 9µg BID) via Symbicort pMDI.

1.3.4 Formoterol urine PK Results from Study D589GC00002

Study D589GC00002 was a Phase 2, single-dose, randomized, partially-blinded, 5-way crossover, active- and placebo-controlled multicenter study comparing the bronchodilating effects following single doses of formoterol (2.25µg, 4.5µg, and 9µg) in combination with budesonide pMDI 160 µg, in children with asthma. A total of 54 patients were randomized and 50 (92.6%) completed the study. 12-hour urine samples were collected following each single dose treatment for determination of unchanged formoterol. The formoterol geometric mean Ae_{0-12} values increased dose proportionally with increase in dose from 2.25 µg to 9.0 µg as delivered by Symbicort pMDI; the result is consistent with relative stable fe_{0-12} values across all three dose groups (Table 3). The same trend was observed when arithmetic mean was used during analysis (Table 4.3).

Table 1.3 Geometric Mean of Formoterol Ae_{0-12} and fe_{0-12} following Single Dose Administration by Symbicort pMDI or Foradil Aerolizer (PK Set)

Treatment Arm	Data Set	N	Ae_{0-12} (pmol)	fe_{0-12}	CV
BUD 160/ FM 2.25	Full set	51	199	3.72%	132%
	Excluding BLQ sample	50	212	3.96%	113%
BUD 160/ FM 4.5	Full set	52	397	3.71%	100%
BUD 160/ FM 9.0	Full set	51	868	4.06%	98%
BUD 160/ Foradil Aerolizer 12*	Full set	49	434	1.82%	392%
	Excluding BLQ samples	43	749	3.15%	94%

BUD, budesonide; FM, formoterol
All the BLOQ samples were imputed with ½ LLOQ value (20 pmol) in the full data set during analysis
* Inhalation dose was set as 10 µg for Foradil 12 during fe_{0-12} calculation
Source: Reviewer's analysis from RSPC.xpt

There were 6 (12%) urine samples from budesonide 160µg/Foradil 12µg treatment arm with formoterol concentration BLOQ. The sponsor stated that *"it is not reasonable that a patient who inhaled Foradil 12 µg correctly would have no formoterol exposure"*. After excluding those 6 samples, the average Ae_{0-12} from budesonide 160µg/formoterol 9µg treatment arm is comparable with Ae_{0-12} from budesonide 160µg/Foradil Aerolizer 12µg (10 µg delivered out of the mouthpiece)[4] treatment arm (Table 1.3).

When using the same Symbicort pMDI device, the pediatric mean urine formoterol fe_{0-12} value (4.06%) following single dose of budesonide 160 µg/formoterol 9µg inhalation obtained from Study D589GC00002 was similar to the fe_{0-12} value (3.74%) following single dose of budesonide 640 µg/formoterol 18µg inhalation obtained from Study D5896C00013.

1.3.5 Hypothalamus-pituitary-adrenal (HPA) axis assessment following long-term use of Symbicort in children

The long-term effect of Symbicort on pediatric HPA axis was evaluated in Study SD-039-0719. The geometric mean of 24-hour urinary cortisol excretion amount reduced from 29.3 nmol at baseline to 24.6 nmol following 26-week BID treatment with Symbicort pMDI (budesonide 320µg/formoterol 9µg) (Figure 1). The extent of reduction was comparable to that following 26-week BID treatment with Pulmicort Turbuhaler [budesonide 400µg (approximately 320µg delivered)].

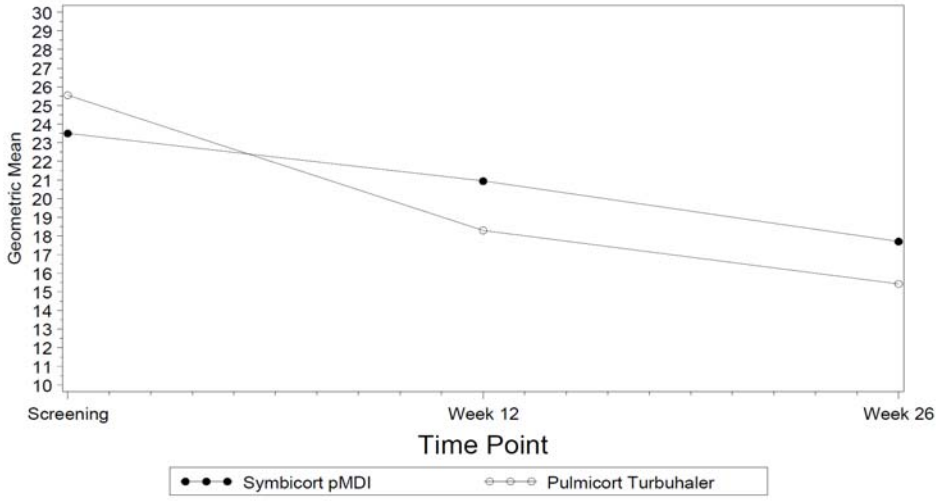


Figure 1 Geometric mean 24-hour urinary cortisol excretion amount following 26-week BID treatment with either Symbicort pMDI (320/9) or Pulmicort turbuhaler [budesonide 400µg (approximately 320µg delivered)]. (Source: CSR SD-039-0719, page 135, Figure 11)

To be noted, Pulmicort Turbuhaler is not marketed in the US.

2. QUESTION BASED REVIEW

2.1 List the in vitro and in vivo Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the sNDA

In total, three pediatric studies were submitted under SDN 1959 (Table 2.1). Among them, only Study D589GC00002 has a PK component which provided formoterol urine concentrations following single dose administration of formoterol (2.25µg, 4.5µg, and 9µg) in combination with budesonide pMDI 160 µg.

Table 2.1 List of Three Clinical Studies in sNDA021929 Pediatric Re-Submission Package

Study ID	Study Date	Phase	Study Objectives	Study Design	Subjects Randomized	Treatments
D589GC00001	08/07/2011 – 04/05/2013	2	Efficacy, safety	R, DB, PC,PG	304 children (6-11yo) with asthma	6-Week treatment: Placebo BUD pMDI 160µg BID
D589GC00002	10/07/2010 – 01/03/2012	2	Efficacy, PK, safety	R, PB, PC, AC, 5-way CO	54 children (6-11yo) with asthma	Single-dose treatment: pMDI: BUD 160µg BUD 160/F2.25µg BUD 160/F4.5µg BUD 160/F9µg Foradil Aerolizer: BUD 160/F12µg
D589GC00003	04/14/2014 – 04/14/2016	3	Efficacy, safety	R, DB, PG	279 children (6-11yo) with asthma	12-Week treatment: pMDI: BUD 160µg BID BUD 160/FM4.5µg BID BUD 160/FM 9µg BID

R=randomized, DB=double blind, PB=partial blind, PC=placebo controlled, PG=parallel group, CO=cross over
Source: section 5.2, tabular-listing.pdf

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physicochemical properties of the drug substance, and the formulation of the drug product?

Symbicort pMDI contains budesonide and formoterol fumarate dihydrate. Budesonide is a corticosteroid designated chemically as (RS)-11β, 16α, 17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S).

Formoterol is a selective beta2-agonist designated chemically as (R*,R*-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide.

Two strengths of Symbicort pMDI have been approved and marketed (the two strengths shared the same pMDI device). Each product has been designed to deliver a minimum of 120 actuations, and delivering either:

- 80 µg budesonide and 4.5 µg formoterol fumarate dihydrate micronized per actuation, ex-actuator (hereafter referred to as Symbicort pMDI 80/4.5), or;
- 160 µg budesonide and 4.5 µg formoterol fumarate dihydrate micronized per actuation, ex-actuator (hereafter referred to as Symbicort pMDI 160/4.5)

The strength of 80/4.5 µg is proposed for children 6 to <12 years in this supplement. The composition of Symbicort pMDI 80/4.5 µg is listed in Table 2.2. Each actuation delivers 80 µg budesonide and 4.5 µg formoterol fumarate dihydrate outside of the mouthpiece.

Table 2.2 Ingredients and Their Quantities per Albuterol MDPI Inhaler Container

Component	Manufacturing concentration (% w/w)	Canister concentration (% w/w)	Quantity per canister[a]	Quantity per actuation, ex-valve	Quantity per actuation, ex-actuator	Function	Standard
Budesonide micronised				(b) (4)	80 µg	Active	AstraZeneca
Formoterol fumarate dihydrate micronised					4.5 µg	Active	AstraZeneca
Povidone K25					(b) (4)	Suspending agent	USP
PEG 1000						Lubricant	NF
HFA 227						Propellant	(b) (4)

[a] Target fill weight = (b) (4)
[b] Manufacturing concentrations include drug overages of (b) (4)% for budesonide micronised and formoterol fumarate dihydrate micronized respectively (b) (4).
[c] Formulation overages of approximately (b) (4)% for both drug substances are included (b) (4)

Source: Section 3.2.P.1 Description and Composition of the Drug Product, Page 3, Table 1

2.2.2 What are the proposed mechanism of action and therapeutic indications?

Refer to the approved label of NDA 021929,
"Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard in vitro and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay.

Formoterol fumarate is a long-acting selective β2 adrenergic agonist with a rapid onset of action. Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. In vitro studies have shown that formoterol has more than 200-fold greater agonist activity at β2 receptors than at β1-receptors."

The proposed therapeutic indication in this supplement is to "Treatment of asthma in patients aged 6 to <12 years".

2.2.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dosage in children aged 6 to <12 years is 2 inhalations of SYMBICORT 80/4.5 twice daily. The route of administration is oral inhalation.

2.3 General Clinical Pharmacology

2.3.1 What are the PK endpoints in clinical pharmacology studies?

Urine formoterol PK parameters (Ae_{0-12} and fe_{0-12}) following single dose administration of formoterol (2.25µg, 4.5µg, and 9µg) in combination with budesonide pMDI 160 µg were among the secondary endpoints in Study D589GC00002.

2.3.2 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The parent compound, formoterol, is the active moiety. Urine concentrations of formoterol were measured using a validated LC-MS/MS method.

2.4 PK Characteristics of the Drug

2.4.1 What are the characteristics of drug absorption?

Refer to the approved label of NDA 021929, "*Budesonide: Healthy Subjects: Orally inhaled budesonide is rapidly absorbed in the lungs and peak concentration is typically reached within 20 minutes. After oral administration of budesonide peak plasma concentration was achieved in about 1 to 2 hours and the absolute systemic availability was 6%-13% due to extensive first pass metabolism. In healthy subjects, 34% of the metered dose was deposited in the lung (as assessed by plasma concentration method and using a budesonide-containing dry powder inhaler) with an absolute systemic availability of 39% of the metered dose.*

Formoterol: Inhaled formoterol is rapidly absorbed; peak plasma concentrations are typically reached at the first plasma sampling time, within 5-10 minutes after dosing. Approximately 8% of the delivered dose of formoterol was recovered in the urine as unchanged drug."

2.4.3 What are the characteristics of drug distribution?

Refer to the approved label of NDA 021929, "*Budesonide: The volume of distribution of budesonide was approximately 3 L/kg. It was 85%-90% bound to plasma proteins.*

Formoterol: Over the concentration range of 10-500 nmol/L, plasma protein binding for the RR and SS enantiomers of formoterol was 46% and 58%, respectively."

2.4.4 What are the characteristics of drug metabolism?

Refer to the approved label of NDA 021929, "*Budesonide: In vitro studies with human liver homogenates have shown that budesonide was rapidly and extensively metabolized. Two major metabolites formed via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4) catalyzed biotransformation have been isolated and identified as 16α-hydroxyprednisolone and 6ß-hydroxybudesonide. The corticosteroid activity of each of these two metabolites was less than 1% of that of the parent compound.*

Formoterol: The primary metabolism of formoterol is by direct glucuronidation and by O-demethylation followed by conjugation to inactive metabolites. Secondary metabolic pathways include deformylation and sulfate conjugation. CYP2D6 and CYP2C have been identified as being primarily responsible for O-demethylation."

2.4.5 What are the characteristics of drug elimination?

Refer to the approved label of NDA 021929, "*Budesonide: Budesonide was excreted in urine and feces in the form of metabolites. Approximately 60% of an intravenous radiolabeled dose was recovered in the urine.*
No unchanged budesonide was detected in the urine. The 22R form of budesonide was preferentially cleared by the liver with systemic clearance of 1.4 L/min vs 1.0 L/min for the 22S form. The terminal half-life, 2 to 3 hours, was the same for both epimers and was independent of dose.

Formoterol: The excretion of formoterol was studied in four healthy subjects following simultaneous administration of radiolabeled formoterol via the oral and IV routes. In that study, 62% of the radiolabeled formoterol was excreted in the urine while 24% was eliminated in the feces."

2.5 Intrinsic Factors

2.5.1 How is the systemic exposure in children compared to that in adults?

- Budesonide
  The dose-normalized budesonide geometric mean $AUC_{0\text{-}inf}$ and C_{max} following 12 inhalations of Symbicort pMDI (160/4.5 per inhalation) in adults were 9.68 pM·h/μg and 2.35 pM/μg, respectively (Table 1.1).

  The dose-normalized budesonide geometric mean $AUC_{0\text{-}inf}$ and C_{max} following 4 inhalations of Symbicort pMDI (160/4.5 per inhalation) in children were 6.59 pM·h/μg and 2.13 pM/μg, respectively (Table 1.1).

  Therefore, the dose-normalized budesonide systemic exposure ($AUC_{0\text{-}inf}$ and C_{max}) in children was numerically lower than that of adults following single dose inhalation from the Symbicort pMDI device.

- Formoterol
  The formoterol geometric mean $AUC_{0\text{-}6}$ and C_{max} following BID inhalation of Symbicort pMDI (320/9) BID in adults with asthma at steady state were 102 pM·h and 27.9 pM, respectively (Table 1.2). Following the same dose and dosing regimen in children with asthma 6-11 years of age, the formoterol geometric mean $AUC_{0\text{-}6}$ and C_{max} at steady state were 110 pM·h and 27.0 pM, respectively (Table 1.2). Therefore, formoterol systemic exposure at steady state in children was comparable to that of adults following administration of Symbicort pMDI (320/9) BID.

2.5.2 Renal Impairment

Refer to the approved label of NDA 021929, "*There are no data regarding the specific use of SYMBICORT in patients with renal impairment.*"

2.5.3 Hepatic Impairment

Refer to the approved label of NDA 021929, "*There are no data regarding the specific use of SYMBICORT in patients with hepatic impairment. Reduced liver function may affect the elimination of corticosteroids. Budesonide pharmacokinetics was affected by compromised liver function as evidenced by a doubled systemic availability after oral ingestion. The intravenous budesonide pharmacokinetics was, however, similar in cirrhotic patients and in healthy subjects. Specific data with formoterol is not available, but because formoterol is primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver impairment.*"

2.6 Drug-drug interactions (DDI)

Refer to the approved label of NDA 021929, "*A single-dose crossover study was conducted to compare the pharmacokinetics of eight inhalations of the following: budesonide, formoterol, and budesonide plus formoterol administered concurrently. The results of the study indicated that there was no evidence of a pharmacokinetic interaction between the two components of SYMBICORT.*

Inhibitors of cytochrome P450 enzymes
Ketoconazole: Ketoconazole, a strong inhibitor of cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4), the main metabolic enzyme for corticosteroids, increased plasma levels of orally ingested budesonide.

Cimetidine: At recommended doses, cimetidine, a nonspecific inhibitor of CYP enzymes, had a slight but clinically insignificant effect on the pharmacokinetics of oral budesonide.

Specific drug-drug interaction studies with formoterol have not been performed."

2.7 Analytical Section

2.7.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

Only urine concentration of unchanged formoterol was measured in Study D589GC00002. Aliquots of 150 µL urine and 50 µL internal standard working solution (or 50 µL 0.1% formic acid for the blank samples) were added to a 5 mL glass tube. After vortex mixing for 10 seconds, 200 µL 1% ammonia in water was added. After vortex mixing for 20 seconds, the samples were slowly loaded onto SPE columns, which had been conditioned with 200 µL methanol, followed by 200 µL 1% ammonia in water. The SPE columns were washed with 200 µL 1% ammonia in water, followed by 200 µL 1% ammonia in acetonitrile, followed by 200 µL 1% ammonia in water : methanol (1 : 1 v/v). After cleaning the column tips with a tissue, the samples were eluted with 50 µL 0.5% formic acid in methanol : water (1 : 1 v/v), followed by 50 µL water into a 2 mL polypropylene deep well collection plate. The plate was covered with a silicone mat. After vortex mixing for 20 seconds and centrifugation at 1500 x g at 20ºC for 1 minute, a volume of 5 µL was injected into the chromatographic system. The method was validated prior to sample analysis and was reported in study number AZE042XL-100423-B / (b) (4)-RD-1208.

2.7.2 For all moieties measured, is free, bound, or total measured?

Due to the nature of the measuring method, it's the total amount of formoterol that was measured.

2.7.3 What is the range of the standard curve? What is the limit of quantitation? What are the accuracy, precision, and selectivity at these limits? What is the sample stability under conditions used in the study?

The summary of the validation results from analyzing formoterol plasma concentrations is listed in Table 2.3. The range of calibration curves is 40.0 pM to 50000 pM. The lower limit of quantitation was 40 pM. The dilution linearity was about 10-fold. The method had acceptable selectivity over matrix as the experiments were assessed using blank human urine from 6 individuals. The precision and accuracy of LLOQ, low, medium and high quality controls were all within ±15% of the nominal value. Formoterol urine samples were stable for at least 4 freeze/thaw cycles, and at least 25 hours at room temperature.

Table 2.3 Summary of Assay Performance of Formoterol Quality Control for Study D589GC00002

Required sample volume	150 µL
LLOQ	40.0 pmol/L
Calibration range	40.0-50 000 pmol/L
Sample minimum required dilution	Not applicable
Dilution linearity (range)	10 fold dilution acceptable (Dilution QC at a concentration of 400 000 pmol/L)
Matrix selectivity	Acceptable selectivity (with and without addition of internal standard) and matrix effects were demonstrated. The experiments were assessed using blank human urine from 6 individuals.
Intra-assay precision (CV%)	Low QC: 5.0; 3.9, 3.8
	Mid QC: 1.5, 1.8, 2.2
	High QC: 1.9, 2.3, 1.1
Inter-assay precision (CV%)	Low QC: 4.5
	Mid QC: 2.4
	High QC: 3.7
Intra-assay accuracy (Diff%)	Low QC: -2.0, -6.3, -3.0
	Mid QC: 2.6, 2.3, -1.2
	High QC: -2.6, -2.4, -8.9
Inter-assay accuracy (Diff%)	Low QC: -3.8
	Mid QC: 1.2
	High QC: -4.6
Freeze/thaw stability	At least 4 times
Room temperature stability	At least 25 h

Source: 2016OCT20-Attachment-response.pdf, page 4-5

2.8 Reference:

1. FDA 04/03/2009 Complete Response Letter:
   http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af80135d7f

2. FDA Clinical Pharmacology Review:
   http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af80165183

3. FDA 03/09/2015 Pediatric - Revised Written Request:
   http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af8037dd7b

4. FDA approved label of NDA 020831 Foradil®
   http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020831s028lbl.pdf

5. FDA approved label of NDA 021929 Symbicort®
   http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021929s021lbl.pdf

3 DETAILED LABELING RECOMMENDATIONS

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

Asthma

Cardiovascular effects: In a single-dose cross-over study involving 201 patients with persistent asthma, single-dose treatments of 4.5, 9, and 18 mcg of formoterol in combination with 320 mcg of budesonide delivered via SYMBICORT were compared to budesonide 320 mcg alone. Dose-ordered improvements in FEV_1 were demonstrated when compared with budesonide. ECGs and blood samples for glucose and potassium were obtained post-dose. For SYMBICORT, small mean increases in serum glucose and decreases in serum potassium (+0.44 mmol/L and -0.18 mmol/L at the highest dose, respectively) were observed with increasing doses of formoterol, compared to budesonide. In ECGs, SYMBICORT produced small dose-related mean increases in heart rate (approximately 3 bpm at the highest dose), and QTc intervals (3-6 msec) compared to budesonide alone. No subject had a QT or QTc value ≥500 msec.

In the United States, five 12-week, active- and placebo-controlled studies and one 6-month active-controlled study evaluated 2976 patients aged 6 years and older with asthma. Systemic pharmacodynamic effects of formoterol (heart/pulse rate, blood pressure, QTc interval, potassium, and glucose) were similar in patients treated with SYMBICORT, compared with patients treated with formoterol dry inhalation powder 4.5 mcg, 2 inhalations twice daily. No patient had a QT or QTc value ≥500 msec during treatment.

In three placebo-controlled studies in adolescents and adults with asthma, aged 12 years and older, a total of 1232 patients (553 patients in the SYMBICORT group) had evaluable continuous 24-hour electrocardiographic monitoring. Overall, there were no important differences in the occurrence of ventricular or supraventricular ectopy and no evidence of increased risk for clinically significant dysrhythmia in the SYMBICORT group compared to placebo.

HPA-axis effects: Overall, no clinically important effects on HPA-axis, as measured by 24-hour urinary cortisol, were observed for SYMBICORT treated adult or adolescent patients at doses up to 640/18 mcg/day compared to budesonide.

(b) (4)

Special Populations

Geriatric

The pharmacokinetics of SYMBICORT in geriatric patients have not been specifically studied.

Pediatric

Plasma concentrations of budesonide were measured following administration of four inhalations of SYMBICORT 160/4.5 in a single-dose study in pediatric patients with asthma, 6 to <12 years of age.

(b) (4)

(b) (4)

. The dose-normalized C_{max} and $AUC_{0\text{-}inf}$ of budesonide

(b) (4)


(b) (4)

4. Appendix

4.1 Individual Study Review of Study D589GC00002

Study Type: Phase 2 efficacy, safety, PK, formoterol dose ranging study in children with asthma
Study Dates: 10/07/2010 – 01/03/2012

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

Objective:
The primary objective of this study was to evaluate the bronchodilating effects of 3 doses of formoterol given in combination with budesonide as Symbicort pMDI in a population of asthmatic children demonstrated to be stable on a medium dose range of inhaled corticosteroid (ICS) therapy.

The secondary objectives were:

- Evaluate the bronchodilating effect of Foradil Aerolizer (formoterol fumarate inhalation powder; Merck) 12 µg;
- Determine the systemic exposure to formoterol following administration of formoterol 2.25 µg, 4.5 µg, and 9 µg, given in combination with budesonide as Symbicort pMDI or Foradil Aerolizer 12 µg.

Study Design and Method:
This was a Phase 2, single-dose, randomized, partially-blinded, 5-way cross-over, active- and placebo-controlled multicenter study comparing the bronchodilating effects following single doses of formoterol in combination with budesonide pMDI 160 µg, in pediatric patients with asthma. A total of 54 patients were randomized to the study. All randomized patients received at least one formoterol treatment; 50 patients (92.6%) received all 5 treatments and completed the study. During each treatment period, FEV1 and urine samples were collected for 12 hours post-dose. The treatment periods were separated by approximately 7-day (range of 3-14 days) wash-out period.

The doses of single dose treatments are summarized in Table 4.1. Each subject received 3 inhalations from two products during each treatment period. Treatments in all the arms except Foradil Aerolizer® active control arm were blinded. Refer to the approved label of NDA 020831; each inhalation of Foradil Aerolizer® 12 µg delivers *"10 mcg of formoterol fumarate from the mouthpiece"*[4].

Table 4.1 Products and Doses of Five Treatment Arms in Study D589GC00002

Treatment Arms	Doses (Budesonide/ Formoterol)	Products					
		Symbicort pMDI 80/2.25*	Symbicort pMDI 80/4.5	Budesonide HFA pMDI 40*	Budesonide HFA pMDI 80*	Placebo HFA pMDI	Foradil Aerolizer 12#
Blinded Arms	160 µg/ 0				2 inhalations	1 inhalation	
	160 µg/ 2.25 µg	1 inhalation		2 inhalations			
	160 µg/ 4.5 µg	2 inhalations				1 inhalation	
	160 µg/ 9.0 µg		2 inhalations			1 inhalation	
Partially Blinded Arm	160 µg/ 12 µg				2 inhalations		1 inhalation

* Investigational HFA MDI products
# 12 µg formoterol fumarate, which equals 9.8 µg formoterol
Source: adapted from CSR Report d589gc00002, page 24-25

Noteworthy inclusion criteria:

- Was between the ages of 6 and <12 years (not having reached his/her 12th birthday at the time of Visit 1)
- Had a documented clinical diagnosis of asthma as defined by the American Thoracic Society for at least 6 months prior to Visit 1.
- Had a FEV1 measured at least 6 hours after the last dose of inhaled, SABA, and at least 48 hours after the last dose of inhaled LABA of ≥60% and ≤85% of predicted normal.
- Demonstrated reversibility of FEV1 of ≥15% from pre-albuterol level within 15 to 30 minutes after administration of a standard dose of albuterol at Visit 2.
- Had required and received treatment with a consistent daily dose of ICS within the corresponding dose range for at least 4 weeks prior to Visit 1.
- If receiving inhalant allergen immunotherapy, the patient must have been on a stable maintenance regimen for at least 6 weeks and was expected to remain on immunotherapy throughout the study.

Noteworthy exclusion criteria:

- Had been hospitalized for >24 hours at least once or has required emergency treatment more than once in an emergency department (or equivalent) for acute deterioration of asthma during the 6 months prior to Visit 1.
- Had required treatment with systemic corticosteroids (e.g., oral, parenteral, or rectal) for any reason within the 12 weeks prior to Visit 1.
- Was receiving treatment with a β-blocker (including eye drops).
- Had taken Xolair®, or any other monoclonal or polyclonal antibody therapy, for any reason within the 6 months prior to Visit 2

12-hour urine samples were collected following each single dose treatment for determination of unchanged formoterol. Unchanged formoterol from urine was extracted by solid phase (SPE column) followed by LC-MS/MS analysis. The calibration range was from 40.0 to 50000 pM. The calibration curve, QC sample and ISR results data met the acceptance criteria. The precision (%CV) for the QC samples at 3 concentrations was ≤8.4% and the accuracy (% bias) for the QC samples at 3 concentrations was between -4.3% and 3.5%.

Efficacy Endpoint:
The primary efficacy endpoint is the average post-dose 12-hour FEV1

PK Endpoints:

- Amount of formoterol excreted in the urine over a 12-hour period after administration (Ae_{0-12})
- Fraction of the formoterol dose excreted in the urine over a 12-hour period after administration (fe_{0-12})

Demographics:
The demographic and key baseline characteristics of study patients are summarized in Table 4.2. Of 54 patients randomized, 31 (57.4%) were boys and 23 (42.6%) were girls. The mean age was 9.2 years (ranging from 6 to 11 years), with 11 patients (20.4%) between the ages of 6 to <8 years. The patients had a mean time of 73.2 months since asthma diagnosis.

Table 4.2 Demographic Information [Randomized/Safety/Efficacy (ITT)] Analysis Set

Parameter	All randomized (N = 54)
Sex	
Male	31 (57.4%)
Female	23 (42.6%)
Age (years)	
Mean	9.2
SD	1.79
Median	10.0
Min	6
Max	11
Age group (years)	
≥6 to <8	11 (20.4%)
≥8 to <12	43 (79.6%)
Race	
White	31 (57.4%)
Black/African American	22 (40.7%)
Asian	0
Native Hawaiian or Other Pacific Islander	0
American Indian or Alaska Native	0
Other	1 (1.9%)
Months since asthma diagnosis	
Mean	73.2
SD	39.16
Median	72.7
Min	10
Max	142

Source: from CSR Report d589gc00002, page 36, Table 8.

PK Results:

In total, 203 urine samples were collected for measuring formoterol urine concentrations. Among them,

- Three urine samples from subjects (Subjects E2812005, E2819010, and E2856023) in budesonide 160 µg treatment arm had detectable formoterol concentrations (BLOQ after re-analysis, 26.3 pM, and 55.1 pM, respectively). All three subjects participated in budesonide 160 µg/formoterol 9 µg treatment arm in the prior period. The wash-out period between the prior period and this period was 5 days for all three subjects. By considering 1) the terminal elimination half-life of formoterol is 10 hours[4], 2) the median unchanged formoterol urine concentration was 2230 pM (ranging from 224-8990 pM) following inhalation of 9µg formoterol; there could be residue formoterol detectable in certain urine samples 5 days post-dose.

- One sample from Subject E2825001 in budesonide 160 µg/formoterol 2.25 µg treatment arm was BLOQ. Considering the geometric mean of formoterol urine concentration from this treatment arm (539.5 pmol) was 13-fold higher than the limit of LOQ, and the coefficient of variation was 146%, the result is not unexpected. Indeed, there were two more samples from this treatment arm with concentrations within 2-fold range of the LOQ.

- Six samples (6/49) from subjects (Subjects E2805001, E2825001, E2827005, E2829004, E2832003, and E2837011) in budesonide 160 µg/Foradil 12 µg treatment arm were BLOQ. The

sponsor considered that *"it is not reasonable that a patient who inhaled Foradil 12 µg correctly would have no formoterol exposure"*.

The arithmetic mean urinary unchanged formoterol Ae_{0-12} and fe_{0-12} values from each treatment arm were summarized in Table 4.3. The formoterol Ae_{0-12} values appeared to increased dose proportionally with dose increase from 2.25 µg to 9.0 µg as delivered by Symbicort pMDI; the result is consistent with relative stable fe_{0-12} values across all three dose groups. The geometric mean urinary unchanged formoterol Ae_{0-12} and fe_{0-12} from Foradil® Aerolizer 12 µg treatment arm were 21% and 29% less than Symbicort pMDI 9.0 µg treatment arm.

Table 4.3 Arithmetic Mean of Formoterol Ae_{0-12} and fe_{0-12} following Single Dose Administration by Symbicort pMDI or Foradil Aerolizer (PK Set)

Time point	Class	Treatment				
		BUD 160/ FM 2.25 (N = 54)	BUD 160/ FM 4.5 (N = 53)	BUD 160/ FM 9.0 (N = 53)	BUD 160/ Foradil 12.0 (N = 51)	
Amount of formoterol excreted (pmol)	N	51	52	51	49[a]	43[b]
	Mean	278.39	532.65	1090.88	860.42	980.47
	SD	204.520	416.762	681.941	806.558	789.274
	Median	229.98	473.63	1036.05	790.78	883.52
	Min	0.0	34.1	27.6	0.0	81.9
	Max	1003.9	2318.1	4204.1	4942.7	4942.7
Fraction of formoterol excreted (%)	N	51	52	51	49	43[b]
	Mean	5.20	4.98	5.10	3.64	4.14
	SD	3.823	3.895	3.187	3.415	3.343
	Median	4.30	4.43	4.84	3.33	3.72
	Min	0.0	0.3	0.1	0.0	0.3
	Max	18.8	21.7	19.6	20.8	20.8

Bud, budesonide; FM, formoterol
[a] All available data
[b] Excluding 6 subjects whose urine formoterol concentrations were BLOQ
Source: from CSR Report d589gc00002, page 52, Table 17

When 6 BLOQ samples in budesonide 160 µg/Foradil 12 µg treatment arm were excluded from the analysis, the arithmetic mean Ae_{0-12} and fe_{0-12} values from budesonide 160 µg/Foradil Aerolizer12 µg treatment arm were closer to those of budesonide 160 µg/formoterol 9.0 µg arm.

Efficacy Results:

Treatment comparisons of average post-dose 12-hour FEV1 showed that all the budesonide/formoterol treatment arms were superior to budesonide-only treatment arm (Table 4.4). In addition, budesonide 160 µg/formoterol 4.5 µg arm and budesonide 160 µg/formoterol 9.0 µg arm were superior to budesonide 160 µg/formoterol 2.25 µg arm, whereas there was no statistically significant difference between budesonide 160 µg/formoterol 4.5 µg arm and budesonide 160 µg/formoterol 9.0 µg arm.

Table 4.4 Treatment Comparison* of Average Post-dose 12-hour FEV1 (L) (Efficacy Analysis Set)

	From ANCOVA		
Contrast	LS Mean (SE)	95% CI	p-value
BUD 160/FM 9.0 vs. BUD 160	0.114 (0.0140)	(0.087, 0.142)	<0.0001
BUD 160/FM 4.5 vs. BUD 160	0.105 (0.0140)	(0.078, 0.133)	<0.0001
BUD 160/FM 2.25 vs. BUD 160	0.058 (0.0141)	(0.030, 0.085)	0.0001
BUD 160/FM 4.5 vs. BUD 160/FM 9.0	-0.009 (0.0139)	(-0.036, 0.018)	0.5223
BUD 160/FM 2.25 vs. BUD 160/FM 9.0	-0.057 (0.0139)	(-0.084, -0.029)	0.0001
BUD 160/FM 2.25 vs. BUD 160/FM 4.5	-0.048 (0.0138)	(-0.075, -0.020)	0.0007
BUD 160 vs. BUD 160/Foradil 12.0	-0.114 (0.0141)	(-0.142, -0.086)	<0.0001
BUD 160/FM 2.25 vs. BUD 160/Foradil 12.0	-0.056 (0.0141)	(-0.084, -0.028)	0.0001
BUD 160/FM 4.5 vs. BUD 160/Foradil 12.0	-0.009 (0.0141)	(-0.036, 0.019)	0.5394
BUD 160/FM 9.0 vs. BUD 160/Foradil 12.0	0.000 (0.0140)	(-0.027, 0.028)	0.9863

* As analyzed by ANCOVA. Factors in the ANCOVA model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit.
BUD, budesonide; FM, formoterol
Source: from CSR Report d589gc00002, page 46, Table 14

Average post-dose12-hour FEV1 increased 16 mL (from 1.603 L to 1.619 L) in budesonide 160 µg/Foradil Aerolizer 12 µg arm when six subjects with BLOQ urine samples were excluded. This small change did not affect the general efficacy conclusion of this study (Table 4.5).

Table 4.5 Sensitivity Analysis*: Treatment Comparison* of Average Post-dose 12-hour FEV1 (L) (Excluding 6 Subjects in BUD/160/Foradil 12.0 Treatment Arm)

Contrast	LS Mean	95% CI	p-value
BUD 160 vs. BUD 160/ Foradil 12.0	-0.131	(-0.158, -0.103)	<0.0001
BUD 160/ FM 2.25 vs. BUD 160/ Foradil 12.0	-0.073	(-0.101, -0.045)	<0.0001
BUD 160/ FM 4.5 vs. BUD 160/ Foradil 12.0	-0.025	(-0.053, 0.003)	0.0753
BUD 160/ FM 9.0 vs. BUD 160/ Foradil 12.0	-0.016	(-0.044, 0.011)	0.2496

* As used the same ANCOVA analysis in Table 4.4.
BUD, budesonide; FM, formoterol
Source: from CSR Report d589gc00002, page 55, Table 19

Vital Sign Results:
Pre-dose vital signs (blood pressure and pulse rate) were recorded in the morning before inhalation of the study drug in each treatment period. No electrocardiogram examinations were performed during this study. The differences between treatment arms on pre-dose blood pressure and pulse rate were all numerically small and not clinically meaningful (Table 4.6).

Table 4.6 Treatment Comparison of Mean (SD) Pre-Dose Vital Signs (Safety Analysis Set)

Treatment Arm	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Pulse Rate (bpm)
BUD 160 (N=51)	102.9 (13.93)	67.4 (10.78)	79.2 (11.38)
BUD 160/ FM 2.25 (N=54)	103.7 (11.00)	66.9 (9.13)	80.5 (10.54)
BUD 160/ FM 4.5 (N=53)	105.1 (9.81)	68.5 (7.82)	79.3 (10.90)
BUD 160/ FM 9.0 (N=53)	104.1 (10.87)	67.9 (8.93)	79.7 (9.12)
BUD 160/ Foradil 12.0 (N=50)	103.7 (11.78)	64.8 (8.59)	80.2 (10.74)

BUD, budesonide; FM, formoterol
Source: from CSR Report d589gc00002, page 283-285, Table 11.3.8.1.1.2

PK Conclusions:
The amount of formoterol excreted in the urine within 12 hour post-single dose increased proportionally with dose increase from 2.25 µg to 9 µg. The fraction of formoterol excreted in the urine within 12 hour post-single dose was about 5% (arithmetic mean).

Reviewer's Analysis:
The geometric mean urinary unchanged formoterol Ae_{0-12} and fe_{0-12} values from each treatment arm were summarized by reviewer in Table 4.7. The formoterol Ae_{0-12} values appeared to increase dose proportionally with dose increase from 2.25 µg to 9.0 µg as delivered by Symbicort pMDI inhaler; the result is consistent with relative stable fe_{0-12} values across all three dose groups. The geometric mean urinary unchanged formoterol Ae_{0-12} and fe_{0-12} from Foradil® Aerolizer12 µg treatment arm were only half the value compared to Symbicort 9.0 µg treatment arm.

Table 4.7 Geometric Mean of Formoterol Ae_{0-12} and fe_{0-12} following Single Dose Administration by Symbicort pMDI or Foradil Aerolizer (PK Set)

Treatment Arm	N	Ae_{0-12} (pmol)	Ae_{0-12} (µg)	fe_{0-12} (%)	CV%
BUD 160/ FM 2.25	51	199	0.0837	3.72%	132%
BUD 160/ FM 4.5	52	397	0.167	3.71%	100%
BUD 160/ FM 9.0	51	868	0.365	4.06%	97.7%
BUD 160/ Foradil 12	49	434	0.182	1.82%	392%

Bud, budesonide; FM, formoterol
All the BLOQ samples were imputed with ½ LLOQ value (20 pmol)
Source: Reviewer's analysis from RSPC.xpt

When 6 BLOQ samples in budesonide 160 µg/Foradil 12 µg treatment arm were excluded from the analysis, the geometric mean Ae_{0-12} and fe_{0-12} value from budesonide 160 µg/Foradil 12 µg treatment arm was 749 (CV=94.3%) pmol and 3.15% (CV=94.3%), respectively.

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/s/

YUNZHAO REN
01/01/2017

BHAWANA SALUJA
01/02/2017