CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-929/S012

Trade Name: Symbicort

Generic Name: Budesonide; Formoterol Fumarate Dihydrate

Sponsor: AstraZeneca

Approval Date: 2/27/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21–929/S012

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	✓
Other Action Letters	
Labeling	✓
REMS	✓
Summary Review	✓
Officer/Employee List	✓
Office Director Memo	
Cross Discipline Team Leader Review	✓
Medical Review(s)	✓
Chemistry Review(s)	✓
Environmental Assessment	
Pharmacology Review(s)	✓
Statistical Review(s)	✓
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	✓
Other Reviews	✓
Risk Assessment and Risk Mitigation Review(s)	✓
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	✓

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21–929/S012

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-929/S-012

AstraZeneca LP
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Attention: Mark DeSiato
Executive Director, Regulatory Affairs

Dear Mr. DeSiato:

Please refer to your supplemental new drug application dated April 28, 2008, received April 29, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for SYMBICORT (budesonide/formoterol) Inhalation Aerosol.

We acknowledge receipt of your submissions dated July 24, August 7, 20, and 25, November 26, and December 3, and 5, 2008 and January 9, 15, 22, and 23, and February 6, 19, 23, 24, and 26, 2009.

This supplemental new drug application provides for the use of SYMBICORT for the treatment of Chronic Obstructive Pulmonary Disease (COPD).

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling text for the package insert submitted February 26, 2009, and Medication Guide submitted February 19, 2009. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 21-929/S-012."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. We are waiving the pediatric study requirement for this supplement because the necessary studies are impossible or highly impracticable since the disease does not exist in children.

RISK EVALUATION AND MITIGATION STRATEGIES REQUIREMENTS

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) for an approved drug if the FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

Since SYMBICORT was approved July 2006, FDA has become aware of an increased incidence of lower respiratory tract infections in patients with COPD who take SYMBICORT. This information is from controlled clinical trials (one 6-month and one 12-month safety and efficacy trial) submitted with this supplemental new drug application. This information was not available when SYMBICORT was granted marketing authorization. Therefore, we consider this information to be "new safety information" as defined in FDAAA.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Your previously approved Medication Guide has been revised to include the new safety information. Pursuant to 21 CFR Part 208, FDA has determined that SYMBICORT poses a serious and significant public health concern requiring distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of SYMBICORT. FDA has determined that SYMBICORT is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use SYMBICORT. FDA has also determined that Symbicort is a product for which patient labeling could help prevent serious adverse events. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed SYMBICORT.

Your proposed REMS, submitted on January 15, 2009, and appended to this letter, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS included in your January 15, 2009, submission.

Your assessment of the REMS should include:

a. An evaluation of patients' understanding of the serious risks of Symbicort.

Prominently identify submissions containing REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission:

- **NDA 21-929 REMS ASSESSMENT**
- **NEW SUPPLEMENT FOR NDA 21-929**
  PROPOSED REMS MODIFICATION
  < other supplement identification > [if included]
  <REMS ASSESSMENT> [if included]

If you do not submit electronically, please send 5 copies of submissions containing REMS assessments or proposed modifications of the REMS.

PROMOTIONAL MATERIALS

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Pulmonary and Allergy Products and two copies of both the promotional materials and the package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Colette Jackson, Regulatory Project Manager, at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: REMS, Package Insert, Medication Guide

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

/s/

Badrul Chowdhury

2/27/2009 12:13:53 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21–929/S012

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SYMBICORT safely and effectively. See full prescribing information for SYMBICORT.

SYMBICORT® 80/4.5
(budesonide 80 mcg and formoterol fumarate dihydrate* 4.5 mcg)
Inhalation Aerosol
SYMBICORT® 160/4.5
(budesonide 160 mcg and formoterol fumarate dihydrate* 4.5 mcg)
Inhalation Aerosol
FOR ORAL INHALATION
Initial US Approval: 2006

WARNING: RISK OF ASTHMA-RELATED DEATH ***(See full prescribing information for complete boxed warning.)***

- **Long-acting beta$_2$-adrenergic agonists (LABA) may increase the risk of asthma-related death. A placebo-controlled study with another LABA (salmeterol) showed an increase in asthma-related deaths in patients receiving salmeterol. The finding of an increase in the risk of asthma-related deaths with salmeterol may apply to formoterol. (5.1)**
- **When treating patients with asthma, prescribe SYMBICORT only for patients not adequately controlled on other asthma-controller medications or whose disease severity clearly warrants initiation of treatment with two maintenance therapies (1.1, 5.1)**

----------RECENT MAJOR CHANGES----------

Indications and Usage, Maintenance Treatment of Chronic Obstructive Pulmonary Disease (1.2)	February 2009
Dosage and Administration, Chronic Obstructive Pulmonary Disease (2. 2)	February 2009
Warnings and Precautions, Pneumonia (5.5)	February 2009

----------INDICATIONS AND USAGE----------

SYMBICORT is a combination product containing a corticosteroid and a long-acting beta$_2$-adrenergic agonist indicated for:

- Maintenance treatment of asthma in patients 12 years of age and older. (1.1)
- Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. (1.2)

Important limitations:

- Not indicated for patients whose asthma can be managed by inhaled corticosteroids with occasional use of inhaled short-acting beta$_2$-agonists. (1.1)
- Not indicated for the relief of acute bronchospasm. (1.1, 1.2)

----------DOSAGE AND ADMINISTRATION----------

For oral inhalation only.

- Maintenance treatment of asthma in patients >12 years: 2 inhalations twice daily of SYMBICORT 80/4.5 or 160/4.5. Starting dosage is based on asthma severity. (2.1)
- Maintenance treatment of airflow obstruction in COPD: 2 inhalations of SYMBICORT 160/4.5 twice daily (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Metered-dose inhaler containing a combination of budesonide (80 or 160 mcg) and formoterol (4.5 mcg) as an inhalation aerosol (3)

----------CONTRAINDICATIONS----------

- Primary treatment of status asthmaticus or acute episodes of asthma or COPD requiring intensive measures. (4)
- Hypersensitivity to any of the ingredients in SYMBICORT (4)

----------WARNINGS AND PRECAUTIONS----------

- Asthma-related death: Long-acting beta$_2$-adrenergic agonists may increase the risk. Prescribe only for recommended patient populations. (5.1)
- Deterioration of disease and acute episodes: Do not initiate in acutely deteriorating asthma or to treat acute symptoms. (5.2)
- Use with additional long-acting beta$_2$-agonist: Do not use in combination because of risk of overdose. (5.3)
- Localized infections: *Candida albicans* infection of the mouth and throat may occur. Monitor patients periodically for signs of adverse effects on the oral cavity. Advise patients to rinse the mouth following inhalation. (5.4)
- Pneumonia: Increased risk in patients with COPD. Monitor patients for signs and symptoms of pneumonia and other potential lung infections. (5.5)
- Immunosuppression: Potential worsening of infections (e.g., existing tuberculosis, fungal, bacterial, viral, or parasitic infection; or ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.6)
- Transferring patients from systemic corticosteroids: Risk of impaired adrenal function when transferring from oral steroids. Taper patients slowly from systemic corticosteroids if transferring to SYMBICORT. (5.7)
- Hypercorticism and adrenal suppression: May occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue SYMBICORT slowly. (5.8)
- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Risk of increased systemic corticosteroid effects. Exercise caution when used with SYMBICORT. (5.9)
- Paradoxical bronchospasm: Discontinue SYMBICORT and institute alternative therapy if paradoxical bronchospasm occurs. (5.10)
- Patients with cardiovascular or central nervous system disorders: Use with caution because of beta-adrenergic stimulation. (5.12)
- Decreases in bone mineral density: Assess bone mineral density initially and periodically thereafter. (5.13)
- Effects on growth: Monitor growth of pediatric patients. (5.14)
- Glaucoma and cataracts: Close monitoring is warranted. (5.15)
- Metabolic effects: Be alert to eosinophilic conditions, hypokalemia, and hyperglycemia. (5.16, 5.18)
- Coexisting conditions: Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.17)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥ 3%) are:

- Asthma: nasopharygitis, headache, upper respiratory tract infection, pharygolaryngeal pain, sinusitis, influenza, back pain, nasal congestion, stomach discomfort, vomiting, and oral candidiasis. (6.3)
- COPD: nasopharyngitis, oral candidiasis, bronchitis, sinusitis, upper respiratory tract infections. (6.3).

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Use with caution. May cause increased systemic corticosteroid effects.
- Monoamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of formoterol on vascular system. (7.2)
- Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. (7.3)
- Diuretics: Use with caution. Electrocardiographic changes and/or hypokalemia associated with nonpotassium-sparing diuretics may worsen with concomitant beta-agonists. (7.4)

----------USE IN SPECIFIC POPULATIONS----------

Hepatic impairment: Monitor patients for signs of increased drug exposure. (8)

--------SEE 17 FOR PATIENT COUNSELING INFORMATION AND MEDICATION GUIDE---------

Revised FEBRUARY, 2009

FULL PRESCRIBING INFORMATION: CONTENTS†

†Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF ASTHMA RELATED DEATH

Long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on other asthma-controller medications (e.g., low-to-medium dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies. Data from a large placebo-controlled U.S. study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol may apply to formoterol (a long-acting beta$_2$-adrenergic agonist), one of the active ingredients in SYMBICORT [*see Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of Asthma

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

Long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death [*see Warnings and Precautions (5.1)*]. One of the active ingredients of SYMBICORT is formoterol, a long-acting beta$_2$-agonist, therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies.

Important Limitations of Use:

- SYMBICORT is NOT indicated for the relief of acute bronchospasm.
- SYMBICORT is not indicated in patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled, short-acting beta$_2$-agonists.

1.2 Maintenance Treatment of Chronic Obstructive Pulmonary Disease (COPD)

SYMBICORT 160/4.5 is indicated for the twice daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. SYMBICORT 160/4.5 is the only approved dosage for the treatment of airflow obstruction in COPD.

Important Limitations of Use: SYMBICORT is not indicated for the relief of acute bronchospasm.

2 DOSAGE AND ADMINISTRATION

SYMBICORT should be administered twice daily every day by the orally inhaled route only. After inhalation, the patient should rinse the mouth with water without swallowing. *[see Patient Counseling Information (17.4)]*

Prime SYMBICORT before using for the first time by releasing two test sprays into the air away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 7 days or when it has been dropped, prime the inhaler again by shaking well before each spray and releasing two test sprays into the air away from the face.

More frequent administration or a higher number of inhalations (more than 2 inhalations twice daily) of the prescribed strength of SYMBICORT is not recommended as some patients are more likely to experience adverse effects with higher doses of formoterol. Patients using SYMBICORT should not use additional long-acting $beta_2$-agonists for any reason. *[See Warnings and Precautions (5.3, 5.12)]*

2.1 Asthma

If asthma symptoms arise in the period between doses, an inhaled, short-acting $beta_2$-agonist should be taken for immediate relief.

Adult and Adolescent Patients 12 Years of Age and Older: For patients 12 years of age and older, the dosage is 2 inhalations twice daily (morning and evening, approximately 12 hours apart).

The recommended starting dosages for SYMBICORT for patients 12 years of age and older are based upon patients' asthma severity.

For patients who are not currently receiving inhaled corticosteroid therapy, but whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies,

the recommended starting dose is SYMBICORT 80/4.5 or 160/4.5, two inhalations twice daily depending upon asthma severity.

The maximum recommended dosage is SYMBICORT 160/4.5 mg twice daily.

For all patients it is desirable to titrate to the lowest effective strength after adequate asthma stability is achieved.

Improvement in asthma control following inhaled administration of SYMBICORT can occur within 15 minutes of beginning treatment, although maximum benefit may not be achieved for 2 weeks or longer after beginning treatment. Individual patients will experience a variable time to onset and degree of symptom relief.

For patients who do not respond adequately to the starting dose after 1-2 weeks of therapy with SYMBICORT 80/4.5, replacement with SYMBICORT 160/4.5 may provide additional asthma control.

If a previously effective dosage regimen of SYMBICORT fails to provide adequate control of asthma, the therapeutic regimen should be re-evaluated and additional therapeutic options, (e.g., replacing the lower strength of SYMBICORT with the higher strength, adding additional inhaled corticosteroid, or initiating oral corticosteroids) should be considered.

2.2 Chronic Obstructive Pulmonary Disease (COPD)

For patients with COPD the recommended dose is SYMBICORT 160/4.5, two inhalations twice daily.

If shortness of breath occurs in the period between doses, an inhaled, short-acting beta$_2$-agonist should be taken for immediate relief.

3 DOSAGE FORMS AND STRENGTHS

SYMBICORT is available as a metered-dose inhaler containing a combination of budesonide (80 or 160 mcg) and formoterol (4.5 mcg) as an inhalation aerosol in the following two strengths: 80/4.5 and 160/4.5. Each dosage strength contains 60 or 120 actuations per/canister. Each strength of SYMBICORT is supplied with a red plastic actuator with a gray dust cap.

4 CONTRAINDICATIONS

The use of SYMBICORT is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required.
- Hypersensitivity to any of the ingredients in SYMBICORT.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Asthma-related Death with Long-Acting Beta$_2$-Adrenergic Agonists

Long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death [*see Warnings and Precautions (5.1)*]. One of the active ingredients of SYMBICORT is formoterol, a long-acting beta$_2$-agonist, therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies.

A 28-week, placebo controlled US study comparing the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death may represent a class effect of the long-acting beta$_2$-adrenergic agonists, including formoterol. No study adequate to determine whether the rate of asthma-related death is increased with SYMBICORT has been conducted.

Clinical studies with formoterol suggested a higher incidence of serious asthma exacerbations in patients who received formoterol than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups.

5.2 Deterioration of Disease and Acute Episodes

SYMBICORT should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma or COPD. SYMBICORT has not been studied in patients with acutely deteriorating asthma or COPD. The initiation of SYMBICORT in this setting is not appropriate.

Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of SYMBICORT with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 2 inhalations twice daily (morning and evening) of SYMBICORT.

SYMBICORT should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta$_2$-agonist, not SYMBICORT, should be used to relieve acute symptoms such as shortness of breath. When prescribing SYMBICORT, the physician must also provide the patient with an inhaled, short-acting beta$_2$-agonist (e.g., albuterol) for treatment of acute symptoms, despite regular twice-daily (morning and evening) use of SYMBICORT.

When beginning treatment with SYMBICORT, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

5.3 Excessive Use of SYMBICORT and Use with Other Long-Acting Beta$_2$-Agonists

As with other inhaled drugs containing beta$_2$-adrenergic agents, SYMBICORT should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing long-acting beta$_2$-agonists, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using SYMBICORT should not use an additional long-acting beta$_2$-agonist (e.g., salmeterol, formoterol fumarate, arformoterol tartrate) for any reason, including prevention of exercise-induced bronchospasm (EIB) or the maintenance treatment of asthma or COPD.

5.4 Local Effects

In clinical studies, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in patients treated with SYMBICORT. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while treatment with SYMBICORT continues, but at times therapy with SYMBICORT may need to be interrupted. Patients should rinse the mouth after inhalation of SYMBICORT.

5.5 Pneumonia and Other Lower Respiratory Tract infections

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap. Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids.

In a 6 month study of 1,704 patients with COPD, there was a higher incidence of lung infections other than pneumonia (e.g., bronchitis, viral lower respiratory tract infections, etc.) in patients receiving SYMBICORT 160/4.5 (7.6%) than in those receiving SYMBICORT 80/4.5 (3.2%), formotero1 4.5 mcg (4.6%) or placebo (3.3%). Pneumonia did not occur with greater incidence in the SYMBICORT 160/4.5 group (1.1 %) compared with placebo (1.3%). In a 12-month study of 1,964 patients with COPD, there was also a higher incidence of lung infections other than pneumonia in patients receiving SYMBICORT 160/4.5 (8.1%) than in those receiving SYMBICORT 80/4.5 (6.9%), formoterol 4.5 mcg (7.1%) or placebo (6.2%). Similar to the 6 month study, pneumonia did not occur with greater incidence in the SYMBICORT 160/4.5 group (4.0%) compared with placebo (5.0%).

5.6 Immunosuppression

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered. The immune responsiveness to varicella vaccine was evaluated in pediatric patients with asthma ages 12 months to 8 years with budesonide inhalation suspension.

An open-label, nonrandomized clinical study examined the immune responsiveness to varicella vaccine in 243 asthma patients 12 months to 8 years of age who were treated with budesonide inhalation suspension 0.25 mg to 1 mg daily (n=151) or noncorticosteroid asthma therapy (n=92) (i.e., $beta_2$-agonists, leukotriene receptor antagonists, cromones). The percentage of patients developing a seroprotective antibody titer of ≥5.0 (gpELISA value) in response to the vaccination was similar in patients treated with budesonide inhalation suspension (85%), compared to patients treated with noncorticosteroid asthma therapy (90%). No patient treated with budesonide inhalation suspension developed chicken pox as a result of vaccination.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

5.7 Transferring Patients From Systemic Corticosteroid Therapy

Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although SYMBICORT may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a

warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to SYMBICORT. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with SYMBICORT. Lung function (mean forced expiratory volume in 1 second [FEV_1] or morning peak expiratory flow [PEF], beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to inhaled corticosteroids or SYMBICORT may unmask conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). Some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

5.8 Hypercorticism and Adrenal Suppression

Budesonide, a component of SYMBICORT, will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since budesonide is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of SYMBICORT in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with SYMBICORT should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when budesonide is administered at higher than recommended

doses over prolonged periods of time. If such effects occur, the dosage of SYMBICORT should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of SYMBICORT with ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to budesonide may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*

5.10 Paradoxical Bronchospasm and Upper Airway Symptoms

As with other inhaled medications, SYMBICORT can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with SYMBICORT, it should be treated immediately with an inhaled, short-acting bronchodilator, SYMBICORT should be discontinued immediately, and alternative therapy should be instituted.

5.11 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of SYMBICORT, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

5.12 Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia *[see Overdosage (10)]*. Therefore, SYMBICORT, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Formoterol, a component of SYMBICORT, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of formoterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been

reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

5.13 Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, post menopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating SYMBICORT and periodically thereafter. If significant reductions in BMD are seen and SYMBICORT is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5, or placebo on BMD was evaluated in a subset of 326 patients (females and males 41 to 88 years of age) with COPD in the 12-month study. BMD evaluations of the hip and lumbar spine regions were conducted at baseline and 52 weeks using dual energy x-ray absorptiometry (DEXA) scans. Mean changes in BMD from baseline to end of treatment were small (mean changes ranged from -0.01 - 0.01 g/cm^2). ANCOVA results for total spine and total hip BMD based on the end of treatment time point showed that all geometric LS Mean ratios for the pairwise treatment group comparisons were dose to 1, indicating that overall, bone mineral density for total hip and total spine regions for the 12 month time point were stable over the entire treatment period.

5.14 Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving SYMBICORT routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT, titrate each patient's dose to the

lowest dosage that effectively controls his/her symptoms. *[See Dosage and Administration (2.1), Use in Specific Populations (8.4).]*

5.15 Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including budesonide, a component of SYMBICORT. Therefore, close monitoring is warranted in patients with a change in vision or with history of increased intraocular pressure, glaucoma, and/or cataracts.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5, or placebo on development of cataracts or glaucoma were evaluated in a subset of 461 patients with COPD in the 12-month study. Opthalmic examinations were conducted at baseline, 24 weeks, and 52 weeks. There were 26 subjects (6%) with an increase in posterior subcapsular score from baseline to maximum value (>0.7) during the randomized treatment period. Changes in posterior subcapsular scores of >0.7 from baseline to treatment maximum occurred in 11 patients (9.0%) in the SYMBICORT 160/4.5 group, 4 patients (3.8%) in the SYMBICORT 80/4.5 group, 5 patients (4.2%) in the formoterol group, and 6 patients (5.2%) in the placebo group.

5.16 Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroids. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between budesonide and these underlying conditions has not been established.

5.17 Coexisting Conditions

SYMBICORT, like all medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist

albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.18 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects *[see Clinical Pharmacology (12.2)]*. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with SYMBICORT at recommended doses.

6 ADVERSE REACTIONS

Long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death. One of the active ingredients of SYMBICORT is formoterol, a long-acting beta$_2$-agonist. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adreneergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. [s*ee Warnings and Precautions (5.1)*].

Systemic and inhaled corticosteroid use may result in the following:

- Candida albicans infection [see *Warnings and Precautions (5.4)*]
- Pneumonia or lower respiratory tract infections in patients with COPD [see *Warnings and Precautions (5.5)*]
- Immunosuppression [see *Warnings and Precautions (5.6)*]
- Hypercorticism and adrenal suppression [see *Warnings and Precautions (5.8)*]
- Growth effects in pediatric patients [see *Warnings and Precautions (5.14)*]
- Glaucoma and cataracts [see *Warnings and Precautions (5.15)*]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience in Asthma

Patients 12 years and older

The overall safety data in adults and adolescents are based upon 10 active- and placebo-controlled clinical trials in which 3393 patients ages 12 years and older (2052 females and 1341 males) with asthma of varying severity were treated with SYMBICORT 80/4.5 or 160/4.5 mcg taken two inhalations once or twice daily for 12 to 52 weeks. In these trials, the patients on SYMBICORT had a mean age of 38 years and were predominantly Caucasian (82%).

The incidence of common adverse events in Table 1 below is based upon pooled data from three 12-week, double-blind, placebo-controlled clinical studies in which 401 adult and adolescent patients (148 males and 253 females) age 12 years and older were treated with two inhalations of SYMBICORT 80/4.5 or SYMBICORT 160/4.5 twice daily. The SYMBICORT group was composed of mostly Caucasian (84%) patients with a mean age of 38 years, and a mean percent predicted FEV_1 at baseline of 76 and 68 for the 80/4.5 mcg and 160/4.5 mcg treatment groups, respectively. Control arms for comparison included two inhalations of budesonide HFA metered dose inhaler (MDI) 80 or 160 mcg, formoterol dry powder inhaler (DPI) 4.5 mcg, or placebo (MDI and DPI) twice daily. Table 1 includes all adverse events that occurred at an incidence of ≥ 3% in any one SYMBICORT group and more commonly than in the placebo group with twice-daily dosing. In considering these data, the increased average duration of patient exposure for SYMBICORT patients should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 1 **Adverse-reactions occurring at an incidence of ≥ 3% and more commonly than placebo in the SYMBICORT groups: pooled data from three 12-week, double-blind, placebo-controlled clinical asthma trials in patients 12 years and older**

Treatment*	**SYMBICORT**		**Budesonide**		**Formoterol**	**Placebo**
Adverse Event	**80/4.5 mcg N = 277 %**	**160/4.5 mcg N =124 %**	**80 mcg N =121 %**	**160 mcg N = 109 %**	**4.5 mcg N = 237 %**	**N = 400 %**
Nasopharyngitis	10.5	9.7	14.0	11.0	10.1	9.0
Headache	6.5	11.3	11.6	12.8	8.9	6.5
Upper respiratory tract infection	7.6	10.5	8.3	9.2	7.6	7.8
Pharyngolaryngeal pain	6.1	8.9	5.0	7.3	3.0	4.8
Sinusitis	5.8	4.8	5.8	2.8	6.3	4.8
Influenza	3.2	2.4	6.6	0.9	3.0	1.3
Back pain	3.2	1.6	2.5	5.5	2.1	0.8
Nasal congestion	2.5	3.2	2.5	3.7	1.3	1.0
Stomach discomfort	1.1	6.5	2.5	4.6	1.3	1.8
Vomiting	1.4	3.2	0.8	2.8	1.7	1.0
Oral Candidiasis	1.4	3.2	0	0	0	0.8
Average Duration of Exposure (days)	**77.7**	**73.8**	**77.0**	**71.4**	**62.4**	**55.9**

*All treatments were administered as two inhalations twice daily.

Long-term safety - asthma clinical trials in patients 12 years and older

Long-term safety studies in adolescent and adult patients 12 years of age and older, treated for up to 1 year at doses up to 1280/36 mcg/day (640/18 mcg twice daily), revealed neither clinically important changes in the incidence nor new types of adverse events emerging after longer periods of treatment. Similarly, no significant or unexpected patterns of abnormalities were observed for up to 1 year in safety measures including chemistry, hematology, ECG, Holter monitor, and HPA-axis assessments.

6.2 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

The incidence of common adverse events in Table 2 below is based upon pooled data from two double-blind, placebo-controlled clinical studies (6 and 12 months in duration) in which 771 adult COPD patients (496 males and 275 females) 40 years of age and older were treated with SYMBICORT 160/4.5, two inhalations twice daily. Of these patients 651

were treated for 6 months and 366 were treated for 12 months. The SYMBICORT group was composed of mostly Caucasian (93%) patients with a mean age of 63 years, and a mean percent predicted FEV_1 at baseline of 33%. Control arms for comparison included two inhalations of budesonide HFA (MDI) 160 mcg, formoterol (DPI) 4.5 mcg or placebo (MDI and DPI) twice daily. Table 2 includes all adverse events that occurred at an incidence of ≥ 3% in the SYMBICORT group and more commonly than in the placebo group. In considering these data, the increased average duration of patient exposure to SYMBICORT should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 2 Adverse reactions occurring at an incidence of ≥ 3% and more commonly than placebo in the SYMBICORT group: pooled data from two double-blind, placebo-controlled clinical COPD trials

Treatment*	**SYMBICORT**	**Budesonide**	**Formoterol**	**Placebo**
	160/4.5 mcg	**160 mcg**	**4.5 mcg**	
	N = 771	**N = 275**	**N = 779**	**N = 781**
Adverse Event	%	%	**%**	%
Nasopharyngitis	7.3	3.3	5.8	4.9
Oral candidiasis	6.0	4.4	1.2	1.8
Bronchitis	5.4	4.7	4.5	3.5
Sinusitis	3.5	1.5	3.1	1.8
Upper respiratory tract infection viral	3.5	1.8	3.6	2.7
Average Duration of Exposure (days)	**255.2**	**157.1**	**240.3**	**223.7**

* All treatments were administered as two inhalations twice daily.

Lung infections other than pneumonia (mostly bronchitis) occurred in a greater percentage of subjects treated with SYMBICORT 160/4.5 compared with placebo (7.9% vs. 5.1%, respectively). There were no clinically important or unexpected patterns of abnormalities observed for up to 1 year in chemistry, haematology, ECG, ECG (Holter) monitoring, HPA-axis, bone mineral density and ophthalmology assessments.

6.3 Postmarketing Experience

The following adverse reactions have been reported during post-approval use of SYMBICORT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or

establish a causal relationship to drug exposure. Some of these adverse reactions may also have been observed in clinical studies with SYMBICORT.

Cardiac disorders: angina pectoris, tachycardia, atrial and ventricular tachyarrhythmias, atrial fibrillation, extrasystoles, palpitations
Endocrine disorders: hypercorticism, growth velocity reduction in pediatric patients
Eye disorders: cataract, glaucoma, increased intraocular pressure
Gastrointestinal disorders: oropharyngeal candidiasis, nausea
Immune system disorders: immediate and delayed hypersensitivity reactions, such as anaphylactic reaction, angioedema, bronchospasm, urticaria, exanthema, dermatitis, pruritus
Metabolic and nutrition disorders: hyperglycemia, hypokalemia
Musculoskeletal, connective tissue, and bone disorders: muscle cramps
Nervous system disorders: tremor, dizziness
Psychiatric disorders: behavior disturbances, sleep disturbances, nervousness, agitation, depression, restlessness
Respiratory, thoracic, and mediastinal disorders: dysphonia, cough, throat irritation
Skin and subcutaneous tissue disorders: skin bruising
Vascular disorders: hypotension, hypertension

7 DRUG INTERACTIONS

In clinical studies, concurrent administration of SYMBICORT and other drugs, such as short-acting $beta_2$-agonists, intranasal corticosteroids, and antihistamines/decongestants has not resulted in an increased frequency of adverse reactions. No formal drug interaction studies have been performed with SYMBICORT.

7.1 Inhibitors of Cytochrome P4503A4

The main route of metabolism of corticosteroids, including budesonide, a component of SYMBICORT, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a strong inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of CYP3A4 may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Caution should be exercised when considering the coadministration of SYMBICORT with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir,

saquinavir, telithromycin) *[see Warnings and Precautions (5.9)]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

SYMBICORT should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of formoterol, a component of SYMBICORT, on the vascular system may be potentiated by these agents. In clinical trials with SYMBICORT, a limited number of COPD and asthma patients received tricyclic antidepressants, and, therefore, no clinically meaningful conclusions on adverse events can be made.

7.3 Beta-Adrenergic Receptor Blocking Agents

Beta-blockers (including eye drops) may not only block the pulmonary effect of beta-agonists, such as formoterol, a component of SYMBICORT, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non−potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of SYMBICORT with non−potassium-sparing diuretics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies of SYMBICORT in pregnant women. SYMBICORT was teratogenic and embryocidal in rats. Budesonide alone was teratogenic and embryocidal in rats and rabbits, but not in humans at therapeutic doses. Formoterol fumarate alone was teratogenic in rats and rabbits. Formoterol fumarate was also embryocidal, increased pup loss at birth and during lactation, and decreased pup weight in rats. SYMBICORT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

SYMBICORT

In a reproduction study in rats, budesonide combined with formoterol fumarate by the inhalation route at doses approximately 1/7 and 1/3, respectively, the maximum recommended human daily inhalation dose on a mg/m^2 basis produced umbilical hernia. No teratogenic or embryocidal effects were detected with budesonide combined with formoterol fumarate by the inhalation route at doses approximately 1/32 and 1/16, respectively, the maximum recommended human daily inhalation dose on a mg/m^2 basis.

Budesonide

Studies of pregnant women have not shown that inhaled budesonide increases the risk of abnormalities when administered during pregnancy. The results from a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-1997 (ie, Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry) indicate no increased risk for congenital malformations from the use of inhaled budesonide during early pregnancy. Congenital malformations were studied in 2014 infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 10-12 weeks after the last menstrual period), the period when most major organ malformations occur. The rate of recorded congenital malformations was similar compared to the general population rate (3.8% vs 3.5%, respectively). In addition, after exposure to inhaled budesonide, the number of infants born with orofacial clefts was similar to the expected number in the normal population (4 children vs 3.3, respectively).

These same data were utilized in a second study bringing the total to 2534 infants whose mothers were exposed to inhaled budesonide. In this study, the rate of' congenital malformations among infants whose mothers were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%).

Budesonide produced fetal loss, decreased pup weight, and skeletal abnormalities at subcutaneous doses in rabbits less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis and in rats at doses approximately 6 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis. In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 3

times the maximum recommended human daily inhalation dose on a mcg/m^2 basis.

Experience with oral corticosteroids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

Formoterol

Formoterol fumarate has been shown to be teratogenic, embryocidal, to increase pup loss at birth and during lactation, and to decrease pup weights in rats when given at oral doses 1400 times and greater the maximum recommended human daily inhalation dose on a mcg/m^2 basis. Umbilical hernia was observed in rat fetuses at oral doses 1400 times and greater the maximum recommended human daily inhalation dose on a mcg/m^2 basis. Brachygnathia was observed in rat fetuses at an oral dose 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis. Pregnancy was prolonged at an oral dose 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis. In another study in rats, no teratogenic effects were seen at inhalation doses up to 500 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis.

Subcapsular cysts on the liver were observed in rabbit fetuses at an oral dose 54,000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis. No teratogenic effects were observed at oral doses up to 3200 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis.

Nonteratogenic Effects

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

8.2 Labor and Delivery

There are no well-controlled human studies that have investigated the effects of SYMBICORT on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of SYMBICORT for management of asthma during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

8.3 Nursing Mothers

Since there are no data from controlled trials on the use of SYMBICORT by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue SYMBICORT, taking into account the importance of SYMBICORT to the mother.

Budesonide, like other corticosteroids, is secreted in human milk. Data with budesonide delivered via dry powder inhaler indicates that the total daily oral dose of budesonide available in breast milk to the infant is approximately 0.3% to 1% of the dose inhaled by the mother [*see Clinical Pharmacology, Pharmacokinetics (12.3)).* For SYMBICORT, the dose of budesonide available to the infant in breast milk, as a percentage of the maternal dose, would be expected to be similar.

In reproductive studies in rats, formoterol was excreted in the milk. It is not known whether formoterol is excreted in human milk.

8.4 Pediatric Use

Safety and effectiveness of SYMBICORT in asthma patients 12 years of age and older have been established in studies up to 12 months. In the two 12-week, double-blind, placebo-controlled US pivotal studies 25 patients 12 to 17 years of age were treated with SYMBICORT twice daily *[see Clinical Studies (14.1)]*. Efficacy results in this age group were similar to those observed in patients 18 years and older. There were no obvious differences in the type or frequency of adverse events reported in this age group compared with patients 18 years of age and older.

The safety and effectiveness of SYMBICORT in asthma patients 6 to <12 years of age has not been established.

Overall 1447 asthma patients 6 to <12 years of age participated in placebo- and active-controlled SYMBICORT studies. Of these 1447 patients, 539 received SYMBICORT twice daily. The overall safety profile of these patients was similar to that observed in patients ≥12 years of age who also received SYMBICORT twice daily in studies of similar design.

Controlled clinical studies have shown that orally inhaled corticosteroids including budesonide, a component of SYMBICORT, may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA-axis suppression, suggesting that growth velocity is a more sensitive indicator of

systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effect of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final height are unknown. The potential for "catch-up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

In a study of asthmatic children 5-12 years of age, those treated with budesonide DPI 200 mcg twice daily (n=311) had a 1.1 centimeter reduction in growth compared with those receiving placebo (n=418) at the end of one year; the difference between these two treatment groups did not increase further over three years of additional treatment. By the end of 4 years, children treated with budesonide DPI and children treated with placebo had similar growth velocities. Conclusions drawn from this study may be confounded by the unequal use of corticosteroids in the treatment groups and inclusion of data from patients attaining puberty during the course of the study.

The growth of pediatric patients receiving orally inhaled corticosteroids, including SYMBICORT, should be monitored. If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect should be considered. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT, each patient should be titrated to the lowest strength that effectively controls his/her asthma [*see Dosage and Administration* (2)].

8.5 Geriatric Use

Of the total number of patients in asthma clinical studies treated with SYMBICORT twice daily, 149 were 65 years of age or older, of whom 25 were 75 years of age or older.

In the COPD studies of 6 to 12 months duration, 349 patients treated with SYMBICORT 160/4.5 twice daily were 65 years old and above and of those, 73 patients were 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

As with other products containing $beta_2$-agonists, special caution should be observed when using SYMBICORT in

geriatric patients who have concomitant cardiovascular disease that could be adversely affected by $beta_2$-agonists.

Based on available data for SYMBICORT or its active components, no adjustment of dosage of SYMBICORT in geriatric patients is warranted.

8.6 Hepatic Impairment

Formal pharmacokinetic studies using SYMBICORT have not been conducted in patients with hepatic impairment, However, since both budesonide and formoterol fumarate are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of budesonide and formoterol fumarate in plasma. Therefore, patients with hepatic disease should be closely monitored.

8.7 Renal Impairment

Formal pharmacokinetic studies using SYMBICORT have not been conducted in patients with renal impairment.

10 OVERDOSAGE

SYMBICORT

SYMBICORT contains both budesonide and formoterol; therefore, the risks associated with overdosage for the individual components described below apply to SYMBICORT. In pharmacokinetic studies, single doses of 960/54 mcg (12 actuations of SYMBICORT 80/4.5) and 1280/36 mcg (8 actuations of 160/4.5), were administered to patients with COPD. A total of 1920/54 mcg (12 actuations of SYMBICORT 160/4.5) was administered as a single dose to both healthy subjects and patients with asthma. In a long-term active-controlled safety study in asthma patients, SYMBICORT 160/4.5 was administered for up to 12 months at doses up to twice the highest recommended daily dose. There were no clinically significant adverse reactions observed in any of these studies.

Clinical signs in dogs that received a single inhalation dose of SYMBICORT (a combination of budesonide and formoterol) in a dry powder included tremor, mucosal redness, nasal catarrh, redness of intact skin, abdominal respiration, vomiting, and salivation; in the rat, the only clinical sign observed was increased respiratory rate in the first hour after dosing. No deaths occurred in rats given a combination of budesonide and formoterol at acute inhalation doses of 97 and 3 mg/kg, respectively (approximately 1200 and 1350 times the maximum recommended human daily inhalation dose on a

mcg/m^2 basis). No deaths occurred in dogs given a combination of budesonide and formoterol at the acute inhalation doses of 732 and 22 mcg/kg, respectively (approximately 30 times the maximum recommended human daily inhalation dose of budesonide and formoterol on a mcg/m^2 basis).

Budesonide

The potential for acute toxic effects following overdose of budesonide is low. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur *[see Warnings and Precautions (5)]*. Budesonide at five times the highest recommended dose (3200 mcg daily) administered to humans for 6 weeks caused a significant reduction (27%) in the plasma cortisol response to a 6-hour infusion of ACTH compared with placebo (+1%). The corresponding effect of 10 mg prednisone daily was a 35% reduction in the plasma cortisol response to ACTH.

In mice, the minimal inhalation lethal dose was 100 mg/kg (approximately 600 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In rats, there were no deaths following the administration of an inhalation dose of 68 mg/kg (approximately 900 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). The minimal oral lethal dose in mice was 200 mg/kg (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis) and less than 100 mg/kg in rats (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Formoterol

An overdose of formoterol would likely lead to an exaggeration of effects that are typical for $beta_2$-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol. No clinically significant adverse reactions were seen when formoterol was delivered to adult patients with acute bronchoconstriction at a dose of 90 mcg/day over 3 hours or to stable asthmatics 3 times a day at a total dose of 54 mcg/day for 3 days.

Treatment of formoterol overdosage consists of discontinuation of the medication together with institution of appropriate symptomatic and/or supportive therapy. The

judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of formoterol. Cardiac monitoring is recommended in cases of overdosage.

No deaths were seen in mice given formoterol at an inhalation dose of 276 mg/kg (more than 62,200 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In rats, the minimum lethal inhalation dose was 40 mg/kg (approximately 18,000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No deaths were seen in mice that received an oral dose of 2000 mg/kg (more than 450,000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Maximum nonlethal oral doses were 252 mg/kg in young rats and 1500 mg/kg in adult rats (approximately 114,000 times and 675,000 times the maximum recommended human inhalation dose on a mcg/m^2 basis).

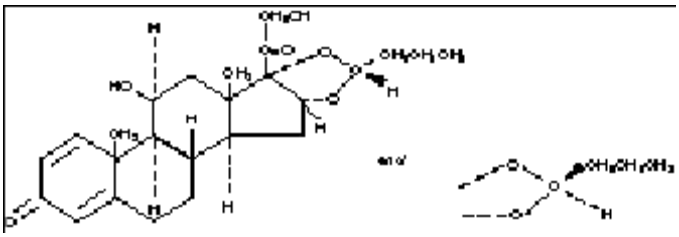
11 DESCRIPTION

SYMBICORT 80/4.5 and SYMBICORT 160/4.5 each contain micronized budesonide and micronized formoterol fumarate dihydrate for oral inhalation only.

Each SYMBICORT 80/4.5 and SYMBICORT 160/4.5 canister is formulated as a hydrofluoroalkane (HFA 227; 1,1,1,2,3,3,3-heptafluoropropane)-propelled pressurized metered dose inhaler containing either 60 or 120 actuations [*see Dosage Forms and Strengths (3) and How Supplied/Storage and Handling (16)*]. After priming, each actuation meters either 91/5.1 mcg or 181/5.1 mcg from the valve and delivers either 80/4.5 mcg, or 160/4.5 mcg (budesonide micronized/formoterol fumarate dihydrate micronized) from the actuator. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between actuation of the device and inspiration through the delivery system. SYMBICORT also contains povidone K25 USP as a suspending agent and polyethylene glycol 1000 NF as a lubricant.

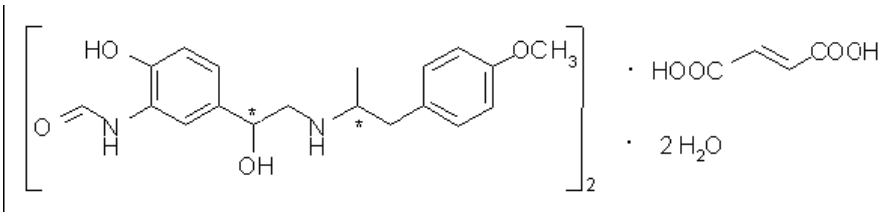
SYMBICORT should be primed before using for the first time by releasing two test sprays into the air away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 7 days or when it has been dropped, prime the inhaler again by shaking well for 5 seconds before each spray and releasing two test sprays into the air away from the face.

One active component of SYMBICORT is budesonide, 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). The empirical formula of budesonide is $C_{25}H_{34}O_6$ and its molecular weight is 430.5. Its structural formula is:



Budesonide is a white to off-white, tasteless, odorless powder which is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform. Its partition coefficient between octanol and water at pH 7.4 is 1.6×10^3.

The other active component of SYMBICORT is formoterol fumarate dihydrate, a selective beta$_2$-agonist designated chemically as (R*,R*)-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butendioate(2:1), dihydrate. The empirical formula of formoterol is $C_{42}H_{56}N_4O_{14}$ and its molecular weight is 840.9. Its structural formula is:



Formoterol fumarate dihydrate is a powder which is slightly soluble in water. Its octanol-water partition coefficient at pH 7.4 is 2.6. The pKa of formoterol fumarate dihydrate at 25°C is 7.9 for the phenolic group and 9.2 for the amino group.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SYMBICORT

SYMBICORT contains both budesonide and formoterol; therefore, the mechanisms of action described below for the individual components apply to SYMBICORT. These drugs represent two classes of medications (a synthetic corticosteroid and a long-acting selective beta$_2$-adrenoceptor agonist) that have different effects on clinical, physiological, and inflammatory indices of Chronic Obstructive Pulmonary Disease (COPD) and asthma.

Budesonide

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.

In glucocorticoid receptor affinity studies, the 22R form of budesonide was two times as active as the 22S epimer. *In vitro* studies indicated that the two forms of budesonide do not interconvert.

Inflammation is an important component in the pathogenesis of COPD and asthma. Corticosteroids have a wide range of inhibitory activities against multiple cell types (eg, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (eg, histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic and non–allergic-mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in COPD and asthma.

Studies in asthmatic patients have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects over a wide range of doses of budesonide. This is explained by a combination of a relatively high local anti-inflammatory effect, extensive first pass hepatic degradation of orally absorbed drug (85%-95%), and the low potency of formed metabolites.

Formoterol

Formoterol fumarate is a long-acting selective beta$_2$-adrenergic agonist (beta$_2$-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 $beta_2$-receptors than at $beta_1$-receptors. The *in vitro* binding selectivity to $beta_2$- over $beta_1$-adrenoceptors is higher for formoterol than for albuterol (5 times), whereas salmeterol has a higher (3 times) $beta_2$-selectivity ratio than formoterol.

Although $beta_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the heart, there are also $beta_2$-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects.

The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Formoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these *in vitro* and animal findings to humans is unknown.

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 postdose. 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 evaluated 2152 patients aged 12 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, two 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.

Chronic Obstructive Pulmonary Disease:
Cardiovascular effects: In 2 clinical studies, 6 months and 12 months in duration including 3668 COPD patients, no clinically important differences were seen in pulse rate, blood pressure, potassium, and glucose between SYMBICORT, the individual components of SYMBICORT, and placebo. [*see Clinical Studies (14.2)*].

ECGs recorded at multiple clinic visits on treatment in both studies showed no clinically important differences for heart rate, PR interval, QRS duration, heart rate, signs of cardiac ischemia or arrhythmias between SYMBICORT 160/4.5 the monoproducts and placebo, all administered as two inhalations twice daily. Based on ECGs, 6 patients treated with SYMBICORT 160/4.5, 6 patients treated with formoterol 4.5, and 6 patients in the placebo group experienced atrial fibrillation or flutter that was not present at baseline. There were no cases of nonsustained ventricular tachycardia in the SYMBICORT 160/4.5, formoterol 4.5, or placebo groups.

In the 12-month study, 520 patients had evaluable continuous 24-hour ECG (Holter) monitoring prior to the first dose and after approximately 1 and 4 months on treatment. No clinically important differences in ventricular or supraventricular arrhythmias, ventricular or supraventricular ectopic beats, or heart rate were observed among the groups treated with SYMBICORT 160/4.5, formoterol or placebo taken as two inhalations twice daily. Based on ECG (Holter) monitoring, one patient on SYMBICORT 160/4.5, no patients on formoterol 4.5, and three patients in the placebo group experienced atrial fibrillation or flutter that was not present at baseline.

HPA axis effects: Twenty-four hour urinary cortisol measurements were collected in a pooled subset (n=616) of patients from two COPD studies. The data indicated approximately 30% lower mean 24-hour urinary free cortisol values following chronic administration (> 6 months) of SYMBICORT relative to placebo. SYMBICORT appeared to exhibit comparable cortisol suppression to budesonide 160 mcg alone or coadministration of budesonide 160 mcg and formoterol 4.5 mcg. For patients treated with SYMBICORT or placebo for up to 12 months, the percentage of patients who shifted from normal to low for this measure were generally comparable.

Other Budesonide Products

To confirm that systemic absorption is not a significant factor in the clinical efficacy of inhaled budesonide, a clinical study in patients with asthma was performed comparing 400 mcg budesonide administered via a pressurized metered dose inhaler with a tube spacer to 1400 mcg of oral budesonide and placebo. The study demonstrated the efficacy of inhaled budesonide but not orally ingested budesonide, despite comparable systemic levels. Thus, the therapeutic effect of conventional doses of orally inhaled budesonide are largely explained by its direct action on the respiratory tract.

Inhaled budesonide has been shown to decrease airway reactivity to various challenge models, including histamine, methacholine, sodium metabisulfite, and adenosine monophosphate in patients with hyperreactive airways. The clinical relevance of these models is not certain.

Pretreatment with inhaled budesonide, 1600 mcg daily (800 mcg twice daily) for 2 weeks reduced the acute (early-phase reaction) and delayed (late-phase reaction) decrease in FEV_1 following inhaled allergen challenge.

The systemic effects of inhaled corticosteroids are related to the systemic exposure to such drugs. Pharmacokinetic studies have demonstrated that in both adults and children with asthma the systemic exposure to budesonide is lower with SYMBICORT compared with inhaled budesonide administered at the same delivered dose via a dry powder inhaler [*see Clinical Pharmacology, Pharmacokinetics, SYMBICORT (12.3)]*. Therefore, the systemic effects (HPA axis and growth) of budesonide delivered from SYMBICORT would be expected to be no greater than what is reported for inhaled budesonide when administered at comparable doses via the dry powder inhaler [*see Use in Specific Populations, Pediatric Use (8.4)*].

HPA Axis Effects: The effects of inhaled budesonide administered via a dry powder inhaler on the hypothalamic-pituitary-adrenal (HPA) axis were studied in 905 adults and 404 pediatric patients with asthma. For most patients, the ability to increase cortisol production in response to stress, as assessed by cosyntropin (ACTH) stimulation test, remained intact with budesonide treatment at recommended doses. For adult patients treated with 100, 200, 400, or 800 mcg twice daily for 12 weeks, 4%, 2%, 6%, and 13%, respectively, had an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL assessed by liquid chromatography following short-cosyntropin test) as compared to 8% of patients treated with placebo. Similar results were obtained in pediatric patients. In another study in adults, doses of 400, 800, and 1600 mcg of inhaled budesonide twice daily for 6 weeks were examined; 1600 mcg twice daily (twice the maximum recommended dose) resulted in a 27% reduction in stimulated cortisol (6-hour ACTH infusion) while 10-mg prednisone resulted in a 35% reduction. In this study, no patient on budesonide at doses of 400 and 800 mcg twice daily met the criterion for an abnormal stimulated-cortisol response (peak cortisol <14.5 mcg/dL assessed by liquid chromatography) following ACTH infusion. An open-label, long-term follow-up of 1133 patients for up to 52 weeks confirmed the minimal effect on the HPA axis (both basal- and stimulated-plasma cortisol) of budesonide when administered at recommended doses. In patients who had previously been oral-steroid−dependent, use of budesonide in recommended doses was associated with higher stimulated-cortisol response compared to baseline following 1 year of therapy.

Other Formoterol Products

While the pharmacodynamic effect is via stimulation of beta-adrenergic receptors, excessive activation of these receptors commonly leads to skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in plasma potassium, and

increases in plasma glucose. Inhaled formoterol, like other beta$_2$-adrenergic agonist drugs, can produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium [*see Warnings and Precautions (5)*]. For SYMBICORT, these effects are detailed in the *Clinical Pharmacology, Pharmacodynamics, SYMBICORT* (12.2) section.

Use of long-acting beta$_2$-adrenergic agonist drugs can result in tolerance to bronchoprotective and bronchodilatory effects.

Rebound bronchial hyperresponsiveness after cessation of chronic long-acting beta-agonist therapy has not been observed.

12.3 Pharmacokinetics

SYMBICORT

Absorption: *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 contrast, most of the budesonide delivered to the lungs was systemically absorbed. 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.

Following administration of SYMBICORT 160/4.5 mcg, two or four inhalations twice daily) for 5 days in healthy subjects, plasma concentration of budesonide generally increased in proportion to dose. The accumulation index for the group that received two inhalations twice daily was 1.32 for budesonide.

Asthma Patients: In a single-dose study, higher than recommended doses of SYMBICORT (12 inhalations of SYMBICORT 160/4.5 mcg) were administered to patients with moderate asthma. Peak budesonide plasma concentration of 4.5 nmol/L occurred at 20 minutes following dosing. This study demonstrated that the total systemic exposure to budesonide from SYMBICORT was approximately 30% lower than from inhaled budesonide via a dry powder inhaler (DPI) at the same delivered dose. Following administration of SYMBICORT, the half-life of the budesonide component was 4.7 hours.

In a repeat dose study, the highest recommended dose of SYMBICORT (160/4.5 mcg, two inhalations twice daily) was administered to patients with moderate asthma and healthy subjects for 1 week. Peak budesonide plasma concentration of 1.2 nmol/L occurred at 21 minutes in asthma patients. Peak budesonide plasma concentration was 27% lower in asthma patients compared to that in healthy subjects. However, the total systemic exposure of budesonide was comparable to that in asthma patients.

Peak steady-state plasma concentrations of budesonide administered by DPI in adults with asthma averaged 0.6 and 1.6 nmol/L at doses of 180 mcg and 360 mcg twice daily, respectively. In asthmatic patients, budesonide showed a linear increase in AUC and C_{max} with increasing dose after both single and repeated dosing of inhaled budesonide.

COPD Patients: In a single-dose study, 12 inhalations of SYMBICORT 80/4.5 mcg (total dose 960/54 mcg) were administered to patients with COPD. Mean budesonide peak plasma concentration of 3.3 nmol/L occurred at 30 minutes following dosing. Budesonide systemic exposure was comparable between SYMBICORT pMDI and coadministration of budesonide via a metered-dose inhaler and formoterol via a dry powder inhaler (budesonide 960 mcg and formoterol 54 mcg). In the same study, an open-label group of moderate asthma patients also received the same higher dose of SYMBICORT. For budesonide, COPD patients exhibited 12% greater AUC and 10% lower C_{max} compared to asthma patients.

In the 6 month pivotal clinical study, steady-state pharmacokinetic data of budesonide was obtained in a subset of COPD patients with treatment arms of SYMBICORT pMDI 160/4.5 mcg, SYMBICORT pMDI 80/4.5 mcg, budesonide 160 mcg, budesonide 160 mcg and formoterol 4.5 mcg given together, all administered as two inhalations twice daily. Budesonide systemic exposure (AUC and C_{max}) increased proportionally with doses from 80 mcg to 160 mcg and was generally similar between the 3 treatment groups receiving the same dose of budesonide (SYMBICORT pMDI 160/4.5 mcg, budesonide 160 mcg, budesonide 160 mcg and formoterol 4.5 mcg administered together).

Formoterol:
Inhaled formoterol is rapidly absorbed; peak plasma concentrations are typically reached at the first plasma sampling time, within 5-10 minutes after dosing. As with many drug products for oral inhalation, it is likely that the

majority of the inhaled formoterol delivered is swallowed and then absorbed from the gastrointestinal tract.

Healthy Subjects: Following administration of SYMBICORT (160/4.5 mcg, two or four inhalations twice daily) for 5 days in healthy subjects, plasma concentration of formoterol generally increased in proportion to dose. The accumulation index for the group that received two inhalations twice daily was 1.77 for formoterol.

Asthma patients: In a single-dose study, higher than recommended doses of SYMBICORT (12 inhalations of SYMBICORT 160/4.5 mcg) were administered to patients with moderate asthma. Peak plasma concentration for formoterol of 136 pmol occurred at 10 minutes following dosing. Approximately 8% of the delivered dose of formoterol was recovered in the urine as unchanged drug.

In a repeat dose study, the highest recommended dose of SYMBICORT (160/4.5 mcg, two inhalations twice daily) was administered to patients with moderate asthma and healthy subjects for 1 week. Peak formoterol plasma concentration of 28 pmol/L occurred at 10 minutes in asthma patients. Peak formoterol plasma concentration was about 42% lower in asthma patients compared to that in healthy subjects. However, the total systemic exposure of formoterol was comparable to that in asthma patients.

COPD patients: Following single-dose administration of 12 inhalations of SYMBICORT 80/4.5, mean peak formoterol plasma concentration of 167 pmol/L was rapidly achieved at 15 minutes after dosing. Formoterol exposure was slightly greater (~16-18%) from SYMBICORT pMDI compared to coadministration of budesonide via a metered-dose inhaler and formoterol via a dry powder inhaler (total dose of budesonide 960 mcg and formoterol 54 mcg). In the same study, an open label group of moderate asthma patients received the same dose of SYMBICORT. COPD patients exhibited 12-15% greater AUC and C_{max} for formoterol compared to asthma patients.

In the 6 month pivotal clinical study, steady-state pharmacokinetic data of formoterol was obtained in a subset of COPD patients with treatment arms of SYMBICORT pMDI 160/4.5 mcg, SYMBICORT pMDI 80/4.5. mcg, formoterol 4.5 mcg, budesonide 160 mcg and formoterol 4.5 mcg given together, all administered as two inhalations twice daily. The systemic exposure of formoterol as evidenced by AUC, was about 30% and 16% higher from SYMBICORT pMDI compared to formoterol alone treatment arm and

coadministration of individual components of budesonide and formoterol treatment arm, respectively.

Distribution: *Budesonide*: The volume of distribution of budesonide was approximately 3 L/kg. It was 85%-90% bound to plasma proteins. Protein binding was constant over the concentration range (1-100 nmol/L) achieved with, and exceeding, recommended inhaled doses. Budesonide showed little or no binding to corticosteroid binding globulin. Budesonide rapidly equilibrated with red blood cells in a concentration independent manner with a blood plasma ratio of about 0.8.

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. The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 54 mcg dose.

Metabolism: *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. No qualitative differences between the *in vitro* and *in vivo* metabolic patterns were detected. Negligible metabolic inactivation was observed in human lung and serum preparations.

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.

Elimination: *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.

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 mcg in a single-dose study in pediatric patients with asthma, 6-11 years of age. Urine was collected for determination of formoterol excretion. Peak budesonide concentrations of 1.4 nmol/L occurred at 20 minutes post-dose. Approximately 3.5% of the delivered formoterol dose was recovered in the urine as unchanged formoterol. This study also demonstrated that the total systemic exposure to budesonide from SYMBICORT was approximately 30% lower than from inhaled budesonide via a dry powder inhaler that was also evaluated at the same delivered dose.

Gender/Race

Specific studies to examine the effects of gender and race on the pharmacokinetics of SYMBICORT have not been conducted. Population PK analysis of the SYMBICORT data indicates that gender does not affect the pharmacokinetics of budesonide and formoterol. No conclusions can be drawn on the effect of race due to the low number of non-Caucasians evaluated for PK.

Nursing Mothers

The disposition of budesonide when delivered by inhalation from a dry powder inhaler at doses of 200 or 400 mcg twice daily for at least 3 months was studied in eight lactating women with asthma from 1 to 6 months postpartum. Systemic exposure to budesonide in these women appears to be comparable to that in non-lactating women with asthma from other studies. Breast milk obtained over eight hours post-dose revealed that the maximum concentration of budesonide for the 400 and 800 mcg total daily doses was 0.39 and 0.78 nmol/L, respectively, and occurred within 45 minutes after dosing. The estimated oral daily dose of budesonide from breast milk to the infant is approximately 0.007 and 0.014 mcg/kg/day for the two dose regimens used in this study, which represents approximately 0.3% to 1% of the dose

inhaled by the mother. Budesonide levels in plasma samples obtained from five infants at about 90 minutes after breastfeeding (and about 140 minutes after drug administration to the mother) were below quantifiable levels (<0.02 nmol/L in four infants and <0.04 nmol/L in one infant) *[see Use in Specific Populations, Nursing Mothers (8.3)]*.

Renal or Hepatic Insufficiency

There are no data regarding the specific use of SYMBICORT in patients with hepatic or renal 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.

Drug-Drug Interactions

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 non-specific 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Budesonide

Long-term studies were conducted in rats and mice using oral administration to evaluate the carcinogenic potential of budesonide.

In a 2-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In two additional 2-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). However, in the male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings.

In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (approximately equal to the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Budesonide was not mutagenic or clastogenic in six different test systems: Ames *Salmonella*/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in *Drosophila melanogaster*, and DNA repair analysis in rat hepatocyte culture.

In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 mcg/kg (approximately equal to the maximum recommended human daily inhalation dose on a mcg/m^2 basis). However, it caused a decrease in prenatal viability and viability in the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg and above (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No such effects were noted at 5 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Formoterol

Long-term studies were conducted in mice using oral administration and rats using inhalation administration to evaluate the carcinogenic potential of formoterol fumarate.

In a 24-month carcinogenicity study in CD-1 mice, formoterol at oral doses of 0.1 mg/kg and above (approximately 20 times

the maximum recommended human daily inhalation dose on a mcg/m^2 basis) caused a dose-related increase in the incidence of uterine leiomyomas.

In a 24-month carcinogenicity study in Sprague-Dawley rats, an increased incidence of mesovarian leiomyoma and uterine leiomyosarcoma were observed at the inhaled dose of 130 mcg/kg (approximately 60 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No tumors were seen at 22 mcg/kg (approximately 10 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Other beta-agonist drugs have similarly demonstrated increases in leiomyomas of the genital tract in female rodents. The relevance of these findings to human use is unknown.

Formoterol was not mutagenic or clastogenic in Ames *Salmonella*/microsome plate test, mouse lymphoma test, chromosome aberration test in human lymphocytes, and rat micronucleus test.

A reduction in fertility and/or reproductive performance was identified in male rats treated with formoterol at an oral dose of 15 mg/kg (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In a separate study with male rats treated with an oral dose of 15 mg/kg (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis), there were findings of testicular tubular atrophy and spermatic debris in the testes and oligospermia in the epididymides. No such effect was seen at 3 mg/kg (approximately 1400 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No effect on fertility was detected in female rats at doses up to 15 mg/kg (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

13.2 Animal Toxicology and/or Pharmacology

Preclinical: Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

Reproductive Toxicology Studies:
SYMBICORT

SYMBICORT has been shown to be teratogenic and embryocidal in rats when given at inhalation doses of 12/0.66 mcg/kg (budesonide/formoterol) and above (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Umbilical hernia, a malformation, was observed for fetuses at doses of 12/0.66 mcg/kg and above (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No teratogenic or embryocidal effects were detected at 2.5/0.14 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Budesonide

As with other corticosteroids, budesonide has been shown to be teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weight, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg/day in rabbits (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis) and 500 mcg/kg/day in rats (approximately 6 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 250 mcg/kg/day (approximately 3 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Formoterol

Formoterol fumarate has been shown to be teratogenic, embryocidal, to increase pup loss at birth and during lactation, and to decrease pup weights in rats when given at oral doses of 3 mg/kg/day and above (approximately 1400 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Umbilical hernia, a malformation, was observed in rat fetuses at oral doses of 3 mg/kg/day and above (approximately 1400 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Brachygnathia, a skeletal malformation, was observed in rat fetuses at an oral dose of 15 mg/kg/day (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Pregnancy was prolonged at an oral dose of 15 mg/kg/day (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In another study in rats, no teratogenic effects were seen at inhalation doses up to 1.2 mg/kg/day (approximately 500 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Formoterol fumarate has been shown to be teratogenic in rabbits when given at an oral dose of 60 mg/kg (approximately 54,000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Subcapsular cysts on the liver were observed in rabbit fetuses at an oral dose of 60 mg/kg (approximately 54,000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No teratogenic effects were observed at oral doses up to 3.5 mg/kg (approximately 3200 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

14 CLINICAL STUDIES

14.1 Asthma

SYMBICORT has been studied in patients with asthma 12 years of age and older. In two clinical studies comparing SYMBICORT with the individual components, improvements in most efficacy end points were greater with SYMBICORT than with the use of either budesonide or formoterol alone. In addition, one clinical study showed similar results between SYMBICORT and the concurrent use of budesonide and formoterol at corresponding doses from separate inhalers.

The safety and efficacy of SYMBICORT were demonstrated in two randomized, double-blind, placebo-controlled US clinical studies involving 1076 patients 12 years of age and older. Fixed SYMBICORT dosages of 160/9 mcg, and 320/9 mcg twice daily (each dose administered as two inhalations of the 80/4.5 and 160/4.5 mcg strengths, respectively) were compared with the monocomponents (budesonide and formoterol) and placebo to provide information about appropriate dosing to cover a range of asthma severity.

Study 1: Clinical Study with SYMBICORT 160/4.5

This 12-week study evaluated 596 patients 12 years of age and older by comparing SYMBICORT 160/4.5 mcg, the free combination of budesonide 160 mcg plus formoterol 4.5 mcg in separate inhalers, budesonide 160 mcg, formoterol 4.5 mcg, and placebo; each administered as two inhalations twice daily. The study included a 2-week run-in period with budesonide 80 mcg, two inhalations twice daily. Most patients had moderate to severe asthma and were using moderate to high doses of inhaled corticosteroids prior to study entry. Randomization was stratified by previous inhaled corticosteroid treatment (71.6% on moderate- and 28.4% on high-dose inhaled corticosteroid). Mean percent predicted FEV_1 at baseline was 68.1% and was similar across treatment groups. The coprimary efficacy end points were 12-hour-average postdose

FEV_1 at week 2, and predose FEV_1 averaged over the course of the study. The study also required that patients who satisfied a predefined asthma worsening criterion be withdrawn. The predefined asthma-worsening criteria were a clinically important decrease in FEV_1 or peak expiratory flow (PEF), increase in rescue albuterol use, nighttime awakening due to asthma, emergency intervention or hospitalization due to asthma, or requirement for asthma medication not allowed by the protocol. For the criterion of nighttime awakening due to asthma, patients were allowed to remain in the study at the discretion of the investigator if none of the other asthma-worsening criteria were met. The percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma is shown in Table 3.

Table 3 The number and percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma (Study 1)

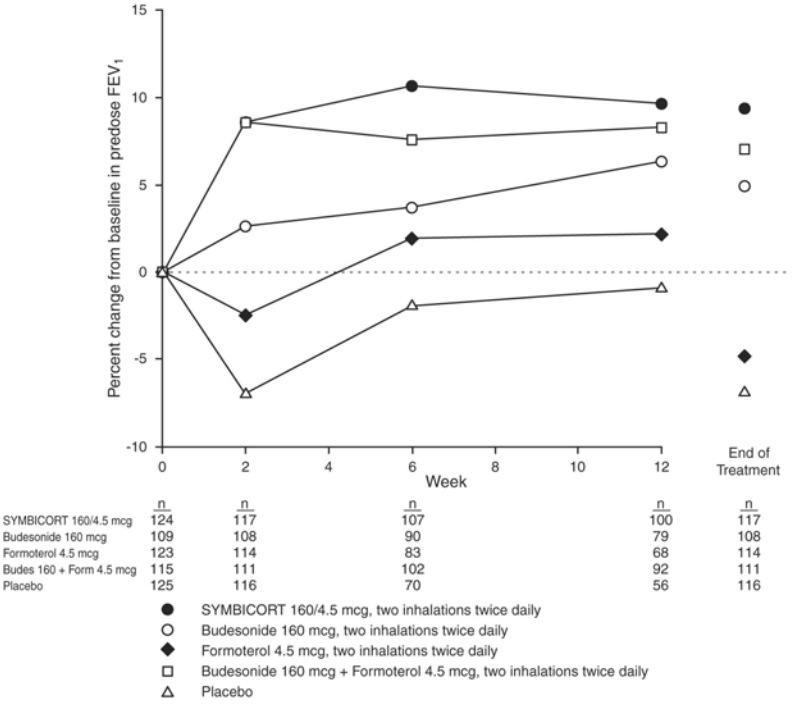
	SYMBICORT 160/4.5 mcg n=124	**Budesonide 160 mcg plus Formoterol 4.5 mcg** n=115	**Budesonide 160 mcg** n=109	**Formoterol 4.5 mcg** n=123	**Placebo** n=125
Patients withdrawn due to predefined asthma event*	13 (10.5)	13 (11.3)	22 (20.2)	44 (35.8)	62 (49.6)
Patients with a predefined asthma event*†	37 (29.8)	24 (20.9)	48 (44.0)	68 (55.3)	84 (67.2)
Decrease in FEV_1	4 (3.2)	8 (7.0)	7 (6.4)	15 (12.2)	14 (11.2)
Rescue medication use	2 (1.6)	0	3 (2.8)	3 (2.4)	7 (5.6)
Decrease in AM PEF	2 (1.6)	5 (4.3)	5 (4.6)	17 (13.8)	15 (12.0)
Nighttime awakenings‡	24 (19.4)	11 (9.6)	29 (26.6)	32 (26.0)	49 (39.2)
Clinical exacerbation	7 (5.6)	6 (5.2)	5 (4.6)	17 (3.8)	16 (12.8)

*These criteria were assessed on a daily basis irrespective of the timing of the clinic visit, with the exception of FEV_1, which was assessed at each clinic visit.

[†]Individual criteria are shown for patients meeting any predefined asthma event, regardless of withdrawal status.
[‡]For the criterion of nighttime awakening due to asthma, patients were allowed to remain in the study at the discretion of the investigator if none of the other criteria were met.

Mean percent change from baseline in FEV_1 measured immediately prior to dosing (predose) over 12 weeks is displayed in Figure 1. Because this study used predefined withdrawal criteria for worsening asthma, which caused a differential withdrawal rate in the treatment groups, predose FEV_1 results at the last available study visit (end of treatment, EOT) are also provided. Patients receiving SYMBICORT 160/4.5 mcg had significantly greater mean improvements from baseline in predose FEV_1 at the end of treatment (0.19 L, 9.4%), compared with budesonide 160 mcg (0.10 L, 4.9%), formoterol 4.5 mcg (-0.12 L, -4.8%), and placebo (-0.17 L, -6.9%).

Figure 1 - Mean Percent Change From Baseline in Predose FEV_1 Over 12 Weeks (Study 1)



The effect of SYMBICORT 160/4.5 mcg two inhalations twice daily on selected secondary efficacy variables, including morning and evening PEF, albuterol rescue use, and asthma symptoms over 24 hours on a 0-3 scale is shown in Table 4.

Table 4 Mean values for selected secondary efficacy variables (Study 1)

Efficacy Variable	SYMBICORT 160/4.5 mcg (n*=124)	Budesonide 160 mcg plus Formoterol 4.5 mcg (n*=115)	Budesonide 160 mcg (n*=109)	Formoterol 4.5 mcg (n*=123)	Placebo (n*=125)
AM PEF (L/min)					
Baseline	341	338	342	339	355
Change from Baseline	35	28	9	-9	-18
PM PEF (L/min)					
Baseline	351	348	357	354	369
Change from Baseline	34	26	7	-7	-18
Albuterol rescue use					
Baseline	2.1	2.3	2.7	2.5	2.4
Change from Baseline	-1.0	-1.5	-0.8	-0.3	0.8
Average symptom score/day (0-3 scale)					
Baseline	0.99	1.03	1.04	1.04	1.08
Change from Baseline	-0.28	-0.32	-0.14	-0.05	0.10

*Number of patients (n) varies slightly due to the number of patients for whom data were available for each variable. Results shown are based on last available data for each variable.

The subjective impact of asthma on patients' health-related quality of life was evaluated through the use of the standardized Asthma Quality of Life Questionnaire (AQLQ(S)) (based on a 7-point scale where 1 = maximum impairment and 7 = no impairment). Patients receiving SYMBICORT 160/4.5 had clinically meaningful improvement in overall asthma-specific quality of life, as defined by a mean difference between treatment groups of

>0.5 points in change from baseline in overall AQLQ score (difference in AQLQ score of 0.70 [95% CI 0.47, 0.93], compared to placebo).

Study 2: Clinical Study with SYMBICORT 80/4.5

This 12-week study was similar in design to Study 1, and included 480 patients 12 years of age and older. This study compared SYMBICORT 80/4.5 mcg, budesonide 80 mcg, formoterol 4.5 mcg, and placebo; each administered as two inhalations twice daily. The study included a 2-week placebo run-in period. Most patients had mild to moderate asthma and were using low to moderate doses of inhaled corticosteroids prior to study entry. Mean percent predicted FEV_1 at baseline was 71.3% and was similar across treatment groups. Efficacy variables and end points were identical to those in Study 1.

The percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma is shown in Table 5. The method of assessment and criteria used were identical to that in Study 1.

Table 5 The number and percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma (Study 2)

	SYMBICORT 80/4.5 mcg (n=123)	Budesonide 80 mcg (n=121)	Formoterol 4.5 mcg (n=114)	Placebo (n=122)
Patients withdrawn due to predefined asthma event*	9 (7.3)	8 (6.6)	21 (18.4)	40 (32.8)
Patients with a predefined asthma event*†	23 (18.7)	26 (21.5)	48 (42.1)	69 (56.6)
Decrease in FEV_1	3 (2.4)	3 (2.5)	11 (9.6)	9 (7.4)
Rescue medication use	1 (0.8)	3 (2.5)	1 (0.9)	3 (2.5)
Decrease in AM PEF	3 (2.4)	1 (0.8)	8 (7.0)	14 (11.5)
Nighttime awakening‡	17 (13.8)	20 (16.5)	31 (27.2)	52 (42.6)

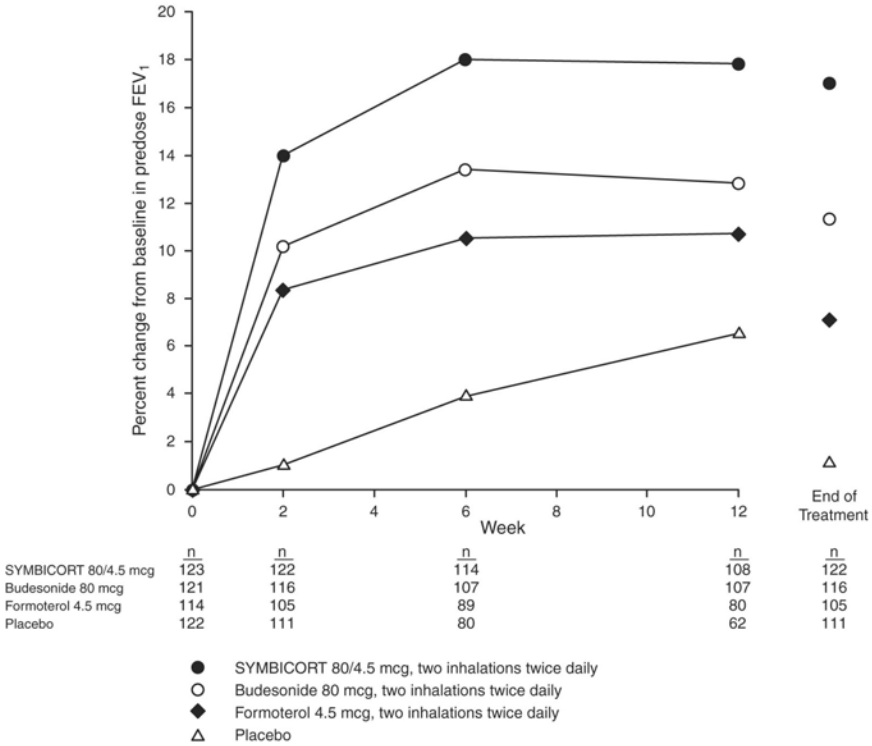
Table 5 The number and percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma (Study 2)

	SYMBICORT 80/4.5 mcg (n=123)	Budesonide 80 mcg (n=121)	Formoterol 4.5 mcg (n=114)	Placebo (n=122)
Clinical exacerbation	1 (0.8)	3 (2.5)	5 (4.4)	20 (16.4)

*These criteria were assessed on a daily basis irrespective of the timing of the clinic visit, with the exception of FEV_1, which was assessed at each clinic visit.
†Individual criteria are shown for patients meeting any predefined asthma event, regardless of withdrawal status.
‡For the criterion of nighttime awakening due to asthma, patients were allowed to remain in the study at the discretion of the investigator if none of the other criteria were met.

Mean percent change from baseline in predose FEV_1 over 12 weeks is displayed in Figure 2.

Figure 2 - Mean Percent Change From Baseline in Predose FEV_1 Over 12 Weeks (Study 2)



Efficacy results for other secondary end points, including quality of life, were similar to those observed in Study 1.

Onset and Duration of Action and Progression of Improvement in Asthma Control

The onset of action and progression of improvement in asthma control were evaluated in the two pivotal clinical studies. The median time to onset of clinically significant bronchodilation (>15% improvement in FEV_1) was seen within 15 minutes. Maximum improvement in FEV_1 occurred within 3 hours, and clinically significant improvement was maintained over 12 hours. Figures 3 and 4 show the percent change from baseline in postdose FEV_1 over 12 hours on the day of randomization and on the last day of treatment for Study 1.

Reduction in asthma symptoms and in albuterol rescue use, as well as improvement in morning and evening PEF, occurred within 1 day of the first dose of SYMBICORT; improvement in these variables was maintained over the 12 weeks of therapy.

Following the initial dose of SYMBICORT, FEV_1 improved markedly during the first 2 weeks of treatment, continued to show improvement at the Week 6 assessment, and was maintained through Week 12 for both studies.

No diminution in the 12-hour bronchodilator effect was observed with either SYMBICORT 80/4.5 mcg or SYMBICORT 160/4.5 mcg, as assessed by FEV_1, following 12 weeks of therapy or at the last available visit.

FEV_1 data from Study 1 evaluating SYMBICORT 160/4.5 mcg is displayed in Figures 3 and 4.

Figure 3 - Mean Percent Change From Baseline in FEV_1 on Day of Randomization (Study 1)

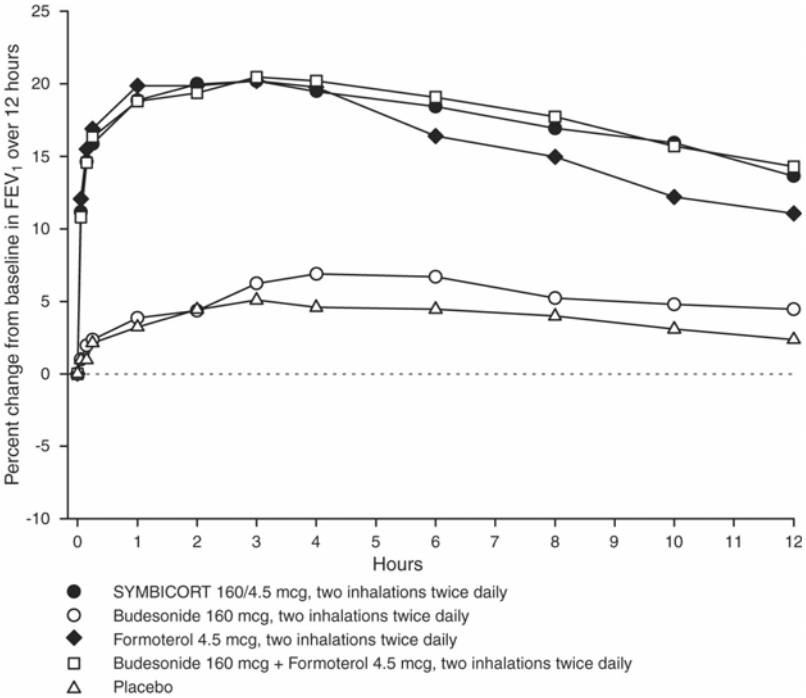
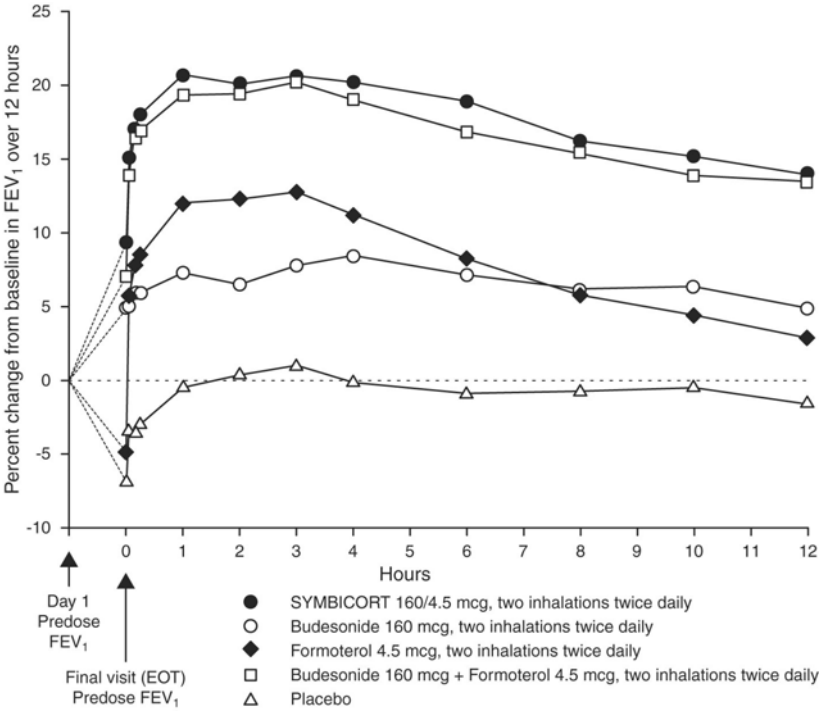


Figure 4 - Mean Percent Change From Baseline in FEV_1 At End of Treatment (Study 1)



14.2 Chronic Obstructive Pulmonary Disease (COPD)

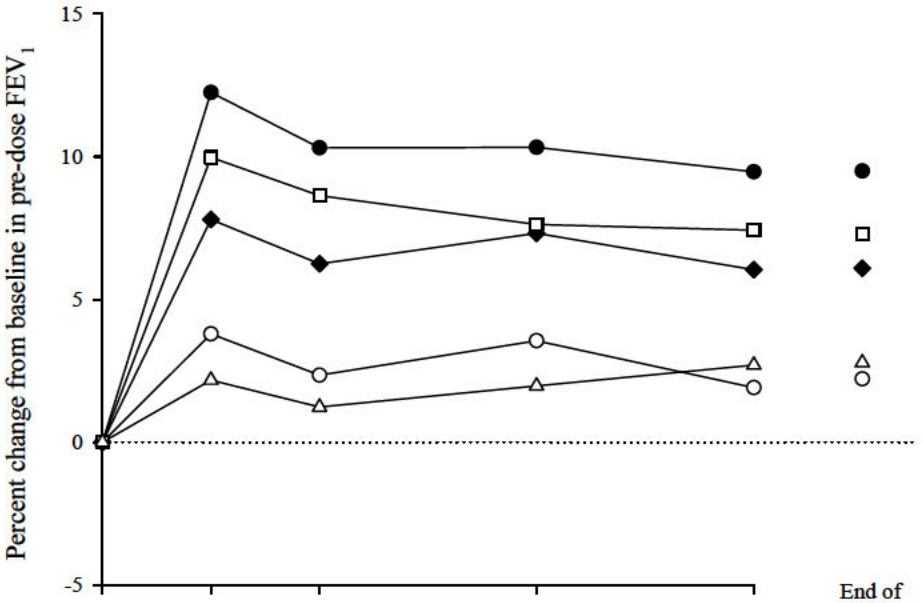
The efficacy of SYMBICORT 80/4.5 and SYMBICORT 160/4.5 in the maintenance treatment of airflow obstruction in COPD patients was evaluated in two randomized, double-blind, placebo-controlled multinational studies, conducted over 6 months (Study 1) and 12 months (Study 2), in a total of

3668 patients (2416 males and 1252 females). The majority of patients (93%) were Caucasian. All patients were required to be at least 40 years of age, with a FEV_1 of less than or equal to 50% predicted, a clinical diagnosis of COPD with symptoms for at least 2 years, and a smoking history of at least 10 pack years, prior to entering the trial. The mean prebronchodilator FEV_1 at baseline of the patients enrolled in the study was 34% predicted. Forty-eight percent of the patients enrolled were on inhaled corticosteroids and 52.7% of patients were on short-acting anticholinergic bronchodilators during run-in. On randomization, inhaled corticosteroids were discontinued, and ipratropium bromide was allowed at a stable dose for those patients previously treated with short-acting anticholinergic bronchodilators. The co-primary efficacy variables in both studies were the change from baseline in average pre-dose and 1-hour post-dose FEV_1 over the treatment period. The results of both studies 1 and 2 are described below.

Study 1

This was a 6-month, placebo-controlled study of 1704 COPD patients (mean % predicted FEV_1 at baseline ranging from 33.5% -34.7%) conducted to demonstrate the efficacy and safety of SYMBICORT in the treatment of airflow obstruction in COPD. The patients were randomized to one of the following treatment groups: SYMBICORT 160/4.5 (n=277), SYMBICORT 80/4.5 (n=281), budesonide 160 mcg + formoterol 4.5 mcg (n=287), budesonide 160 mcg (n=275), formoterol 4.5 mcg (n=284), or placebo (n=300). Patients receiving SYMBICORT 160/4.5 mcg, two inhalations twice daily, had significantly greater mean improvements from baseline in pre-dose FEV_1 averaged over the treatment period [0.08 L, 10.7%] compared with formoterol 4.5 mcg [0.04 L, 6.9%] and placebo [0.01 L, 2.2%] (See Figure 5). Patients receiving SYMBICORT 80/4.5 mcg, two inhalations twice daily, did not have significantly greater improvement from baseline in the pre-dose FEV_1 averaged over the treatment period compared with formoterol 4.5 mcg.

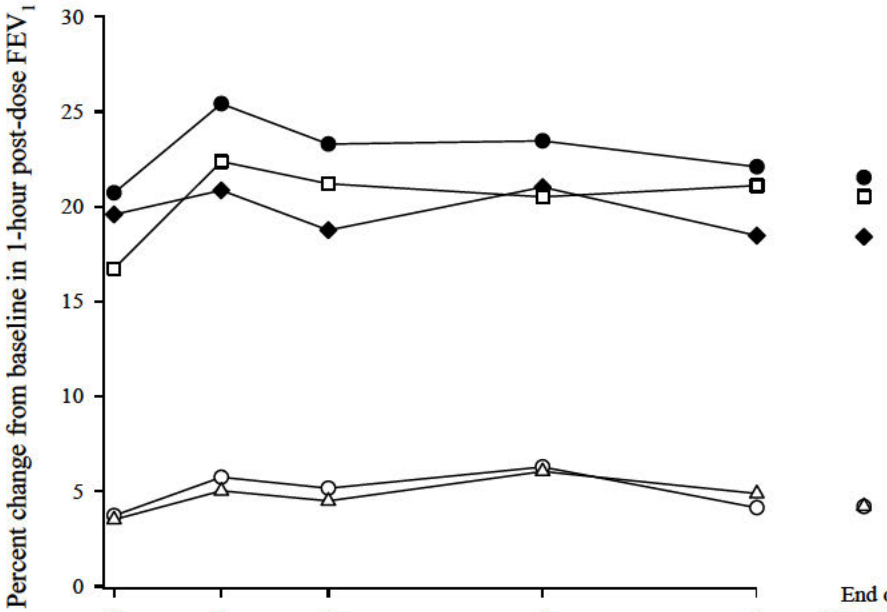
Figure 5 Mean Percent Change From Baseline in Pre-dose FEV_1 Over 6 months (Study 1)



	N	N	N	N	N	N
Symbicort 160/4 5 mcg	275	266	259	250	238	266
Budesonide 160 mcg	274	262	242	227	210	265
Formoterol 4.5 mcg	283	263	250	235	223	263
Budes 160+Form 4 5 mcg	286	278	267	253	238	279
Placebo	299	266	245	238	230	270

Patients receiving SYMBICORT 160/4.5 mcg, two inhalations twice daily, had significantly greater mean improvements from baseline in 1-hour post-dose FEV_1 averaged over the treatment period [0.20 L, 22.6%], compared with budesonide 160 mcg [0.03 L, 4.9%] and placebo [0.03 L, 4.1%] (See Figure 6)

Figure 6 Mean Percent Change From Baseline in 1-hour Post-dose FEV_1 Over 6 months (Study 1)



	0	1	2	4	6	End of Treatment
	N	N	N	N	N	N
Symbicort 160/4.5 mcg	271	267	257	250	237	275
Budesonide 160 mcg	274	255	241	224	210	274
Formoterol 4 5 mcg	282	259	248	234	221	283
Budes 160+Form 4.5 mcg	283	277	267	252	239	286
Placebo	298	262	243	238	230	299

● SYMBICORT MDI 160/4.5 mcg, two inhalations twice daily
○ Budesonide 160 mcg, two inhalations twice daily
◆ Formoterol 4.5 mcg, two inhalations twice daily
□ Budesonide 160 mcg + Formoterol 4.5 mcg, two inhalations twice daily
△ Placebo

Study 2

This was a 12-month, placebo-controlled study of 1964 COPD patients (mean % predicted FEV_1 at baseline ranging from 33.7% -35.5%) conducted to demonstrate the efficacy and safety of SYMBICORT in the treatment of airflow obstruction in COPD. The patients were randomized to one of the following treatment groups: SYMBICORT 160/4.5 (n=494), SYMBICORT 80/4.5 (n=494), formoterol 4.5 mcg (n=495), or placebo (n=48l). Patients receiving SYMBICORT 160/4.5 mcg, two inhalations twice daily, had significantly greater improvements from baseline in mean pre-dose FEV_1 averaged over the treatment period [0.10 L, 10.8%] compared with formoterol 4.5 mcg [0.06 L, 7.2%] and placebo [0.01 L, 2.8%]. Patients receiving SYMBICORT 80/4.5 mcg, two inhalations twice daily, did not have significantly greater improvements from baseline in the mean pre-dose FEV_1 averaged over the treatment period compared to formoterol. Patients receiving SYMBICORT 160/4.5 mcg, two inhalations twice daily, also had significantly greater mean improvements from baseline in 1-hour post-dose FEV_1 averaged over the treatment period [0.21 L, 24.0%] compared with placebo [0.02 L, 5.2%].

Serial FEV_1 measures over 12 hours were obtained in a subset of patients in Study 1 (n=99) and Study 2 (n=121). The median time to onset of bronchodilation, defined as an FEV_1 increase of 15% or greater from baseline, occurred at 5 minutes post-dose. Maximum improvement (calculated as the average change from baseline at each timepoint) in FEV_1 occurred at approximately 2 hours post-dose.

In both Studies 1 and 2, improvements in secondary endpoints of morning and evening peak expiratory flow and reduction in rescue medication use were supportive of the efficacy of SYMBICORT 160/4.5.

16 HOW SUPPLIED/STORAGE AND HANDLING

SYMBICORT is available in two strengths and is supplied in the following package sizes:

Dosage Forms and Strengths

Package Size	NDC
SYMBICORT 80/4.5, 120 inhalations	0186-0372-20
SYMBICORT 80/4.5, 60 inhalations (institutional pack)	0186-0372-28
SYMBICORT 160/4.5, 120 inhalations	0186-0370-20
SYMBICORT 160/4.5, 60 inhalations (institutional pack)	0186-0370-28

Each strength is supplied as a pressurized aluminium canister with an attached counting device, a red plastic actuator body with a white mouthpiece, and attached gray dust cap. Each 120 inhalation canister has a net fill weight of 10.2 grams and each 60 inhalation canister has a net fill weight of 6.9 grams (SYMBICORT 80/4.5) or 6 grams (SYMBICORT 160/4.5). Each canister is packaged in a foil overwrap pouch with desiccant sachet and placed into a carton. Each carton contains one canister and a Medication Guide.

The SYMBICORT canister should only be used with the SYMBICORT actuator, and the SYMBICORT actuator should not be used with any other inhalation drug product.

The correct amount of medication in each inhalation cannot be ensured after the labeled number of inhalations from the canister have been used, even though the inhaler may not feel completely empty and may continue to operate. The inhaler should be discarded when the labeled number of inhalations have been used or within 3 months after removal from the foil pouch. Never immerse the canister into water to determine the amount remaining in the canister ("float test").

Store at controlled room temperature 20°C to 25°C (68°F to 77°F) [see USP]. Store the inhaler with the mouthpiece down.

For best results, the canister should be at room temperature before use. Shake well for 5 seconds before using.

Keep out of the reach of children.

CONTENTS UNDER PRESSURE.

Do not puncture or incinerate. Do not store near heat or open flame. Exposure to temperatures over 120ºF may cause bursting. Never throw container into fire or incinerator.

17 PATIENT COUNSELING INFORMATION

See Medication Guide (17.6)

17.1 Risk of Asthma-Related Death

Patients with asthma should be informed that formoterol fumarate dihydrate, one of the active ingredients in SYMBICORT, may increase the risk of asthma-related death.

They should also be informed that data are not adequate to determine whether the concurrent use of inhaled corticosteroids, the other component of SYMBICORT, or other asthma-controller therapy modifies this risk.

17.2 Not for Acute Symptoms

SYMBICORT is not meant to relieve acute asthma symptoms or exacerbations of COPD and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist such as albuterol. (The physician should provide the patient with such medication and instruct the patient in how it should be used.)

Patients should be instructed to notify their physician immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting $beta_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting $beta_2$-agonists

- Significant decrease in lung function as outlined by the physician

Patients should not stop therapy with SYMBICORT without physician/provider guidance since symptoms may recur after discontinuation.

17.3 Do Not Use Additional Long-Acting Beta$_2$-Agonists
When patients are prescribed SYMBICORT, other long-acting beta$_2$-agonists for asthma and COPD should not be used.

17.4 Risks Associated With Corticosteroid Therapy
Local Effects: Patients should be advised that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with SYMBICORT, but at times therapy with SYMBICORT may need to be temporarily interrupted under close medical supervision. Rinsing the mouth after inhalation is advised.

Pneumonia: Patients with COPD have a higher risk of pneumonia and should be instructed to contact their healthcare provider if they develop symptoms of pneumonia.

Immunosuppression: Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles and, if exposed, to consult their physician without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex.

Hypercorticism and Adrenal Suppression: Patients should be advised that SYMBICORT may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to SYMBICORT.

Reduction in Bone Mineral Density: Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk.

Reduced Growth Velocity: Patients should be informed that orally inhaled corticosteroids, component of SYMBICORT, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the

growth of children and adolescents taking corticosteroids by any route.

Ocular Effects: Long-term use of inhaled corticosteroids may increase the risk of some eye problems (cataracts or glaucoma); regular eye examinations should be considered.

17.5 Risks Associated With Beta-Agonist Therapy

Patients should be informed of adverse effects associated with $beta_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

17.6 Medication Guide

SYMBICORT is a trademark of the AstraZeneca group of companies.

Manufactured for: AstraZeneca LP, Wilmington, DE 19850
By: AstraZeneca Dunkerque Production, Dunkerque, France

Product of France
31152-XX

MEDICATION GUIDE

SYMBICORT 80/4.5

(budesonide 80 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalation Aerosol

SYMBICORT 160/4.5

(budesonide 160 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalation Aerosol

Read the Medication Guide that comes with SYMBICORT before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about SYMBICORT?

- **SYMBICORT contains 2 medicines:**
  - **Budesonide (the same medicine found in PULMICORT FLEXHALER®),** an inhaled corticosteroid medicine. Inhaled corticosteroids help to decrease inflammation in the lungs. Inflammation in the lungs can lead to asthma symptoms.
  - **Formoterol (the same medicine found in FORADIL® AEROLIZER®),** a long-acting $beta_2$-agonist medicine or LABA. LABA medicines are used in patients with chronic obstructive pulmonary disease (COPD) and asthma. LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent asthma symptoms, such as wheezing and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and may lead to death if not treated right away.

- **In patients with asthma, LABA medicines such as formoterol (one of the medicines in SYMBICORT)**

may increase the chance of death from asthma problems. In a large asthma study, more patients who used another LABA medicine died from asthma problems compared with patients who did not use that LABA medicine. Talk with your healthcare provider about this risk and the benefits of treating your asthma with SYMBICORT.

- **SYMBICORT does not relieve sudden symptoms. Always have an inhaled short-acting beta$_2$-agonist medicine with you to treat sudden symptoms. If you do not have this type of medicine, contact your healthcare provider to have one prescribed for you.**

- **Do not stop using SYMBICORT unless told to do so by your healthcare provider because your symptoms might get worse.**

- **SYMBICORT should be used only if your healthcare provider decides that another asthma-controller medicine alone does not control your asthma or that you need two asthma-controller medicines.**

- **Call your healthcare provider if breathing problems worsen over time while using SYMBICORT. You may need different treatment.**

- **Get emergency medical care if:**
  - **Breathing problems worsen quickly, and**
  - **You use your short-acting beta$_2$-agonist medicine, but it does not relieve your breathing problems.**

What is SYMBICORT?
SYMBICORT combines an inhaled corticosteroid medicine, budesonide (the same medicine found in PULMICORT FLEXHALER), and a long-acting beta$_2$-agonist medicine (LABA), formoterol (the same medicine found in FORADIL AEROLIZER).

Asthma

SYMBICORT is used long-term, two times each day to control symptoms of asthma, and prevent symptoms such as wheezing in patients age 12 year and older.

SYMBICORT contains formoterol (the same medicine found in FORADIL AEROLIZER). Because LABA medicines such as formoterol may increase the chance of death from asthma problems, SYMBICORT is not for patients with asthma who:

- are well controlled with another asthma-controller medicine such as a low to medium dose of an inhaled corticosteroid medicine
- only need short-acting beta$_2$-agonist medicines once in awhile

The safety and effectiveness of SYMBICORT in asthma patients 6 to <12 years of age has not been established.

Chronic Obstructive Pulmonary Disease (COPD)
COPD is a chronic lung disease that includes chronic bronchitis, emphysema, or both. SYMBICORT 160/4.5 mcg is used long term, two times each day to help improve lung function for better breathing in adults with COPD.

Who should not use SYMBICORT?

Do not use SYMBICORT:
• to treat sudden severe symptoms of asthma or COPD.
• if you are allergic to any of the ingredients in SYMBICORT. See the end of the Medication Guide for a list of ingredients in SYMBICORT.

What should I tell my healthcare provider before using SYMBICORT?
Tell your healthcare provider about all of your health conditions, including if you:

- **have heart problems**
- **have high blood pressure**
- **have seizures**
- **have thyroid problems**
- **have diabetes**
- **have liver problems**

- **have osteoporosis**
- **have an immune system problem**
- **have eye problems such as increased pressure in the eye, glaucoma, or cataracts**
- **are allergic to any medicines**
- **are exposed to chicken pox or measles**
- **are pregnant or planning to become pregnant.** It is not known if SYMBICORT may harm your unborn baby.
- **are breastfeeding.** Budesonide, one of the active ingredients in SYMBICORT, passes into breast milk. You and your healthcare provider should decide if you will take SYMBICORT while breast-feeding.

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. SYMBICORT and certain other medicines may interact with each other. This may cause serious side effects. Especially tell your healthcare provider if you take antifungal and anti-HIV medicines.

Know all the medicines you take. Keep a list and show it to your healthcare provider and pharmacist each time you get a new medicine.

How do I use SYMBICORT?

See the step-by-step instructions for using SYMBICORT at the end of this Medication Guide. Do not use SYMBICORT unless your healthcare provider has taught you and you understand everything. Ask your healthcare provider or pharmacist if you have any questions.

- Use SYMBICORT exactly as prescribed. **Do not use SYMBICORT more often than prescribed.** SYMBICORT comes in two strengths. Your healthcare provider has prescribed the strength that is best for you. Note the differences between SYMBICORT and your other inhaled medications, including the differences in prescribed use and physical appearance.

- SYMBICORT should be taken every day as two puffs in the morning and two puffs in the evening.

- If you miss a dose of SYMBICORT, you should take your next dose at the same time you normally do. Do not take SYMBICORT more often or use more puffs than you have been prescribed.

- Rinse your mouth with water and spit the water out after each dose (two puffs) of SYMBICORT. Do not swallow the water. This will help to lessen the chance of getting a fungus infection (thrush) in the mouth and throat.

- Do not spray SYMBICORT in your eyes. If you accidentally get SYMBICORT in your eyes, rinse your eyes with water, and if redness or irritation persists, consult your healthcare provider.

- Do not change or stop any medicines used to control or treat your breathing problems. Your healthcare provider will change your medicines as needed.

- **While you are using SYMBICORT do not use other medicines that contain a long-acting beta$_2$-agonist (LABA) for any reason, such as SEREVENT DISKUS (salmeterol xinafoate inhalation powder), ADVAIR DISKUS or ADVAIR HFA (fluticasone propionate and salmeterol), or formoterol containing products (FORADIL AEROLIZER, Brovana, Performist)**

- Make sure you always have a short-acting beta$_2$-agonist medicine with you. Use your short-acting beta$_2$-agonist medicine if you have breathing problems between doses of SYMBICORT.

- **Call your healthcare provider or get medical care right away if:**
    - your breathing problems worsen with SYMBICORT
    - you need to use your short-acting beta$_2$-agonist medicine more often than usual
    - your short-acting beta$_2$-agonist medicine does not work as well for you at relieving symptoms

- you need to use four or more inhalations of your short-acting beta$_2$-agonist medicine for 2 or more days in a row
- you use one whole canister of your short-acting beta$_2$-agonist medicine in 8 weeks' time
- your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
- your symptoms do not improve after using SYMBICORT regularly for 1 week.

What are the possible side effects with SYMBICORT?

- **SYMBICORT contains formoterol. In patients with asthma, LABA medicines such as formoterol may increase the chance of death from asthma problems.** See "What is the most important information I should know about SYMBICORT?"

- **Pneumonia and other lower respiratory tract infections.** People with COPD have a higher chance of getting pneumonia and other lung infections. Inhaled corticosteroids may increase the chance of getting pneumonia. Call your healthcare provider if you notice any of these symptoms:
  - increase in mucus (sputum) production
  - change in mucus color
  - fever
  - chills
  - increased cough
  - increased breathing problems.

Other possible side effects with SYMBICORT include:

- **serious allergic reactions including rash, hives, swelling of the face, mouth, and tongue, and breathing problems.** Call your healthcare provider

or get emergency medical care if you get any symptoms of a serious allergic reaction.

- **chest pain**
- **increased blood pressure**
- **a fast and irregular heartbeat**
- **headache**
- **tremor**
- **nervousness**
- **immune system effects and a higher chance for infections**
- **eye problems including glaucoma and cataracts.** You should have regular eye exams while using SYMBICORT.
- **lower bone mineral density.** This may be a problem for people who already have a higher chance for low bone mineral density (osteoporosis).
- **slowed growth in children.** A child's growth should be checked often.
- **thrush in the mouth and throat**
- **throat pain**

The most common side effects with SYMBICORT include:
Adults and children with asthma:

- throat irritation
- headache
- upper respiratory tract infection
- throat pain
- inflammation of mucous membranes of the sinuses (sinusitis)
- flu
- back pain

- nasal congestion
- stomach discomfort
- vomiting
- thrush in the mouth and throat

Patients with COPD:

- throat irritation
- thrush in the mouth and throat
- lower respiratory tract infections, mostly infections and/or inflammation of the mucous membranes of the bronchial tubes (bronchitis)
- inflammation of mucous membranes in the sinuses (sinusitis)
- upper respiratory tract infection

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the side effects of SYMBICORT. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088 and/or ASTRAZENECA at 1-800-236-9933.

How do I store SYMBICORT?

- Store SYMBICORT at room temperature between 68°F to 77°F (20°C to 25°C).
- Store with the mouthpiece down.
- The contents of your SYMBICORT canister are under pressure. Do not puncture or throw the canister into a fire or incinerator. Do not use or store it near heat or open flame. Storage above 120ºF may cause the canister to burst.
- Throw away SYMBICORT when the counter reaches zero (“0”) or 3 months after you take SYMBICORT out of its foil pouch, whichever comes first.

- **Keep SYMBICORT and all medicines out of the reach of children.**

General Information about SYMBICORT
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SYMBICORT for a condition for which it was not prescribed. Do not give your SYMBICORT to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about SYMBICORT. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about SYMBICORT that was written for healthcare professionals. For more information, call 1-800-236-9933 or go to www.MySymbicort.com.

What are the ingredients in SYMBICORT?
Active ingredient: micronized budesonide and micronized formoterol fumarate dihydrate

Inactive ingredients: hydrofluroalkane (HFA 227), povidone K25 USP, and polyethylene glycol 1000 NF

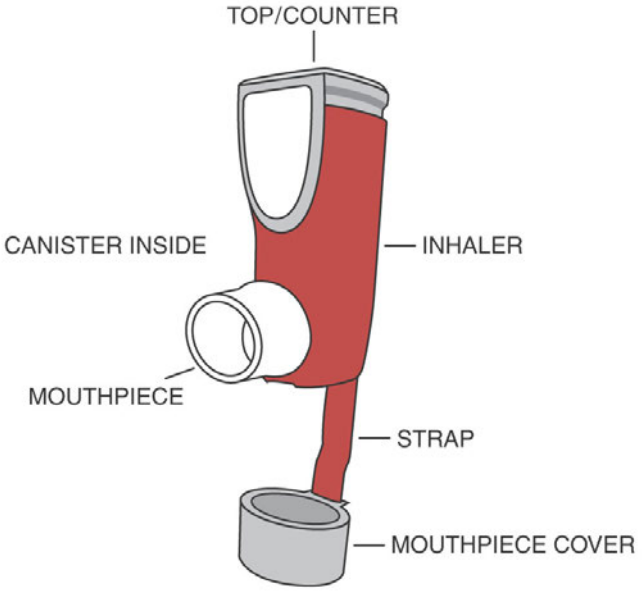


Figure 1

Upright Position

How to Use SYMBICORT

Follow the instructions below for using SYMBICORT. You will breathe-in (inhale) the medicine. If you have any questions, ask your doctor or pharmacist.

Preparing your inhaler for use

1. Take your SYMBICORT out of the moisture-protective foil pouch before you use it for the first time and throw the foil away. Write the date that you open the foil pouch on the box.

2. A counter is attached to the top of the metal canister. The counter will count down each time you release a puff of SYMBICORT. The arrow points to the number of inhalations (puffs) left in the canister. The counter will stop counting at zero ("0").

3. Use the SYMBICORT canister only with the red SYMBICORT inhaler supplied with the product. Parts of the SYMBICORT inhaler should not be used with parts from any other inhalation product.

4. Shake your SYMBICORT inhaler well for 5 seconds right before each use. Remove the mouthpiece cover. Check the mouthpiece for foreign objects before use.

5. **Priming** Before you use SYMBICORT for the first time, you will need to prime it. To prime SYMBICORT, hold it in the upright position. See figure 1 above. Shake the SYMBICORT inhaler well for 5 seconds. Hold your SYMBICORT inhaler facing away from you and then release a test spray. Then shake it again for 5 seconds and release a second test spray. Your SYMBICORT inhaler is now primed and ready for use. After you have primed the SYMBICORT inhaler for the first time, the counter will read either 120 or 60, depending on which size was provided to you.

If you do not use your SYMBICORT inhaler for more than 7 days or if you drop it, you will need to prime again.

Ways to hold the SYMBICORT inhaler for use

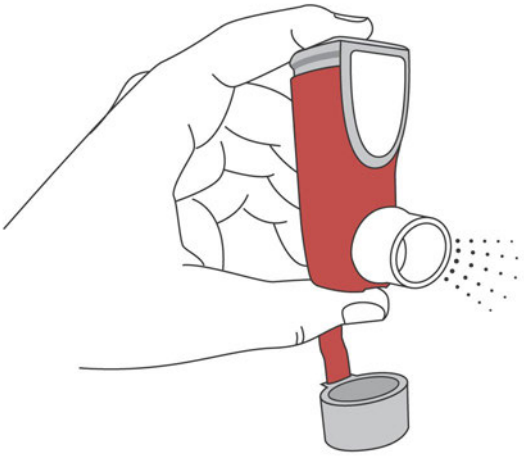


Figure 2

OR

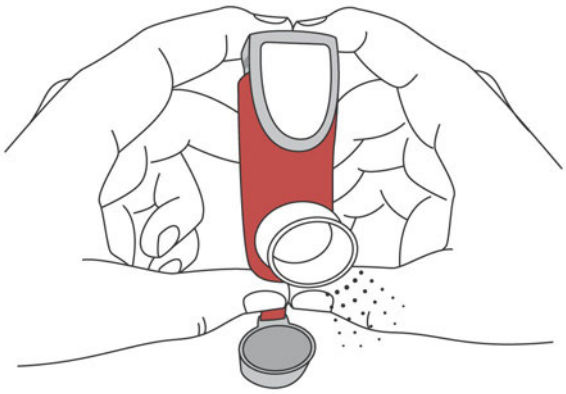


Figure 3

Using your SYMBICORT inhaler

6. Shake your SYMBICORT inhaler well for 5 seconds. Remove the mouthpiece cover. Check the mouthpiece for foreign objects.

7. Breathe out fully (exhale). Hold the SYMBICORT inhaler up to your mouth. Place the white mouthpiece fully into your mouth and close your lips around it. Make sure that the SYMBICORT inhaler is upright and that the opening of the mouthpiece is pointing towards the back of your throat (see Figure 4).

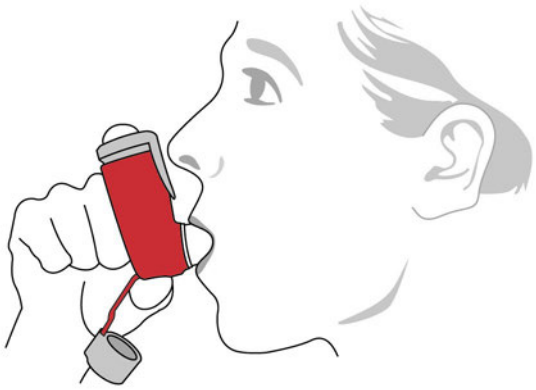


Figure 4

8. Breathe in (inhale) deeply and slowly through your mouth. Press down firmly and fully on the top of the counter on the SYMBICORT inhaler to release the medicine (see Figures 2 and 3).

9. Continue to breathe in (inhale) and hold your breath for about 10 seconds, or for as long as is comfortable. Before you breathe out (exhale), release your finger from the top of the counter. Keep the SYMBICORT inhaler upright and remove from your mouth.

10. Shake the SYMBICORT inhaler again for 5 seconds and repeat steps 7 to 9.

After using your SYMBICORT inhaler

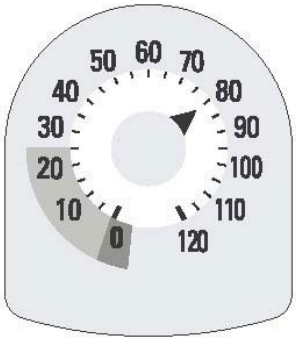
11. Replace the mouthpiece cover after use.

12. After you finish taking SYMBICORT (two puffs), rinse your mouth with water. Spit out the water. Do not swallow it.

Reading the counter

- The arrow on the counter on the top of the SYMBICORT inhaler points to the number of inhalations (puffs) left in your inhaler.

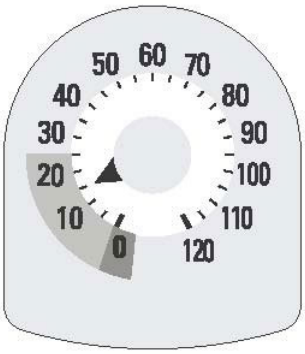
COUNTER



- The counter will count down each time you release a puff of medicine (either when preparing your SYMBICORT inhaler for use or when taking the medicine).

- When the arrow on the counter approaches 20, you will notice the beginning of a yellow area letting you know that it is time to call your healthcare provider for a refill.

COUNTER



- It is important that you pay attention to the number of inhalations (puffs) left in your SYMBICORT inhaler by reading the counter. Throw away SYMBICORT when the counter shows zero ("0"). Your SYMBICORT inhaler may not feel empty and it may continue to operate, but you will not get the right amount of medicine if you keep using it. Use a new SYMBICORT inhaler and follow the instructions for priming (instruction 5 above).

How to clean your SYMBICORT inhaler

Clean the white mouthpiece of your SYMBICORT inhaler every 7 days. To clean the mouthpiece:

- Remove the grey mouthpiece cover
- Wipe the inside and outside of the white mouthpiece opening with a clean, dry cloth
- Replace the mouthpiece cover
- **Do not put the SYMBICORT inhaler into water**
- Do not try to take apart your **SYMBICORT** inhaler

31154-XX
Rev. XX/XX

Manufactured for: AstraZeneca LP, Wilmington, DE 19850

By: AstraZeneca Dunkerque Production, Dunkerque, France

Product of France

This Medication Guide has been approved by the U.S. Food and Drug Administration.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21–929/S012

REMS

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS) FOR SYMBICORT

I. GOAL

The goal of this REMS is to communicate the risks of SYMBICORT.

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each SYMBICORT prescription. SYMBICORT is packaged as a single unit of use. The Medication Guide is inserted inside the carton during insertion of the overwrapped MDI unit. Each Medication Guide is barcode scanned to ensure that the correct version is being used and that the component is available for insertion into each carton.

Because the Medication Guide is included as part of the secondary package for SYMBICORT, AstraZeneca has met the requirements of 21 CFR 208.24 for distribution and dispensing of the Medication Guide.

B. Communication Plan

The REMS for SYMBICORT does not include a communication plan.

C. Element To Assure Safe Use

The REMS for SYMBICORT does not include elements to assure safe use.

D. Implementation System

Because the REMS for SYMBICORT does not include elements to assure safe use, an implementation system is not required.

III. ASSESSMENT OF REMS

Because the Medication Guide is included as part of the secondary package for SYMBICORT, AstraZeneca has met the requirements of 21 CFR 208.24 for distribution and dispensing of the Medication Guide. Accordingly, AstraZeneca will not be required to assess the distribution and dispensing of the Medication Guide or failures to adhere to distribution and dispensing requirements. However, AstraZeneca will be required to assess patients' understanding of the serious risks of SYMBICORT.

NDA 21-929/S-012 -- SYMBICORT (budesonide/formoterol fumarate dihydrate)

The Timetable for Assessments is as follows:

1st FDAAA assessment: August 2010 (18 months from approval)
2nd FDAAA assessment: February 2012 (3 years from approval)
3rd FDAAA assessment: February 2016 (7 years from approval)

AstraZeneca will submit the assessment within 60 days of the close of the intervals as noted above.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21–929/S012

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	February 27, 2009
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary and Allergy Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	21-929, SE-01, S012
Applicant Name:	AstraZeneca
Date of Submission:	April 28, 2008
PDUFA Goal Date:	February 28, 2009
Proprietary Name:	Symbicort Inhalation Aerosol
Established Name:	Budesonide and formoterol fumarate
Dosage form:	Inhalation Aerosol
Strength:	Budesonide 160 mcg, and formoterol fumarate 4.5 mcg
Proposed Indications:	Chronic Obstructive Pulmonary Disease
Action:	Approval

1. Introduction

AsraZeneca submitted this supplemental 505(b)(1) application for use of Symbicort 160/4.5 (budesonide 160 mcg, and formoterol fumarate 4.5 mcg) for maintenance treatment of airflow obstruction in patients with Chronic Obstructive Pulmonary Disease (COPD), including chronic bronchitis and emphysema. The proposed dose is two inhalations twice daily. The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

There are several drug classes available for the relief of airflow obstruction in patients with COPD. These include beta-adrenergic agents, anticholinergic agents, combination products containing beta-adrenergic agents and anticholinergic agents, combination of long-acting beta-adrenergic agents and corticosteroids, and methylxanthines. Advair, a combination of long-acting beta-adrenergic salmeterol and corticosteroid fluticasone propionate, available as a Diskus and as an inhalation aerosol, is approved for maintenance treatment of airflow obstruction in patients with COPD. Advair Diskus is also approved for use in COPD patients to reduce exacerbations. Symbicort 160/4.5 will provide another choice for maintenance treatment of airflow obstruction in patients with COPD.

3. Chemistry, Manufacturing, and Controls

Symbicort 160/4.5 is an approved product and there are no CMC issues.

4. Nonclinical Pharmacology and Toxicology

No new pharmacology and toxicology studies were submitted with this application. The pharmacology and toxicology data were reviewed in the original NDA.

5. Clinical Pharmacology and Biopharmaceutics

The general clinical pharmacology and biopharmaceutic considerations for Symbicort 160/4.5 were addressed in the original NDA. There are no major issues with this application. AstraZeneca submitted PK data in COPD patients and HPA axis data in COPD patients, which are described in the product label.

6. Clinical Microbiology

Not applicable.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the pivotal studies that form the basis of review and regulatory decision for this application are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

Table 1. Pivotal Advair Diskus clinical studies

ID	Study type	Study duration	Patient Age, yr	Treatment groups*	N (ITT)	Study Year#	Countries
D002, SHINE	Efficacy and safety	6 months	≥ 40	Sym 80/4.5 BID Sym 160/4.5 BID Bud 160 + For 4.5 BID Bud 160 BID For 4.5 BID Pbo	281 277 287 275 284 300	2006	USA, Poland, Netherlands, South Africa, Czech Republic
D001, SUN	Efficacy and safety	12 months	≥ 40	Sym 80/4.5 BID Sym 160/4.5 BID For 4.5 BID Pbo	494 494 495 481	2007	USA, Hungary, Germany, Denmark, Bulgaria, Mexico, Greece, Iceland, Romania

* Sym = Symbicort Inhalation Aerosol; For = Formoterol Turbohaler as Oxis Turbohaler, which is a non-US product; Bud: Budesonide; Pbo = Placebo
# Year study subject enrollment ended

b. Design and conduct of the studies

Studies SHINE and SUN:

These studies were randomized, double-blind, double-dummy, parallel-group in design, conducted in patients with moderate-to-severe COPD. Patients were required to be 40 years of age and older; have a clinical diagnosis of COPD with symptoms for 2 years or longer, FEV1/FVC <70%, FEV1 ≤ 50% predicted; be a current or previous smoker with a smoking history of ≥10 pack years; and have a history of at least one COPD exacerbation requiring a course of oral steroids within 1-12 months before the first visit. The studies had an initial screening period, followed by 6 months (for SHINE) or 12 moths (for SUN) double-blind treatment period. The treatment arms are shown in Table 1. There are two issues with the treatment arms worth noting. First, unlike typical factorial design study for combination products where the active comparators are pharmaceutically the same as the combination product, in these studies the formoterol comparator was delivered via the Oxis Turbuhaler, which is different than the inhalation aerosol device in Symbicort. This was acceptable because for the asthma development program AstraZeneca conducted a pharmacodynamic study that resolved the pharmaceutical differences to support the use of different devices to deliver formoterol. Second, in the SHINE study AstraZeneca included a free combination of budesonide and formoterol to evaluate for a pharmaceutic interaction when budesonide and formoterol are administered in one device versus two devices.

The studies had two co-primary efficacy variables: pre-dose FEV1 to demonstrate the contribution of budesonide, and post-dose FEV1 to show the contribution of formoterol. The primary analysis was the change from baseline in the average of all FEV1, pre-dose or 1 hour post-dose, measurements during the randomized treatment period. Multiplicity was accounted for by a pre-specified hierarchical order requiring the higher dose to be positive to move to the lower dose. Other efficacy variables of interest were Saint Georges Respiratory Questionnaire (SGRQ), Breathlessness Diary Score, and COPD exacerbation. A COPD exacerbation was defined as worsening of COPD that at the discretion of the investigator required a course of oral corticosteroid treatment or hospitalization or both. There is no generally accepted definition of COPD exacerbations, but it usually includes some combination of symptoms and a change of treatment. [1] The definition of COPD exacerbation used in these two studies was entirely based upon oral corticosteroid use or hospitalization, which is not sufficient.

Safety assessment in these studies included adverse event recording, vital signs, physical examination, laboratory measure, ECGs, and urinary free cortisol measurement in a subgroup of patients (437 in SHINE and 179 in SUN studies). In the SUN study, 24 hour Holter monitoring, ophthalmologic assessment, and bone mineral density were included in a subgroup of patients.

[1] Cazzola M, MacNee W, Martizez FJ, et al. ATS/ERS Task Force Report: Outcomes for COPD pharmacological trials, from lung function to biomarkers. Eur Resp J 2008; 31: 416-468.

c. Efficacy findings and conclusions

The clinical program supports efficacy of Symbicort 160/4.5 at a dose of two inhalations twice daily for maintenance treatment of airflow obstruction in patients with COPD.

Patients enrolled in these studies were of mean age of 63 years and had mean baseline pre-bronchodilator FEV1 of approximately 1 liter, which is approximately 34% of predicted. Results of the primary efficacy variables are shown in Table 2. These results demonstrate efficacy of Symbicort 160/4.5, and the contribution of budesonide (Symbicort vs. formoterol comparison in pre-dose FEV1) and contribution of formoterol (Symbicort vs. budesonide comparison in 1 hour post-dose FEV1). In both the studies pre-dose FEV1 and 1 hour post-dose FEV1 were statistically significantly superior for Symbicort 160/4.5 compared to formoterol, but Symbicort 80/4.5 was not statistically significantly superior compared to formoterol. Contribution of budesonide in Symbicort 160/4.5 is replicated in both studies, which is necessary because inhaled corticosteroids do not have the COPD indication. Contribution of budesonide in Symbicort 80/4.5 was not shown in either of the study. Contribution of formoterol in Symbicort 160/4.5 was tested in one study, which is adequate because formoterol has a COPD indication. Nevertheless, contribution of formoterol was replicated within the one study where it was tested with both doses of Symbicort being statistically significantly superior compared to budesonide. Although the two doses of Symbicort were not statistically different, Symbicort 160/4.5 was consistently numerically better than Symbicort 80/4.5. The overall data support approval of Symbicort 160/4.5, but not Symbicort 80/4.5.

In a subset of patients, serial FEV1 measures over 12 hours were obtained (99 in SHINE and 121 in SUN). In this subset, onset of bronchodilation, defined as an FEV1 increase of 15% or greater from baseline, calculated by using a linear interpolation method, occurred in 6.6 minutes in SHINE and 4.2 minutes in SUN, and maximum improvement occurred at approximately 2 hours post-dose. This information will be included in the label to stay consistent with the labels of two single ingredient formoterol products approved for COPD - Perforomist (formoterol fumarate) Inhalation Solution, and Brovana (arformoterol tartrate) Inhalation solution. The third single ingredient formoterol product approved for COPD, Foradil Aerolizer (formoterol fumarate inhalation powder), does not have such statement in the label.

Table 2. Results of primary efficacy variables for studies SHINE and SUN, pre-specified primary comparisons are shaded

	Pre-dose FEV_1 Change from baseline in average during treatment period (p-value)		**1 hr post-dose FEV_1** Change from baseline in average during treatment period (p-value)	
	SHINE	**SUN**	**SHINE**	**SUN**
Symbicort 80/4.5 vs. placebo	0.05 (0.002)	0.07 (<0.001)	0.16 (<0.001)	0.16 (<0.001)
Symbicort 160/4.5 vs. placebo	0.08 (<0.001)	0.09 (<0.001)	0.17 (<0.001)	0.18 (<0.001)
Symbicort 80/4.5 vs. budesonide 160	0.06 (0.001)	-	0.16 (<0.001)	-
Symbicort 160/4.5 vs. budesonide 160	0.08 (<0.001)	-	0.17 (<0.001)	-
Symbicort 80/4.5 vs. formoterol 4.5 TBH	0.02 (0.335)	0.02 (0.161)	0.03 (0.116)	0.01 (0.420)
Symbicort 160/4.5 vs. formoterol 4.5 TBH	0.04 (0.026)	0.04 (0.008)	0.04 (0.039)	0.03 (0.023)
Symbicort 160/4.5 vs. free combination	0.01 (0.479)		0.01 (0.461)	-
Budesonide 160 vs. placebo	0.00 (0.902)	-	0.00 (0.997)	-
Formoterol 4.5 TBH vs. placebo	0.04 (0.037)	0.05 (<0.001)	0.14 (<0.001)	0.15 (<0.001)

	Pre-dose FEV_1 Change from baseline in average during treatment period (p-value)		**1 hr post-dose FEV_1** Change from baseline in average during treatment period (p-value)	
Symbicort 160/4.5 vs. Symbicort 80/4.5	0.02 (0.198)	0.02 (0.206)	0.01 (0.615)	0.02 (0.144)

Other efficacy variables were supportive of efficacy of Symbicort in COPD, but the findings were not robus (b) (4) For SGRQ, the differences between Symbicort and placebo were statistically significantly different, but the minimal clinically important difference of 4 units was not reached in any study. For the Breathlessness Diary Score, the differences between Symbicort and placebo were also statistically significantly different, but the minimal clinically important difference of 0.2 units was only reached for Symbicort 160/4.5 in the SUN study. For COPD exacerbation, the findings were less convincing. The difference in rates of COPD exacerbation between Symbicort and placebo was significantly different in the SUN study for Symbicort 160/4.5, but the rates were not different in the SHINE study. The events were primarily driven by events requiring corticosteroid treatment.

8. Safety

a. Safety database

The safety assessment of Symbicort for COPD patients is based on studies shown in Table 1. The safety database is adequate and typical for other similar applications.

b. Safety findings and conclusion

The submitted data support the safety of Symbicort in patients with COPD.

There were a total of 26 deaths in the two clinical studies. The number of deaths was generally similar across treatment groups and from causes expected in this study population. The percentage of patients with serious adverse events were higher in the Symbicort groups compared to placebo, but similar to formoterol group. Evaluation of these serious adverse events did not show any safety concerns. Adverse events occurring more in Symbicort group compared to placebo were typical of this class of drug and included events such as nasopharyngitis, oral candidiasis, bronchitis, and upper respiratory tract infections.

The incidence of pneumonia and other lung infection was carefully evaluated because of the known risk of lung infection in COPD patients on inhaled corticosteroids. The incidence of pneumonia was not increased in the two studies, but there was higher incidence of lung infection other than pneumonia (e.g., bronchitis, viral lower respiratory tract infections, etc.) in patients receiving Symbicort 160/4.5 compared to formoterol or placebo.

In a subset of patients, bone mineral density (n=326), ophthalmologic assessment (n=461), and Holter monitoring (n=520) were done. The changes in bone mineral density in these studies were small and not different between treatment groups. Ophthalmologic assessment did not show any differential changes in intraocular pressure among treatment groups. Opacification of the lens as assessed by lenticular opacity scale (LOCS III score)

increased in all treatment groups over the course of the study with the largest increase occurring in the Symbicort 160/4.5 group. The Holter monitoring did not show any findings suggestive of a new safety signal.

c. REMS/RiskMAP

Symbicort has a Boxed Warning and a Medication Guide because of risk of asthma related death. In consultation with the Office of New Drugs and Office of Surveillance and Epidemiology (OSE) it was decided that the Medication Guide will now be considered part of a Risk Evaluation and Mitigation Strategy (REMS) for the lower respiratory tract infections, as required by the FDAAA. Astra Zeneca will submit three assessments of the REMS at 18 month, 3 years, and 7 years from approval of this supplement. Information for the assessment of REMS may include but may not be limited to an evaluation of patients' understanding of the serious risks of Symbicort.

9. Advisory Committee Meeting

An advisory committee was not convened for this application. Symbicort is an approved product for asthma and this application was based on a typical COPD drug development program. There were no new or unique efficacy or safety findings in the program.

10. Pediatric

COPD is an adult disease, therefore, specific pediatric studies would not be required that relate to this action specific to COPD. This application was discussed at the January 28, 2009, PeRC meeting where it was agreed that a full waiver should be granted because studies would be impossible or highly impracticable because the disease does not exist in pediatric patients.

11. Other Relevant Regulatory Issues

a. DSI Audits

No DSI audit was conducted for this application. During review of this application the clinical team did not identify any irregularities that would raise concerns regarding data integrity. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. The applicant certified that it did not enter into financial arrangements with any investigator whereby the value of the compensation could affect the outcome of the studies. Some investigators received payments or had equity interest in AstraZeneca, but these investigators contributed relatively small number of patients in the studies. Furthermore, the multi-center nature of the studies makes it unlikely that equity interests could have influenced or biased the results of these studies.

c. Others

There are no outstanding issues with consults received from DDMAC, DRISK, or from other groups in CDER.

12. Labeling

a. Proprietary Name

There are no issues with the proprietary name as the name Symbicort was previously reviewed and found to be acceptable.

b. Physician Labeling

The labeling of Symbicort was reviewed in the past with approval of the asthma indication. With this application the existing label has undergone changes to include the new information related to the COPD indication, and the format was changed to the new Physician's Labeling Rule (PLR) format. There were some content changes to make the label consistent with the expectations of the labeling language under the PLR format, and to make the language consistent with some other single ingredient inhaled long-acting beta-agonist and inhaled corticosteroid labels that are in PLR format. The label was reviewed by various disciplines of this Division, and by DDMAC, OSE, and DRISK. The Division and the applicant have agreed to the final version of the label.

c. Carton and Immediate Container Labels

Symbicort is a marketed product and there were no changes to the carton and immediate container labels with this application. These were reviewed previously by various disciplines of this Division, and the current version was found to be acceptable.

d. Patient Labeling and Medication Guide

The Patient Counseling Information was reviewed by various disciplines of this Division, and DRISK, and found to be acceptable.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The applicant has submitted adequate data to support approval of Symbicort 160/4.5 for maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema. The action on this application will be Approval.

b. Risk Benefit Assessment

The overall risk benefit assessment support approval of Symbicort 160/4.5 for maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema. The risks associated with use of Symbicort in patients with COPD are typical of drug of this class that are associated with the use of inhaled budesonide and inhaled formoterol, which are described in the product label. There is a risk of lung infection with Symbicort in COPD patients, a finding that was also seen with Advair. Lung infection is a serious safety finding, but it is reasonable to expect that health care providers taking care of patients with COPD will be able to readily diagnose

them, differentiate them from a COPD exacerbation, and treat these appropriately. The REMS will also assure that health care providers and patients are aware of lung infection with Symbicort. The benefits of Symbicort 160/4.5 outweigh these risks and justify approval. Relief of airflow obstruction is a clinically meaningful improvement in COPD patients and by itself is not a trivial benefit. There are limited treatment choices for patients with COPD and additional treatment options for COPD are desired.

c. Post-marketing Risk Management Activities

Symbicort currently has a Medication Guide, which will now be considered part of REMS. Risk management activities will fall under the provision of REMS (discussed in section 8c above).

d. Post-marketing Study Commitments

There will be no post-marketing studies required.

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

/s/

Badrul Chowdhury
2/27/2009 10:51:49 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21–929/S012

OFFICER/EMPLOYEE LIST

Consent for the Officer Employee List for NDA 21-929/S-012

Badrul A. Chowdhury
Sandy Barnes
Lydia Gilbert-McClain
Sally Seymour
Timothy Robison
Luqi Pei
Qian Li
Ted Guo
Partha Roy
Ramesh Raghavachari
Lori Cantin
Colette Jackson
Denise Toyer
Kristina Arnwine
Sharon Mills
Iris Masucci

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21–929/S012

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 9, 2009
From	Sally Seymour, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA# 21-929 SE01, S 012
Applicant	AstraZeneca
Date of Submission	April 28, 2008
PDUFA Goal Date	February 27, 2009
Proprietary Name / **Established (USAN) names**	Symbicort Inhalation Aerosol budesonide/formoterol inhalation aerosol
Dosage forms / Strength	Inhalation aerosol 160/4.5 mcg
Proposed Indication(s)	1. (b) (4) maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema
Recommended:	Approval

1. Introduction

Astra Zeneca (AZ) submitted an efficacy supplement to new drug application (NDA# 21-929) on April 28, 2008 for the use of Symbicort 160/4.5 for the (b) (4) maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The PDUFA date for this application is February 27, 2009. Symbicort is a fixed dose combination of corticosteroid budesonide and the long acting beta agonist (LABA) formoterol that was approved for the maintenance treatment of asthma on July 21, 2006. Symbicort is a metered dose inhaler (MDI) that uses the propellant hydrofluoroalkane (HFA 227). For the asthma indication, Symbicort is currently approved in two different dosage strengths: 80/4.5 and 160/4.5, where the first number represents the amount of budesonide and the second number represents the amount of formoterol per actuation.

This memo provides a summary of the development program with a focus on the issues that warrant further discussion, including satisfaction of the combination policy. Since the Applicant seeks (b) (4) these will also be a focus of discussion.

2. Background

Symbicort is a fixed dose combination of corticosteroid budesonide and the LABA formoterol. Formoterol is currently approved as the Foradil Aerolizer and Foradil Certihaler for the long term, maintenance treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema. Formoterol is also available as the Oxis Turbuhaler outside of the US. Budesonide is approved for the treatment of asthma in two inhalation formulations

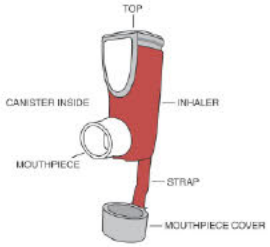
(Pulmicort Flexhaler and Pulmicort Respules). Currently there are no inhaled corticosteroids approved for the treatment of COPD; however, Advair is another fixed dose combination product which is approved for the maintenance treatment of airflow obstruction in patients with COPD as well as for the reduction of exacerbations of COPD in patients with a history of exacerbations. Advair contains the corticosteroid fluticasone and the LABA, salmeterol, and is approved as a Diskus dry powder inhaler and an HFA Inhalation Aerosol. AZ seeks the same maintenance treatment of airflow obstruction indication as Advair. (b) (4) However, there is currently no approved product (b) (4)

The Division and AZ had several interactions regarding the COPD program. The key regulatory history is outlined below:

- April 19, 2004 – End of phase 2 meeting
  - Independent substantiation of the contribution of the components to the combination product will be required. DPAP suggested adding formoterol group to 12 month study to determine contribution of budesonide. Substantiating contribution of formoterol less critical.
  - The Oxis Turbuhaler 9mcg is an acceptable mono-product comparator.
  - Consider a free combination arm in the 6 month study.
  - Endpoints are acceptable – pre-dose FEV_1 and post-dose 1 hour FEV_1
  - Health related QOL instruments must be appropriately validated and MID should be justified.
  - Safety database satisfactory, but perform ECGs at 3 months, add Holter monitoring, and an ophthalmologic assessment at 6 months.
  - Provide results by country.
  - It is necessary to demonstrate a dose response to support approval (b) (4)

3. CMC/Device

Symbicort Inhalation Aerosol is a fixed dose combination pressurized metered dose inhaler, which contains the active pharmaceutical ingredients budesonide and formoterol. Symbicort Inhalation Aerosol contains 120 actuations, each of which delivers (after priming) 160mcg budesonide and 4.5mcg formoterol from the actuator. The Applicant plans to use the same Symbicort Inhalation Aerosol 160/4.5 product approved for use in asthma; therefore, no new CMC information was provided in this efficacy supplement. Symbicort also contains the propellant hydrofluoroalkane (HFA) – 227, as well as excipients polyethylene glycol 1000, and polyvinylpyrrolidone K25. The CMC reviewer, Dr. Ramesh Raghavachari, recommends approval of this supplemental NDA.



4. Nonclinical Pharmacology/Toxicology

The Applicant plans to use the same Symbicort Inhalation Aerosol product approved for use in asthma and (b) (4) To support the asthma indication, AZ submitted a complete pharmacology/toxicology package; therefore, no new pharmacology/toxicology information was provided in this efficacy supplement. The pharmacology/toxicology reviewer, Dr. Timothy Robison, recommends approval of this supplemental NDA.

5. Clinical Pharmacology/Biopharmaceutics

Since Symbicort is an approved product, the Applicant submitted a complete clinical pharmacology package in the original NDA to support the asthma indication. In this supplemental NDA, the Applicant submitted data to assess the pharmacokinetic (PK) profile of budesonide and formoterol delivered via Symbicort in patients with COPD and to assess the effect of Symbicort on the HPA axis in patients with COPD. PK assessments were included in a subset of patients in SHINE (6 month study) and HPA axis assessments were included in a subset of patients in SHINE and SUN (12 month study). The results were reviewed by the clinical pharmacology reviewer, Dr. Partha Roy, who recommends approval of this supplemental NDA pending agreement on labeling. The findings are summarized briefly below.

The PK results show that formoterol exposure from Symbicort 160/4.5 was 16-18% higher compared to the monotherapy products administered together and 30% higher compared to formoterol delivered via the Oxis Turbuhaler. This suggests a formulation effect and a possible drug-drug interaction effect. Regarding budesonide exposure, the exposure for Symbicort is similar to the monotherapy products administered together and budesonide alone. Comparing patients with asthma and COPD, there is a 12-16% increase in budesonide and formoterol exposure in COPD patients compared to asthma patients.

Regarding the HPA axis assessments, 24 hour urinary free cortisol (UFC) was measured in a subset of patients in SHINE (n=437) and SUN (n=179). Urine was collected over 24 hours at baseline, Month 6 and Month 12 (SUN only). The results suggest that there is a dose dependent effect on the 24 hour UFC with Symbicort: a 17% decrease in 24 hour UFC with Symbicort 80/4.5 and a 30% decrease in 24 hour UFC with Symbicort 160/4.5 compared to placebo, which was statistically significant. These results will be described in the product label.

6. Clinical Microbiology

Symbicort Inhalation Aerosol 160/4.5 is an approved product and there are no clinical microbiology issues.

7. Clinical/Statistical- Efficacy

To support the proposed COPD indication, AZ submitted the results of two phase 3, placebo controlled clinical trials of 6 and 12 months duration, Study D589900002 and Study D589900001, hereafter referred to as SHINE and SUN, respectively. In addition there were some support clinical pharmacology studies in patients with COPD as shown in the table

below. The clinical pharmacology studies were discussed in Section 5. The focus of the efficacy discussion will be the clinical trials, SHINE and SUN.

Table 1 Clinical Development Program for Symbicort Inhalation Aerosol for COPD

Study	Design	Duration	Population	Treatment Groups
D589900001 **SUN** Apr 2005-Sept 2007 International	R, DB, DD, MC **P3 Efficacy and safety**	12 months	1964 patients with COPD	Symbicort MDI 80/4.5 BID (n=494) Symbicort MDI 160/4.5 BID (n=494) Formoterol TBH 4.5 BID (n=495) Placebo BID (n=481)
D589900002 **SHINE** Apr 2005- Dec 2006 International – US, South Africa, Poland, Netherlands, Czech Republic	R, DB, DD, MC **P3 Efficacy and safety**	6 months	1704 patients with COPD	Symbicort MDI 80/4.5 BID (n=281) Symbicort MDI 160/4.5 BID (n=277) Budesonide MDI* 160 + Oxis TBH 4.5 BID (n=287) Budesonide MDI* 160 BID (n=275) Formoterol TBH 4.5 BID (n=284) Placebo (n=300)
748 Mar 2004-Feb 2005 Sweden	R, PC, DB, DD, XO **PD** **Onset of action**	Single dose (2 puffs)	90 patients with COPD	Symbicort MDI 160/4.5 Seretide (salmeterol/fluticasone) Evohaler 25/250 Ventoline (salbutamol) Evohaler 100mcg
738 Nov 2002-Dec 2002 US	OL, R, 2 way XO **Relative BA**	Single dose (8 puffs)	30 patients with COPD	Symbicort MDI 160/4.5 Budesonide MDI* 160 + Formoterol TBH 4.5
00006 Aug 2003-Oct 2003 US	OL, R, 2 way X0 **Relative BA** **PK asthma vs. COPD**	Single dose (12 puffs)	26 patients with asthma 26 patients with COPD	Symbicort MDI 80/4.5 Budesonide MDI* + Formoterol TBH

OL – open-label; R – randomized; XO – crossover; DB – double blind; DD – double dummy; MC – multicenter
*Budesonide MDI – same product as Symbicort without formoterol
TBH – Oxis Turbuhaler is a dry powder inhaler available outside the US, which contains formoterol and lactose

Dose Selection

Currently there are two dosage strengths of Symbicort Inhalation Aerosol that are approved for asthma, Symbicort 80/4.5 and Symbicort 160/4.5, which have different amounts of the corticosteroid, budesonide. AZ included both strengths in both of the phase 3 studies and selected a dose for the proposed COPD indication based upon the results of the phase 3 studies. This approach is acceptable as inhaled corticosteroids are not approved for a COPD indication which makes dose-ranging with budesonide alone impractical.

SHINE Study Design

The SHINE trial was a phase 3, 6 month, randomized, double-blind, double-dummy, parallel group, multicenter, placebo controlled trial in patients with COPD. Patients $\geq$ 40 years of age with the following were enrolled: a clinical diagnosis of COPD with symptoms for $\geq$ 2 years, FEV_1/FVC <70% pre-bronchodilator, $FEV_1 \leq$ 50% of predicted normal value pre-bronchodilator, current or previous smoker with a smoking history of $\geq$10 pack years, and a history of at least one COPD exacerbation requiring a course of oral steroids within 1-12 months before the first visit.

Eligible patients were randomized to one of six treatment groups for 26 weeks:

- Symbicort HFA MDI 160/4.5 and placebo Turbuhaler – two inhalations BID
- Symbicort HFA MDI 80/4.5 and placebo Turbuhaler – two inhalations BID
- budesonide HFA MDI 160mcg and formoterol OXIS Turbuhaler 4.5mcg – two inhalations BID
- budesonide HFA MDI 160mcg and placebo Turbuhaler – two inhalations BID
- formoterol OXIS Turbuhaler and placebo Turbuhaler – two inhalations BID
- placebo HFA MDI and placebo Turbuhaler – two inhalations BID

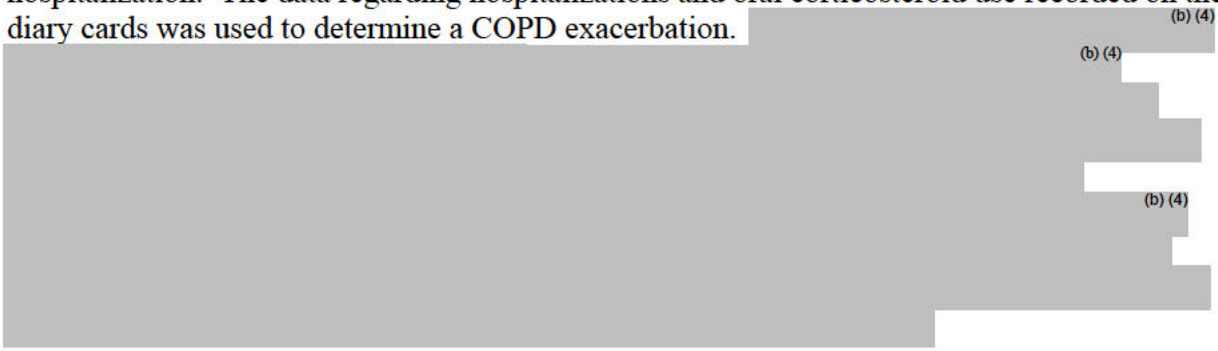
A brief discussion of the treatment groups is warranted because typically for combination product programs, we recommend that the comparator groups are the same formulation and device as the combination product. The budesonide comparator is the same formulation and device as Symbicort without the formoterol. However, the formoterol comparator is delivered via the Oxis Turbuhaler, which is not the same formulation or device as Symbicort. Formoterol Oxis Turbuhaler is a dry powder formulation of formoterol which is available outside the US. In the asthma development program, AZ conducted a pharmacodynamic study that resolved the pharmaceutic differences from the use of different devices to deliver formoterol. Therefore, the use of formoterol Oxis Turbuhaler in this program is acceptable. In addition, the Applicant included a free combination of budesonide and formoterol to evaluate for a pharmaceutic interaction when budesonide and formoterol are administered in one device as Symbicort.

Long acting beta agonists and long acting anticholinergics were not allowed and were converted to short acting beta agonists and anticholinergics, respectively. Inhaled corticosteroids (other than randomized study medication), xanthine derivatives, and chronic oral corticosteroids were not allowed during the randomized treatment period. Albuterol was provided as rescue medication. Patients were evaluated during a clinic visit approximately once a month.

There were two co-primary efficacy variables: pre-dose FEV1 and 1 hour post-dose FEV1. The primary analysis was the change from baseline in the average of all the FEV1 (pre-dose or 1 hour post-dose) measurements during the randomized treatment period. The contribution of formoterol to the combination was evaluated by comparing Symbicort and budesonide for 1-hour post-dose FEV1. The contribution of budesonide to the combination was evaluated by comparing Symbicort and formoterol for pre-dose FEV1. Because there are two doses of Symbicort with comparison of each to dose to monotherapies, multiplicity was accounted for by pre-specifying a hierarchical order requiring statistical significance in order to move onto the next comparison. First, the higher dose of Symbicort was specified to be compared with the monotherapies, followed by the lower dose. Serial spirometry (pre-dose, 5, 15, 30, 60, 120, 180, 240, 360, 480, 600, and 720 minutes post-dose) was performed in a subset of patients.

Secondary efficacy variables included the Saint Georges Respiratory Questionnaire (SGRQ), Breathlessness Diary scores, and COPD exacerbations. In addition, patients were given diaries to record daily AM and PM PEF, rescue medication use, oral corticosteroid use, Breathlessness Diary, cough, and sputum symptoms, nighttime awakenings, and hospitalization. A COPD exacerbation was defined as worsening of COPD that at the

discretion of the investigator required a course of oral steroids for treatment and/or hospitalization. The data regarding hospitalizations and oral corticosteroid use recorded on the diary cards was used to determine a COPD exacerbation. (b) (4)



SUN Study Design

The SUN trial was very similar to SHINE with the exception that SUN was of 12 months duration. In addition, SUN did not include a free combination budesonide+formoterol treatment group or a budesonide 160 treatment group. The entry criteria were similar to SHINE and eligible patients were randomized to one of four treatment groups for 52 weeks:

- Symbicort HFA MDI 160/4.5 and placebo Turbuhaler – two inhalations BID
- Symbicort HFA MDI 80/4.5 and placebo Turbuhaler – two inhalations BID
- formoterol OXIS Turbuhaler and placebo Turbuhaler – two inhalations BID
- placebo HFA MDI and placebo Turbuhaler – two inhalations BID

The co-primary efficacy variables were the same as in SHINE: pre-dose FEV1 and 1 hour post-dose FEV1. Secondary efficacy variables included the SGRQ, Breathlessness Diary scores, and COPD exacerbations. In addition, patients were given diaries to record daily AM and PM PEF, rescue medication use, oral corticosteroid use, Breathlessness Diary, cough, and sputum symptoms, nighttime awakenings, and hospitalization. COPD exacerbations were also a key secondary efficacy variable in SUN, but the definition has the same limitations as was discussed for SHINE.

Safety variables monitored during SHINE and SUN are described in the following section.

Phase 3 Efficacy Results

There were 1704 patients enrolled in SHINE and 1964 patients enrolled in SUN. The majority of patients were primarily white males with a mean age of 63 years and a mean baseline pre-bronchodilator FEV_1 of approximately 1 liter (~34% predicted). Approximately 40-45% of patients were from the US. The demographic profile was generally balanced between treatment groups in the trials. The Symbicort treatment groups had the lowest percentage of discontinuations compared to the other treatment groups.

The following table shows the results for the co-primary endpoints for the various treatment group comparisons in the two phase 3 clinical trials. The results shown are the change from baseline in the average pre-dose or 1 hour post-dose FEV1 over the randomized treatment period. Although the baselines are not shown, baselines were generally similar across

[1] Cazzola M, MacNee W, et. al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J* 2008; 31: 416-418.

treatment groups with the note that the placebo group had a slightly higher baseline for pre-dose FEV1 and post dose FEV1 of 1.08-1.10L vs. 1.02-1.05L in the other treatment groups. In the table below, the pre-specified primary comparisons are shaded.

Table 1 – Efficacy Results for SHINE and SUN

	Pre-dose FEV_1 Change from baseline in average during treatment period (p-value)		**1 hr post-dose FEV_1** Change from baseline in average during treatment period (p-value)	
	SHINE	**SUN**	**SHINE**	**SUN**
Symbicort 80/4.5 vs. placebo	0.05 (0.002)	0.07 (<0.001)	0.16 (<0.001)	0.16 (<0.001)
Symbicort 160/4.5 vs. placebo	0.08 (<0.001)	0.09 (<0.001)	0.17 (<0.001)	0.18 (<0.001)
Symbicort 80/4.5 vs. budesonide 160	0.06 (0.001)		0.16 (<0.001)	
Symbicort 160/4.5 vs. budesonide 160	0.08 (<0.001)		0.17 (<0.001)	
Symbicort 80/4.5 vs. formoterol 4.5 TBH	0.02 (0.335)	0.02 (0.161)	0.03 (0.116)	0.01 (0.420)
Symbicort 160/4.5 vs. formoterol 4.5 TBH	0.04 (0.026)	0.04 (0.008)	0.04 (0.039)	0.03 (0.023)
Symbicort 160/4.5 vs. free combination	0.01 (0.479)		0.01 (0.461)	
Budesonide 160 vs. placebo	0.00 (0.902)		0.00 (0.997)	
Formoterol 4.5 TBH vs. placebo	0.04 (0.037)	0.05 (<0.001)	0.14 (<0.001)	0.15 (<0.001)
Symbicort 160/4.5 vs. Symbicort 80/4.5	0.02 (0.198)	0.02 (0.206)	0.01 (0.615)	0.02 (0.144)

The results for SUN and SHINE are consistent and the following results are worth noting:

- Both Symbicort groups were significant compared to placebo for pre-dose as well as 1 hour post dose FEV1.
- For the pre-dose FEV1 and 1 hour post-dose FEV1, only the Symbicort 160/4.5 group was statistically significant compared to the formoterol group in both trials. The Symbicort 80/4.5 group was not significantly different compared to formoterol.
- As inhaled corticosteroids are not approved for a COPD indication, it is not surprising that the budesonide group was not significant compared to placebo in SHINE.
- There was no significant difference between the free combination group and Symbicort 160/4.5 delivered in a single device.
- Although there was no statistical significance between the two Symbicort groups, there was a numerical difference favoring the Symbicort 160/4.5 group compared to the Symbicort 80/4.5 group.

These results demonstrate the efficacy of Symbicort 160/4.5 and the contribution of formoterol (Symbicort vs. budesonide 160 in 1-hr post-dose FEV1) and contribution of budesonide (Symbicort vs. formoterol in pre-dose FEV1) as well as a numerical benefit over the Symbicort 80/4.5 treatment group. The results do not support the efficacy of Symbicort 80/4.5 as the results failed to show the contribution of budesonide 80 to the combination product.

Breathlessness Diary (BD)

The results for the BD in both SHINE and SUN support the efficacy of Symbicort 160/4.5 and 80/4.5 in that there was a statistically significant reduction in BD scores in the Symbicort groups compared to placebo; however the minimal clinically important difference (0.2) was only reached for the Symbicort 160/4.5 group in SUN. (b) (4)

However, the results do provide support of the efficacy of Symbicort.

Saint Georges Respiratory Questionnaire (SGRQ)

With regards to the SGRQ, the results in both SHINE and SUN support the efficacy of Symbicort 160/4.5 and 80/4.5 in that there was a statistically significant reduction in the SGRQ total score compared to placebo; however the minimal clinically important difference (4 units) was not reached.

COPD Exacerbations

(b) (4) (b) (4) however the information is useful to evaluate the efficacy of Symbicort. As shown in the table below, the rates of exacerbations in the Symbicort treatment groups were lower than the placebo group. The rates in the Symbicort 160/4.5 group were statistically significant compared to placebo in SUN (rate ratio 0.632, $p<0.001$), but the rates were not statistically significant different compared to placebo in SHINE (rate ratio of 0.796, $p=0.109$). The results were primarily driven by the events requiring corticosteroid treatment.

Table 2 – Efficacy Results for SHINE and SUN

	Total # Exacerbations per Subject-Treatment Year	
	SHINE	**SUN**
Symbicort 80/4.5	0.786	0.529
Symbicort 160/4.5	0.769	0.564
Free combination bud 160 + form 4.5	0.636	
Budesonide 160	0.771	
Formoterol 4.5 TBH	0.967	0.750
Placebo	1.008	0.892

Other

The Applicant includes (b) (4) using the definition of a 15% improvement in FEV1 as the onset of action. Because this combination product is a maintenance medication and an onset of action based upon post-dose FEV1 is primarily due to the formoterol component, (b) (4)

The Applicant (b) (4) peak expiratory flow (PEF), nighttime awakenings, and albuterol rescue medication use. While the results for these variables in the Symbicort treatment groups were statistically significant compared to placebo as discussed in Dr. Karimi-Shah's review, these variables are not typically followed in COPD patients and are more common measures of control in asthma patients. Therefore, (b) (4) a general statement that PEF, nighttime awakenings, and rescue medication use improved and support the efficacy of Symbicort would be reasonable.

The Applicant also (b) (4)

In summary, SHINE and SUN support the efficacy of Symbicort 160/4.5 for the maintenance treatment of airflow obstruction in patients with COPD based upon the results for the co-primary efficacy variables, pre-dose FEV1 and 1-hour post dose FEV1. The FEV1 results

establish the contribution of formoterol and budesonide and numerically favor Symbicort 160/4.5 over Symbicort 80/4.5. Secondary efficacy variables, including SGRQ, COPD exacerbations (as defined by the Sponsor), symptoms, PEF, and rescue medication use also support the efficacy of Symbicort. Dr. Guo has verified the Applicant's primary efficacy results and Dr. Karimi-Shah has concluded that the efficacy results of SHINE and SUN support the efficacy of Symbicort 160/4.5 for the proposed indication. I concur with this conclusion.

8. Safety

While Symbicort is an approved product for the treatment of asthma, this efficacy supplement would extend the indication to COPD patients, which is a new population. Therefore, extensive safety monitoring was included in the phase 3 program. Safety monitoring in SHINE and SUN included adverse events, vital signs, physical examination, ECGs, chemistry, hematology, urinalysis, and urinary free cortisol in a subgroup of patients (n=437 in SHINE and n=179 in SUN). SUN also included the following safety measurements: 24 hour Holter monitoring, ophthalmologic assessment, and bone mineral density (BMD) in a subgroup of patients. Of special interest in both clinical trials is the risk of pneumonia and lower respiratory tract infections that was noted in the COPD program for another ICS/LABA combination product, Advair Diskus.

In SHINE and SUN, there were 558 and 988 patients treated with Symbicort for 6 months and one year, respectively. In addition, there were 287 patients treated with the free combination of budesonide and formoterol in SHINE. The number of patients and duration of exposure to Symbicort is acceptable to assess the safety of Symbicort in the COPD population.

In both SHINE and SUN, fewer patients discontinued in the Symbicort treatment groups compared to the other treatment groups. The primary reason for discontinuation was adverse events followed by withdrawal of consent/not willing to continue. In SHINE, there were fewer discontinuations due to AEs in the Symbicort treatment groups compared to placebo, budesonide or formoterol treatment groups. In SUN, discontinuations due to AEs were similar among the treatment groups.

There were a total of 26 deaths during the randomized treatment period in SHINE and SUN. The number of deaths in each treatment group was few and generally similar across treatment groups; however, there was a numerically higher number of deaths in the Symbicort 80/4.5 group (10) compared to Symbicort 160/4.5 (6), budesonide (2), formoterol (3), and placebo (5). It is difficult to draw any conclusions from this numerical imbalance for the lower dose of Symbicort due to the fact that the number of deaths was overall low and the causes of death do not support a specific etiology. In addition, there does not appear to be a dose ordering effect as the number of deaths with the higher dose of Symbicort was similar to placebo.

The percentage of patients with SAEs was numerically higher in the Symbicort treatment groups compared to placebo, but was similar to the formoterol group. The most common SAE was COPD, which was more common in the Symbicort groups compared to placebo, but occurred in a similar percentage of patients in the formoterol group. There was no increase in

pneumonia SAEs in the Symbicort treatment groups compared to placebo. Review of the SAEs does not suggest a specific signal.

In SHINE, adverse events (AEs) in the Symbicort 160/4.5 treatment group (57.4%) were reported in a similar percentage of patients as the budesonide (57.5%) and formoterol (56.7%) groups, but slightly higher than in the free combination (49.5%) and placebo groups (50.7%). The most common AEs included: COPD, nasopharyngitis, oral candidiasis, bronchitis, sinusitis, and diarrhea. In SUN, AEs were more common in the Symbicort treatment groups (65%) compared to placebo (55%). The most common AEs were similar to SHINE and also included upper respiratory tract infection, back pain and muscle spasms.

Of particular interest were the pneumonia and lower respiratory tract AEs, as these AEs have been noted in the COPD program for another ICS/LABA combination product, Advair Diskus. In general, pneumonia AEs were not increased in the Symbicort groups compared to placebo. However, there was an increase in other lower respiratory tract infections in the Symbicort 160/4.5 compared to other treatment groups. These other lower respiratory tract infections included: bronchitis, tracheobronchitis, and lower respiratory tract infection – bacterial or viral. The specific data is as follows. In the 1,704 patients with COPD in SHINE, there was a higher incidence of lung infections other than pneumonia (e.g., bronchitis, viral lower respiratory tract infections, etc.) in patients receiving SYMBICORT 160/4.5 (7.6%) than in those receiving Symbicort 80/4.5 (3.2%), formoterol 4.5 mcg (4.6%) or placebo (3.3%). Pneumonia did not occur with greater incidence in the Symbicort 160/4.5 group (1.1%) compared with placebo (1.3%). In 1,964 patients with COPD in SUN, there was also a higher incidence of lung infections other than pneumonia in patient receiving SYMBICORT 160/4.5 (8.1%) than in those receiving Symbicort 80/4.5 (6.9%), formoterol 4.5 mcg (7.1%) or placebo (6.2%). Similar to the 6 month study, pneumonia did not occur with greater incidence in the Symbicort 160/4.5 group (4.0%) compared with placebo (5.0%).

The increase in lower respiratory tract infections may be secondary to the budesonide component and is consistent with the findings in the COPD program for the other combination product, Advair Diskus. This information will be highlighted in the product label in the Warnings and Precautions section.

Bone mineral density (n=326), ophthalmologic assessments (n=461) and Holter monitoring (n=520) were performed in a subset of patients in SUN. BMD was measured as the change from baseline to endpoint in total lumbar spine bone mineral density. At the end of the treatment period, the change from baseline in BMD was small and the difference between treatment groups was small. The effects of Symbicort on the eye were assessed by the lenticular opacity scale (LOCSIII score) and intraocular pressure. At the end of the treatment period, there was an increase in intraocular pressure in all treatment groups. The change from baseline was small and similar across treatment groups, with the Symbicort 80/4.5 group showing the largest increase from baseline (0.69mmHg). For the posterior subcapsular opacity assessment, there was an increase across treatment groups. The change from baseline was small with the Symbicort 160/4.5 group showing the largest increase (0.18). The Holter monitoring results did not suggest a new safety signal. The results for the BMD and ophthalmologic assessments will be described in the product label.

There were no new safety signals noted in the laboratory, ECG, vital sign, and physical examination data.

In summary, SHINE and SUN support the safety of Symbicort 160/4.5 for the maintenance treatment of airflow obstruction in patients with COPD. Overall, there were fewer discontinuations in the Symbicort treatment groups compared to the other treatment groups. Although there was no increase in pneumonia AEs in the Symbicort 160/4.5 group, there was an increase in lower respiratory tract infection AEs compared to the other treatment groups and this will be included in the product label. This new safety information will also be the basis for a Risk Evaluation and Mitigation Strategy or REMS. See Section 13 for more discussion. Dr. Karimi-Shah has concluded that the results of SHINE and SUN support the safety of Symbicort 160/4.5 for the proposed indication. I concur with this conclusion.

9. Advisory Committee Meeting

An advisory committee meeting was not held for this efficacy supplement because Symbicort Inhalation Aerosol is an approved product for asthma and there is an established regulatory pathway for the proposed COPD indication.

10. Pediatrics

This efficacy supplement triggers PREA because the application is for a new indication, COPD. The Applicant submitted a request for waiver for pediatric study requirements as COPD is a disease of adults. The request for a waiver is reasonable as COPD is a disease of adults; therefore, the pediatric study requirements should be waived. It should be noted that at the time of finalization of this review, the discussion regarding a pediatric waiver at the Pediatric Review Committee (PERC) is pending.

11. Other Relevant Regulatory Issues

A DSI audit was not requested for this application as Symbicort Inhalation Aerosol is an approved drug product for asthma and the combination of ICS/LABA is already approved for the COPD indication. The Applicant did close a clinical site in Poland (Site 209) due to data quality issues. There were no data integrity issues identified during the review process and no significant financial disclosures that could have compromised the outcome of the data.

12. Labeling

The approved labeling for Symbicort Inhalation Aerosol includes a Medication Guide because of the risk of asthma related death. The Applicant submitted the label for Symbicort Inhalation Aerosol in the new physician labeling (PLR) format. The labeling was extensively revised to be consistent with the other ICS/LABA combination product, Advair, which is in the PLR format. An exhaustive discussion of the labeling is not included in this memo, but a summary of high level issues are noted below:

- Revision of the Warnings and Precautions section to be consistent with the other ICS/LABA product, Advair Diskus.
- Inclusion of pneumonia and other lung infections as a Warning/Precaution class labeling since there was a signal of other lung infections in the Symbicort COPD program.

- More detailed description of results of the bone mineral density data and the ophthalmologic data from SUN will be included.
- (b) (4) A more general statement regarding these endpoints would be more reasonable.
- There are no issues with the proprietary name and carton/container labels as Symbicort Inhalation Aerosol is a currently approved product.

At the time of finalization of this review, labeling negotiations are ongoing.

13. Recommendations/Risk Benefit Assessment

- Recommended regulatory action

The recommended regulatory action is **Approval**. The submitted data are adequate to support the efficacy of Symbicort 160/4.5 Inhalation Aerosol for the maintenance treatment of airflow obstruction in patients with COPD. Efficacy was based primarily upon the results for the co-primary efficacy variables, pre-dose FEV1 and 1-hour post dose FEV1 from two randomized, double-blind, placebo controlled clinical trials of 6 and 12 months duration. Secondary efficacy variables, including SGRQ, COPD exacerbations (as defined by the Sponsor), symptoms, PEF, and rescue medication use also support the efficacy of Symbicort 160/4.5. The submitted data do not support the efficacy of Symbicort 80/4.5 and the Applicant is not seeking approval of this dosage strength. Review of the safety data identified an increase in lower respiratory tract infections. A similar signal of pneumonia/lower respiratory tract infections was noted in another ICS/LABA program for COPD; therefore, lower respiratory tract infections may be a class effect likely related to the corticosteroid component. This finding will be described in the Warnings/Precautions section of the product label and will be the basis for a Risk Evaluation and Mitigation Strategy (REMS).

- Risk Benefit Assessment

The data submitted support a favorable benefit risk assessment for Symbicort 160/4.5 in patients with COPD, but a REMS will be required to ensure that patients are aware of the risks of lower respiratory tract infections with Symbicort. There are limited therapies for patients with COPD and additional treatment options for this population are desired. The submitted data demonstrate a clear benefit in pulmonary function as well as a benefit in other supportive secondary efficacy variables. The identification of a safety signal of lower respiratory tract infections is of concern and will be communicated to healthcare providers in the product label and to patients in the Medication Guide. The review team recommends approval and there are no differences in opinion to address.

- Recommendation for Postmarketing Risk Management Activities

Currently, Symbicort Inhalation Aerosol labeling includes a Medication Guide because of the risk of asthma related death with the long acting beta agonists. Review of the submitted data in COPD patients identified a safety signal of lower respiratory tract infections with use of Symbicort. A similar signal of pneumonia/lower respiratory tract infections was noted in another ICS/LABA program for COPD; therefore, lower respiratory tract infections are believed to be a class effect likely related to the corticosteroid component. This finding will be described in the Warnings/Precautions section of the product label and will be described in

the Medication Guide. This new safety information will be the basis for a Risk Evaluation and Mitigation Strategy (REMS). This will be Medication Guide only REMS.

- Recommendation for other Postmarketing Study Commitments

There are no recommendations for post-marketing commitments.

- Recommended Comments to Applicant

None.

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

/s/

Sally Seymour
1/9/2009 11:18:36 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21–929/S012

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 21-929
Submission Number	S-012
Submission Code	SE01
Letter Date	28-APR-2008
Stamp Date	29-APR-2008
PDUFA Goal Date	27-Feb-2009
Reviewer Name	Banu A. Karimi-Shah, MD
Review Completion Date	December 24, 2008
Established Name	Budesonide/Formoterol
(Proposed) Trade Name	Symbicort Inhalation Aerosol
Therapeutic Class	Combination ICS/LABA
Applicant	AstraZeneca
Priority Designation	S
Formulation	160 mcg/4.5 mcg
Dosing Regimen	320 mcg/9 mcg BID
Indication	COPD
Intended Population	≥ 40 years old

Table of Contents

LIST OF TABLES

List of Figures

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The clinical recommendation for this application is **Approval**.

The purpose of this 505(b)1 efficacy supplement (sNDA) is to provide data supporting an indication for the (b) (4) maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including bronchitis and emphysema, with Symbicort. Symbicort is a fixed-dose combination product of budesonide (corticosteroid) and formoterol fumarate dihydrate (long-acting beta-agonist). The drug product is a pressurized metered dose inhaler (pMDI) using HFA 227 as the propellant. Although two dosage strengths are approved for treatment of asthma (80/4.5 and 160/4.5), the dose proposed for registration in this COPD efficacy supplement is 320/9 mcg (2 puffs of 160/4.5 budesonide/formoterol) BID. Symbicort is already approved for the maintenance treatment of asthmatic patients 12 years of age and older, at total daily doses from 160/9 mcg BID to 320/9 mcg BID. The efficacy and safety of Symbicort in this COPD population is supported by two pivotal trials, of 6 months and 12 months duration, respectively. The Applicant has adequately demonstrated the efficacy and safety Symbicort for COPD.

1.2 Recommendation on Post-marketing Actions

1.2.1 Risk Management Activity

A Medication Guide (MG) will be required and updated to include the new safety information regarding the increased incidence of lower respiratory tract infections with the use of Symbicort in COPD patients. Also, the Applicant will be required to have a Risk Evaluation and Mitigation Strategy (REMS), in which the Applicant will need to evaluate the effectiveness of the MG and provide an assessment regarding whether the MG is being dispensed. These activities will be required in addition to routine pharmacovigilance.

1.2.2 Required Phase 4 Commitments

No Phase 4 commitments are sought for Symbicort with regard to the COPD indication.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The Symbicort COPD clinical program included two pivotal, placebo- and active-controlled, double-dummy, parallel group, and multinational phase 3 studies (D5899C0001 [a 12 month study, hereafter referred to as "SUN"] and D5899C0002 [a 6-month study, hereafter referred to as "SHINE"]). Two dosage strengths of Symbicort (budesonide formoterol: 80/4.5 and 160/4.5

per actuation were evaluated in SUN and SHINE. These dosage strengths, each administered as 2 actuations twice daily (BID), correspond to total daily doses of 320/18 mcg and 640/18 mcg; hereafter, these study medications will be referred to as Symbicort LD (low-dose) and HD (high-dose), respectively. The clinical development program for COPD was designed to characterize the efficacy and safety of two dosage strengths of Symbicort as long-term maintenance therapy in patients with COPD, and to demonstrate that Symbicort meets the FDA combination rule regarding the development of fixed-combination prescription drugs for use in humans [21 CFR 300.50].

1.3.2 Efficacy

Two pivotal clinical trials demonstrated the efficacy of Symbicort in patients with COPD. These trials were multicenter, randomized, double-blind, placebo-controlled, parallel group studies that were 6 and 12 months in duration, named SHINE and SUN respectively. In SHINE, patients were assigned to one of six treatment arms: Symbicort HD BID, Symbicort LD BID, budesonide 160 mcg + 4.5 mcg formoterol in free combination BID, budesonide 2 x 160 mcg BID, formoterol 2 x 4.5 mcg BID, or placebo BID. The study consisted of an initial visit, a 2-week run-in period, 5 further visits during a 26-week treatment period, and a 4-week follow-up telephone call. In SUN, patients were assigned to one of four treatment arms: Symbicort HD BID, Symbicort LD BID, formoterol 2 x 4.5 mcg BID, or placebo BID for a randomized treatment period of 52 weeks. The design was identical to that of SHINE, except that there were seven visits over the longer treatment period. Efficacy was assessed via pulmonary function testing at each visit.

The co-primary efficacy endpoints in both studies were the change from baseline to endpoint in pre-dose FEV1, to demonstrate the anti-inflammatory contribution of budesonide, and 1-hr post-dose FEV1, to demonstrate the bronchodilator contribution of formoterol, to the efficacy of the combination product, Symbicort. Each co-primary variable was calculated as an average over the randomized treatment period. In SUN and SHINE, the primary comparison for the pre-dose FEV1 endpoint was between each of the Symbicort groups and formoterol. Results indicate that only the higher dose of Symbicort (320/9 mcg BID) demonstrated a statistically significantly greater increase from baseline in pre-dose FEV1 when compared with formoterol. Symbicort LD failed to show the contribution of the inhaled corticosteroid to the efficacy of the combination product..

In SHINE, the primary comparison for the post-dose FEV1 endpoint was between each of the Symbicort groups and budesonide alone. For post-dose FEV1, results indicate that both dosage strengths of Symbicort demonstrated a statistically significantly greater increase from baseline when compared with budesonide. These results demonstrated that formoterol contributes to the efficacy of the combination product. These results were supported by the SUN study, however, this 12 month study did not include a budesonide group for comparison, so the primary comparison was between the Symbicort treatment groups and placebo.

Key secondary endpoints were defined by the Applicant as dyspnea (as measured by the Breathlessness Diary), the St. George's Respiratory Questionnaire (SGRQ), and COPD

exacerbations. COPD exacerbations, as defined by the applicant, occurred at a numerically lower rate in both pivotal studies. The SGRQ and Breathlessness Diary were also generally supportive of the efficacy of Symbicort. However, for various reasons, including failure to meet minimal clinically important differences, issues with the instrument, or concerns regarding endpoint definition, these key secondary variables (b) (4). Other secondary variables that were measured included serial FEV1 measurements, morning and evening peak expiratory flow (PEF), COPD symptoms (rescue medication use, cough, sputum, and sleep score. These secondary variables were generally supportive of the efficacy of Symbicort.

In conclusion, findings from two pivotal COPD studies (SUN and SHINE) support the efficacy of Symbicort HD therapy for the long-term treatment of airway obstruction in patients with COPD, including chronic bronchitis and emphysema.

1.3.3 Safety

The safety of Symbicort in COPD patients was assessed in two pivotal studies with reports of deaths, adverse events, laboratory values, vital signs, and physical exams. Additional safety information regarding effect on the ophthalmologic exam, bone mineral density, and 24 hour Holter monitoring was assessed in the SUN (12 month) study only. Effect on the hypothalamic-pituitary-adrenal (HPA) axis was also assessed in a subset of patients from both studies (see 7.1.12 Special Safety Studies). A summary of the safety information is presented below.

There were 26 deaths reported during the randomized treatment period in the two pivotal trials: 6 in the Symbicort HD group, 10 in the Symbicort LD group, 2 in the budesonide group, 3 in the formoterol group, and 5 in the placebo group. Nineteen of the 26 deaths were reported in the non-US regions, and 7 were reported in the US region. The most frequently reported SAE leading to death was COPD exacerbation: 3 subjects in the Symbicort LD group and 1 subject in the budesonide group. Other causes of death included cardiac and malignancy-related SAEs. Overall, there were relatively few deaths in this study, considering the severity of COPD in the study population and the presence of co-morbid conditions in this older population. Review of the narratives and the causes of death did not suggest a particular safety signal.

Across the Phase 3 studies, the profile of the most commonly reported adverse events (COPD, nasopharyngitis, oral candidiasis, bronchitis and sinusitis), was generally similar in the Symbicort and the mono-products groups, but the incidence of AEs and SAEs was higher on active treatments compared to placebo. Most AEs were mild to moderate in intensity with Symbicort treatment. Overall, the percentage of subjects with SAEs was slightly higher in the Symbicort and formoterol 4.5 groups compared to placebo. COPD was the most common SAE reported with a similar frequency across the Symbicort and formoterol groups, with a slightly higher frequency in these groups compared to placebo. Discontinuations from the study due to adverse events (DAEs) were similarly distributed across the treatment groups.

Reviewer's comment: The frequency of COPD SAEs may reflect the underlying severity of the enrolled COPD population. This finding may be related to the greater and earlier discontinuation in the placebo group, which may have reduced the chance for discontinued subjects in this group with very severe COPD to contribute SAEs.

Pneumonia-related preferred terms and "potential lung infections other than pneumonia" containing preferred terms that could represent lower respiratory tract infections were evaluated due to findings in recent studies (1-3) of the fluticasone/salmeterol combination in subjects with COPD that indicated a higher rate of pneumonia in all groups receiving fluticasone. For pneumonia-related preferred terms, no clinically important differences were seen between treatment groups. However, when the incidence of "potential lung infections other than pneumonia" was evaluated, there was a higher incidence in those groups treated with budesonide as compared with placebo. In SUN, there was a numerical trend towards increased lung infections with higher doses of inhaled corticosteroid. This is consistent with the findings with fluticasone/salmeterol in patients with COPD and will be described in the product label. This safety signal of increased "lung infections other than pneumonia" is new information that will be the basis of a Risk Evaluation Mitigation Strategy (REMS) [see Section 1.2.1].

Additional safety analyses of vital signs, laboratory findings, bone mineral density assessments, ophthalmologic examinations, and holter monitoring did not reveal clinically significant results between treatment groups. Symbicort did exhibit statistically significant (~30%) suppression of 24-hour urinary free cortisol, indicating a suppression of hypothalamic-pituitary-adrenal (HPA) axis function in patients with COPD (see 7.1.12 Special Safety Studies).

In general, the adverse event profile of Symbicort was consistent with known effects of inhaled corticosteroids and beta-agonists, the safety findings in asthma patients, as well as with what would be expected in a COPD population. In summary, the clinical trial results support the safety of Symbicort in COPD patients. Review of the safety data indicates that lung infections other than pneumonia, (including bronchitis, lower respiratory tract infection, etc.) may be a new safety signal noted with Symbicort in COPD patients and is consistent with another ICS/LABA combination product. No other new safety concerns arose from the review of the data in COPD patients as compared with what has been reported in the Symbicort product label and other ICS/LABA combination products.

1.3.4 Dosing Regimen and Administration

A dose of 320/9 mcg (budesonide/formoterol) BID is recommended in COPD patients. The dose is to be delivered via 2 actuations of the 160/4.5 mcg dosage strength.

1.3.5 Drug-Drug Interactions

The Applicant did not conduct any new investigations specifically evaluating drug-drug interactions as part of this supplemental NDA.

1.3.6 Special Populations

The Applicant did not conduct any new investigations specifically targeted towards any special populations as part of this supplemental NDA.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Symbicort is a fixed-dose combination product of budesonide (corticosteroid) and formoterol fumarate dihydrate (LABA). The drug product is a pressurized metered dose inhaler (MDI or pMDI) using HFA 227 as a propellant. Two dosage strengths are currently approved for different asthma severities, 80/4.5 and 160/4.5, containing 80 or 160 mcg of budesonide and 4.5 mcg of formoterol, respectively. Each is approved to be given as 2 actuations twice daily.

2.2 Currently Available Treatment for Indications

Currently available treatment includes various formulations of both budesonide and formoterol single-ingredient products. Also, available are multiple approved HFA or DPI formulations of other orally inhaled corticosteroids, and several approved formulations of other long-acting beta agonists, either as single ingredient or together with other corticosteroids (e.g. Advair). Other major pharmaceutical therapies available for the maintenance treatment of COPD include the orally inhaled anticholinergics (i.e. tiotropium bromide and ipratropium bromide) and the methylxanthines.

2.3 Availability of Proposed Active Ingredient in the United States

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

Formoterol is available in several formulations for inhaled use: Foradil® Aerolizer® (formoterol fumarate inhalation powder) (NDA 20-831, 2/16/2001, Novartis), Foradil Certihaler (formoterol fumarate dry powder,) (NDA 21-592, 12/15/2006), Brovana (arformoterol tartrate inhalation solution) (NDA 21-912, 10/6/2006), and Perforomist (formoterol fumarate inhalation solution) (NDA 22-007, 5/11/2007).

2.5 Pre-submission Regulatory Activity

Symbicort was approved in the US under NDA 21-929 in July 2006, with US market introduction in June 2007. An End-of-Phase 2 (EOP2) meeting was held with the Division in April 2004 to discuss the COPD development program. The two pivotal Phase 3 protocols were submitted to IND 63,394 (Serial No. 0336) in March 2005. Review of the protocol revealed that the Applicant had incorporated the Division's suggestions from the EOP2 meeting. No major recommendations were issued at that time. The Division also responded to questions in a pre-NDA briefing document in December 2007. Based on the Division's responses, the Applicant did not feel that a pre-sNDA meeting was necessary.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

This COPD efficacy supplement does not propose any changes to the currently approved Symbicort drug product. There have been no proposed changes to the manufacturing process or to packaging configuration. The CMC review team is recommending an **Approval** action for this efficacy supplement. For a more complete analysis of CMC issues, see the CMC review of NDA 21-929/ S-012 by Dr. Ramesh Raghavachari.

3.2 Animal Pharmacology/Toxicology

AstraZeneca submitted complete pre-clinical general toxicology studies with the original NDA submission. The current product label includes the information from these non-clinical studies. No new animal pharmacology/toxicology studies were performed nor required for this efficacy application. The Pharmacology/Toxicology review team is recommending an **Approval** action for this pediatric efficacy supplement. Refer to the Pharmacology/Toxicology review of NDA 21-929/S-012 by Dr. Timothy Robison for further details.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The studies conducted by the Applicant and included in this application were the primary source of clinical data for this review. The application does not rely on reports in the medical literature or other sources of data. Additional clinical information that could not be located in the NDA, or data clarifications, were obtained from the Applicant in response to information requests made during the review process. In all cases, the Applicant provided the requested information in usable format and the information was incorporated into the review.

4.2 Tables of Clinical Studies

Table 1: Pivotal Clinical Studies

Study #	Study Type	Design/Centers	Treatment Groups	Population[a]	Duration
D5899C0001 **(SUN)**	Efficacy/Safety	R, DB, DD, PG, PC, AC, MC Countries (# centers) US (144) Germany (26) Hungary (26) Denmark (13) Bulgaria (9) Greece (6) Romania (6) Mexico (5) Iceland (2)	SYMB 320/9 BID SYMB 160/9 BID *Formoterol 9 BID Placebo	Moderate to Severe COPD ≥ 40 years old, male or female **N = 1964**	12 months
D5899C0002 **(SHINE)**	Efficacy/Safety	R, DB, DD, PG, PC, AC, MC Countries (# centers) Czech Republic (18) Netherlands (11) Poland (30) South Africa (12) United States (123)	SYMB 320/9 BID SYMB 160/9 BID (BUD 320 + *FF 9) BID BUD 320 BID *Formoterol 9 BID Placebo	Moderate to Severe COPD ≥ 40 years old, male or female **N = 1704**	6 months

R = randomized, DB = double blind, PC = placebo controlled, AC = active controlled, MC = multicenter, DD = double dummy, PG = parallel group, SYMB = Symbicort, BUD = budesonide, FF = formoterol fumarate.
*Note: In both trials, the formoterol mono-product was delivered via the DPI formulation, the OXIS Turbuhaler.
Reviewer's Comment In general, we do not usually advise the use of mono-comparator in a different formulation and delivered by a different device, as is the case here with the OXIS Turbuhaler. However, in the original NDA for asthma, the Applicant has provided a PK/PD bridging study that demonstrates the comparability of the formoterol dose delivered by the OXIS TBH and Symbicort. Therefore, the use of this mono-product was accepted by the Division at the time of the original NDA review, and still remains acceptable for this program.

4.3 Review Strategy

Equal emphasis was placed on both pivotal studies during the course of this review. Reviews of these studies were based primarily on the clinical study reports, original protocols, and statistical analysis plans. The Applicant's summary data tables were reviewed in detail. Appendix tables were also reviewed in varying amounts of detail, depending upon the endpoint and review issue. Case report forms and narratives were reviewed for all deaths during randomized treatment.

4.4 Data Quality and Integrity

Review of the data from the pivotal studies by the Biometrics reviewer (Dr. Ted Guo) did not show any evidence of treatment-by-site interaction. DPAP did not request audits by the Division of Scientific Investigation (DSI). DSI audits were considered to be unnecessary because:

- this submission is an efficacy supplement of a drug with an established safety and efficacy profile in asthma patients 12 years of age and older.
- no treatment-by-site interaction was detected on statistical analysis.
- each site enrolled relatively small numbers of patients, with no specific site showing a positive response that was driving the outcome of the trial.

4.5 Compliance with Good Clinical Practices

The Applicant states that they did not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with the application [*Module 1.3.3]*. Clinical studies were conducted in compliance with recognized Good Clinical Practices.

4.6 Financial Disclosures

The Applicant's compliance with the Final Rule on Financial Disclosure by Clinical Investigators is attested to in Module 1.3.4 of this NDA application. The Applicant certifies that it did not enter into financial arrangements with any investigator whereby the value of compensation could be affected by the outcome of the study (Category 1), that no investigator received significant payments (Category 2), that none of the investigators disclosed a proprietary interest in the product (Category 3), or possessed a significant equity interest in the Applicant (Category 4) as defined in 21 CFR 54 with a few exceptions. However, the investigators that did receive significant payments or have an equity interest in the Applicant contributed relatively small numbers of patients to these large multinational, multicenter trials, so that it was unlikely that the outcome would be affected by their participation.

5 CLINICAL PHARMACOLOGY

The objectives of the clinical pharmacology program in this efficacy supplement were:

- PK characterization / Formulation evaluation in COPD patients
- PK interaction as a result of combining the two active ingredients
- Systemic exposure in COPD vs. asthma pts.
- HPA-axis assessment

The clinical pharmacology program consisted of:

- Study D5899C00006 – Relative BA, OL, R, 2-way X-over, SD study with treatments: 1) SYM 80/4.5 x 12 actuations, total dose 960/54 mcg in COPD pts; 2) BUD pMDI (80 µg x 12 actuations, total dose 960 µg) plus FORM TBH (4.5 µg x 12 inhalations, total dose 54 µg) in COPD pts; 3) SYM 80/4.5 x 12 actuations, total dose 960/54 mcg in asthma pts
- Study D5899C00002 (SHINE) – 6 month, R, double-dummy, parallel Phase III study with treatments: 1) SYM 160/4.5, 2) SYM 80/4.5, 3) BUD 160, 4) FORM 4.5, 5) BUD 160 + FORM 4.5, 6) Placebo. An extensive 12-hr post-dose PK sampling in a sub-set (n = 238) of COPD patients.

- In addition, HPA-axis assessment (24h urine free cortisol) was also conducted in a subset of COPD patients in both the Ph. 3 studies [SUN (179 pts) and SHINE (437 pts)]

For full details of the clinical pharmacology results, refer to the review of the Biopharmaceutics reviewer, Dr. Partha Roy. A summary of the results is provided below:

1. Generally comparable systemic exposure between Symbicort, budesonide pMDI and co-administration of budesonide pMDI and Form TBH
2. A slight formulation effect for formoterol with an increase in exposure by 16-18% from Symbicort compared to co-administration of individual products.
3. Budesonide appears have a small effect (~12% increase in AUC) on formoterol exposure while there was lack of any measurable effect on budesonide exposure in the presence of formoterol.
4. Formoterol exposure (AUC) from Symbicort 160/4.5 mcg appears to be about 30% higher compared to formoterol TBH
5. Budesonide as well as formoterol exposure (AUC) in COPD patients appear to be about 12-16% higher compared to asthma patients.
6. Symbicort 160/4.5 mcg exhibited statistically significant (~30%) suppression of 24h-UFC levels following chronic twice daily inhalation administration in COPD patients relative to placebo.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The purpose of this supplemental NDA is to provide data supporting an indication for the (b) (4) (b) (4) maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema with Symbicort.

6.1.1 Methods

The efficacy review is based on the two pivotal studies conducted by Astra Zeneca, SUN (12 month study) and SHINE (6 month study). Both studies were multicenter, randomized, double-blind, double-dummy, placebo-controlled, active-controlled, parallel group trials. Equal emphasis was placed on each study throughout the course of this review.

6.1.2 General Discussion of Endpoints

Primary Efficacy Endpoints

- Pre-dose FEV1 – to assess the contribution of budesonide (ICS)
- Post-dose FEV1- to assess the contribution of formoterol (LABA)

- Separate mean FEV1 (for both pre-dose and 1 hour post-dose measurements) was calculated for each patient for the treatment period (Visit 3 to 6) as follows:

  $$\text{Mean FEV1} = \frac{\sum \text{Available FEV1 measurements over the treatment period}}{\text{\# of available FEV1 measurements}}$$

- The change from baseline to the mean of FEV1 was calculated for both pre-dose and 1 hour post-dose measurements:

  Change in FEV1 = Mean FEV1 – Baseline FEV1

Secondary Efficacy Endpoints

❖ Patient-Reported Outcomes (PROs)
- St. George's Respiratory Questionnaire (SGRQ)
- Diary cards variables
  - AM and PM PEF
  - B2-agonist or ipratropium use prior to PEF measurement
  - Breathlessness diary
  - Cough scores
  - Sputum scores
  - Night time awakenings
  - Use of beta-agonist rescue medication and oral steroids
  - Hospitalization

❖ Exacerbations

Exacerbation was defined as worsening of COPD that at the discretion of the investigator requires a course of oral steroids for treatment and/or hospitalization.

Reviewer's comment: A COPD exacerbation was defined solely on the basis of treatment with oral steroids and/or hospitalization. Generally, the Division requires a more rigorous definition of exacerbation, including symptoms, severity, and definitive identification of the beginning and end of an exacerbatio (b) (4)

ue to concerns with the Applicant's definition of exacerbation, *however this information is still useful to evaluate the overall efficacy of Symbicort.*

❖ Pharmacokinetic Variables (in SHINE only)
- $AUC_{(0\text{-}t)}$: area under the curve from time zero to the last quantifiable concentration using the actual timing of blood draws
- C_{max}: largest observed concentration after inhalation

❖ Pharmacodynamic/Efficacy Variables
- FVC – the best of 3 maneuvers; mean change calculated similar to primary efficacy variables

- Serial FEV1 – from 5 to 720 minutes in a subset of 300 patients; change from baseline will be the difference at each time point minus the value at pre-dose.
- Inspiratory Capacity – means change calculated similar to primary efficacy variables

❖ Health Care Economics
1. Resource utilization
   a) Unscheduled health care provider visits - Proportion of patients with unscheduled healthcare provider visits due to COPD and number of such visits
   b) Urgent care clinic visits - Proportion of patients with urgent care clinic visits due to COPD and number of such visits
   c) Emergency room Visits - Proportion of patients with ER visits due to COPD an number of such visits
   d) Total COPD cost (imputed)

6.1.3 Study Design

The two pivotal trials had the same general design. Both were phase III, multi-center, randomized, double-blind, double-dummy, placebo-controlled, active-controlled, parallel group trials in patients with COPD. The patients enrolled were of either sex, ≥ 40 years of age with a FEV_1 ≤ 50% of predicted normal value pre-bronchodilator, a FEV_1/FVC <70% pre-bronchodilator, had a clinical diagnosis of COPD with symptoms for ≥ 2 years, were current or previous smokers with a smoking history of ≥10 pack years, had a score of ≥ 2 on the MMRC dyspnea scale, a total symptom score (based on breathlessness, cough and sputum) of ≥ 2 per day for at least half of the run-in period, had a history of at least one COPD exacerbation requiring a course of oral steroids within 1-12 months before Visit 1, used short-acting inhaled bronchodilator (β_2-agonists or anticholinergics) as rescue medication, had no history of asthma, and no history of allergic rhinitis before 40 years of age. The duration of SHINE was 6 months; the duration of SUN was 12 months.

Both studies consisted of an initial visit, a 2 week-run in period, 5 further visits during a 26-week treatment period (in SHINE), 7 further visits during a 52-week treatment period (in SUN), and a 4-week follow-up telephone call. Prior to Visit 1, fixed dose combination therapy was to be replaced with a comparable dose of ICS monotherapy and a short-acting inhaled beta agonist. Patients using either long-acting beta agonists or anticholinergics were to be converted to a short-acting bronchodilator of the same class. Between Visits 1 and 2, patients were allowed to continue use of inhaled steroids and/or short-acting inhaled bronchodilators. At Visit 2, treatment with ICS was to be discontinued, and all eligible patients were randomized to receive one of the study treatments.

The co-primary efficacy endpoints in both studies were change from baseline in pre-dose FEV1, to demonstrate the anti-inflammatory contribution of budesonide, and post-dose FEV1, to demonstrate the bronchodilator contribution of formoterol, to the efficacy of the combination product, Symbicort. Each co-primary variable was calculated as an average over the randomized treatment period (primary analysis). Dyspnea scores as measured by the

Breathlessness Diary (BD), SGRQ, and COPD exacerbations were defined as key secondary endpoints. Additional secondary endpoints, including spirometric and non-spirometric variables, were also examined. These other secondary endpoints included AM and PM peak expiratory flow, serial FEV1, FVC, rescue medication use, oral steroid use, symptom scores, sleep scores, health care economics, and pharmacokinetic variables (in SHINE only). The primary analysis for all efficacy variables was performed using all-randomized subjects (ITT population).

6.1.4 Efficacy Findings

6.1.4.1 SHINE

Demographics and Baseline Characteristics

A total of 1704 patients were randomized at 180 centers. Overall, discontinuation from the study was higher in the single ingredient treatment arms as compared with the Symbicort and free combination arms, and highest in the placebo arm. In each of the treatment arms, either adverse events or withdrawal of consent was the most likely reason for discontinuation. Of the 1704 patients randomized, 1378 patients completed the study, and a total of 326 patients discontinued. There was a greater percentage of male (68%) than female (32%) subjects consistent with the disease prevalence in the target population. Most subjects were Caucasian, with fewer than 7% non-Caucasian patients. Approximately half of the subjects were over age 65, with approximately 12% of subjects over the age of 75 years. Baseline percent predicted FEV1, post-bronchodilator percent predicted FEV1, and smoking history (pack years) were well-balanced across all treatment groups. Severity classification, based on the GOLD 2006 criteria applied to post-bronchodilator FEV1 at Visit 1, indicated that approximately 80% of the study population had severe or very severe COPD, while 20% had moderate COPD at entry. In general, demographic and key baseline characteristics were similar across treatment groups and geographic regions (US vs. non-US). Exceptions included a higher percentage of women in the US (41.5% of the total) than in the non-US region (24.8%). In addition, a larger percentage of enrolled subjects in the US were African Americans (8.4%) compared with the percentage enrolled in non-US countries (0.5%). The study population included a representative number of subjects with co-morbid conditions, including hypertension (42%), lipid profile abnormalities (24%), cardiac disease (18%), diabetes (10%), and osteoporosis (8%). Treatment groups were generally balanced with respect to demographic, key baseline, and medical history characteristics.

Primary Efficacy Endpoint

The co-primary efficacy endpoints were change from baseline in pre-dose FEV1, to demonstrate the anti-inflammatory contribution of budesonide, and post-dose FEV1, to demonstrate the bronchodilator contribution of formoterol, to the efficacy of the combination product, Symbicort. Each co-primary variable was calculated as an average over the randomized treatment period (primary analysis) and at the end-of-treatment.

1. Pre-dose FEV1

Treatment means and treatment comparisons for change in baseline averaged over the randomized treatment period and at the end of treatment are shown in Table 2 and Table 3.

Table 2 SHINE: Pre-dose FEV1 (L): Treatment means

			Average Of Randomized Treatment Period		End of Treatment	
	N	Baseline value Mean (SD)	Change from Baseline LS Mean (SEM)	95% CI	Change from Baseline LS Mean (SEM)	95% CI
Symbicort HD	266	1.04 (0.42)	0.08 (0.01)	0.06, 0.11	0.07 (0.02)	0.04, 0.11
Symbicort LD	275	1.04 (0.40)	0.06 (0.01)	0.03, 0.08	0.05 (0.02)	0.02, 0.08
Free combo	279	1.05 (0.37)	0.07 (0.01)	0.04, 0.09	0.06 (0.02)	0.03, 0.09
Budesonide 160	265	1.04 (0.39)	0.00 (0.01)	-0.02, 0.03	0.00 (0.02)	-0.03, 0.03
Formoterol 4.5	263	1.03 (0.40)	0.04 (0.01)	0.02, 0.07	0.03 (0.02)	0.00, 0.06
Placebo	270	1.10 (0.39)	0.01 (0.01)	-0.02, 0.03	0.01 (0.02)	-0.02, 0.04

Source: SHINE CSR, Section 7.2.1.1, Tables 24 and 26, p. 132, 135

Table 3 SHINE: Pre-dose FEV1 (L): Treatment comparisons for change from baseline

Comparison	Average Of Randomized Treatment Period		End of Treatment	
	LS Mean (95% CI)	p-value	LS Mean (95% CI)	p-value
Symbicort LD vs. placebo	0.05 (0.02, 0.09)	0.002	0.03 (-0.01, 0.07)	0.119
Symbicort HD vs. placebo	0.08 (0.04, 0.11)	< 0.001	0.06 (0.02, 0.10)	0.004
Symbicort LD vs. budesonide	0.06 (0.02, 0.09)	0.001	0.05 (0.00, 0.09)	0.033
Symbicort HD vs. budesonide	0.08 (0.04, 0.11)	< 0.001	0.07 (0.03, 0.12)	< 0.001
Symbicort LD vs. formoterol	**0.02 (-0.02, 0.05)**	**0.335**	**0.01 (-0.03, 0.06)**	**0.488**
Symbicort HD vs. formoterol	**0.04 (0.00, 0.07)**	**0.026**	**0.04 (0.00, 0.09)**	**0.044**
Symbicort HD vs. free comb.	0.01 (-0.02, 0.05)	0.479	0.01 (-0.03, 0.05)	0.525
Budesonide vs. placebo	0.00 (-0.04, 0.03)	0.902	-0.01 (-0.05, 0.03)	0.559
Formoterol vs. placebo	0.04 (0.00, 0.07)	0.037	0.02 (-0.02, 0.06)	0.395
Symbicort HD vs. LD	0.02 (-0.01, 0.06)	0.198	0.03 (-0.01, 0.07)	0.179

Source: SHINE CSR, Tables 25 and 27, Section 7.2.1.1, p. 133, 135
Bold Text indicates pre-specified primary comparisons

In terms of the pre-specified primary comparisons, results indicate that only Symbicort HD demonstrated a statistically significantly greater increase from baseline in pre-dose FEV1 when compared with formoterol. This result was consistent when analyzed as the average of the randomized treatment period or at the end of treatment.

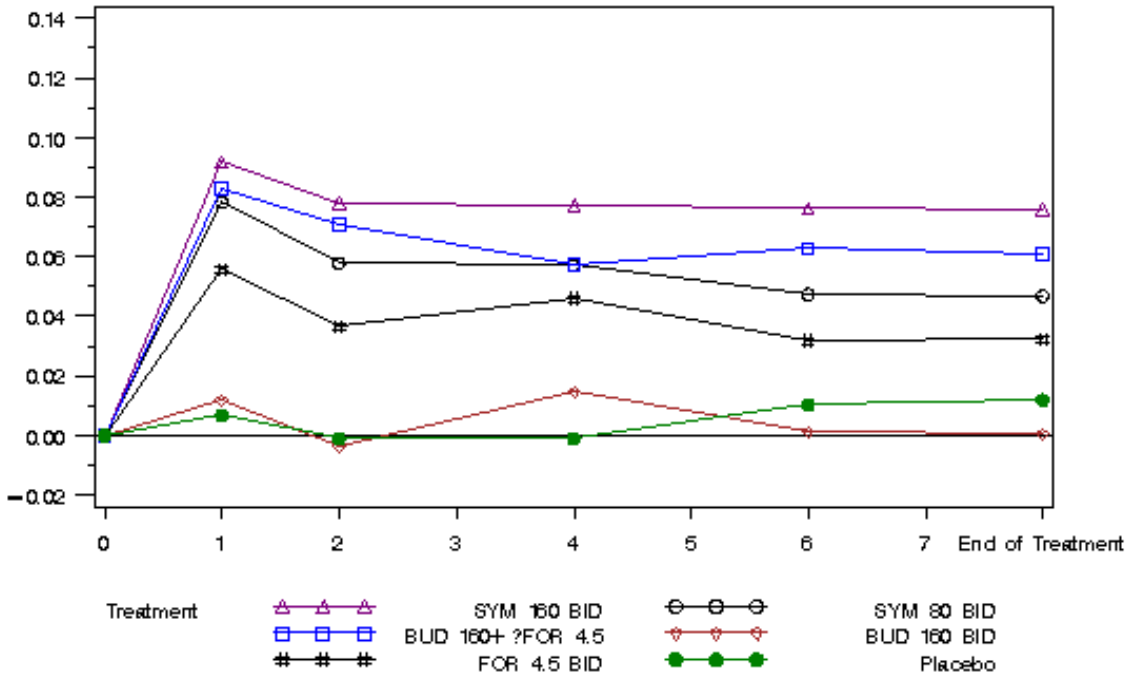
Reviewer's Comment: It is of note that the difference between Symbicort HD and formoterol, though statistically significant, was quantitatively small, approximately 40 mL.

Symbicort LD failed to show the contribution of the inhaled corticosteroid to the efficacy of the combination product in both analyses. Both dosage strengths of Symbicort demonstrated a statistically significant difference in pre-dose FEV1 vs. placebo when examined as the average of the randomized treatment period, but Symbicort LD was not statistically different from placebo at the end of treatment. In both analyses, Symbicort HD was not statistically different when compared with Symbicort LD in terms of change from baseline in pre-dose FEV1, but the results numerically favored the Symbicort HD group.

Reviewer's Comment: Based on the above analysis, the Sponsor has decided only to pursue the Symbicort HD BID for the COPD indication, as Symbicort LD failed to show the contribution of budesonide to the efficacy of the combination product.

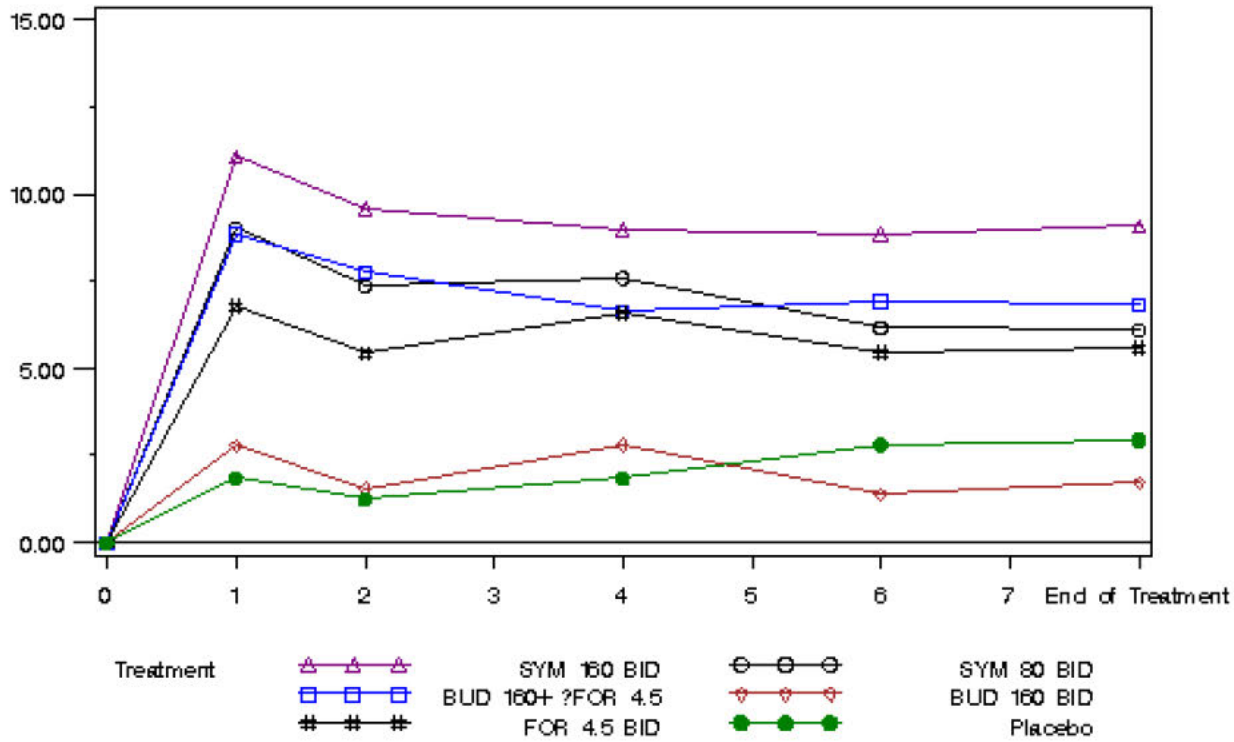
Figure 1 and Figure 2 depict the LS mean change and percent change from baseline in pre-dose FEV1 by visit, respectively. The accompanying table provides information for the number of subjects included in the analysis at each time point. Symbicort HD demonstrated improvements in pre-dose FEV1 that were apparent at Month 1 and were generally maintained over the 6-month study period.

Figure 1 SHINE: LS Mean change from baseline in pre-dose FEV1 by Visit



[Source: NDA 21-929, Biometrics Review, Dr. Ted Guo]

Figure 2 SHINE: Percent change from baseline in pre-dose FEV1 by visit



[Source: NDA 21-929, Biometrics Review, Dr. Ted Guo]

Treatment group	Months				
	1	2	4	6	EOT
Symbicort HD N = 275	266	259	250	238	266
Symbicort LD N = 280	273	265	254	246	275
Free Combo N = 286	278	267	253	238	279
Budesonide N = 274	262	242	227	210	265
Formoterol N = 283	263	250	235	223	263
Placebo N = 299	266	245	238	230	270

Reviewer's comment: Of note, although the pre-specified primary endpoint is the mean change in pre-dose and post-dose FEV1 averaged over the treatment period (as portrayed in Figure 1), (b) (4) *Graphically the figures do not appear to be strikingly different.*

2. Post-dose FEV1

Treatment means and treatment comparisons for change in baseline averaged over the randomized treatment period and at the end of treatment are shown Table 4 and Table 5.

Table 4 SHINE: Post-dose FEV1 (L): Treatment means

			Average Of Randomized Treatment Period		End of Treatment	
	N	Baseline value Mean (SD)	Change from Baseline LS Mean (SEM)	95% CI	Change from Baseline LS Mean (SEM)	95% CI
Symbicort HD	275	1.04 (0.41)	0.20 (0.01)	0.18, 0.23	0.19 (0.02)	0.15, 0.23
Symbicort LD	280	1.04 (0.40)	0.19 (0.01)	0.17, 0.22	0.18 (0.02)	0.14, 0.22
Free combo	286	1.05 (0.36)	0.19 (0.01)	0.16, 0.21	0.20 (0.02)	0.16, 0.24
Budesonide 160	274	1.04 (0.40)	0.03 (0.01)	0.01, 0.06	0.02 (0.02)	-0.02, 0.06
Formoterol 4.5	283	1.02 (0.40)	0.17 (0.01)	0.14, 0.19	0.15 (0.02)	0.11, 0.18,
Placebo	299	1.08 (0.38)	0.03 (0.01)	0.01, 0.06	0.02 (0.02)	-0.01, 0.06

Source: SHINE CSR, Section 7.2.1.2, Tables 28 and 30, p. 137 and 140

Table 5 SHINE: 1-hr Post-dose FEV1 (L): Treatment comparisons for change from baseline

Comparison	Average Of Randomized Treatment Period		End of Treatment	
	LS Mean (95% CI)	p-value	LS Mean (95% CI)	p-value
Symbicort LD vs. placebo	0.16 (0.13, 0.20)	< 0.001	0.15 (0.11, 0.20)	< 0.001
Symbicort HD vs. placebo	0.17 (0.14, 0.20)	< 0.001	0.16 (0.12, 0.21)	< 0.001
Symbicort LD vs. budesonide	**0.16 (0.13, 0.20)**	**< 0.001**	**0.16 (0.11, 0.21)**	**< 0.001**
Symbicort HD vs. budesonide	**0.17 (0.14, 0.21)**	**< 0.001**	**0.17 (0.12, 0.22)**	**< 0.001**
Symbicort HD vs. free comb.	0.01 (-0.02, 0.05)	0.461	-0.01 (-0.06, 0.04)	0.671
Budesonide vs. placebo	0.00 (-0.03, 0.03)	0.997	-0.01 (-0.05, 0.04)	0.808
Formoterol vs. placebo	0.14 (0.10, 0.17)	<0.001	0.12 (0.07, 0.17)	<0.001
Symbicort HD vs. LD	0.01 (-0.03, 0.04)	0.615	0.01 (-0.04, 0.06)	0.693

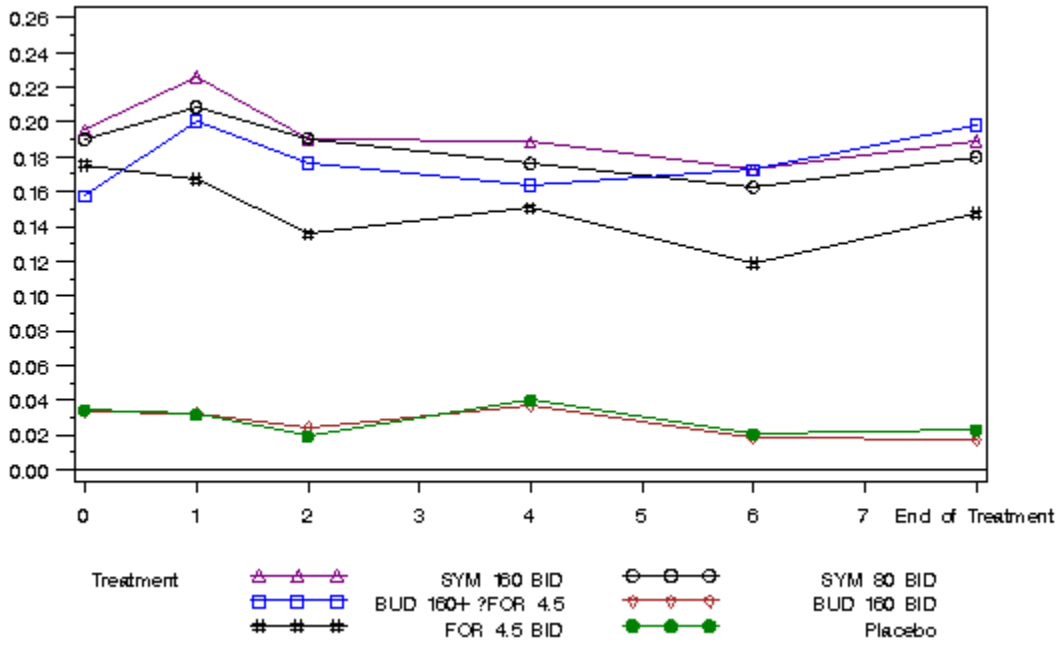
Source: SHINE CSR, Section 7.2.1.2, Tables 29 and 31, p. 137 and 140
Bold Text indicates primary comparisons

In terms of the pre-specified primary comparisons, results indicate that both dosage strengths of Symbicort demonstrated a statistically significantly greater increase from baseline in post-dose FEV1 when compared with budesonide. This result was consistent when analyzed as the average of the randomized treatment period and at the end of treatment. Both dosage strengths of Symbicort demonstrated a statistically significant difference in post-dose FEV1 vs. placebo when examined as the average of the randomized treatment period and at the end of treatment. These results demonstrate that formoterol makes a contribution to the efficacy of both strengths of the combination product.

Figure 3 and Figure 4 depict the LS mean change and percent change from baseline in post-dose FEV1 by visit, respectively. The accompanying table provides information for the number of subjects included in the analysis at each time point. Symbicort LD and HD demonstrated

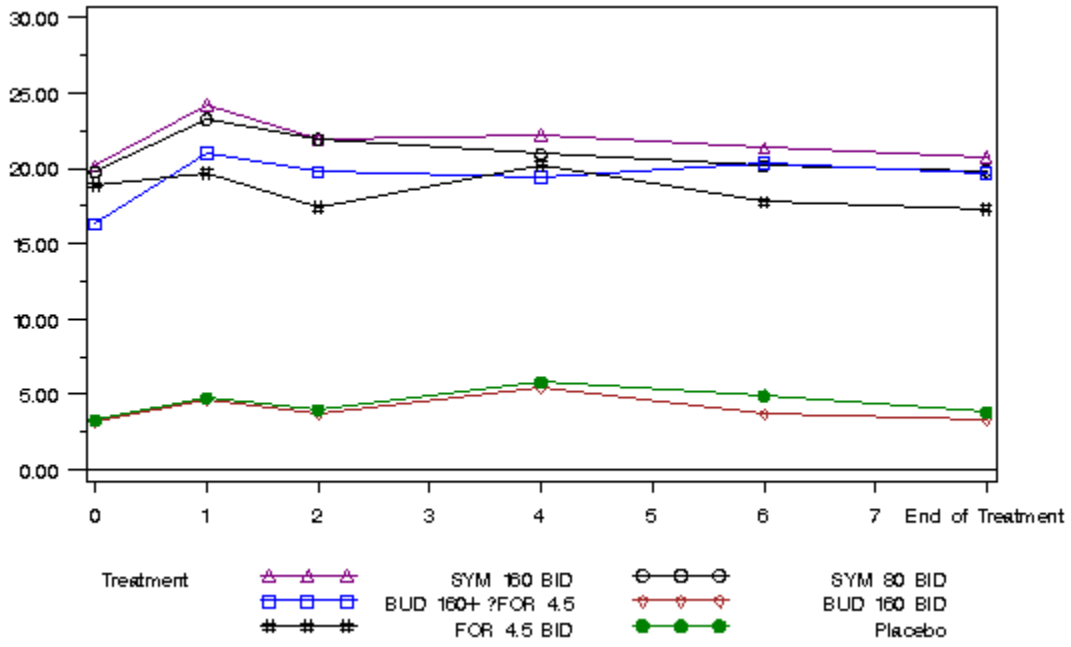
improvements in 1-hour post-dose FEV1 that were apparent on the day of randomization and were generally maintained over the 6-month study period.

Figure 3 SHINE: LS mean change from baseline in 1-hour post-dose FEV1 by visit



[Source: NDA 21-929, Biometrics Review, Dr. Ted Guo]

Figure 4 SHINE: Mean Percent Change from Baseline in 1-hr Post-dose FEV1 Over 6 months (Figure 2, proposed product label)



[Source: NDA 21-929, Biometrics Review, Dr. Ted Guo]

Treatment group	Months				
	1	2	4	6	EOT
Symbicort HD N = 271	267	257	250	237	275
Symbicort LD N = 280	270	264	254	244	280
Free Combo N = 283	277	267	252	239	286
Budesonide N = 274	255	241	224	210	274
Formoterol N = 282	259	248	234	221	283
Placebo N = 298	262	243	238	230	299

Reviewer's comment: Of note, although the pre-specified primary endpoint is the mean change in pre-dose and post-dose FEV1 averaged over the treatment period (as portrayed in Figure 14), (b) (4) *(see Figure 15). Graphically, the figures do not appear to be strikingly different.*

In summary, SHINE results indicate that only Symbicort HD demonstrated a statistically significantly greater increase from baseline in pre-dose FEV1 when compared with formoterol. This result was consistent when analyzed as the average of the randomized treatment period or at

the end of treatment. Symbicort LD failed to show the contribution of the inhaled corticosteroid to the efficacy of the combination product in both analyses. In both analyses, Symbicort HD was not statistically different when compared with Symbicort LD in terms of change from baseline in pre-dose FEV1. Symbicort HD demonstrated improvements in pre-dose FEV1 that were apparent at Month 1 and were generally maintained over the 6-month study period. These results demonstrate that the higher dose of budesonide makes a contributed to the efficacy of the combination product, while the lower dose does not. For post-dose FEV1, results indicate that both dosage strengths of Symbicort demonstrated a statistically significantly greater increase from baseline in post-dose FEV1 when compared with budesonide. This result was consistent when analyzed as the average of the randomized treatment period or at the end of treatment. These results demonstrate that formoterol makes a contribution to the efficacy of both strengths of the combination product.

6.1.4.2 SUN

Demographics and Baseline Characteristics

A total of 1964 patients were randomized at 225 centers. Overall, discontinuation from the study was slightly higher in the formoterol treatment arm as compared with the Symbicort arms, and highest in the placebo arm. In each of the treatment arms, either adverse events or withdrawal of consent was the most likely reason for discontinuation. Of the 1964 patients randomized, 1355 patients completed the study, and a total of 609 patients discontinued. There was a greater percentage of male (64%) than female (36%) subjects consistent with the disease prevalence in the target population. Most subjects were Caucasian, with fewer than 8% non-Caucasian patients. Approximately half of the subjects were over age 65, with approximately 11% of subjects over the age of 75 years. Baseline percent predicted FEV1, post-bronchodilator percent predicted FEV1, and smoking history (pack years) were well-balanced across treatment groups. Severity classification, based on the GOLD 2006 criteria applied to post-bronchodilator FEV1 at Visit 1, indicated that approximately 80% of the study population had severe or very severe COPD, while 20% had moderate COPD at entry. Severity varied somewhat across treatment groups, with approximately 30% more subjects in the most severe category in the Symbicort HD and formoterol groups. In general, demographic and key baseline characteristics were similar across treatment groups and geographic regions (US vs. non-US). Exceptions included a higher percentage of women in the US (43.7% of the total) than in the non-US region (29.9%). In addition, a larger percentage of enrolled subjects in the US were African Americans (5.3%) compared with none in non-US countries. The study population included a representative number of subjects with co-morbid conditions, including hypertension (42%), lipid profile abnormalities (22%), cardiac disease (18%), diabetes (11%), osteoporosis (11%), cataracts (5%), atrial fibrillation and/or arrhythmia (4%), and congestive heart failure (3%). Treatment groups were generally balanced with respect to demographic, key baseline, and medical history characteristics.

Primary Efficacy Endpoint

The co-primary efficacy endpoints were change from baseline in pre-dose FEV1, to demonstrate the anti-inflammatory contribution of budesonide, and post-dose FEV1, to demonstrate the bronchodilator contribution of formoterol, to the efficacy of the combination product, Symbicort. Each co-primary variable was calculated as an average over the randomized treatment period (primary analysis) and at the end-of-treatment.

1. Pre-dose FEV1

Treatment means and treatment comparisons for change in baseline averaged over the randomized treatment period and at the end of treatment are shown in Table 6 and Table 7.

Table 6 SUN: Pre-dose FEV1 (L): Treatment means

			Average Of Randomized Treatment Period		End of Treatment	
	N	Baseline value Mean (SD)	Change from Baseline LS Mean (SEM)	95% CI	Change from Baseline LS Mean (SEM)	95% CI
Symbicort HD	471	1.03 (0.39)	0.10 (0.01)	0.08, 0.10	0.09 (0.02)	0.06, 0.12
Symbicort LD	479	1.04 (0.39)	0.08 (0.01)	0.06, 0.11	0.06 (0.02)	0.03, 0.10
Formoterol 4.5	465	1.03 (0.40)	0.06 (0.01)	0.04, 0.09	0.07 (0.02)	0.03, 0.10
Placebo	436	1.08 (0.42)	0.01 (0.01)	-0.02, 0.03	-0.00 (0.02)	-0.03, 0.03

Source: SUN CSR, Section 7.2.1.1, Tables 25 and 27, p. 136, 138

Table 7 SUN: Pre-dose FEV1 (L): Treatment comparisons for change from baseline

Comparison	Average Of Randomized Treatment Period		End of Treatment	
	LS Mean (95% CI)	p-value	LS Mean (95% CI)	p-value
Symbicort HD vs. placebo	0.09 (0.06, 0.12)	< 0.001	0.09 (0.06, 0.13)	< 0.001
Symbicort HD vs. formoterol	**0.04 (0.01, 0.07)**	**0.008**	**0.03 (-0.01, 0.06)**	**0.150**
Symbicort LD vs. placebo	0.07 (0.05, 0.10)	< 0.001	0.07 (0.03, 0.10)	< 0.001
Symbicort LD vs. formoterol	**0.02 (-0.01, 0.05)**	**0.161**	**-0.00 (-0.04, 0.04)**	**0.972**
Formoterol vs. placebo	0.05 (0.03, 0.08)	< 0.001	0.07 (0.03, 0.10)	< 0.001
Symbicort HD vs. LD	0.02 (-0.01, 0.05)	0.206	0.03 (-0.01, 0.06)	0.137

Source: SUN CSR, Section 7.2.2.1, Tables 26 and 28, p. 136, 138
Bold Text indicates pre-specified primary comparisons

In terms of the pre-specified primary comparisons, results indicate that only Symbicort HD demonstrated a statistically significantly greater increase from baseline in pre-dose FEV1 when compared with formoterol. However, this result was not consistent when analyzed at the end of treatment.

Reviewer's Comment: It is of note that the difference between Symbicort HD and formoterol, though statistically significant, was quantitatively small, approximately 40 mL, similar to what it was in the 6 month study.

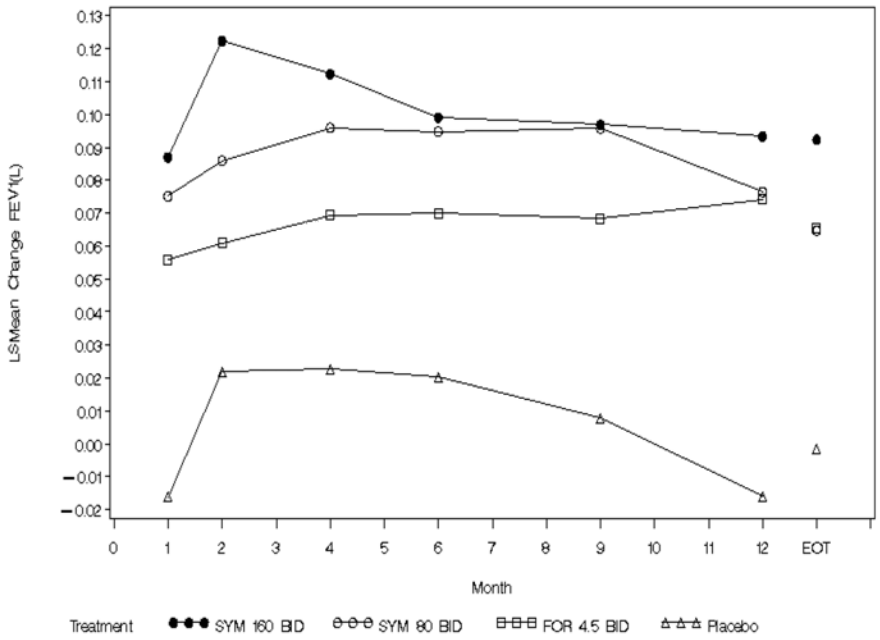
Symbicort LD failed to show the contribution of the inhaled corticosteroid to the efficacy of the combination product in both analyses. Both dosage strengths of Symbicort demonstrated

statistically significant difference in pre-dose FEV1 vs. placebo when examined as the average of the randomized treatment period and at the end of treatment. Symbicort HD was not statistically different when compared with Symbicort LD in terms of change from baseline in pre-dose FEV1, but the results numerically favored the Symbicort HD group.

Reviewer's Comment: Based on the above analysis as well as the findings from the 6 month SHINE study, the Sponsor has decided only to pursue the Symbicort HD BID for the COPD indication, as the lower dose failed to show the contribution of budesonide to the efficacy of the combination product.

Figure 5 depicts the LS mean change from baseline in pre-dose FEV1 by visit. The accompanying table provides information for the number of subjects included in the analysis at each time point. Symbicort HD demonstrated improvements in pre-dose FEV1 that were apparent at Month 1 and were generally maintained over the 12-month study period.

Figure 5 SUN: LS mean change from baseline in pre-dose FEV1 by visit



Treatment group	Months						
	1	2	4	6	9	12	EOT
Symbicort HD N = 494	470	451	433	408	386	361	471
Symbicort LD N = 494	474	453	418	398	369	354	479
Formoterol N = 495	462	437	403	386	362	337	465
Placebo N = 481	434	400	371	347	327	307	436

Reviewer's comment: This figure is not included in the proposed product label. Only the figures from the 6-month study are included.

2. Post-dose FEV1

Treatment means and treatment comparisons for change in baseline averaged over the randomized treatment period and at the end of treatment are shown in Table 8 and Table 9.

Table 8 SUN: Post-dose FEV1 (L): Treatment means

			Average Of Randomized Treatment Period		**End of Treatment**	
	N	Baseline value Mean (SD)	Change from Baseline LS Mean (SEM)	95% CI	Change from Baseline LS Mean (SEM)	95% CI
Symbicort HD	494	1.02 (0.39)	0.21 (0.01)	0.18, 0.23	0.20 (0.02)	0.16, 0.23
Symbicort LD	494	1.04 (0.39)	0.19 (0.01)	0.16, 0.21	0.16 (0.02)	0.13, 0.20
Formoterol 4.5	495	1.03 (0.40)	0.18 (0.01)	0.15, 0.20	0.17 (0.02)	0.14, 0.20
Placebo	479	1.08 (0.42)	0.02 (0.01)	0.00, 0.05	0.01 (0.02)	-0.02, 0.04

Source: SUN CSR, Section 7.2.1.2, Tables 29 and 31, p. 140, 143

Table 9 SUN: 1-hr Post-dose FEV1 (L): Treatment comparisons for change from baseline

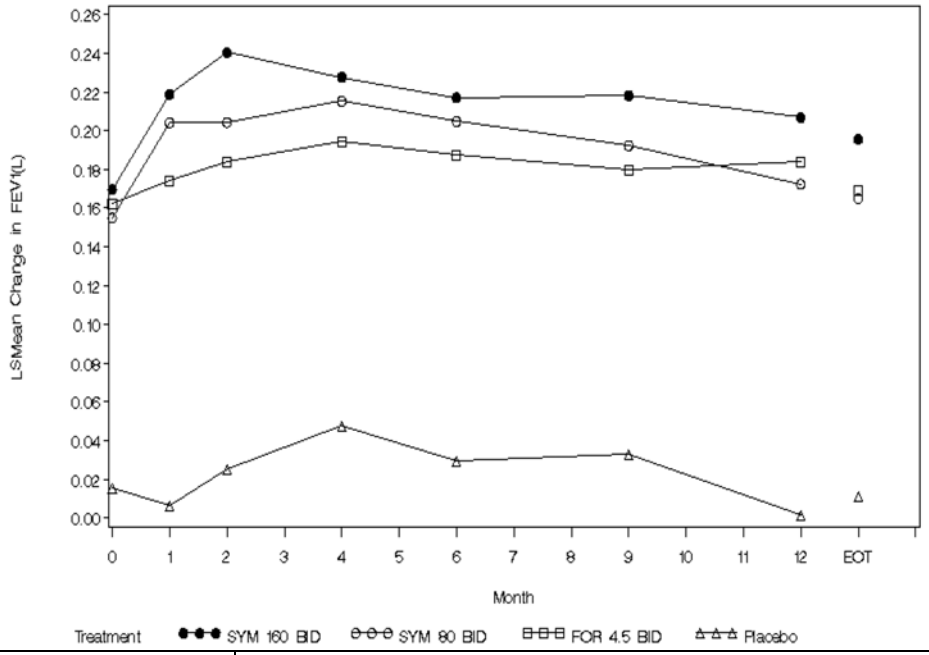
Comparison	**Average Of Randomized Treatment Period**		**End of Treatment**	
	LS Mean (95% CI)	p-value	LS Mean (95% CI)	p-value
Symbicort HD vs. placebo	**0.18 (0.16, 0.21)**	**< 0.001**	**0.18 (0.15, 0.22)**	**< 0.001**
Symbicort HD vs. formoterol	0.03 (0.00. 0.06)	0.23	0.03 (-0.01, 0.06)	0.164
Symbicort LD vs. placebo	**0.16 (0.13, 0.19)**	**< 0.001**	**0.15 (0.12, 0.19)**	**< 0.001**
Symbicort LD vs. formoterol	0.01 (-0.02, 0.04)	0.420	-0.00 (-0.04, 0.03)	0.807
Formoterol vs. placebo	0.15 (0.12, 0.18)	< 0.001	0.16 (0.12, 0.20)	< 0.001
Symbicort HD vs. LD	0.02 (-0.01, 0.05)	0.144	0.03 (-0.01, 0.07)	0.102

Source: SUN CSR, Section 7.2.1.2, Tables 30 and 32, p. 140 and 143
Bold Text indicates primary comparisons

In terms of the pre-specified primary comparisons, results indicate that both dosage strengths of Symbicort demonstrated a statistically significantly greater increase from baseline in post-dose FEV1 when compared with placebo. This result was consistent when analyzed as the average of the randomized treatment period or at the end of treatment.

Figure 6 depicts the LS mean change from baseline in post-dose FEV1 by visit. The accompanying table provides information for the number of subjects included in the analysis at each time point. Symbicort LD and HD demonstrated improvements in 1 hour post-dose FEV1 that were apparent on the day of randomization and were generally maintained over the 12-month study period.

Figure 6 SUN: LS mean change from baseline in 1-hour post-dose FEV1 by visit



Treatment group	Months						
	1	2	4	6	9	12	EOT
Symbicort HD N = 490	467	450	430	405	384	361	494
Symbicort LD N = 494	473	449	416	393	370	353	494
Formoterol N = 495	459	436	401	384	361	337	495
Placebo N = 478	428	397	368	345	323	306	479

In summary, SUN results indicate that only Symbicort HD demonstrated a statistically significantly greater increase from baseline in pre-dose FEV1 when compared with formoterol. However, this result was not consistent when analyzed at the end of treatment. Symbicort LD failed to show the contribution of the inhaled corticosteroid to the efficacy of the combination product in both analyses. Both dosage strengths of Symbicort demonstrated statistically significant difference in pre-dose FEV1 vs. placebo when examined as the average of the randomized treatment period and at the end of treatment. Symbicort HD was not statistically different when compared with Symbicort LD in terms of change from baseline in pre-dose

FEV1. These results demonstrate that the higher dose of budesonide makes a contribution to the efficacy of the combination product, however the lower dose does not. For post-dose FEV1, results indicate that both dosage strengths of Symbicort demonstrated a statistically significantly greater increase from baseline in post-dose FEV1 when compared with placebo and/or budesonide. This result was consistent when analyzed as the average of the randomized treatment period or at the end of treatment. These results demonstrate that formoterol makes a contribution to the efficacy of both strengths of the combination product.

Table 10 Summary of the Primary Efficacy Endpoints: Treatment comparisons averaged over the randomized treatment period for both SUN and SHINE

	Pre-Dose FEV1 (L)		Post-Dose FEV1 (L)	
	SUN 12 months	**SHINE 6 months**	**SUN 12 months**	**SHINE 6 months**
Symbicort LD vs. placebo	0.07 (0.05, 0.10)	0.05 (0.02, 0.09)	**0.16 (0.13, 0.19)**	0.16 (0.13, 0.20)
Symbicort HD vs. placebo	0.09 (0.06, 0.12)	0.08 (0.04, 0.11)	**0.18 (0.16, 0.21)**	0.17 (0.14, 0.20)
Symbicort LD vs. budesonide		0.06 (0.02, 0.09)		**0.16 (0.13, 0.20)**
Symbicort HD vs. budesonide		0.08 (0.04, 0.11)		**0.17 (0.14, 0.21)**
Symbicort LD vs. formoterol	**0.02 (-0.01, 0.05)**	**0.02 (-0.02, 0.05)**	0.01 (-0.02, 0.04)	0.03 (-0.01, 0.06)
Symbicort HD vs. formoterol	**0.04 (0.01, 0.07)**	**0.04 (0.00, 0.07)**	0.03 (0.00, 0.06)	0.04 (0.00, 0.07)
Symbicort HD vs. free comb.		0.01 (-0.02, 0.05)		0.01 (-0.02, 0.05)
Budesonide HD vs. placebo		0.00 (-0.04, 0.03)		0.00 (-0.03, 0.03)
Formoterol vs. placebo	0.05 (0.03, 0.08)	0.04 (0.00, 0.07)	0.15 (0.12, 0.18)	0.14 (0.10, 0.17)

Bolded text indicates the primary comparisons for each efficacy variable; highlighted values indicate statistically significant results
Gray boxes indicate that budesonide was not a treatment arm in the SUN study, therefore the comparison could not be made.

Table 10 summarizes the results for the primary efficacy endpoints from both the SUN and SHINE studies. In terms of the pre-specified primary analysis, the results are replicated in both studies. Symbicort HD was statistically significantly superior to formoterol with regard to pre-dose FEV1, and both doses of Symbicort were statistically superior to either budesonide or placebo with regard to post-dose FEV1, thus demonstrating the contribution of both components to the efficacy of the combination product.

6.1.4.3 Subgroup Analyses of the Primary Endpoint

Subgroup analyses by sex, age, and race were conducted by the Applicant. The subgroup analyses are summarized by study below.

SHINE

1) Pre-Dose FEV1

Similar patterns of results seen in the primary analysis were seen in the sensitivity analyses adjusting for sex and age groups. A statistically significant interaction was observed for race, particularly for black subjects, who showed a large variability across LS mean treatment effects. However, when this interaction was examined more closely, the large increase in treatment effect was noted in the free combination, budesonide, and placebo arms. For these same subjects, the primary treatment group comparison of Symbicort HD versus formoterol was equivalent to the primary analysis. Therefore, it was concluded that there was no clear evidence of a differential treatment effect across race groups.

2) 1-hour Post-Dose FEV1

Similar patterns of results seen in the primary analysis were seen in the sensitivity analyses adjusting for sex and age groups. A statistically significant interaction was observed for race, particularly for black subjects, who showed a large variability across LS mean treatment effects. Most notable was the large increase in 1-hour post-dose FEV1 for the free combination, budesonide, and placebo arms (LS means: 0.45L, 0.19L, and 0.28L, respectively), which was not consistent with primary results. For these same subjects, the primary treatment group comparison for Symbicort HD versus budesonide was 0.02L, which was also not consistent with the primary analysis. When the reason for this is further investigated, it appears that the inconsistency in the treatment effect is due to unexpected increase in the budesonide treatment group rather than a lack of effect in the Symbicort HD group, which was 0.20L. Results for subjects reporting “other” for race, show similar results to the primary analysis.

SUN

1) Pre-Dose FEV1

Similar patterns of results seen in the primary analysis were seen in the sensitivity analyses adjusting for sex and age groups. A statistically significant interaction was observed for race ($p=0.05$), however this was deemed by the Applicant to be due to the large variability across race groups. Therefore, it was concluded that there was no clear evidence of a differential treatment effect across race groups.

2) 1-hour Post-Dose FEV1

Similar patterns of results seen in the primary analysis were seen in the sensitivity analyses adjusting for sex, age, and race groups.

6.1.4.4 Secondary efficacy endpoints

The Applicant identified dyspnea (as measured by the Breathlessness Diary), St. George's Respiratory Questionnaire (SGRQ), and COPD exacerbations as key secondary efficacy variables. Other secondary efficacy variables of interest were 12-hour serial FEV1 (onset of action), morning and evening peak expiratory flow (PEF), Breathlessness Cough Sputum Score (BCSS), Sleep Score, and rescue medication use.

Dyspnea Scores

Dyspnea scores, as measured by the Breathlessness Diary, range from 0-4 with higher scores indicating more severe dyspnea. A reduction of 0.2 units has been defined as the minimally important clinical difference (MCID) based on prior validation. The primary comparison was between the Symbicort treatments and placebo.

In SHINE, the LS mean difference between Symbicort HD and placebo averaged over the randomized treatment period was -0.16 (95% CI -0.25, -0.06, p = 0.001); Symbicort LD versus placebo yielded a LS mean difference of -0.16 (95% CI -0.26, -007, p < 0.001). Both Symbicort HD and LD demonstrated a statistically significant reduction from baseline in dyspnea scores when compared with placebo, but the pre-specified MCID was not achieved. In SUN, the LS mean difference between Symbicort HD and placebo averaged over the randomized treatment period was -0.20 (95% CI -0.27, -0.12, p < 0.001); Symbicort LD versus placebo yielded a LS mean difference of -0.15 (95% CI -0.23, -0.08, p < 0.001). Both Symbicort HD and LD demonstrated a statistically significant reduction from baseline in dyspnea scores when compared with placebo, but the pre-specified MCID was only achieved for Symbicort HD

Reviewer's comment: The Sponsor ha (b) (4) *Although the MCID was met in SUN when Symbicort HD was compared with placebo, this was not replicated in the 6-month SHINE study in which the MCID was not met, despite the statistical significance of the finding. Given that finding was not replicated, and more importantly, that the Division does not currently accept the Breathlessness Diary as an instrument that can adequately measure dyspnea reduction,* (b) (4)

St. George's Respiratory Questionnaire (SGRQ)

The SGRQ total score and scores for each of the 3 domains (symptoms, activity, impact) were analyzed at the end of treatment. The validated MCID for the SGRQ total score and the impact domain score has been defined as a mean change in score of 4 units. The primary comparison was between the Symbicort treatment groups and placebo. In SHINE, the LS mean difference between Symbicort HD and placebo in SGRQ total score change from baseline at the end of treatment was -3.12 (95% CI -5.201, -1.036, P = 0.003); Symbicort LD versus placebo yielded a LS mean difference of -2.95 (95% CI -5.011, -0.884, p = 0.005).

In SUN, The LS mean difference between Symbicort HD and placebo in SGRQ total score change from baseline at the end of treatment was -2.39 (95% CI -4.085, -0.690, P = 0.006); Symbicort LD versus placebo yielded a LS mean difference of -3.66 (95% CI -5.351, -1.975, p < 0.001). Symbicort HD and LD groups demonstrated statistically significant reductions in SGRQ total scores compared with placebo in both studies, but did no achieve the pre-specified MCID of 4 units.

COPD exacerbations

A COPD exacerbation was pre-defined as a worsening of COPD that required a course of oral steroids and/or hospitalization for treatment. Episodes of COPD worsening that were treated with parenteral steroids alone, or with antibiotics without systemic steroids or hospitalization, were not included in the definition of exacerbation, but were listed separately. The primary comparison was between Symbicort treatment groups and placebo.

In SHINE, the results for the primary analysis of the number of protocol-defined COPD exacerbations per subject-treatment year indicated that there were no statistically significant differences in the rate of exacerbations between treatment groups. Specifically, the rate ratio of the comparison of Symbicort HD versus placebo was 0.796 [95% CI 0.603, 1.052, p = 0.109]. The rate ratio of the comparison of Symbicort LD versus placebo was 0.766 [95% CI 0.581, 1.011, p = 0.60]. Additionally, there were no differences between treatment groups for time to first exacerbation. In SUN, the results for the primary analysis of the number of protocol-defined COPD exacerbations per subject-treatment year indicate that there were statistically significant differences in the rate of exacerbations between treatment groups. Specifically, the rate ratio of the comparison of Symbicort HD versus placebo was 0.632 [95% CI 0.522, 0.765, p =< 0.001]. The rate ratio of the comparison of Symbicort LD versus placebo was 0.593 [95% CI 0.487, 0.722, p < 0.001]. There was no statistical difference between Symbicort treatment groups.

Reviewer's Comment: The Applicant has included the following statement in (b) (4) [redacted] *It is of note that the rate ratio result in the 6 month study was not statistically significant. A COPD exacerbation was defined solely on the basis of treatment with oral steroids and/or hospitalization. Generally, the Division requires a more rigorous definition of exacerbation, including symptoms, severity, and definitive identification of the beginning and end of an exacerbation to* (b) (4) [redacted] *however this information is still useful to evaluate the overall efficacy of Symbicort.*

Serial 12-hour FEV1

At Visits 2, 4, and 6, FEV1 was measured pre-dose and at 5, 15, 30, 60, 120, 180, 240, 360, 480, 600, and 720 minutes post-dose in a subset of 618 subjects. The 12 hour FEV1 curves from SHINE , based on mean percent change from baseline pre-dose FEV1 values are shown in Figure 7 and Figure 8. The same curves from SUN are shown in Figure 9 and Figure 10.

Figure 7 SHINE: Mean percent change from baseline in FEV1 on day of randomization

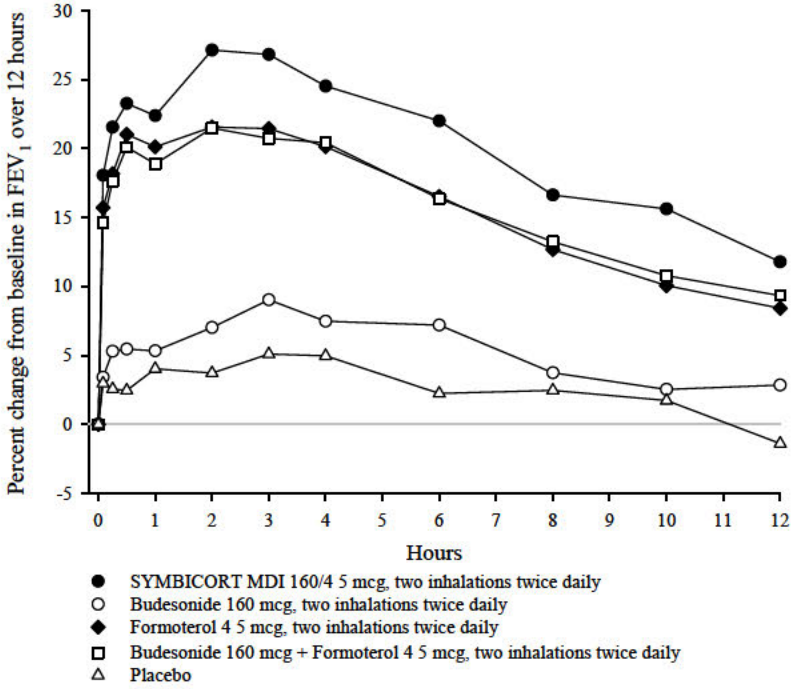


Figure 8 SHINE: Mean percent change from baseline in FEV1 at end of treatment

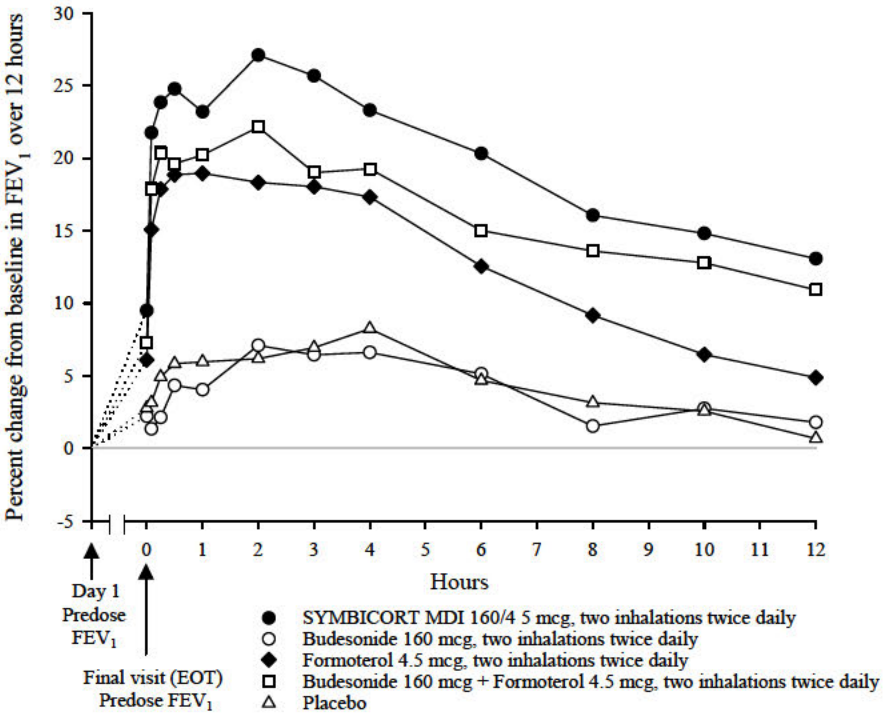


Figure 9 SUN: Mean percent change from baseline FEV1 over 12 hours – day of randomization

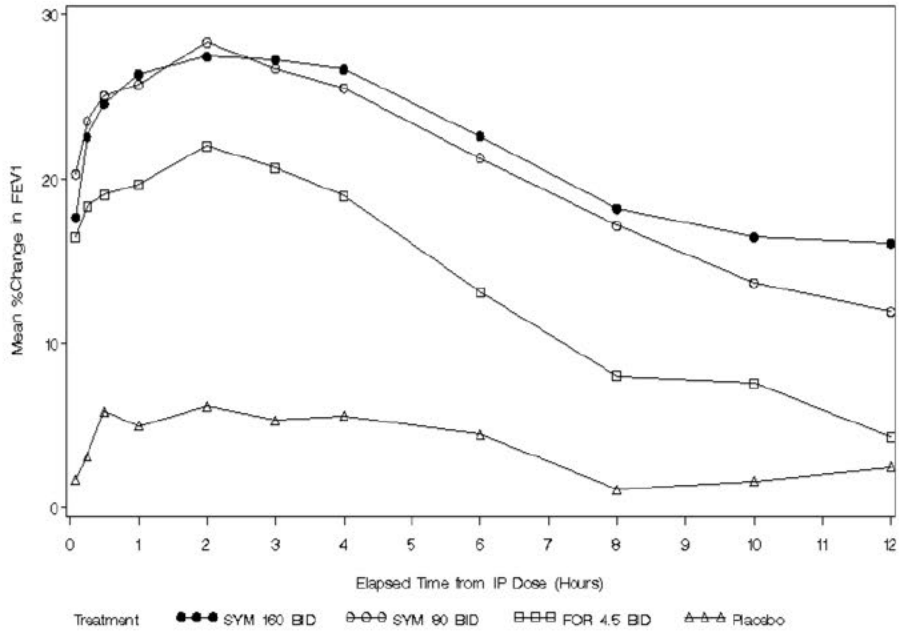
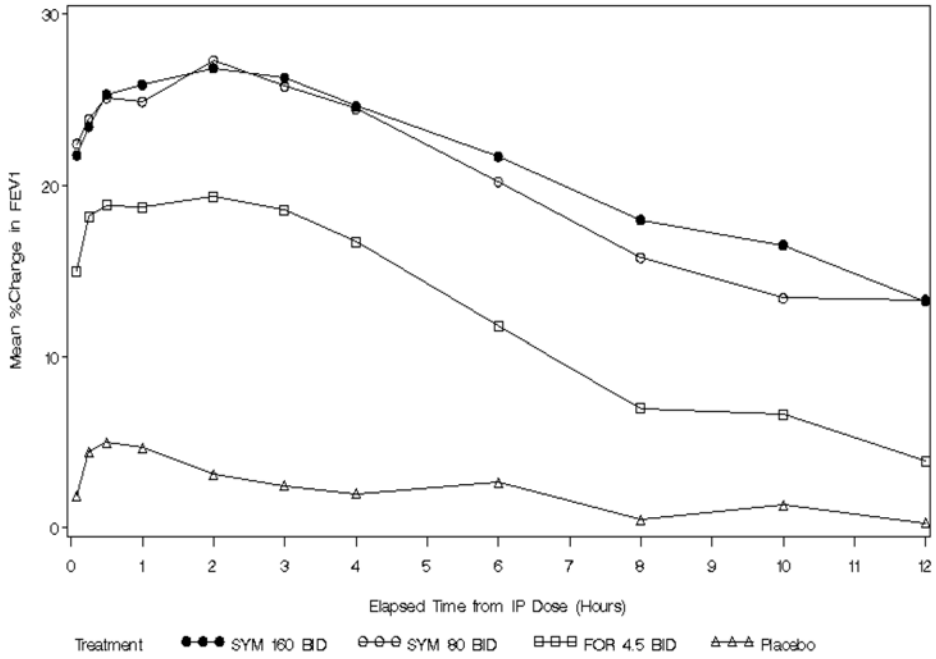


Figure 10 SUN: Mean percent change from baseline in FEV1 over 12 hours – end of treatment



The serial FEV1 graphs above indicate that all Symbicort-containing treatment groups demonstrated bronchodilation at 5 minutes after dosing, compared with placebo, which reached a maximum between 2 and 3 hours, and was maintained over 12 hours. The response was present at the end of treatment as well. The serial FEV1 curves in the 12-month study differ in one notable way when compared with the 6 month study. In SUN, the formoterol treatment group did not have a sustained improvement in FEV1 compared to placebo over 12 hours. The reason for this finding is unclear given the curves in the 6-month study and that formoterol is approved as a twice-daily drug.

Reviewer's comment: Of note, (b) (4) *the SHINE serial FEV1 curves are included by the Applicant in the proposed product label.*

Morning and Evening PEF

A Mini-Wright peak flow meter was dispensed at Visit 1. The patients were instructed to perform 3 maneuvers twice daily (morning and evening). The highest value on each occasion was to be recorded in the diary. The morning measurement was to be done immediately on rising; the evening measurement was to be done before going to bed and prior to inhalation of the evening dose of study drug. The variable to be measured was change from baseline (mean over the last 10 days of the run-in period) to treatment (mean over all available measurements) in both morning and evening PEF. Treatment means and treatment comparisons for change in baseline averaged over the randomized treatment period in SHINE are shown in Table 11 and Table 12; the results from SUN are shown in Table 13 and Table 14.

Table 11 SHINE: AM and PM PEF – Treatment means

			Average Over Randomized Treatment Period	
	N	Baseline value Mean (SD)	Change from Baseline LS Mean (SEM)	95% CI
Morning PEF (L/min)				
Symbicort HD	271		(b) (4)	15.45, 23.24
Symbicort LD	278	181.30 (67.87)	16.43 (1.96)	12.60, 20.27
Free combo	282	185.00 (66.96)	18.68 (1.96)	14.84, 22.52
Budesonide 160	272	177.02 (64.58)	5.25 (1.98)	1.36, 9.15
Formoterol 4.5	281	182.73 (66.19)	9.82 (1.95)	5.99, 13.65
Placebo	291		(b) (4)	-3.31, 4.20
Evening PEF (L/min)				
Symbicort HD	270		(b) (4)	11.91, 19.81
Symbicort LD	278	191.19 (70.78)	14.48 (1.98)	10.60, 18.36
Free combo	280	195.10 (70.35)	17.17 (1.99)	13.27, 21.06
Budesonide 160	272	186.11 (65.15	3.19 (2.00)	-0.74, 7.13
Formoterol 4.5	279	192.09 (67.05)	8.13 (1.98)	4.25, 12.02
Placebo	289		(b) (4)	-3.25, 4.37
(b) (4)		(D) (4)		

Source: SHINE CSR, Section 7.2.6.1, Table 54, p. 170

Table 12 SHINE: AM and PM PEF (L/min): Primary treatment comparisons for change from baseline

Comparison	Average Of Randomized Treatment Period	
	LS Mean (SEM)	95% CI, p-value
Morning PEF (L/min)		
Symbicort HD vs. Placebo	18.91(2.61)	13.79, 24.02 ($p < 0.001$)
Symbicort LD vs. Placebo	15.99 (2.59)	10.92, 21.07 ($p < 0.001$)
Evening PEF (L/min)		
Symbicort HD vs. Placebo	15.30 (2.64)	10.12, 20.48 ($p < 0.001$)
Symbicort LD vs. Placebo	13.92 (2.62)	8.78, 19.06 ($p < 0.001$)

Source: SHINE CSR, Section 7.2.6.1, Table 55, p. 171

Table 13 SUN: AM and PM PEF (L/min) – Treatment means

			Average Over Randomized Treatment Period	
	N	Baseline value Mean (SD)	Change from Baseline LS Mean (SEM)	95% CI
Morning PEF (L/min)				
Symbicort HD	487	(b) (4)		17.42, 24.80
Symbicort LD	488	183.13 (62.04)	15.90 (1.88)	12.21, 19.58
Formoterol 4.5	489	184.50 (72.74)	10.54 (1.88)	6.85, 14.23
Placebo	466	(b) (4)		-1.07, 6.43
Evening PEF (L/min)				
Symbicort HD	486	(b) (4)		13.97, 21.38
Symbicort LD	484	191.83 (64.07)	13.45 (1.89)	9.74, 17.16
Formoterol 4.5	484	193.87 (74.70)	7.86 (1.89)	4.14, 11.57
Placebo	466	(b) (4)		-1.64, 5.88

(b) (4) (b) (4)

Source: SUN CSR, Section 7.2.6.1, Table 55, p. 173

Table 14 SUN: AM and PM PEF (L/min): Primary treatment comparisons for change from baseline

Comparison	Average Of Randomized Treatment Period	
	LS Mean (SEM)	95% CI, p-value
Morning PEF (L/min)		
Symbicort HD vs. Placebo	18.42 (2.27)	13.98, 22.88 ($p < 0.001$)
Symbicort LD vs. Placebo	13.21 (2.26)	8.77, 17.65 ($p < 0.001$)
Evening PEF (L/min)		
Symbicort HD vs. Placebo	15.56 (2.27)	11.10, 20.01 ($p < 0.001$)
Symbicort LD vs. Placebo	11.33 (2.27)	6.87, 15.78 ($p < 0.001$)

Source: SUN CSR, Section 7.2.6.1, Table 56, p. 174

In terms of the primary comparisons, results indicate that both dosage strengths of Symbicort demonstrated a statistically significant change for morning and evening PEF compared with placebo in both studies. The AM and PM PEF findings are generally supportive of the primary endpoints.

Reviewer's comment: (b) (4) *The magnitude of the change is much smaller than what is reported for asthma. Further, PEF is not a measure that is usually followed for COPD patients.* (b) (4) *As a result, a more generalized statement indicating that AM and PM PEF are supportive of the primary endpoint (i.e. efficacy) may be more appropriate* (b) (4)

Breathlessness Cough Sputum Score, Sleep Score, and Rescue Medication Use

- **Breathlessness Cough Sputum Score (BCSS):** comprised of the dyspnea, cough, and sputum scores, each rated from 0-4, with higher scores indicating a more severe manifestation of symptoms.
- **Sleep score:** is also rated on a 0-4 scale with a higher score indicating greater sleep disturbance.
  Reviewer's comment: [redacted] (b) (4)
- **Rescue medication use**: is specifically referring to total daily use in puffs/day of study-provided B2-agonist rescue medication (albuterol or salbutamol).

Treatment means and treatment comparisons for each of the aforementioned secondary efficacy variables, concentrating on the primary comparison of Symbicort HD versus placebo from both SHINE and SUN are presented in Table 15 and Table 16, respectively.

Table 15 SHINE: BCSS, Sleep Score, and Rescue Medication Use: Treatment means and primary treatment comparisons for change from baseline

Comparison	Average Of Randomized Treatment Period			
	Baseline value Mean (SD)	**Change from Baseline LS Mean (SEM) [95% CI]**	**LS Mean (SEM)**	**95% CI (p-value)**
BCSS (0-12)				
Symbicort HD [N=271]	(b) (4)	[-0.83, -0.46]		
Placebo [N = 291]		[-0.50, -0.15]		
Symbicort HD vs. Placebo			-0.32 (0.12)	-0.56, -0.08 P = 0.010
Sleep Score (0-4)				
Symbicort HD [N = 269]	(b) (4)	[-0.35, -0.21]		
Placebo [N = 290]		[-0.22, -0.09]		
Symbicort HD vs. Placebo			-0.12 (0.05)	-0.21, -0.03 P = 0.007
Rescue Medication use (puffs/day)				
Symbicort HD [N = 269]	(b) (4)	[-1.41, -0.81]		
Placebo [N = 289]		[-0.57, 0.01]		
Symbicort HD vs. Placebo			-0.83 (0.20)	-1.22, -0.44 P < 0.001
(b) (4) (b) (4)				

Source: SHINE CSR, Section 7.2.6.2, Tables 56 and 57, p. 172-177.

Table 16 SUN: BCSS, Sleep Score, and Rescue Medication Use: Treatment means and primary treatment comparisons for change from baseline

Comparison	Average Of Randomized Treatment Period			
	Baseline value Mean (SD)	**Change from Baseline LS Mean (SEM) [95% CI]**	**LS Mean (SEM)**	**95% CI (p-value)**
BCSS (0-12)				
Symbicort HD [N = 489]	(b) (4)	-1.01, -0.68]		
Placebo [N = 467]		-0.54, -0.21]		
Symbicort HD vs. Placebo			-0.47 (0.10)	-0.66, -0.28 P < 0.001
Sleep Score (0-4)				
Symbicort HD [N = 489]	(b) (4)	-0.33, -0.20]		
Placebo [N = 463]		-0.16, -0.03]		
Symbicort HD vs. Placebo			-0.17 (0.04)	-0.25, -0.10 P < 0.001
Rescue Medication use (puffs/day)				
Symbicort HD [N = 490]	(b) (4)	-1.26, -0.75]		
Placebo [N = 467]		[-0.12, 0.40]		
Symbicort HD vs. Placebo			-1.15 (0.16)	-1.45, -0.84 P < 0.001

(b) (4) (b) (4)

Source: SUN CSR, Section 7.2.6.2, Tables 57 and 58, p. 175-178.

The results for COPD symptoms and rescue medication use as measured by the BCSS, Sleep score, and rescue medication use averaged over the randomized treatment period indicate Symbicort HD was statistically better than placebo in terms of all variables.

Reviewer's comment: Although statistical significance was achieved for the BCSS, Sleep Score, and rescue medication use, the clinical significance of these findings remains uncertain. Further, for the reasons stated in the previous reviewer's comment (b) (4)

6.1.5 Clinical Microbiology

Symbicort is not an antimicrobial and therefore this section is not applicable.

6.1.6 Efficacy Conclusions

Two pivotal clinical trials demonstrated the efficacy of Symbicort in patients with COPD. These trials were multicenter, randomized, double-blind, placebo-controlled, parallel group studies that were 6 and 12 months in duration, named SHINE and SUN respectively. In SHINE, patients

were assigned to one of six treatment arms: Symbicort HD BID, Symbicort LD BID, budesonide 160 mcg + 4.5 mcg formoterol in free combination BID, budesonide 2 x 160 mcg BID, formoterol 2 x 4.5 mcg BID, or placebo BID. The study consisted of an initial visit, a 2-week run-in period, 5 further visits during a 26-week treatment period, and a 4-week follow up telephone call. In SUN, patients were assigned to one of four treatment arms: Symbicort HD BID, Symbicort LD BID, formoterol 2 x 4.5 mcg BID, or placebo BID for a randomized treatment period of 52 weeks. The design was identical to that of SHINE, except that there were 7 visits over the longer treatment period. Efficacy was assessed via pulmonary function testing at each visit.

The co-primary efficacy endpoints in both studies were the change from baseline to endpoint in pre-dose FEV1, to demonstrate the anti-inflammatory contribution of budesonide, and 1-hr post-dose FEV1, to demonstrate the bronchodilator contribution of formoterol, to the efficacy of the combination product, Symbicort. Each co-primary variable was calculated as an average over the randomized treatment period. In SUN and SHINE, the primary comparison for the pre-dose FEV1 endpoint was between each of the Symbicort groups and formoterol. In SHINE, the primary comparisons for the post-dose FEV1 endpoint was between each of the Symbicort groups and budesonide alone. For post-dose FEV1, results indicate that both dosage strengths of Symbicort demonstrated a statistically significantly greater increase from baseline when compared with budesonide. These results demonstrated that formoterol contributes to the efficacy of the combination product. These results were supported by the SUN study, however, this 12 month study did not include a budesonide group for comparison, so the primary comparison was between the Symbicort treatment groups and placebo. Symbicort HD showed superiority over formoterol for pre-dose FEV1 in both pivotal studies, demonstrating the contribution of the higher dose of budesonide to the efficacy of the combination product. Symbicort HD also showed superiority over budesonide in SHINE and over placebo in SUN for post-dose FEV1, demonstrating the contribution of formoterol to the efficacy of the combination product. Symbicort LD failed to show the contribution of the inhaled corticosteroid to the efficacy of the combination product.

Key secondary endpoints were defined by the Applicant as dyspnea (as measured by the Breathlessness Diary), the St. George's Respiratory Questionnaire (SGRQ), and COPD exacerbations. COPD exacerbations, as defined by the applicant, occurred at a numerically lower rate in both pivotal studies. The SGRQ and Breathlessness Diary were also generally supportive of the efficacy of Symbicort. However, for various reasons, including failure to meet minimal clinically important differences, issues with the instrument, or concerns regarding endpoint definition, these key secondary variables (b) (4) Other secondary variables that were measured included serial FEV1 measurements, morning and evening peak expiratory flow (PEF), COPD symptoms (rescue medication use, cough, sputum, and sleep score. These secondary variables were generally supportive of the efficacy of Symbicort.

In conclusion, findings from two pivotal COPD studies (SUN and SHINE) support the efficacy of Symbicort HD therapy for the long-term treatment of airway obstruction in patients with COPD, including chronic bronchitis and emphysema.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety was assessed in the two pivotal studies with reports of deaths, adverse events, laboratory values, vital signs, and physical exams. Equal emphasis was placed on each study throughout the course of this review. Additional safety information regarding effect on ophthalmologic exam, bone mineral density, and 24-hour Holter monitoring was provided in the SUN (12 month) study only. A total of 3668 subjects received randomized treatment in the two pivotal trials with 1546 patients receiving Symbicort: 1302 (84.2%) of these subjects were treated for at least 24 weeks and 720 subjects (46.6%) were treated for more than 50 weeks.

In general, analysis of the safety results revealed that Symbicort has a similar safety profile in patients with COPD as was known for asthma patients with the exception that COPD patients treated with Symbicort 160/4.5 had a greater incidence of lung infections other than pneumonia. The incidence of pneumonia was not increased in the Symbicort groups relative to the formoterol or placebo treatment arms.

7.1.1 Deaths

There were 26 deaths reported during the randomized treatment period in two pivotal trials: 6 in the Symbicort HD group, 10 in the Symbicort LD group, 2 in the budesonide group, 3 in the formoterol group, and 5 in the placebo group. No deaths were reported in the budesonide + formoterol co-administration group during the randomized treatment period. Nineteen of the 26 deaths were reported in the non-US regions, and 7 were reported in the US region. The most frequent reported SAE leading to death was COPD: 3 subjects in the Symbicort LD group and 1 subject in the budesonide group. All 4 deaths occurred due to COPD exacerbations. Other causes of death included cardiac and malignancy-related SAEs.

Overall, there were relatively few deaths in this study, considering the severity of COPD in the study population and the presence of co-morbid conditions. Review of the narratives and the causes of death did not suggest a particular safety signal.

7.1.2 Other Serious Adverse Events

Table 17 Most commonly reported non-fatal SAEs with onset during the randomized treatment period, by MedDRA PT; pooled SHINE and SUN

MedDRA Preferred Term	Treatment , Number (%) of subjects						
	SYMB (all) (N=1546)	SYMB HD (N=771)	SYMB LD (N = 775)	Bud/Form (N = 287)	Budesonide (N = 275)	Formoterol (N = 779)	Placebo (n = 781)
Mean exposure (days)	253.4	255.2	251.6	164.6	157.1	240.3	223.7
Subjects with any SAE	205 (13.3)	108 (14.0)	97 (12.5)	26 (9.1)	26 (9.5)	111 (14.2)	83 (10.6)
COPD	98 (6.3)	52 (6.7)	46 (5.9)	13 (4.5)	10 (3.6)	50 (6.4)	40 (5.1)
Pneumonia	13 (0.8)	6 (0.8)	7 (0.9)	2 (0.7)	3 (1.1)	9 (1.2)	13 (1.7)
Atrial Fibrillation	9 (0.6)	2 (0.3)	7 (0.9)	0	2 (0.7)	4 (0.5)	2 (0.3)
Bronchitis	7 (0.5)	1 (0.1)	6 (0.8)	0	0	2 (0.3)	0
Angina Pectoris	1 (0.1)	1 (0.1)	0	1 (0.3)	0	4 (0.5)	1 (0.1)
Coronary artery disease	3 (0.2)	2 (0.3)	1 (0.1)	0	0	3 (0.4)	1 (0.1)
Acute myocardial infarction	3 (0.2)	1 (0.1)	2 (0.3)	0	1 (0.4)	2 (0.3)	0
Cardiac failure	4 (0.3)	2 (0.3)	2 (0.3)	0	2 (0.7)	0	0
Respiratory failure	2 (0.1)	0	2 (0.3)	1 (0.3)	0	2 (0.3)	1 (0.1)
Aortic aneurysm	2 (0.1)	0	2 (0.3)	0	1 (0.4)	2 (0.3)	0

Source: Module 5, ISS, Table 23, p. 89

Results in Table 17 show that the percentage of subjects with any SAEs during the randomized treatment period was similar across the Symbicort and formoterol groups, but slightly higher than placebo. COPD was the most common SAE, but occurred in a similar percentage of patients across treatment groups. Other events occurred in only a few patients or did not show a consistent pattern (e.g. dose ordering) to suggest a safety signal. Review of the narratives for the non-fatal SAEs does not suggest a new safety signal for Symbicort.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The pooled disposition data from both SUN and SHINE is presented in Table 18 below.

Table 18 SUN and SHINE: Subject disposition

Disposition	Treatment , Number (%) of subjects						
	SYMB (all) (N=1546)	SYMB HD (N=771)	SYMB LD (N = 775)	Bud/Form (N = 287)	Budesonide (N = 275)	Formoterol (N = 779)	Placebo (n = 781)
Number (%) of subjects							
Completed	1192 (77.1)	598 (77.6)	594 (76.6)	239 (83.3)	212 (77.1)	561 (72.0)	529 (67.7)
Discontinued	354 (22.9)	173 (22.4)	181 (23.4)	48 (16.7)	63 (22.9)	218 (28.0)	252 (32.3)
Reasons for discontinuation							
Eligibility criteria not fulfilled	22 (1.4)	13 (1.7)	9 (1.2)	4 (1.4)	2 (0.7)	18 (2.3)	13 (1.7)
AE	166 (10.7)	81 (10.5)	85 (11.0)	14 (4.9)	26 (9.5)	99 (12.7)	93 (11.9)
Not willing to continue	100 (6.5)	47 (6.1)	53 (6.8)	14 (4.9)	26 (9.5)	99 (12.7)	93 (11.9)
Lost to follow-up	28 (1.8)	13 (1.7)	15 (1.9)	6 (2.1)	4 (1.5)	13 (1.7)	20 (2.6)
Other	38 (2.5)	19 (2.5)	19 (2.5)	10 (3.5)	10 (3.6)	24 (3.1)	22 (2.8)

Source: Module 5, ISS, Table 10, page 46.

Overall, the percentage of subjects who completed the study was higher in the Symbicort groups compared with placebo. The most common reason for discontinuation was the occurrence of an AE. The overall discontinuation rate was much higher in the US (Symbicort 33.4%, Placebo 47.1%) than in non-US countries (Symbicort 13.9%, Placebo 20.9%), which may reflect differences in clinical practice.

7.1.3.2 Adverse events associated with dropouts

There was a total of 371 discontinuations due to adverse events (DAEs) during randomized treatment. A summary of the most commonly reported DAEs by PT in both SHINE and SUN is presented in Table 19.

Table 19 SUN and SHINE: Most commonly reported MedDRA PTs for DAEs

MedDRA Preferred Term	Treatment , Number (%) of subjects						
	SYMB (all) (N=1546)	SYMB HD (N=771)	SYMB LD (N = 775)	Bud/Form (N = 287)	Budesonide (N = 275)	Formoterol (N = 779)	Placebo (n = 781)
Mean exposure (days)	253.4	255.2	251.6	164.6	157.1	240.3	223.7
Subjects with any DAE	155 (10.0)	75 (9.7)	80 (10.3)	13 (4.5)	25 (9.1)	93 (11.9)	85 (10.9)
COPD	68 (4.4)	28 (3.6)	40 (5.2)	11 (3.8)	16 (5.8)	57 (7.3)	44 (5.6)
Dyspnea	10 (0.6)	4 (0.5)	6 (0.8)	0	1 (0.4)	4 (0.5)	11 (10.9)
Bronchitis	3 (0.2)	2 (0.3)	1 (0.1)	1 (0.3)	1 (0.4)	2 (0.3)	4 (0.5)
Pneumonia	1 90.1)	1 (0.1)	0	0	1 (0.4)	1 (0.1)	7 (0.9)
Oral Candidiasis	5 (0.3)	2 (0.3)	3 (0.4)	0	1 (0.4)	0	1 (0.1)
Cardiac failure, congestive	2 (0.1)	1 (0.1)	1 (0.1)	0	2 (0.7)	1 (0.1)	1 (0.1)
Cough	1 (0.1)	0	1 (0.1)	0	0	2 (0.3)	2 (0.3)
Fatigue	2 (0.1)	1 (0.1)	1 (0.1)	0	2 (0.7)	1 (0.1)	0
Ventricular Extrasystoles	4 (0.3)	1 (0.1)	3 (0.4)	0	0	1 (0.1)	0
Myocardial infarction	3 (0.2)	0	3 (0.4)	0	0	1 (0.1)	0

Source: Module 5, ISS, Table 24, page 92.

Reviewer's comment: Although no definitive conclusions can be drawn from this data, it is notable that the most discontinuations for COPD related adverse events occurred in the formoterol groups in both studies. In SHINE, the incidence of discontinuations in the formoterol treatment arm due to COPD was more than twice that of the Symbicort arms. This difference was not as great in the 12 month study, so pooling of the data dilutes this result somewhat. . This finding is of interest given the information we know about LABAs in asthma.

The overall incidence of subjects with DAEs during randomized treatment was similar across treatment groups. The most frequently reported DAE was COPD, which was less frequent in the Symbicort HD group compared to other treatment groups. This profile of discontinuation due to adverse events does not suggest a new safety signal for Symbicort in COPD.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In both SUN and SHINE, an adverse event was defined as "the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product."

Adverse events were collected by means of a standard question: "Have you had any health problems since the previous visit?" The question was put to each subject in the local language at the beginning of each visit, starting with Visit 2, but after completion of the SGRQ. The subject's response to this question and spontaneously reported and/or observed AEs were recorded in the CRF with information about seriousness, action taken, date of onset, stop date, maximum intensity, causality assessment and outcome. Subjects were provided with a diary card to record study variables. It was the investigator's responsibility to review the diary card with the subject and transfer any indications of AEs to the AE form.

COPD symptoms or signs such as bronchitis, cough, phlegm, increased sputum, dyspnea, and wheeze were defined in the clinical study protocol as disease under study events and were to be reported as adverse events if: the sign or symptom was serious according to definitions, the subject discontinued the study due to the sign or symptom, and/or the sign/symptom was new to the subject or not consistent with the subject's pre-existing COPD history, as judged by the investigator. Additional adverse events of interest, which were specific categories of interest potentially associated with ICS and/or beta-agonist medications were also tabulated. The following events of interest were defined:

- Events representing typical and potential steroid class effects, subcategorized as:
    - Local effects: aphonia, dysphonia, oral candidiasis, and thrush
    - Systemic steroid effects: weight gain, adrenal suppression, ocular effects, skin effects, psychiatric disorders, diabetes control, thirst, taste effects, and bone effects
    - Pneumonia and potential lung infections other than pneumonia: due to findings in 2 recent studies (1-3) of the fluticasone/salmeterol combination in subjects with COPD that indicated a higher rate of pneumonia in all groups receiving ICS

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The nomenclature for reported clinical AEs was standardized using the Medical Dictionary for Regulatory Activities (MedDRA) Version 10 (i.e., the version used in SUN, the last study to report data during the clinical development program for COPD). AEs coded in earlier versions of MedDRA were recoded using MedDRA Version 10.

7.1.5.3 Incidence of common adverse events

The adverse event profile of Symbicort HD and LD was reviewed in studies SUN and SHINE.

Overall, report of AEs was 62.4% in the Symbicort HD group and 60.6% in the Symbicort LD group, versus 53.8% in the placebo group. The most commonly reported AEs (>3%) were COPD, nasopharyngitis, oral candidiasis, bronchitis, sinusitis, viral upper respiratory tract infection, and pneumonia. All AEs with the exception of pneumonia, occurred with greater frequency in the Symbicort treatment groups compared to placebo. The number of subjects with oral candidiasis was higher in the Symbicort HD and LD groups compared to formoterol and

placebo, with a dose-ordered response observed for budesonide. When interpreting these results, it is important to note that more patients discontinued from the placebo group. This differential discontinuation may contribute to the greater number of AEs observed in the Symbicort groups. In summary, the AEs noted are not unusual for a COPD patient population. See Table 20.

7.1.5.4 Common adverse event tables

Table 20 Most commonly reported AEs (≥ 3%) during randomized treatment , by MedDRA PT; pooled SHINE and SUN

MedDRA Preferred Term	Treatment , Number (%) of subjects						
	SYMB (all) (N=1546)	SYMB HD (N=771)	SYMB LD (N = 775)	Bud/Form (N = 287)	Budesonide (N = 275)	Formoterol (N = 779)	Placebo (n = 781)
Mean exposure (days)	253.4	255.2	251.6	164.6	157.1	240.3	223.7
Number (%) of subjects							
Total	951 (61.5)	481 (62.4)	470 (60.6)	142 (49.5)	158 (57.5)	460 (59.1)	420 (53.8)
COPD	230 (14.9)	103 (13.4)	127 (16.4)	30 (10.5)	34 (12.4)	133 (17.1)	112 (14.3)
Nasopharyngitis	111 (7.2)	56 (7.3)	55 (7.1)	12 (4.2)	9 (3.3)	45 (5.8)	38 (4.9)
Oral Candidiasis	74 (4.8)	46 (6.0)	28 (3.6)	8 (2.8)	12 (4.4)	9 (1.2)	14 (1.8)
Bronchitis	71 (4.6)	42 (5.4)	29 (3.7)	15 (5.2)	13 (4.7)	35 (4.5)	27 (3.5)
Sinusitis	55 (3.6)	27 (3.5)	28 (3.6)	9 (3.1)	4 (1.5)	24 (3.1)	14 (1.8)
Viral Upper Respiratory Tract Infection	56 (3.6)	27 (3.5)	29 (3.7)	3 (1.0)	5 (1.8)	28 (3.6)	21 (2.7)
Pneumonia	39 (2.5)	18 (2.3)	21 (2.7)	3 (1.0)	5 (1.8)	20 (2.6)	26 (3.3)

Source: Module 5, ISS, Table 15, page 65.

7.1.5.5 Identifying common and drug-related adverse events

The adverse events noted were typical of what is seen in COPD studies. It is often difficult to determine if the adverse events are drug-related, or related to the underlying disease process (i.e. COPD, bronchitis). Oral candidiasis is a known adverse event of inhaled corticosteroid use, and the incidence of this adverse event was of typical frequency in this development program.

7.1.6 Less Common Adverse Events

Pneumonia-related preferred terms and "potential lung infection other than pneumonia" containing preferred terms that could represent lower respiratory infections were evaluated due

to findings in 2 recent studies of the fluticasone/salmeterol combination in subjects with COPD that indicated a higher rate of pneumonia in all groups receiving fluticasone (1-3).

A summary of events of interest representing pneumonia-related events during randomized treatment for the Phase 3A studies is presented in Table 21; lung infections other than pneumonia are presented in Table 22.

Table 21 Pneumonia adverse events by MedDRA preferred term during randomized treatment; pooled SHINE and SUN

MedDRA Preferred Term	Treatment , Number (%) of subjects						
	SYMB (all) (N=1546)	SYMB HD (N=771)	SYMB LD (N = 775)	Bud/Form (N = 287)	Budesonide (N = 275)	Formoterol (N = 779)	Placebo (n = 781)
Mean exposure (days)	253.4	255.2	251.6	164.6	157.1	240.3	223.7
All Pneumonia events	47 (3.0)	23 (3.0)	24 (3.1)	3 (1.0)	5 (1.8)	22 (2.8)	28 (3.6)
Pneumonia	39 (2.5)	18 (2.3)	21 (2.7)	3 (1.0)	5 (1.8)	20 (2.6)	26 (3.3)
Bronchopneumonia	4 (0.3)	2 (0.3)	2 (0.3)	0	0	1 (0.1)	2 (0.3)
Lobar pneumonia	2 (0.1)	2 (0.3)	0	0	0	0	0
Pneumonia staphylococcal	2 (0.1)	1 (0.1)	1 (0.1)	0	0	0	0
Pneumonia pneumococcal	0	0	0	0	0	1 (0.1)	0

Source: Module 5, ISS, Table 27, page 99.

Overall the incidence of pneumonia related events ranged from 1.0-3.6% across treatment groups. The incidence of pneumonia was numerically lower in both Symbicort treatment groups (HD and LD: 3.0%) versus placebo (3.6%). Among pneumonia-related events, there were 47 subjects with events assessed as serious (9 each in Symbicort HD and LD, 2 in budesonide + formoterol, 3 in budesonide, 11 in formoterol, and 14 in placebo) and 13 subjects with DAEs (2 in Symbicort HD, 1 in Symbicort LD, 1 in budesonide, 2 in formoterol, and 7 in placebo).

Table 22 Potential lung infections other than pneumonia by MedDRA preferred term during randomized treatment; pooled SHINE and SUN

MedDRA Preferred Term	Treatment , Number (%) of subjects						
	SYMB (all) (N=1546)	SYMB HD (N=771)	SYMB LD (N = 775)	Bud/Form (N = 287)	Budesonide (N = 275)	Formoterol (N = 779)	Placebo (n = 781)
Mean exposure (days)	253.4	255.2	251.6	164.6	157.1	240.3	223.7
All events	**104 (6.7)**	**61 (7.9)**	**43 (5.5)**	**18 (6.3)**	**17 (6.2)**	**48 (6.2)**	**40 (5.1)**
Bronchitis	71 (4.6)	42 (5.4)	29 (3.7)	15 (5.2)	13 (4.7)	35 (4.5)	27 (3.5)
Lower respiratory tract infection viral	13 (0.8)	6 (0.8)	7 (0.9)	0	2 (0.7)	5 (0.6)	3 (0.4)
Lower respiratory tract infection bacterial	11 (0.7)	9 (1.2)	2 (0.3)	2 (0.7)	1 (0.4)	5 (0.6)	5 (0.6)
Bronchitis bacterial	2 (0.1)	1 (0.1)	1 (0.1)	0	0	3 (0.4)	2 (0.3)
Lower respiratory tract infection	3 (0.2)	2 (0.3)	1 (0.1)	1 (0.3)	0	1 (0.1)	1 (0.1)
Obstructive chronic bronchitis with acute exacerbation	2 (0.1)	1 (0.1)	1 (0.1)	0	0	1 (0.1)	1 (0.1)
Tracheobronchitis	3 (0.2)	0	3 (0.4)	0	0	0	0
Bronchitis chronic	1 (0.1)	1 (0.1)	0	0	0	1 (0.1)	1 (0.1)
Sinobronchitis	1 (0.1)	0	1 (0.1)	0	0	0	1 (0.1)
Lung Infection	0	0	0	0	1 (0.4)	0	0
Sputum purulent	0	0	0	0	0	1 (0.1)	0

Source: Module 5, ISS, Table 28, page 100.

Results in Table 22 demonstrate that potential lung infections other than pneumonia were numerically higher in the Symbicort HD group (7.9%) versus placebo (5.1%). The most common potential lung infection was bronchitis in all treatment groups, occurring more frequently in the Symbicort HD group (5.4%) versus placebo (3.5%).

Among these potential lung infections, there were 15 subjects with events assessed as serious (3 in Symbicort HD, 9 in Symbicort LD, 3 in formoterol, and none reported in the other treatment groups) and 18 subjects with DAEs (3 in Symbicort HD, 2 in Symbicort LD, 1 in budesonide plus formoterol, 1 in budesonide, 6 in formoterol, and 5 in placebo).

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Blood and urine samples for determination of hematology, clinical chemistry, and urinalysis parameters were taken at baseline and endpoint. HPA-axis assessment was evaluated in a subset of patients from both the SUN and SHINE studies and is described in Section 7.1.12.

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

Routine laboratory results were reviewed for each of the submitted studies. HPA axis function was assessed in a subset of patients in both studies.

7.1.7.3 Standard analyses and explorations of laboratory data

In each of the two Phase 3 studies (SUN and SHINE), there were no clinically relevant mean changes from baseline within the Symbicort groups or mean differences between treatment groups for hematology and other clinical chemistry assessments. Although some small differences were identified among treatment groups in the percentage of subjects with shifts from baseline using the potentially significant and significant range limits, there were no significant increases in the percentage of subjects with potentially significant or significant abnormalities in the Symbicort groups for hematology or any of the clinical chemistry assessments. There were small changes in mean serum glucose and potassium levels from baseline in each treatment group and small differences across treatment groups. The percentage of subjects with potentially significant or significant abnormalities relating to an increase in serum glucose or decrease in serum potassium was low and generally similar for Symbicort groups compared to its mono-products and to placebo. Urinalysis was performed in both Phase 3 studies. In these 2 studies, the percentage of subjects with abnormalities was generally low, with similar incidences noted across treatment groups.

7.1.7.5 Special assessments

<u>Holter Monitor Recordings</u>
A total of 520 subjects from the SUN study were included in the Holter monitoring subset. The data from changes in mean values across treatments, shift table results, and physician blinded review of all abnormal Holter results were reviewed. For change in mean values across treatments, there were increases in ventricular ectopy (VE, beats/hour) and heart rate for the formoterol-containing treatment groups at Cmax. However, the differences between treatment groups was not clinically important (Symbicort HD: 15.8, Symbicort LD: 22.7, Formoterol 15.6, placebo: 5.4). The findings for supraventricular ectopy (SVE) were not consistently related to formoterol-containing treatment groups.

For VE rate, the percentage of subjects with shifts from normal at baseline to high on-treatment values was highest in the Symbicort HD group (18.6%) and lowest in the placebo group (12.2%). For SVE rate, the percentage of subjects with shifts from normal at baseline to high on-treatment values was highest for Symbicort LD (16.0%) and lowest for placebo (10.8%). For SVE, shift from normal to high was lowest in the placebo group (8.9%) and highest in the formoterol group (16.8%). For overall Holter assessment, the percentage of subjects with normal assessment at baseline who shifted to abnormal at treatment maximum was highest in the formoterol group (30.9%) and other treatment groups were similar, ranging from 23.0% to 23.7%.

The number and percentage of subjects with specific Holter findings were slightly increased in the Symbicort HD group (33, 6.7%), Symbicort LD group (39, 7.9%), and formoterol 4.5 (40, 8.1%), compared with placebo (27, 5.6%) The increase was driven by the increased supraventricular and ventricular ectopic hourly rate categories. Flags that could indicate new atrial fibrillation were infrequent and balanced across treatment groups. Overall, there was no new safety signal seen.

Bone Mineral Density Assessment

A total of 326 patients from the SUN study had baseline and post-baseline BMD results and were included in the BMD analysis subset. Total lumbar spine BMD was the primary variable to be analyzed, while total hip BMD was the secondary variable. Mean baseline BMD values were similar across all treatment groups for each of the spine and hip regions. Mean changes in BMD from baseline to end of treatment were very close to zero for each of the treatment groups for both spine and hip regions (mean changes ranged from –0.01 to 0.01). ANCOVA results for total spine and total hip BMD based on the end of treatment time point showed that all geometric LS Mean ratios for the pairwise treatment group comparisons were close to 1. Statistically significant differences by ANCOVA were seen between Symbicort HD and each of the other treatment groups for total lumbar spine BMD, and between Symbicort HD and formoterol 4.5 for total hip BMD. However, the geometric LS Mean ratio was either 0.99 or 0.98 for these treatment group comparisons with a 95% confidence interval upper limit of 1.00.

No subjects in any treatment group presenting with a normal BMD T-score at baseline shifted to the osteoporosis category at the end of treatment for either the hip or spine regions. There were 14 subjects who had normal BMD T-scores at baseline (spine) who shifted to the osteopenia category and 11 subjects (hip) who shifted to the osteopenia category at end of treatment, and there were no treatment group differences. Additionally, there were 3 subjects with total hip BMD T-score shifts from the osteopenia category at baseline to the osteoporosis category at the end of treatment, and 9 subjects with total spine BMD T-score shifts from the osteopenia category at baseline to the osteoporosis category at the end of treatment. The numbers of subjects exhibiting categorical shifts were distributed similarly across the 4 treatment groups.

Bone mineral density results for total hip and total spine regions for the 12-month time point were similar to the end of treatment results presented above. Overall, across all treatment groups, bone mineral density for total hip and total spine regions for the 12 month time point were stable over the entire 1-year treatment period.

Ophthalmologic Exams

A total of 461 patients from the SUN study were included in the ophthalmology analysis set. The 4 separate lenticular opacity assessments ([nuclear opalescence (NO), nuclear color (NC), cortical cataract (C), and posterior subcapsular (P)] along with intraocular pressure measurements were to be conducted at baseline, 6 months, and 12 months. Results for posterior subcapsular (P) only are presented here as the most accurate measure of lenticular opacification associated with the use of corticosteroids.

The LS mean change from baseline to end of treatment for posterior subcapsular and intraocular pressures were small for each treatment group. The ANCOVA results in Table 57 showed a statistically significant difference in the treatment group LS Mean changes from baseline for Symbicort HD vs. Symbicort LD ($p = 0.022$). No other treatment group comparisons were statistically significant for posterior subcapsular or intraocular pressure.

In examining the shifts of individual patients from baseline to end of treatment, the percentage of patients with changes in IOP from ≥10 to ≤20 mm Hg at baseline to >20 mm Hg at the end of treatment was highest in the Symbicort HD group (11%) and lowest in the Symbicort LD groups (3%). In the Symbicort HD group, 9 of the 13 subjects had actual intraocular pressure changes of ≤ 4 mm Hg. Overall, changes from 10 to 20 mmHg, inclusive, at baseline to >20 mmHg at the end of randomized treatment in intraocular pressure considered clinically important (i.e. ≥5mmHg) were few and showed no association with a particular treatment.

There were 26 of 461 subjects (6%) with an increase in the posterior subcapsular score from baseline to the maximum value during the randomized treatment period of ≥0.7 (i.e. a worsening of 0.7 or more, a change of ≥0.7 is considered clinically important). Changes in posterior subcapsular scores of ≥0.7 from baseline to treatment maximum occurred more often in the Symbicort HD group (11 subjects, 9%), and least often in the Symbicort LD group (4 subjects, 4%). Results were similar for the end of treatment. Review of these subjects did not reveal any consistent commonalities among subjects exhibiting posterior subcapsular changes of ≥0.7.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs, including systolic and diastolic blood pressures, pulse rate, BMI, and weight, were analyzed using change from baseline. Results of the ANCOVA analysis of mean change from baseline in these parameters showed no clinically meaningful differences between treatment groups at the end of treatment.

Shift table results were used to categorize the change from baseline for systolic and diastolic blood pressure and pulse rate. In general, the percentage of subjects shifting into either low or high categories was low. For systolic blood pressure at treatment maximum, there were small increases in the percentage of subjects in the Symbicort and formoterol 4.5 groups with shifts from normal to high values compared with placebo. There were no clinically meaningful

treatment group differences for the percentage of subjects with shifts from normal to either high or low for diastolic blood pressure, or for pulse rate at any time point or at maximum throughout treatment.

7.1.9 Electrocardiograms (ECGs)

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

Twelve-lead ECGs were obtained pre-dose and 30 to 60 minutes after administration of the morning dose of study drug in all subjects in the Phase 3 studies. The timing of the post-dose measurements corresponds to the time of peak sustained pharmacodynamic effects of formoterol. Assessments were obtained at protocol-specified visits (baseline and Months 2 and 6 in SHINE, and baseline and Months 2, 6 and 12 in SUN). Change from baseline refers to changes from the last pre-dose value before the first dose of randomized study drug. In the two pivotal studies, there were 1544 Symbicort subjects assessed with 5028 ECGs performed during treatment. The number of ECGs per subject was similar for the Symbicort, formoterol, and placebo groups.

7.1.9.4 Additional analyses and explorations

Mean changes in QRS and PR intervals from baseline were small, and not clinically meaningful. There were no clinically relevant treatment group differences when change from baseline was assessed for these parameters. Small increases from baseline in heart rate were noted at treatment maximum in all treatment groups. There were no significant differences in heart rate at treatment maximum across treatment groups. For QT, QTcB and QTcF, LS mean change from baseline at treatment maximum showed moderate increases across all treatment groups. There were some statistically significant between-group differences; however, these differences were small and not clinically meaningful.

Shift data analysis of the ECGs showed that the percentage of subjects with shifts from normal to abnormal at treatment maximum in the Symbicort treatment groups was slightly higher than placebo (16.7% vs. 12.3%.) and similar to formoterol (17.7%).

Assessment of outliers revealed that for QRS duration, the percentage of subjects who met change criteria of an increase of at least 30 msec from baseline or had values that crossed the extended reference range of >120 msec (or both) was lowest in the placebo group, but was similar across all other treatment groups. For PR interval, the percentage of unique subjects who met change criteria of an increase of at least 40 msec from baseline or had values that crossed the extended reference range of >220 msec (or both) at any time during the study was low and similar across all treatment groups. For heart rate, a similar percentage of subjects in the Symbicort HD group crossed the high threshold (>100 bpm) or met the change criteria (increase of at least 20 bpm) relative to the formoterol 4.5 and placebo treatment groups. For QT, the percentage of subjects with potentially significant findings (values that crossed the high

threshold [450 msec] or with changes ≥30 msec) was slightly higher in the Symbicort treatment groups compared to the formoterol 4.5 and placebo treatment groups, with the majority of subjects manifesting changes ≥30 msec. For QTcB, the percentage of subjects with potentially significant findings was similar across treatment groups and for QTcF, the percentage of subjects with potentially significant findings was slightly higher in all formoterol-containing treatment groups compared to placebo.

Overall, the ECG changes described are typical of the beta agonist class of medications, and are described in the current product label. These findings do not suggest a new safety signal.

7.1.10 Immunogenicity

Immunogenicity is not applicable for an inhaled corticosteroid/long-acting beta-agonist combination product.

7.1.11 Human Carcinogenicity

Carcinogenicity was not formally assessed in this COPD efficacy supplement, but it was examined in the original clinical development program. Per the approved product label, in a 2-year carcinogenicity study in Sprague Dawley rats, In a 2-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In two additional 2-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). However, in the male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings.
In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (approximately equal to the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

In a 24-month carcinogenicity study in Sprague-Dawley rats, an increased incidence of mesovarian leiomyoma and uterine leiomyosarcoma were observed at the inhaled dose of 130 mcg/kg (approximately 60 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No tumors were seen at 22 mcg/kg (approximately 10 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

7.1.12 Special Safety Studies

HPA-axis function in COPD patients was assessed by measuring 24-hour urinary free cortisol (24h-UFC) in a subgroup of subjects in both SUN (179 subjects) and SHINE (437 subjects) studies. In both studies, 24-hour urine specimens were collected at baseline (prior to randomization), at Month 6 (SUN and SHINE), and at Month 12 (SUN). Urine samples were analyzed for urinary free cortisol and creatinine. Creatinine levels were measured to adjust for variations in urine volume by expressing results as the 24-hour urinary cortisol/creatinine ratio.

Urinary free cortisol and cortisol:creatinine ratio were analyzed using a multiplicative ANCOVA. The multiplicative ANCOVA model involved the natural logarithm of the values on treatment, adjusting for the factors of the natural logarithm of the baseline value, country, and treatment group.

The following high-level conclusions can be drawn from the combined 24h-UFC data collected from the two Phase 3 studies (SUN and SHINE):

1. Both higher and lower strengths of Symbicort exhibited measurable suppression of 24h-UFC levels following chronic twice daily inhalation administration in COPD patients relative to placebo. While the cortisol suppression of 30% from Symbicort 160/4.5 mcg was statistically significant (p=0.001), 17% suppression from Symbicort 80/4.5 mcg did not achieve statistical significance (p=0.102). This suggests a dose-dependent response in the budesonide dose range of 160 to 320 mcg following twice daily administration.

2. Symbicort 160/4.5 exhibited comparable cortisol suppression to budesonide 160 mcg alone treatment or free combination of budesonide 160 mcg and formoterol 4.5 mcg.

[Source: Dr. Partha Roy, Clinical Pharmacology Review, sNDA 21-929, December 23, 2008]

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No special studies to investigate withdrawal phenomena and/or abuse potential were provided nor warranted for this efficacy supplement.

7.1.14 Human Reproduction and Pregnancy Data

Symbicort is currently labeled as “Teratogenic Effects: Pregnancy Category C”.
There are no adequate and well-controlled studies with Symbicort or formoterol in pregnant women. No pregnancies were reported in the COPD clinical development program.

7.1.15 Assessment of Effect on Growth

No studies were submitted nor warranted to assess the effect of Symbicort on growth for this COPD efficacy supplement.

7.1.16 Overdose Experience

There were no case reports of overdose in COPD subjects in either of the pivotal phase 3 studies. Per the approved product label, Symbicort HD was tolerated for up to 12 months at doses up to twice the highest recommended daily dose. The potential for acute toxic effects following overdose with budesonide is low. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur. Budesonide at five times the highest recommended dose (3200 mcg daily) administered to humans for 6 weeks caused a significant reduction in the plasma cortisol response. An overdose of formoterol would likely lead to an exaggeration of effects that are typical for beta-agonist medications. Formoterol was well-tolerated at a delivered dose of 90 mcg/day over 3 hours in adult patients with acute bronchoconstriction and when given three times daily for a total dose of 54 mcg/day for 3 days to stable asthmatics.

7.1.17 Post-marketing Experience

Symbicort was first approved for use in the US for the treatment of asthma on July 21, 2006. As of December 2007, Symbicort has been licensed for use in 5 countries for the treatment of asthma. As of September 6, 2006, Symbicort has been licensed for use in Venezuela for the treatment of COPD. Symbicort has been marketed in the US since June 25, 2007. As of December 2007, Symbicort has not been marketed in any additional countries.

As of December 2007, the post-marketing experience for Symbicort has been estimated to be approximately (b) (4) treatment days. An overview of all post-marketing reports received by the applicant through December 31, 2007 revealed 372 reports (29 serious reports, 343 non-serious reports). Of the serious reports, there were a total of 52 serious events, which included bronchospasm, urticaria, asthma, cardio-respiratory arrest, dizziness, tachycardia, tremor, and vision blurred. There were 4 post-marketing reports of death. Three reports concerned patients ≥ 12 years of age (and in one case was ≥ 65 years and had received treatment for COPD). In one case, the patient was < 12 years of age. The causes of death were severe asthma exacerbation, food aspiration, morphine toxicity, and GI hemorrhage. In summary, 3 of the 4 patients with a fatal outcome had asthma; the fourth patient had COPD. One of the 4 reports described a pediatric patient. In the 3 adult reports, alternative explanations for the patients deaths were identified.

The most frequently reported AEs occurred in the respiratory, thoracic, and mediastinal disorders system organ class. When analyzed by preferred term, the most frequently reported post-marketing AEs were tremor, palpitations, cough, headache, dyspnea, and feeling jittery. Of these symptoms, most are well known reactions associated with the use of inhaled beta-agonists, or are related to the underlying disease. Overall there is no information in the post-marketing database that identifies any new safety issues.

7.2 Adequacy of Patient Exposure and Safety Assessments

The designs of the studies in this application, patient demographics, exposure of sub-populations, and duration of exposure to Symbicort are sufficient to allow for an assessment of safety.

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

7.2.1.1 Study type and design/patient enumeration

Table 1 provides a summary of the studies that comprise the clinical development program. This table includes descriptive information on study type, treatment groups, design, patient population, subject numbers, dosing schedule, and indication.

7.2.1.2 Demographics

Demographic and baseline characteristics for the 3668 randomized subjects in both the pivotal trials are summarized by treatment in Table 23.

Table 23 SHINE and SUN: Patient demographics

	SYMB Total	SYMB HD	SYMB LD	BUD + Formoterol	Budesonide	Formoterol	Placebo
N	1546	771	775	287	275	779	781
Male (N and %)	987 (63.8)	496 (64.3)	491 (63.4)	213 (74.2)	186 (67.6)	509 (65.3)	521 (66.7)
Race (N and %)	1440 (93.1)	718 (93.1)	722 (93.2)	264 (92.0)	259 (94.2)	719 (92.3)	725 (92.8)
Caucasian	49 (3.2)	22 (2.9)	27 (3.5)	14 (4.9)	8 (2.9)	21 (2.7)	19 (2.4)
Black	2 (0.1)	1 (0.1)	1 (0.1)	2 (0.7)	1 (0.4)	6 (0.8)	3 (0.4)
Oriental	55 (3.6)	30 (3.9)	25 (3.2)	7 (2.4)	7 (2.5)	33 (4.2)	34 (4.4)
Other							
Age (years)							
Mean (SD)	63.38 (9.03)	63.15 (8.95)	63.6 (9.12)	63.72 (8.99)	63.44 (8.80)	63.14 (9.28)	63.01 (9.32)
Min	40	40	40	40	40	41	40
Max	90	86	90	84	90	89	86
Age group (n, %)	833 (53.9)	422 (54.7)	411(53.0)	147 (51.2)	154 (56.0)	426 (54.7)	432 (55.3)
40 to 65	540 (34.9)	276 (35.8)	264 (34.1)	110 (38.3)	85 (30.9)	264 (33.9)	254 (32.5)
65 to 75	173 (11.2)	73 (9.5)	100 (12.9)	30 (10.5)	36 (13.1)	89 (11.4)	95 (12.2)
> 75 yrs							
Baseline % predicted FEV1 Mean (SD)	33.93 (11.44)	33.7 (11.89)	34.16 (10.99)	33.55 (10.8)	33.54 (10.84)	33.64 (11.4)	34.65 (10.59)
Post-BD % predicted FEV1 (N and %)	338 (21.9)	191 (24.8)	147 (19.0)	67 (23.3)	62 (22.5)	189 (24.3)	142 (18.2)
	930 (60.2)	443 (57.5)	487 (62.8)	167 (58.2)	160 (58.2)	439 (56.4)	482 (61.7)
<30%	274 (17.7)	136 (17.6)	138 (17.8)	53 (18.5)	51 (18.5)	148 (19.0)	152 (19.5)
30-50%	1 (0.1)	0	1 (0.1)	0	1 (0.4)	2 (0.3)	3 (0.4)
50-80%	3 (0.2)	1 (0.1)	2 (0.3)	0	1 (0.4)	1 (0.1)	2 (0.3)
≥ 80%							
Missing							
Pack Years							
Mean (SD)	46.08 (26.37)	44.78 (24.48)	47.36	48.3 (29.90)	47.46 (26.07)	46.06 (24.98)	46.55 (29.19)
Min, Max	10, 210	10, 184	10, 210	10, 188	10, 171	10, 165	10, 225

Source: . Module 5, Integrated Summary of Safety, Table 12, page 53.

The majority of the subjects were male (65.9%) and Caucasian (92.9%). The mean age was 63 years, with 34.2% of the subjects aged 65 to <75 years and 11.5% aged ≥ 75 years. COPD severity (as graded by post-bronchodilator % predicted FEV1) and smoking history were fairly similar across treatment groups. The overall study population in the phase 3 studies included a representative number of subjects with a history of co-morbid conditions (not shown in table), which included hypertension (42%), lipid profile abnormalities (23%), cardiac disease (18%), diabetes mellitus 911%), osteoporosis/osteopenia (9%0, cataracts 95%) and atrial fibrillation/arrhythmia (4%). Overall, there were no significant differences in most baseline

demographic characteristics among the treatment groups that would adversely impact the interpretation of safety results.

7.2.1.3 Extent of exposure (dose/duration)

The 2 pivotal studies included 3668 COPD patients who received randomized treatment. Among these subjects, 1546 received treatment with Symbicort: 1442 (93.3%) for ≥8 weeks, 1302 (84.2%) for at least 6 months (i.e., ≥24 weeks), and 720 (46.6%) for approximately 1 year (i.e., >50 weeks). Duration of exposure differed between the 2 studies, as 1 study (SHINE) evaluated 6 months of treatment and the other (SUN) evaluated 12 months of treatment. The duration of exposure is summarized by treatment in Table 24.

Table 24 SHINE and SUN: Duration of exposure

	SYMB Total	SYMB HD	SYMB LD	BUD + Formoterol	Budesonide	Formoterol	Placebo
N	1546	771	775	287	275	779	781
n (%) of subjects							
>0 to ≤4 weeks	50 (3.2)	29 (3.8)	21 (2.7)	5 (1.7)	15 (5.1)	39 (5.0)	81 (10.4)
>4 to ≤8 weeks	57 (3.7)	25 (3.2)	32 (4.1)	10 (3.5)	11 (4.0)	45 (5.8)	46 (5.9)
>8 to ≤14 weeks	62 (4.0)	31 (4.0)	31 (4.0)	15 (5.2)	17 (6.2)	42 (5.4)	28 (3.6)
>14 to ≤24 weeks	76 (4.9)	36 (4.7)	40 (5.2)	21 (7.3)	17 (6.2)	39 (5.0)	49 (6.3)
>24 to ≤50 weeks	581 (37.6)	284 (36.8)	297 (38.3)	236 (82.2)	216 (78.5)	271 (34.8)	272 (34.8)
>50 weeks	720 (46.6)	366 (47.5)	354 (45.7)	0	0	343 (44.0)	305 (39.1)
Days on treatment							
Mean (SD)	253.4 (115.70)	255.2 (116.22)	251.6 (115.21)	164.6 (40.27)	157.1 (51.31)	240.3 (123.74)	223.7 (129.08)
Median	225.5	273.0	197.0	180.0	181.0	188.0	183.0
Min	1	1	1	1	1	1	1
Max	415	415	406	197	215	393	397
Total days of exposure	391716	196751	194965	47240	43216	187208	174679

Source: . Module 5, Integrated Summary of Safety, Table 11, page 49.

Mean exposure was highest and similar in both Symbicort treatment groups, followed by the formoterol group, and lowest in placebo. The proportion of subjects who discontinued within the first 4 weeks of treatment was higher in the placebo and formoterol 4.5 groups, compared to the Symbicort groups. Overall, the numbers of subjects exposed to Symbicort met the International Conference on Harmonization (ICH) Guidance E1 for extent of population exposure to assess clinical safety.

7. 2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary clinical data sources were used to evaluate the safety of Symbicort in COPD patients.

7.2.3 Adequacy of Overall Clinical Experience

The study number, design, and duration are sufficient to assess the efficacy and safety of Symbicort in patients with COPD. Both studies were double-blind, randomized, and placebo controlled. All of the subjects had an appropriate diagnosis of COPD for at least 2 years and had been using inhaled corticosteroids for at least 30-60 days prior to Screening. Change in pre-dose and 1-hour post-dose FEV1, accepted measures to evaluate the efficacy ICS and beta agonists in COPD, respectively, were used as the co-primary efficacy variables. The statistical analysis was appropriate. In addition, there were an adequate number of subjects exposed to the drug, although racial subsets were small to allow for an adequate assessment of safety in these subgroups.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal or in vitro studies were performed for this COPD efficacy supplement.

7.2.5 Adequacy of Routine Clinical Testing

Adverse events were collected daily and reviewed by the investigators at all clinic visits, as were vital signs. Routine laboratory testing was performed at baseline and endpoint in both studies. Given that both budesonide and formoterol are in well-characterized pharmaceutical classes about which there is extensive information, and that Symbicort is an approved product with significant post-marketing experience, the degree of safety monitoring is adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

These areas of evaluation were not necessary for this COPD efficacy supplement.

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

As Symbicort is not a new molecular entity or a new drug, this section is not applicable to this efficacy supplement.

7.2.8 Assessment of Quality and Completeness of Data

The quality of data available for a safety review was generally adequate. Narrative, CRTs, and CRFs were available, accessible, and complete.

7.2.9 Additional Submissions, Including Safety Update

7.2.9.1 4-month Safety Update (August 2008)

The 4-month safety update summarizes safety information received by the Applicant between Sept 7, 2007 and April 30, 2008 for the ongoing COPD study as well as safety information that has been reported through the AstraZeneca Global Drug Safety Database between January 1, 2008 and April 30, 2008. In addition, a literature search has been conducted to identify any relevant safety information published from January 1, 2008 through April 30, 2008 that relates to the use of Symbicort in patients with COPD.

There is one on-going Symbicort phase 3 study included in this 4-month safety update. Study D589CC00003 is a Phase 3B, 12-month, double-blind, double-dummy, randomized, parallel-group, multicenter exacerbation study of Symbicort HD, Symbicort LD, and formoterol in patients with COPD. As Study 00003 is ongoing, all safety data are preliminary in nature and still blinded to the treatment each subject received. Case report forms for fatal and non-fatal serious adverse events and discontinuations due to adverse events are not included in this safety update. A total of 1200 subjects are planned for randomization into Study 0003; during the reporting period of this safety update, 588 COPD patients have been randomized. The most-commonly reported post-enrollment adverse events (>2% of subjects) were COPD, headache, bronchitis, nasopharyngitis, sinusitis, and supper respiratory tract infection. These are similar to what was observed in the pivotal phase 3 trials submitted to support registration. The most commonly reported SAEs were COPD (42 events), pneumonia (20 events), bronchitis (3 events) and dyspnea (3 events). The reported SAEs are consistent with what has been reported during the clinical development program for COPD. There have been 12 deaths during the course of study 0003 thus far. Six of the twelve deaths were respiratory-related (including acute respiratory failure, emphysema, respiratory failure, COPD, COPD exacerbation, hospital-acquired pneumonia). The post-marketing AEs reported during the 4-month safety update period were consistent with the overall expected safety profile for inhaled beta-agonists, inhaled glucocorticoids, and/or were associated with the underlying disease. A search of the medical literature did not identify any new or relevant safety information in patients receiving Symbicort off-label for the treatment of COPD, bronchitis, or emphysema. In summary, there are no new safety signals noted in the 4-month safety update.

7.2.9.2 Periodic Safety Update Report (October 2008)

The periodic safety update report (PSUR) summarizes the safety information received by the Applicant from worldwide sources between August 25, 2007 and August 24, 2008. Of relevance to the current development program, a review of lower respiratory tract infections and pneumonia in asthma and COPD is provided in this PSUR.

In seven COPD clinical studies analyzed by the Applicant for either Symbicort or Pulmicort, there were 4 (0.11%) deaths due to pneumonia, 58 (1.5%) pneumonia SAEs, and a total of 152 (4.0%) pneumonia AEs. The incidence of pneumonia in all cases was similar to or less than that of the placebo or non-ICS group. Overall, the incidence of pneumonia events was low, and there was no increased reporting rate of pneumonia events in patients treated with budesonide compared with patients that were not ICS treated. Because the reporting of lower respiratory tract infections were not handled consistently across studies, the Applicant cautions pooling of the results of these studies. However, per the Applicant's analysis, no obvious imbalance was detected in the incidence of LRTIs between budesonide and non-ICS treated patients.

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

The adverse event profile of Symbicort has been characterized in asthmatic patients 12 years of age and older. These adverse events are listed in the currently approved product label and include nasopharyngitis, headache, upper respiratory tract infection, pharyngolaryngeal pain, sinusitis, influenza, back pain, nasal congestion, stomach discomfort, vomiting, and oral candidiasis.

In the COPD patient population, the adverse events occurring most commonly include nasopharyngitis, oral candidiasis, bronchitis, sinusitis, and viral upper respiratory tract infection. Known local AEs associated with inhaled corticosteroids, such as oral candidiasis, were seen with expected incidence in these studies. Pneumonia-related preferred terms and other lung infections were evaluated in both the pivotal studies due to recent findings in studies with salmeterol/fluticasone in subjects with COPD that indicated a higher rate of pneumonia in all groups receiving ICS. For pneumonia-related preferred terms, no clinically important differences were seen between treatment groups. However, when the incidence of "potential lung infections other than pneumonia" were evaluated, there was a higher incidence in those groups treated with budesonide as compared with placebo. In SUN, there was a numerical trend towards increased lung infections with higher doses of steroids.

Since market introduction in June 2007, subject exposure to Symbicort is estimated to be about (b) (4) subject treatment days as of the end of December 2007. During this period, a total of 52 serious events have been reported. The most frequently reported post-marketing serious adverse events included bronchospasm (3 cases), urticaria (3 cases), asthma, cardio-respiratory arrest, dizziness, tachycardia, tremor, and blurred vision (all in 2 cases). There were four post-marketing reports of death (status asthmaticus, choking/food aspiration, morphine toxicity, and GI bleed and cardiac ischemia) that occurred in patients that were intermittently on Symbicort, but alternative explanations for the patient's deaths were identified.

To summarize, "lung infections other than pneumonia", including events such as bronchitis, lower respiratory tract infection (viral and bacterial), may be a new safety signal noted with Symbicort in COPD patients. No other new safety concerns arose from the review of the data in COPD patients as compared with what has been reported in the Symbicort product label and other ICS/LABA combination products.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Data were pooled across studies, as the dosing regimens examined in each study were the same.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Two doses were examined in both the pivotal clinical studies submitted in this application. Overall, there were no meaningful difference in adverse events with increasing doses of budesonide within the combination product, Symbicort.

7.4.2.2 Explorations for time dependency for adverse findings

In general, there were more adverse events reported in the 52-week safety trial than in the 6 month trial. This is not unexpected as longer exposure generally results in more adverse events being reported. No other relevant effect of duration of exposure was noted on incidence of adverse findings in this development program.

7.4.2.3 Explorations for drug-demographic interactions

There were no significant differences noted in adverse events when subsets were analyzed according to age, sex, and race.

7.4.2.4 Explorations for drug-disease interactions

No specific drug-disease interactions were assessed in this COPD clinical development program for Symbicort.

7.4.2.5 Explorations for drug-drug interactions

Explorations for drug-drug interaction were not conducted during this COPD development program.

7.4.3 Causality Determination

There were no unusual or rare adverse events that required a causality determination. All of the common adverse events observed were those commonly seen in this class of drug, in this patient population, and in this mode of administration.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

A dose of 320/9 mcg BID (2 actuations of the 160/4.5 dosage strength) is recommended for the (b) (4) maintenance treatment of airflow obstruction in patients with COPD, including bronchitis and emphysema.

8.2 Drug-Drug Interactions

The Applicant did not conduct any new investigations specifically evaluating drug-drug interactions as part of this supplemental NDA.

8.3 Special Populations

The Applicant did not conduct any new investigations specifically targeted towards any special populations as part of this supplemental NDA.

8.4 Pediatrics

(b) (4) Symbicort is already approved for children 12 years of age and older. The applicant has requested and has been granted a waiver for studies in children < 4 years of age.

8.5 Advisory Committee Meeting

A Pulmonary Allergy Advisory Committee was neither held nor required for this efficacy supplement.

8.6 Literature Review

Other than the study reports already included in this application, there were no additional relevant published reports when this reviewer searched the MEDLINE database on November 20, 2008.

8.7 Post-marketing Risk Management Plan

A Medication Guide (MG) will be required and updated to include the new safety information regarding the increased incidence of lower respiratory tract infections with the use of Symbicort in COPD patients. Also, the Applicant will be required to have a Risk Evaluation and Mitigation Strategy (REMS), in which the Applicant will need to evaluate the effectiveness of the MG and provide an assessment regarding whether the MG is being dispensed. These activities will be required in addition to routine pharmacovigilance.

9 OVERALL ASSESSMENT

9.1 Conclusions

9.2 Recommendation on Regulatory Action

The regulatory action recommended for this application is **Approval**.

9.3 Recommendation on Post-marketing Actions

None.

9.3.1 Risk Management Activity

A Medication Guide (MG) will be required and updated to include the new safety information regarding the increased incidence of lower respiratory tract infections with the use of Symbicort in COPD patients. Also, the Applicant will be required to have a Risk Evaluation and Mitigation Strategy (REMS), in which the Applicant will need to evaluate the effectiveness of the MG and provide an assessment regarding whether the MG is being dispensed. These activities will be required in addition to routine pharmacovigilance.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

This reviewer performed a line-by-line review of the product label as submitted by the Applicant in the new PLR format. Most changes made to the format of the label were made in order to harmonize the Symbicort PLR label with the recently approved Advair label in PLR format. As of the completion of this review, line-by-line revision of the product label is ongoing. The following preliminary comments communicated with the Applicant on December 12, 2008 outline the major changes we have made in the label:

The FDA-proposed revisions to your draft labeling for Symbicort have been made using the clean copy of the word version of the label submitted on April 28, 2008. In the revised labeling, FDA insertions are underlined and deletions are strike-out. Be advised that these labeling changes are not the Agency's final recommendations and that certain sections of the Package Insert (in particular Clinical Pharmacology) are still under review. Additional labeling changes will be forthcoming as the label continues to be reviewed. FDA-proposed changes to the Medication Guide and Patient Instructions for Use will be sent to you in a subsequent fax. We have the following comments

1. We note that throughout the package insert you have [(b) (4)] with chronic obstructive disease (COPD) [(b) (4)] asthma. Revise the label placing asthma first followed by COPD throughout the label, since asthma was the first disease studied, and COPD is an add-on indication to the already approved Symbicort product.

2. Several changes in the label (Warnings and Precautions, Clinical Trials Experience) and general changes related to drug class and indications were made throughout the label to harmonize the Symbicort label with the new Advair Diskus label in PLR format.

The following comments pertain to specific sections of the package insert

Section 1: Indications and Usage

- Revise this section so that Asthma is [(b) (4)] and COPD [(b) (4)]

Section 2: Dosage and Administration

- This section was revised to follow the format and content of Advair Diskus label
- Information that has been struck out is not appropriate in this section per the new PLR format and has been moved to more appropriate sections.
- Section 2.3 Geriatric Use in COPD and Asthma is not required as there is no recommended dosing adjustment.

Section 3: Dosage Forms and Strengths

Information that has been struck out has been moved to the How Supplied section of the label.

Section 5: Warnings and Precautions

- Section 5.5 "Pneumonia and Other Lung Infections." Although – the Symbicort COPD studies did not show a pneumonia signal, the Agency considers pneumonia to be a class effect of corticosteroids in COPD. The Symbicort COPD program showed an increase in "Lung infections other than pneumonia) and data from both SHINE and SUN studies (tables 11.3.2.6.14) have been incorporated into the text.
- Section 5.6 Immunosuppression: The paragraph regarding the open label study on responsiveness to varicella vaccine was relocated here from the Drug-Drug interaction section as it is more appropriate here under "Immunosuppression" where the issue of varicella and VZIG is discussed per class labeling.
- Section 5.9: Drug Interactions with Strong Cytochrome P450 3A4 inhibitors) is under review.
- Section 5.13: Reduction in Bone Mineral Density: The study results from the SUN (12 month) study are described in more detail.
- Section 5.15: Glaucoma and Cataracts : The study results from the SUN (12 month) study are presented in more detail.

Section 6: Adverse Reactions

- Revise this section as per our comment #1 so that (b) (4) is Asthma and (b) (4) COPD
- Revise the adverse reactions for the COPD program into short term (6 month) and long-term, and revise the table to present the adverse reactions for the short term (6 month) study only.

Section 8: Use in Special Populations

Revise section 8.5 to comply with the regulatory language in 21 CFR 201.57 (b) (9) (v)

Section 14: Clinical Studies

- Revise the format so that asthma is (b) (4) and COPD is (b) (4)
- For the COPD section, please fill in the appropriate data where "XX" is denoted.
- The (b) (4) because a definition of COPD exacerbation based solely on a change in therapy is inadequate to assess this endpoint. Furthermore, the results were not replicated, as the result was not statistically significant in the 6 month study.
- Th (b) (4)
- (b) (4) a general statement regarding their supportiveness added.
- Additional changes to the Clinical trial section – specifically the inclusion of figure 3 and 4 and the acute bronchodilation response language in the COPD studies are under review.

Section 16: How Supplied/Storage and Handling

- Information from Dosage Forms and Strengths section of the label has been moved to this section.

Section 17: Patient Counseling Information

- This section was revised to be consistent with Advair Diskus.

9.5 Comments to Applicant

This reviewer has no comments to the Applicant at the time of completion of this review.

10 APPENDICES

10.1 Individual Study Report: Study D5899C0002 (SHINE)

Protocol #:	D5899C0002
Title:	A 6-Month Double-blind, Double-dummy, Randomized, Parallel group, Multicenter Efficacy & Safety Study of SYMBICORT pMDI 2 x 160/4.5 mcg & 80/4.5 mcg BID Compared to Formoterol TBH, Budesonide pMDI (& the combination) & placebo in COPD Patients (SHINE)
Study Dates:	Initiated April 4, 2005. Completed December 28, 2006.
Sites:	123 centers in the U.S. 12 centers in South Africa. 30 centers in Poland. 11 centers in the Netherlands. 18 centers in the Czech Republic.
Investigator:	Donald P. Tashkin University of California, Los Angeles (UCLA) Division of Pulmonary and Critical Care Medicine

Reviewer's Comment: For the purposes of this review, the following notations will be used:

- *Symbicort HD or Symbicort 320/9 mcg will be used to denote 2 actuations of the 180/4.5 mcg device*
- *Symbicort LD or Symbicort 160/9 mcg will be used to denote 2 actuations of the 80/4.5 mcg device*
- *Formoterol 9 mcg will be used to denote 2 actuations of the 4.5 mcg Turbuhaler (TBH) device*
- *Budesonide 320 mcg will be used denote 2 actuations of the 160 mcg device*

10.1.1 Study Design/Protocol

The objective of this study was to demonstrate the efficacy and safety of Symbicort for the maintenance treatment of patients with COPD compared to its mono-products and placebo.

Objectives

The **primary objectives** of this study in hierarchical order were:

- Comparison of Symbicort 320/9 mcg BID vs. Formoterol 9 mcg BID – Pre-dose FEV1
- Comparison of Symbicort 320/9 mcg BID vs Budesonide 320 mcg BID – Post-dose FEV1
- Comparison of Symbicort 160/9 mcg BID vs. Formoterol 9 mcg BID - Pre-dose FEV1
- Comparison of Symbicort 160/9 mcg BID vs. Budesonide 320 mcg BID – Post-dose FEV1

The **secondary objectives** of the study were:

- Comparison of Symbicort 320/9 mcg BID vs. placebo – Pre-dose FEV1 and Post-dose FEV1
- Comparison of Symbicort 160/9 mcg BID vs. placebo - Pre-dose FEV1 and Post-dose FEV1

Pertinent **secondary variables** to be measured included:

- Dyspnea using Breathlessness Diary
- Health-related quality of life as measured by SGRQ total score
- Number of COPD exacerbations

Other **secondary variables** to be measured included:

- Serial FEV1 – onset of effect and maintenance of effect at 12 hours (in a subgroup of patients)
- FVC
- Morning and evening PEF
- Inspiratory capacity (pre dose and 1 hour post-dose) (in a sub-group of patients)
- COPD symptoms (excluding dyspnea which is listed above)
    - Rescue medication use (B2 agonists)
    - Cough
    - Sputum
    - Night-time awakenings (sleep score)
- Health care utilization

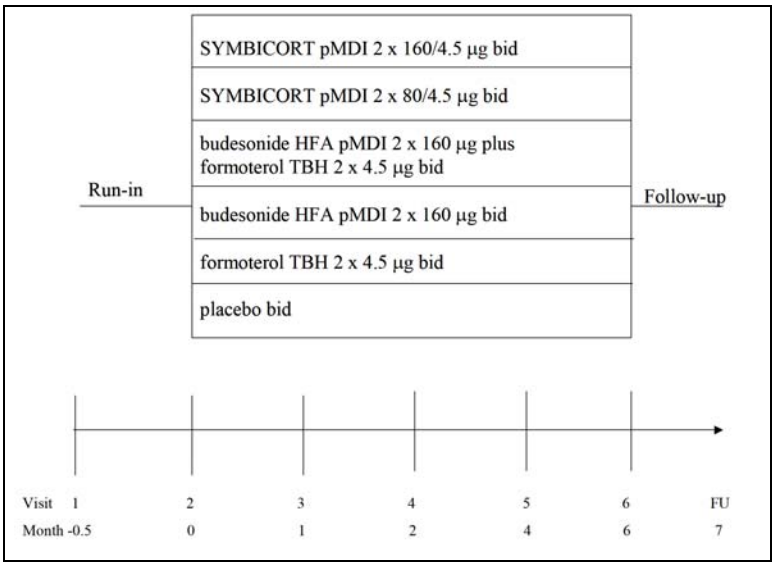
Safety objectives of the study included measurement of:

- Adverse Events (AEs)
- Laboratory Evaluation (Hematology/Chemistry/Urinalysis/24 hour urinary free cortisol)
- 12-lead ECGs
- Vital Signs
- Physical Examination

Description

SHINE was a double-blind, double-dummy, randomized, parallel group, multicenter study in patients with COPD, 6 months (26 weeks) in duration, in which patients were assigned to one of six treatment arms (see Figure **11**).

Figure 11 SHINE, Study Design Diagram



The study consisted of an initial visit, a 2 week-run in period, 5 further visits during a 26-week treatment period and a 4-week follow-up telephone call. Prior to Visit 1, fixed dose combination therapy was to be replaced with a comparable dose of ICS monotherapy and a short-acting inhaled B2 agonist. Patients using either long-acting beta agonists or anticholinergics were to be converted to a short-acting bronchodilator of the same class. Between Visits 1 and 2, patients were allowed to continue use of inhaled steroids and/or short-acting inhaled bronchodilators. At Visit 2, treatment with ICS was to be discontinued, and all eligible patients were randomized to receive one of the six study treatments listed in

Figure **11**. In addition, at Visit 2, all patients will also be given albuterol/salbutamol pMDI rescue medication to be used as required for the relief of bronchospasm. The study schedule is depicted in Table 25.

Table 25 SHINE: Study schedule

Study plan	Run-In	Treatment					FU[a]
Month	**-0.5**	**0**	**1**	**2**	**4**	**6**	**7**
Visit	**1**	**2**	**3**	**4**	**5**	**6[b]**	**FU**
Informed consent[c]	x						
Demography	x						
Medical and smoking use	x						
Inclusion/exclusion criteria	x	x					
Full physical examination	x					x	
Brief physical examination		x	x	x	x		
Vital signs	x[d]	x[e]	x	x	x	x[e]	
Clinical chemistry, hematology & urinalysis	x					x	
Pregnancy test	x					x	
24-hour urine collection[f] (I=issue, C=collect)	I	C			I	C	
PK sampling[f]			x				
ECG		x				x	
Reversibility Test	x						
Lung function (FEV_1, FVC)	x	x[g]	x[g]	x[g]	x[g]	x[g]	
Serial FEV_1 and IC[f]		x	x				
Adverse events		x	x	x	x	x	x
Concomitant medication	x	x	x	x	x	x	x
SGRQ	x	x[h]	x[h]	x[h]		x[h]	
Resource utilization		x	x	x	x	x	x
Diary card (I=issue, R=return and review)	I	I/R	I/R	I/R	I/R	R	
Dispense peak flow meter and instruct in use	x						
Randomization		x					
Study drug (D=dispense, R=return)		D		D/R	D/R	R	
Genetic sampling[i]		x					
Informed consent for genetic sampling[i]	x						

a Follow-up telephone contact
b To be completed by patients that prematurely discontinue
c Signed and dated informed consent may be obtained at an information visit prior to Visit 1
d Including height
e Including weight
f Tests to be performed in a subgroup of patients
g Pre-dose and 1 hour post-dose
h SGRQ performed before all other assessments

Population

Approximately 1250 patients were to be randomized from 150 centers from the US and other countries. The patients enrolled were to be of either sex, ≥ 40 years of age with a FEV_1 ≤ 50% of predicted normal value pre-bronchodilator, have FEV_1/FVC <70% pre-bronchodilator, a clinical diagnosis of COPD with symptoms for ≥ 2 years, current or previous smoker with a smoking

history of ≥10 pack years, score of ≥ 2 on the MMRC dyspnea scale, a total symptom score (based on breathlessness, cough and sputum) of ≥ 2 per day for at least half of the run-in period, a history of at least one COPD exacerbation requiring a course of oral steroids within 1-12 months before Visit 1, use short-acting inhaled bronchodilator (B_2-agonists or anticholinergics) as rescue medication, no history of asthma, and no history of allergic rhinitis before 40 years of age.

- Summary of Inclusion Criteria
  1. Outpatients, men or women ≥ 40 years of age
  2. A clinical diagnosis of COPD with symptoms for more than 2 years
  3. A current or previous smoker with a smoking history ≥ 10 pack years.
  4. Pre-bronchodilator FEV1 ≤ 50% of predicted.
  5. Pre-bronchodilator FEV1/FVC ≤ 70% of predicted.
  6. Documented use of short-acting inhaled bronchodilator (B2-agonists or anticholinergics) as rescue medication.
  7. A score of ≥ 2 on the Modified Medical Research Council dyspnea scale (MMRC)
  8. A history of at least one COPD exacerbation requiring a course of oral steroids and/or antibiotics within 1-12 months before Visit 1 (i.e., not within the 30 days prior to Visit 1
  9. Breathlessness-cough-sputum total symptom score (BCSS) of 2 or more per day for at least half of the run-in period, as measured at Visit 2.

- Summary of Exclusion Criteria
  1. A history of asthma (NAEPP 2003)
  2. A history of allergic rhinitis prior to 40 years of age
  3. Known alpha-1-antitrypsin deficiency
  4. Patients who have needed additions or alterations to their usual maintenance or rescue therapy for COPD due to worsening symptoms within the 30 days prior to Visit 1.
  5. Patients taking oral or ophthalmic non-cardioselective beta-blocking agents.
  6. Patients taking oral steroids.
  7. Patients who have participated in a COPD rehabilitation program within 6 months prior to the study or who are scheduled for such a program during the study.
  8. Known or suspected hypersensitivity to the study drugs including excipients.
  9. Scheduled in-patient hospitalization during the course of the study.
  10. Pregnancy, breastfeeding, or planned pregnancy during the study. Fertile women not using acceptable contraceptive measures, as judged by the investigator. Female patients who are not post-menopausal or surgically sterile must have a negative pregnancy test prior to randomization.

- Discontinuation Criteria
  1. Voluntary discontinuation
  2. Investigator discretion
  3. Incorrect enrollment or randomization
  4. Pregnancy
  5. Requirement for chronic oral corticosteroid treatment

6. Requirement to adjust existing cardioselective beta-blocking therapy
7. Alterations or adjustment to maintenance or rescue therapy for COPD due to worsening symptoms between Visits 1 and 2.

Of note, patients discontinued due to deterioration of COPD were to be recorded as an adverse event.

Treatments

- Study Treatments

Table 26 SHINE: Study Treatments		
Treatment Group	**Dosage Strength (mcg)**	**Dosing Regimen**
Symbicort HD (budesonide/FF)	160/4.5	2 x 160/4.5 mcg BID = **320/9 mcg BID**
Symbicort LD (budesonide/FF)	80/4.5	2 x 80/4.5 mcg BID = **160/9 mcg BID**
Budesonide HFA	160	2 x 160 mcg BID = **320 mcg BID**
Formoterol DPI (Oxis Turbuhaler)	4.5	2 x 4.5 mcg BID = **9 mcg BID**
Placebo pMDI + Placebo Turbuhaler	N/A	**2 x pMDI + 2 x TBH BID**

Reviewer's Comment: In general, we do not advise the use of mono-comparator in a different formulation and delivered by a different device, as is the case here with the OXIS Turbuhaler. However, in the original NDA for asthma, the Applicant has provided a PK/PD bridging study that demonstrates the comparability of the formoterol dose delivered by the OXIS TBH and Symbicort. Therefore, the use of this mono-product was accepted by the Division at the time of the original NDA review, and still remains acceptable for this program.

To maintain the double-dummy blinding of study medication, subjects randomized to active treatment delivered by a pMDI device also received placebo delivered by a TBH device, and vice versa. Rescue medications of albuterol/salbutamol were also provided.

- Permitted Therapies

The following medications were permitted from Visit 1 and throughout the study:

- Antitussives prn not containing ephedrine or other bronchodilators
- Mucolytics not containing ephedrine
- Nasal steroids
- Ipratropium at a stable dose throughout the study if the patient has been on this treatment before the study
- Oral or ophthalmic cardioselective beta-blocking agents if that patient has been on a constant dose for the 6 months prior to Visit 1 without evidence of bronchospasm.

The following medications were permitted between Visit 1 and Visit 2:

- Inhaled steroids and/or short acting bronchodilators (beta-agonists and/or anticholinergics)

Prior to Visit 1, fixed dose combination therapy (ICS and beta agonists) were to be replaced with a comparable dose of ICS monotherapy and a short-acting inhaled beta-agonist. Patients using

long-acting beta agonists and/or anticholinergics were to be converted to a short acting bronchodilator of the same class.

The following medications were permitted for exacerbations after Visit 2 and throughout the study:

- Oral steroids (30 to 40 mg/day for 7 to 14 days) i.e., prednisolone/prednisone
- Parenteral steroids (single injections but not depot formulations). Each day of parenteral steroids will account for a day of the allowed 7- to 14-day course of oral steroids
- Acute use of xanthines and/or increased use of inhaled b2-agonists and ipratropium
- Nebulized treatment with b2-agonists and ipratropium.

- Excluded Therapies

The following drugs were to be withdrawn prior to Visit 1 and withheld throughout the study (See Table 27).

Table 27 SHINE: Excluded therapies

Drug	Time of withdrawal prior to Visit 1
Long acting anticholinergics ie, tiotropium (Spiriva®)	48 hours
Inhaled long-acting β_2-agonists Note: If the β_2-agonist is combined with an inhaled GCS in the same device (eg, SYMBICORT, Advair®, Seretide®), the patient has to stop treatment with the combined product and continue with an inhaled GCS monoproduct at a comparable steroid dose.	48 hours
Inhaled short-acting β_2-agonists (except albuterol or salbutamol as required for relief of bronchospasm) Note: If the β_2-agonist is combined with an anticholinergic in the same device (eg, Combivent®), the patient has to stop treatment with the combined product and continue with ipratropium (ie, Atrovent®) and albutamol/salbutamol as required.	6 hours
Oral β_2-agonists: Short-acting Slow release	 6 hours 24 hours
Ephedrine-containing medication	48 hours
Leukotriene antagonists (eg, Accolate® and Singulair®) and 5-lipoxygenase inhibitors (eg, Zyflo®)	48 hours
Xanthine-containing derivatives, once daily	48 hours
Xanthine-containing derivatives, twice daily	24 hours

- Compliance

Patients were required to enter data in the diary card regarding the use of study and rescue medications. These data were monitored to assess patients' compliance. Patients with a

compliance rate of less than 80% were to be counseled by the investigator and monitored for possible withdrawal from the study.

Efficacy Assessments

Primary Efficacy Endpoints

- Pre-dose FEV1 – to assess the contribution of budesonide (ICS)
- Post-dose FEV1- to assess the contribution of formoterol (LABA)
  - Separate mean FEV1 (for both pre-dose and 1 hour post-dose measurements) was calculated for each patient for the treatment period (Visit 3 to 6) as follows:

    $$\text{Mean FEV1} = \frac{\sum \text{Available FEV1 measurements over the treatment period}}{\text{\# of available FEV1 measurements}}$$
  - The change from baseline to the mean of FEV1 was calculated for both pre-dose and 1 hour post-dose measurements:

    Change in FEV1 = Mean FEV1 – Baseline FEV1

Secondary Efficacy Endpoints

- Patient-Reported Outcomes (PROs)
  - St. George's Respiratory Questionnaire (SGRQ)
    1. Contains 3 domains: Symptoms (8 questions), Activity (16 questions), Impacts (26 questions)
    2. Self-administered during clinic Visits 1, 2, 3, 4, and 6
    3. Secondary outcome variable: the change in mean total scores from Visit 2 to Visit 6. The domain scores were to be handled in the same way.

  - Diary cards: to be completed by the patient each day and reviewed by investigator at each visit. Variables recorded:
    1. AM and PM PEF

    A Mini-Wright peak flow meter was dispensed at Visit 1. The patients were instructed to perform 3 maneuvers twice daily (morning and evening). The highest value on each occasion was to be recorded in the diary. The morning measurement was to be done immediately on rising; the evening measurement was to be done before going to be and prior to inhalation of the evening dose of study drug. The variable to be measured was change from baseline (mean over the last 10 days of the run-in period) to treatment (mean over all available measurements) in both morning and evening PEF.

    2. B2-agonist or ipratropium use prior to PEF measurement

    3. Breathlessness diary (prior to evening dose)

    Patients were asked daily to evaluate their breathlessness on a 5-point Likert-type scale, ranging from 0-4, with higher scores indicating a more severe manifestation of the symptom. The content of the rating system is as follows:
    HOW MUCH DIFFICULT DID YOU HAVE BREATHING TODAY?

0 = none – unaware of any difficulty
1= Mild – noticeable during strenuous activity (eg, running)
2= Moderate – noticeable during light activity (eg, bed making)
3 =Marked – noticeable when washing or dressing
4= Severe – almost constant present even when resting
The variable to be calculated based on this scale was the mean breathlessness score over the treatment period.

4. Cough scores (prior to evening dose)
Patient were asked daily to evaluate their cough based on the following scale:
HOW WAS YOUR COUGH TODAY?
0 = No cough – unaware of coughing
1 = Rare – cough now and then
2 = Occasional – less than hourly
3 = Frequent – one or more times an hour
4 = Almost constant – never free of cough or need to cough
The variable to be calculated from this data was the mean cough score over the treatment period.

5. Sputum scores (prior to evening dose)
Patient were asked daily to evaluate their sputum based on the following scale:
HOW MUCH TROUBLE WAS YOUR SPUTUM TODAY?
0 = none – unaware of any difficulty
1 = Mild – rarely caused a problem
2 = Moderate – noticeable as a problem
3 = Marked – caused a great deal of inconvenience
4 = Severe – an almost constant problem
The variable to be calculated from this scale was the mean sputum score over the treatment period.

6. Night time awakenings (prior to morning dose)
Patients were asked daily to evaluate night time awakenings caused by symptoms of COPD, including, but not limited to dyspnea, cough or chest tightness based on the following scale:
HOW WAS YOUR SLEEP DURING THE NIGHT?
0 = Slept through the night
1 = Symptoms causing you to wake once or wake early
2 = Symptoms causing you to wake twice or more (including waking early)
3 = Symptoms causing you to wake most of the night
4 = Symptoms so severe that you did not sleep at all
The variables to be calculated from this scale were the number and percentage of nights with at least one awakening as well as the number and percentage of symptom free nights

7. Use of beta-agonist rescue medication and oral steroids
The variables to be calculated from this data were a change from baseline (mean over the last 10 days of the run-in period) in mean day-time usage, mean night-time usage, and mean daily usage over the treatment period. Use of oral steroids was to be used to define exacerbation (see Exacerbations below).

8. Hospitalization
a) Proportion of patients hospitalized and number of hospitalizations due to COPD
b) Number of hospitalization days due to COPD among patients who are hospitalized
This data was also used in the definition of exacerbation (see Exacerbations below).

❖ Health Care Economics

2. Resource utilization
a) Unscheduled health care provider visits - Proportion of patients with unscheduled healthcare provider visits due to COPD and number of such visits
b) Urgent care clinic visits - Proportion of patients with urgent care clinic visits due to COPD and number of such visits
c) Emergency room Visits - Proportion of patients with ER visits due to COPD an number of such visits
d) Total COPD cost (imputed)

❖ Exacerbations

Exacerbation was defined as worsening of COPD that at the discretion of the investigator requires a course of oral steroids for treatment and/or hospitalization. From the data regarding hospitalizations and oral corticosteroid use recorded on the diary cards, the following variables were to be derived/calculated:

- The number and percentage of patients with one or more exacerbations adjusting for the time that each patient is in the study.
- The time to first exacerbation for all patients after Visit 2 from the date of first treatment until the start of the exacerbation. Patients who did not experience an exacerbation during the treatment period had the time to their first exacerbation censored at date of last dose. Patients who withdrew prematurely without experiencing an exacerbation, also had time to first exacerbation censored at the date of withdrawal. Patients known to have had an exacerbation but for whom there was no start date recorded, had their date of first exacerbation assumed to be the date of their previous clinic visit.
- The duration of each exacerbation defined as the difference between the start and end date of exacerbation. Patients for whom there was no end date recorded had their date assumed as the date of their following clinic visit.
- The number and percentage of COPD-related hospitalizations, the total number and percentage of steroid courses used for each patient, the number and percentage of patients taking at least one oral steroid course, and the man number of days on oral steroid/patient/year.

Reviewer's comment: A COPD exacerbation as been defined solely on the basis of treatment with oral steroids and/or hospitalization. The beginning and end of an exacerbation, as well as the severity, have also not been adequately defined. (b) (4)

- Pharmacokinetic Variables
  - $AUC_{(0-t)}$: area under the curve from time zero to the last quantifiable concentration using the actual timing of blood draws
  - C_{max}: largest observed concentration after inhalation

- Pharmacodynamic/Efficacy Variables
  - FVC – the best of 3 maneuvers; mean change calculated similar to primary efficacy variables
  - Serial FEV1 – from 5 to 720 minutes in a subset of 300 patients; change from baseline will be the difference at each time point minus the value at pre-dose.
  - Inspiratory Capacity – means change calculated similar to primary efficacy variables

Safety Assessments
- Adverse Events (includes discontinuations)
- Vital Signs – blood pressure, heart rate – abnormalities analyzed descriptively
- Physical Examination
- 12 lead ECG – HR, PR/QT/RR intervals, QRS duration, T-wave morphology
- Hematology – abnormalities analyzed by descriptive statistics
- Clinical Chemistry – abnormalities analyzed by descriptive statistics
- Urinalysis
- Urine free cortisol – 24 hour urine collection in a subgroup of n = 250 patients.

Statistical Plan

Sample Size Determination

A sample size in each treatment group of 190 was considered to allow 90% power to detect a 0.10 L difference between treatments in FEV1 based on an estimated standard deviation of 0.3 L and assuming a significance level of 0.05. A sample size of approximately 250 patients per treatment arm was chosen to allow for an estimated 25% withdrawal rate.

Primary Efficacy Analysis

The primary efficacy endpoints in this study were the change from baseline to endpoint (mean over the treatment period) in 1-hr post dose and pre-dose FEV1. The contribution of formoterol to the combination was to be accomplished by demonstrating a statistically significant difference between Symbicort and budesonide for 1-hour post-dose FEV1. The contribution of budesonide to the combination was to be assessed by demonstrating a statistically significant difference between Symbicort and formoterol for pre-dose FEV1. The efficacy analysis was to be performed on the intention-to-treat (ITT) population. All primary objectives were to be considered in a hierarchical manner. Each hypothesis was to be tested at the 5% level of

significance and each hypothesis test needs to be found to be significant at 5% level before continuing to the next.

This study had 2 primary variables, pre-dose FEV1 and 1 hour post-dose FEV1 to be compared with the monotherapies and placebo at the 2 dose levels of Symbicort. Therefore, to address multiplicity, each of the 4 comparisons versus the monotherapies was performed in hierarchical order and each must have been found to be statistically significant at the 5% level in order to move onto the next comparison and declare superiority of the drug. When testing for statistical significance, the higher dose of Symbicort was first compared with the monotherapies, followed by the lower dose.

The change in pre-dose and post-dose FEV1 from Visit 2 to the average value recorded during Visits 3 to 6 were analyzed using an ANCOVA model with treatment and country as fixed factors and the Visit 2 value as a covariate. Treatment effects were to be expressed as adjusted means. The possibility of treatment by country interaction was to be investigated for both primary efficacy variables separately by including the interaction in the model. A sensitivity analysis may also have been performed for FEV1 using the average of data from Visit 4 to 6 or, in cases of early withdrawals, the last available visit.

FEV1 at each visit and the change from baseline in FEV1 at each visit was to be summarized using standard summary statistics for both pre- and post-dose FEV1 separately. The mean FEV1 over the 6 month treatment period were to be calculated for each patient as the mean of available values and summarized along with the change from baseline in mean FEV1 by treatment group using standard summary statistics. The adjust means and 95% confidence intervals and p-values for the difference between treatments was to be presented.

Secondary Efficacy Analysis
All secondary objectives were to be considered as supportive to the primary endpoints, and as such, no corrections of the significance level were planned to compensate for multiple statistical tests being performed for the secondary variables. For all secondary variables, nominal p-values were to be reported.

- **Patient Reported Outcomes (PROs)**
    - **SGRQ:** Values averaged over the final 10 days preceding randomization were to serve as the patient's baseline value. The treatment period value was defined as the patient's average value of all days during the treatment period. The change from baseline to the last visit measurement on treatment for the 3 domains individually and the total score were analyzed with ANCOVA, with treatment and country as factors and the baseline score as a covariate.
    - **Breathlessness Diary and Symptom Scores:** Breathlessness Diary and symptom scores for cough, sputum and night-time awakenings will be recorded daily by the patient. Rescue medication use will also be recorded. Values averaged over the final 10 days preceding randomization will serve as a patient's baseline value. The treatment period value is defined as the patient's average value of all days during the treatment period. The change from baseline for all variables will be analyzed using

ANCOVA, with treatment and country as factors and the mean run-in period as covariate.

- **Exacerbations**

The number and percentage of patients with exacerbations and occurrences of exacerbations were to be tabulated. Differences in the number of exacerbations were compared using a Generalized Linear Model (GLM) assuming the data follows a Poisson distribution using the logarithmic link function, with treatment and country as factors and allowing for over deviance if appropriate. The time to first exacerbation was to be described using a Kaplan-Meier plot and analyzed using a long-rank test to compare the curves between treatment regimens. In the analysis, patients reporting no exacerbations will be censored to date of last dose, or if withdrawn, date of decision of study discontinuation.

- **Serial FEV1**

Serial FEV1 measurements were to be made on a subset of patients at Visit 2 and 3 to address onset of effect and assess the effect of Symbicort at 12 hours post-dose. Analysis of onset of effect was to be addressed by comparing the two Symbicort treatment groups with placebo at 5 minutes post-dosing. AUC was analyzed to address the overall effect during the 12 hours.

- **Peak Expiratory Flow**

The change from baseline in morning and evening peak expiratory flow (mPEF, ePEF) was compared between treatment regimens by an analysis of covariance model (ANCOVA), with factors for treatment and country included in the model and using the baseline variable as a covariate. Baseline was defined as the average PEF over the 10 days immediately preceding randomization. The treatment period value was defined as the patient's average value of all days during the treatment period.

- **Pharmacokinetic variables**

The pharmacokinetic variables $AUC_{(0-t)}$ and C_{max} for budesonide and formoterol were calculated for patients who provide samples for this purpose. These variables were summarized descriptively for each treatment group and compared between treatment groups, primarily through the use of confidence intervals, using analysis of variance techniques on log-transformed data. This was neither designed nor intended as a bioequivalence study, therefore there will be no decision rule associated with these data.

Safety Variables

- **Adverse Events -** summarized by preferred term and system organ class using MedDRA. Inferential comparisons of adverse event data were not planned.
    - **Adverse Events of Interest:** Specific categories of interest potentially associated with ICS and/or B2 agonists were to be tabulated. Events representing typical and potential steroid class effects were subcategorized as:

      ICS
        - Local effects of ICS: aphonia, dysphonia, oral candidiasis, and thrush

- Systemic steroid effects: growth, weight gain, adrenal suppression, ocular effects, skin effects, psychiatric disorder, diabetes control, thirst, taste effects, bone effects
- Pneumonia
  - Pneumonia related terms
  - "Potential lung infections other than pneumonia" – included preferred terms that could potentially represent lower respiratory tract infections

Reviewer's comment: It is unclear from the definition provided for "pneumonia related terms" and "potential lung infections other than pneumonia" which MedDRA preferred terms are included in these categories.

B2 Agonists

- Class effects: tremor, palpitation, tachycardia, potassium changes, glucose changes, headache, agitation, anxiety, sleep effects, etc.
- Cardiac events: all events in the cardiac system organ class (SOC) and relevant cardiac-related events from other SOCs are included

- **Laboratory Values -** all values outside of the extended reference ranges will be identified and summarized. Shift table and shift plots were provided if deemed necessary.
- **Vital Signs and Physical Exam Values -** summarized by treatment group. Shift tables and shift plots were provided if deemed necessary for vital signs.
- **12-lead ECG –** summarized using standard summary statistics and proportions. Shift tables and plots were provided if deemed necessary.
- **Urinary Free Cortisol -** a subgroup of approximately 250 patients will have UFC and creatinine measured at Visits 2 and 6. The variables of interest will be cortisol and the cortisol:creatinine ratio. These data will be listed and summarized by treatment group using standard summary statistics. The change from Visit 2 to Visit 6 will be analyzed using an ANCOVA approach. Shift tables and shift plots may be provided.

Protocol Amendments

The original protocol, dated February 9, 2005, was submitted to IND 63,394 on March 7, 2005. Subsequently, there was one amendment to the protocol in July 2006. This amendment clarified that albuterol CFC was used as an alternative to albuterol HFA for study rescue medication at US study cites (local amendment).

The statistical analysis plan dated March 1, 2007 contained the following modifications which were made prior to unlocking the study data:

- Definition of additional analysis sets: all randomized subjects, serial spirometry, PK, and urine cortisol
- Clarification that the secondary variables were to be tested after each individual dose of study medication

- Exclusion of average of visits 4-6 as a sensitivity analysis for the primary variables. Instead, use of imputation methods, i.e. LOCF, subjects who dropped out early were still included in the sensitivity analysis.
- Clarification that total symptom score and rescue medication-free days were to be analyzed as outcome variables.

10.1.2 Results

Patient Disposition

A total of 1704 patients were randomized at 180 centers. Patient disposition for the SHINE study is presented in Table 28. Overall, discontinuation from the study was higher in the single ingredient treatment arms as compared with the Symbicort and free combination arms, and highest in the placebo arm. In each of the treatment arms, either adverse events or withdrawal of consent was the most likely reason for discontinuation. Of the 1704 patients randomized, 1378 patients completed the study, and a total of 326 patients discontinued:

- 143 (8.4%) experienced adverse events
- 87 (5.1%) withdrew consent
- 53 (3.1%) for other reasons
- 25 (1.5%) were lost to follow up
- 17 (1.0%) did not meet eligibility criteria
- 1 (0.1%) was missing

Table 28 SHINE: Patient disposition

	SYMB HD	SYMB LD	BUD + Formoterol	Budesonide	Formoterol	Placebo
Total N	277	281	287	275	284	300
Discontinuations	39 (14.1%)	38 (13.5%)	48 (16.7%)	63 (22.9%)	61 (21.5%)	77 (25.7%)
Not eligible	3 (1.1%)	1 (0.3%)	4 (1.4%)	2 (0.7%)	4 (1.4%)	3 (1%)
Adverse event	21 (7.6%)	20 (7.1%)	14 (4.9%)	26 (9.5%)	34 (12%)	28 (9.3%)
Withdrawal of consent	6 (2.2%)	8 (2.8%)	14 (4.9%)	20 (7.3%)	12 (4.2%)	27 (9%)
Lost to follow-up	4 (1.4%)	3 (1.1%)	6 (2.1%)	4 (1.5%)	1 (0.3%)	7 (2.3%)
Other	5 (1.8%)	6 (2.1%)	10 (3.5%)	10 (3.6%)	10 (3.5%)	12 (4%)
Missing	0	0	0	1 (0.3%)	0	0

SYMB HD: Symbicort 320/9 mcg BID, SYMB LD: Symbicort 160/9 mcg BID, BUD + Formoterol: co-administration of the free combination of budesonide + formoterol
Source: SHINE CSR, Section 6.2, Figure 2, p. 106.

- Protocol Deviations

The Applicant reports a total of 206 (12.1%) subjects had at least 1 protocol deviation. Most protocol deviations were minor and did not impact subject safety or efficacy assessments. The most common protocol deviations were related to use of disallowed concomitant medications [174 (10.2%) subjects] and failure to meet eligibility criteria at Visit 1 [24 (1.4%) subjects]. Overall, 21(1.2%) subjects in the efficacy analysis set were excluded from the per-protocol analysis set (See Table 29). Three subjects were given the incorrect randomized treatment. These 3 subjects were handled on an intent-to-treat bases, but were excluded from the per-protocol analysis set. Of note, due to concerns of data quality, the Applicant closed site 209 in

Poland. The 7 patients randomized at this site were not included in the efficacy analyses; however, all safety data have been included in the appropriate analysis sets.

Table 29 SHINE: Protocol deviations

	SYMB HD	SYMB LD	BUD + Formoterol	Budesonide	Formoterol	Placebo
Total N	277	281	287	275	284	300
All Deviations (%)	**39 (14.1%)**	**35 (12.5%)**	**25 (8.7%)**	**36 (13.1%)**	**33 (11.6%)**	**38 (12.7%)**
Use of Prohibited CMs	36 (13.0%)	29 (10.3%)	20 (7.0%)	31 (11.3%)	27 (9.5%)	31 (10.3%)
Failure to Meet EC	3 (1.1%)	3 (1.1%)	3 (1.0 %)	5 (1.8%)	6 (2.1%)	4 (1.3%)
Excluded from PP Analysis	**2 (0.7%)**	**5 (1.8%)**	**3 (1.0%)**	**1 (0.4%)**	**4 (1.4%)**	**6 (2.0%)**
FEV1 > 50% predicted	0	0	0	1 (0.4%)	2 (0.7%)	2 (0.7%)
FEV1/FVC ≥ 70%	0	1 (0.4%)	0	1 (0.4%)	1 (0.4%)	1 (0.3%)
< 2 on MMRC scale	0	0	0	0	1 (0.4%)	0
History of Asthma	1 (0.4%)	0	1 (0.3%)	0	0	1 (0.3%)
History of AR	1 (0.4%)	0	0	0	0	0
Homozygous A1AT	0	0	1 (0.3%)	0	0	0
Chronic OCS use	1 (0.4%)	1 (0.4%)	0	0	0	0
TSS < 2 for run-in	0	1 (0.4%)	0	0	0	3 (1.0%)
Unblinded in study	0	1 (0.4%)	0	0	0	0
Incorrect study med.	0	2 (0.7)	1 (0.3%)	0	0	0

SYMB HD: Symbicort 320/9 mcg BID, SYMB LD: Symbicort 160/9 mcg BID, BUD + Formoterol: co-administration of the free combination of budesonide + formoterol, CMs: Concomitant medications, EC: Eligibility Criteria, MMRC: Modified Medical Research Council, AR: Allergic rhinitis, A1AT: Alpha-1 anti-trypsin, OCS: oral corticosteroids
Source: SHINE CSR, Tables 11.1.3.3 (p. 519) and 11.1.2.5 (p. 413)

Datasets Analyzed

The Applicant has defined the following analysis sets:

- Intention-to-Treat (ITT) (N=1697): also known as the efficacy analysis set (EAS). This analysis set was considered the primary efficacy analysis set, and defined as those patients who had been randomized, received at least one dose of study drug, and contributed sufficient data for at least 1 co-primary or secondary outcome endpoint to be calculated during the randomized treatment period. Of note, the site in Poland was excluded from this population (n=7).
- Per Protocol (PP) (N=1676): The PP population was a subset of the ITT population including only those patients who completed the study without major detected protocol deviations.
- Safety (N=1704): This population was defined as all randomized patients who received at least one dose of study drug and from whom any data after randomization are available.
- Serial spirometry (N=618): all subjects who were randomized, received at least one dose of study medication, and had a baseline pre-dose FEV1 value and at least one post-dose FEV1 value that were from a serial spirometry procedure during the randomized treatment period.

- PK (N=238): based on the safety analysis set and included subjects who had least 1 quantifiable PK concentration
- Urinary free cortisol (N=437): subjects who were randomized, received at least one dose of study medication, and had a baseline and on-treatment value for 24-hr urinary cortisol, urine cortisol concentration, 24-hour urinary creatinine, or urine creatinine concentration during the randomized treatment period.

Demographics and Baseline Characteristics

- Demographics

Demographics and baseline characteristics are summarized in Table 30.

Table 30 SHINE: Patient demographics

	SYMB HD	SYMB LD	BUD + Formoterol	Budesonide	Formoterol	Placebo
ITT population	277	281	287	275	284	300
Male (N and %)	188 (67.9)	181 (64.4)	213 (74.2)	186 (67.6)	186 (65.5)	207 (69)
Race (N and %)						
Caucasian	261 (94.2)	262 (93.2)	264 (92.0)	259 (94.2)	262 (94.7)	284 (94.7)
Black	9 (3.2)	14 (5.0)	14 (4.9)	8 (2.9)	11 (3.9)	8 (2.7)
Oriental	0	0	2 (0.7)	1 (0.4)	2 (0.7)	1 (0.3)
Other	7 (2.5)	5 (1.8)	7 (2.4)	7 (2.5)	9 (3.2)	7 (2.3)
Age (years)						
Mean (SD)	63.11 (9.01)	63.64 (8.97)	63.72 (8.99)	63.44 (8.80)	63.54 (9.52)	63.23 (9.58)
Median	63	63	64	63	64	63
Range	41 to 86	40 to 90	40 to 94	40 to 90	42 to 89	40 to 86
Country (N and %)						
US	114 (41.2)	118 (42.0)	127 (44.3)	112 (40.7)	120 (42.3)	129 (43.0)
Poland	84 (30.3)	81 (28.8)	80 (27.9)	83 (30.2)	84 (29.6)	85 (28.3)
Czech Rep	43 (15.5)	43 (15.3)	46 (16.0)	46 (16.7)	44 (15.5)	44 (14.7)
S. Africa	22 (7.9)	21 (7.5)	21 (7.3)	21 (7.6)	21 (7.4)	23 (7.7)
Netherlands	14 (5.1)	18 (6.4)	13 (4.5)	13 (4.7)	15 (5.3)	19 (6.3)
Baseline % predicted FEV1 Mean (SD)	33.70 (11.89)	34.16 (10.99)	33.55 (10.79)	33.54 (10.84)	33.64 (11.39)	34.65 (10.59)
Post-BD % predicted FEV1 (N and %)						
<30%	71 (25.6)	53 (18.9)	67 (23.3)	62 (22.5)	70 (24.6)	52 (17.3)
30-50%	153 (55.2)	173 (61.6)	167 (58.2)	160 (58.2)	154 (54.2)	184 (61.3)
50-80%	52 (18.8)	53 (18.9)	53 (18.5)	51 (18.5)	59 (20.8)	61 (20.3)
≥ 80%	0	1 (0.4)	0	1 (0.4)	1 (0.4)	2 (0.7)
Missing	1 (0.4)	1 (0.4)	0	1 (0.4)	0	1 (0.3)
Pack Years						
Median	40.0	40.0	42.0	41.0	40.0	40.0
Min, Max	10 to 184	10 to 196	10 to 188	10 to 171	10 to 144	10 to 200

Source: SHINE CSR, Table 15, Section 6.5, page 113.

There was a greater percentage of male than female subjects consistent with the disease prevalence in the target population. Most subjects were Caucasian, with fewer than 7% non-

Caucasian patients. Approximately half of the subjects were over age 65, with approximately 12% of subjects over the age of 75 years. Baseline percent predicted FEV1, post-bronchodilator percent predicted FEV1, and smoking history (pack years) were well balanced across all treatment groups. Severity classification, based on the GOLD 2006 criteria applied to post-bronchodilator FEV1 at Visit 1, indicated that approximately 80% of the study population had severe or very severe COPD, while 20% had moderate COPD at entry. In general, demographic and key baseline characteristics were similar across treatment groups and geographic regions (US vs. non-US). Exceptions included a higher percentage of women in the US (41.5% of the total) than in the non-US region (24.8%). In addition, a larger percentage of enrolled subjects in the US were African Americans (8.4%) compared with the percentage enrolled in non-US countries (0.5%) [Module 5, SHINE CSR, Table 11.1.4.1.3, p. 575].

- Baseline Medical History

The study population included a representative number of subjects with co-morbid conditions, including:

  - Hypertension (42%)
  - Lipid profile abnormalities (24%)
  - Cardiac disease (18%)
  - Diabetes (10%)
  - Osteoporosis (8%)

These baseline conditions were also well-balanced across treatment groups (Module 5, SHINE CSR, Table 11.1.6, p. 833).

- Concomitant Medication Use

The most common COPD medications were inhaled short-acting anticholinergic (ipratropium bromide), systemic corticosteroids, antibiotics, mucolytics, and oxygen, used by at least 5% of subjects during randomized treatment. The most common non-COPD medications were diuretics, platelet aggregation inhibitors (excluding heparin), ace inhibitors, antibiotics, HMG CoA reductase inhibitors, proton pump inhibitors, and anilides, used by at least 5% of the randomized patient population. In general, use of the most common COPD medications during randomized treatment was similar across treatment groups. (Module 5, SHINE CSR, Table 19, p.121)

Compliance

Study medication compliance was determined based on asking subjects twice daily as a part of diary entry whether they used their study medication. The number of "Yes" responses were used to calculate compliance in two ways. The first method was based on the number of "yes" responses to the study medication question from the diary relative to the expected number of study drug intakes based on the duration of the randomized treatment period for each subject. This method assumes that days the diary was not used were also days that the subject did not take study medication. The second method was calculated using the number of "Yes" responses to the study medication question from the diary relative to the total number of actual responses ("Yes" or "No") to the study medication question. Using both methods, study medication

compliance was ≥ 80% in more than 90% of the subjects during randomized treatment. Compliance was similar across treatment groups (SHINE CSR, Table 17, p 118).

Efficacy Endpoint Outcomes

Primary Endpoint Analysis

The co-primary variables were change from baseline in pre-dose FEV1, to demonstrate the anti-inflammatory contribution of budesonide, and post-dose FEV1, to demonstrate the bronchodilator contribution of formoterol, to the efficacy of the combination product, Symbicort. Each co-primary variable was calculated as an average over the randomized treatment period (primary analysis) and at the end-of-treatment.

2. Pre-dose FEV1

Treatment means and treatment comparisons for change in baseline averaged over the randomized treatment period and at the end of treatment are shown in Table 31 and Table 32.

Table 31 SHINE: Pre-dose FEV1 (L): Treatment means

			Average Of Randomized Treatment Period		End of Treatment	
	N	Baseline value Mean (SD)	Change from Baseline LS Mean (SEM)	95% CI	Change from Baseline LS Mean (SEM)	95% CI
Symbicort HD	266	1.04 (0.42)	0.08 (0.01)	0.06, 0.11	0.07 (0.02)	0.04, 0.11
Symbicort LD	275	1.04 (0.40)	0.06 (0.01)	0.03, 0.08	0.05 (0.02)	0.02, 0.08
Free combo	279	1.05 (0.37)	0.07 (0.01)	0.04, 0.09	0.06 (0.02)	0.03, 0.09
Budesonide 160	265	1.04 (0.39)	0.00 (0.01)	-0.02, 0.03	0.00 (0.02)	-0.03, 0.03
Formoterol 4.5	263	1.03 (0.40)	0.04 (0.01)	0.02, 0.07	0.03 (0.02)	0.00, 0.06
Placebo	270	1.10 (0.39)	0.01 (0.01)	-0.02, 0.03	0.01 (0.02)	-0.02, 0.04

Source: SHINE CSR, Section 7.2.1.1, Tables 24 and 26, p. 132, 135

Table 32 SHINE: Pre-dose FEV1 (L): Treatment comparisons for change from baseline

Comparison	Average Of Randomized Treatment Period		End of Treatment	
	LS Mean (95% CI)	p-value	LS Mean (95% CI)	p-value
Symbicort LD vs. placebo	0.05 (0.02, 0.09)	0.002	0.03 (-0.01, 0.07)	0.119
Symbicort HD vs. placebo	0.08 (0.04, 0.11)	< 0.001	0.06 (0.02, 0.10)	0.004
Symbicort LD vs. budesonide	0.06 (0.02, 0.09)	0.001	0.05 (0.00, 0.09)	0.033
Symbicort HD vs. budesonide	0.08 (0.04, 0.11)	< 0.001	0.07 (0.03, 0.12)	< 0.001
Symbicort LD vs. formoterol	**0.02 (-0.02, 0.05)**	**0.335**	**0.01 (-0.03, 0.06)**	**0.488**
Symbicort HD vs. formoterol	**0.04 (0.00, 0.07)**	**0.026**	**0.04 (0.00, 0.09)**	**0.044**
Symbicort HD vs. free comb.	0.01 (-0.02, 0.05)	0.479	0.01 (-0.03, 0.05)	0.525
Budesonide vs. placebo	0.00 (-0.04, 0.03)	0.902	-0.01 (-0.05, 0.03)	0.559
Formoterol vs. placebo	0.04 (0.00, 0.07)	0.037	0.02 (-0.02, 0.06)	0.395
Symbicort HD vs. LD	0.02 (-0.01, 0.06)	0.198	0.03 (-0.01, 0.07)	0.179

Source: SHINE CSR, Tables 25 and 27, Section 7.2.1.1, p. 133, 135
Bold Text indicates pre-specified primary comparisons

In terms of the pre-specified primary comparisons, results indicate that only Symbicort HD demonstrated a statistically significantly greater increase from baseline in pre-dose FEV1 when compared with formoterol. This result was consistent when analyzed as the average of the randomized treatment period or at the end of treatment.

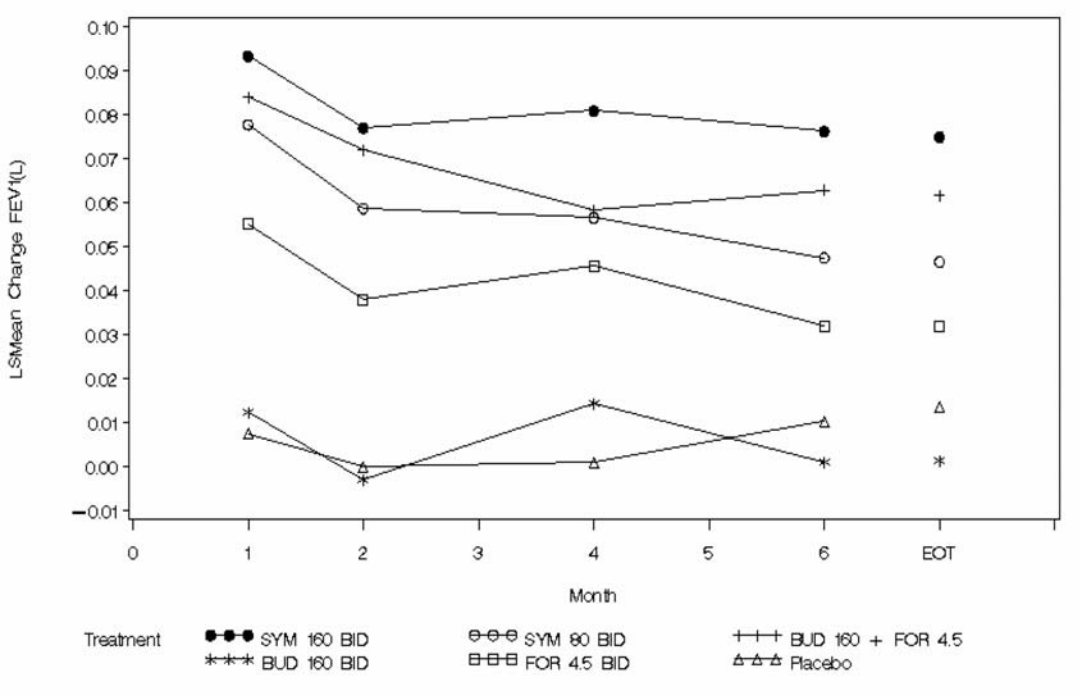
Reviewer's Comment: It is of note that the difference between Symbicort HD and formoterol, though statistically significant, was quantitatively small, approximately 40 mL.

Symbicort LD failed to show the contribution of the inhaled corticosteroid to the efficacy of the combination product in both analyses. Both dosage strengths of Symbicort demonstrated statistically significant difference in pre-dose FEV1 vs. placebo when examined as the average of the randomized treatment period, but Symbicort LD was not statistically different from placebo at the end of treatment. In both analyses, Symbicort HD was not statistically different when compared with Symbicort LD in terms of change from baseline in pre-dose FEV1.

Reviewer's Comment: Based on the above analysis, the Sponsor has decided only to pursue the Symbicort high dose of 320/9 mcg BID for the COPD indication, as the lower dose failed to show the contribution of budesonide to the efficacy of the combination product.

Figure 12 depicts the LS mean change from baseline in pre-dose FEV1 by visit. The accompanying table provides information for the number of subjects included in the analysis at each time point. Symbicort HD demonstrated improvements in pre-dose FEV1 that were apparent at Month 1 and were generally maintained over the 6-month study period.

Figure 12 SHINE: LS Mean change from baseline in pre-dose FEV1 by visit

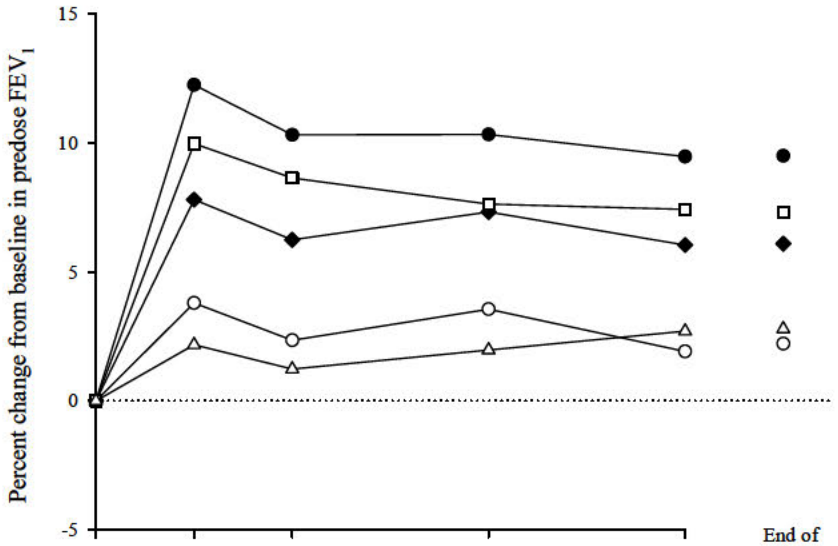


Treatment group	Months				
	1	2	4	6	EOT
Symbicort HD N = 275	266	259	250	238	266
Symbicort LD N = 280	273	265	254	246	275
Free Combo N = 286	278	267	253	238	279
Budesonide N = 274	262	242	227	210	265
Formoterol N = 283	263	250	235	223	263
Placebo N = 299	266	245	238	230	270

Reviewer's comment: Of note, the although the pre-specified primary endpoint is the mean change in pre-dose and post-dose FEV1 averaged over the treatment period (as portrayed in

Figure 12, (b) (4)
(see Figure 13 taken from the product label below.) Of note, the figures do not appear to be strikingly different, graphically.

Figure 13 SHINE: Mean Percent Change from Baseline in Pre-Dose FEV1 Over 6 months (Figure 1, proposed product label)



	N	N	N	N	N	N
Symbicort 160/4 5 mcg	275	266	259	250	238	266
Budesonide 160 mcg	274	262	242	227	210	265
Formoterol 4 5 mcg	283	263	250	235	223	263
Budes 160+Form 4 5 mcg	286	278	267	253	238	279
Placebo	299	266	245	238	230	270

● SYMBICORT MDI 160/4.5 mcg, two inhalations twice daily
○ Budesonide 160 mcg, two inhalations twice daily
◆ Formoterol 4.5 mcg, two inhalations twice daily
□ Budesonide 160 mcg + Formoterol 4.5 mcg, two inhalations twice daily
△ Placebo

2. Post-dose FEV1

Treatment means and treatment comparisons for change in baseline averaged over the randomized treatment period and at the end of treatment are shown in Table 33 and Table 34.

Table 33 SHINE: Post-dose FEV1 (L): Treatment means

			Average Of Randomized Treatment Period		End of Treatment	
	N	Baseline value Mean (SD)	Change from Baseline LS Mean (SEM)	95% CI	Change from Baseline LS Mean (SEM)	95% CI
Symbicort HD	275	1.04 (0.41)	0.20 (0.01)	0.18, 0.23	0.19 (0.02)	0.15, 0.23
Symbicort LD	280	1.04 (0.40)	0.19 (0.01)	0.17, 0.22	0.18 (0.02)	0.14, 0.22
Free combo	286	1.05 (0.36)	0.19 (0.01)	0.16, 0.21	0.20 (0.02)	0.16, 0.24
Budesonide 160	274	1.04 (0.40)	0.03 (0.01)	0.01, 0.06	0.02 (0.02)	-0.02, 0.06
Formoterol 4.5	283	1.02 (0.40)	0.17 (0.01)	0.14, 0.19	0.15 (0.02)	0.11, 0.18,
Placebo	299	1.08 (0.38)	0.03(0.01)	0.01, 0.06	0.02 (0.02)	-0.01, 0.06

Source: SHINE CSR, Section 7.2.1.2, Tables 28 and 30, p. 137 and 140

Table 34 SHINE: 1-hr Post-dose FEV1 (L): Treatment comparisons for change from baseline

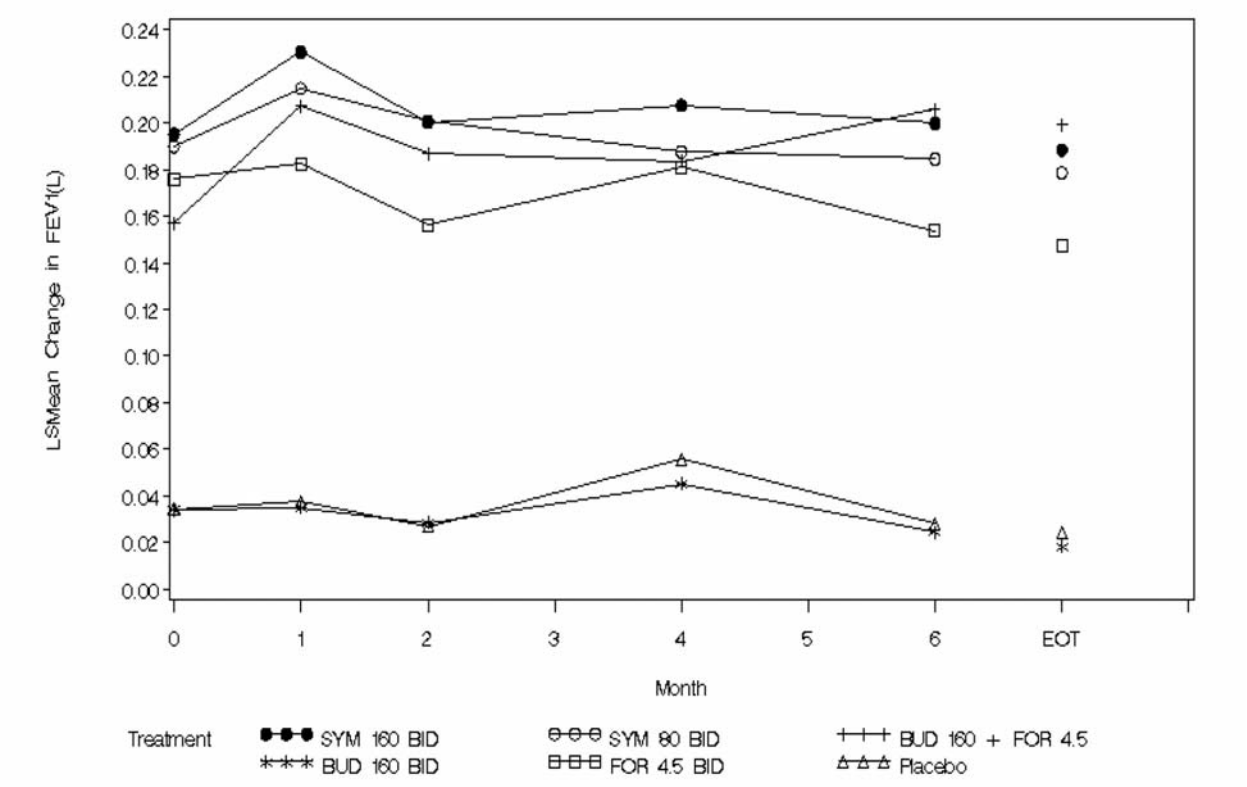
Comparison	Average Of Randomized Treatment Period		End of Treatment	
	LS Mean (95% CI)	p-value	LS Mean (95% CI)	p-value
Symbicort LD vs. placebo	0.16 (0.13, 0.20)	< 0.001	0.15 (0.11, 0.20)	< 0.001
Symbicort HD vs. placebo	0.17 (0.14, 0.20)	< 0.001	0.16 (0.12, 0.21)	< 0.001
Symbicort LD vs. budesonide	**0.16 (0.13, 0.20)**	**< 0.001**	**0.16 (0.11, 0.21)**	**< 0.001**
Symbicort HD vs. budesonide	**0.17 (0.14, 0.21)**	**< 0.001**	**0.17 (0.12, 0.22)**	**< 0.001**
Symbicort HD vs. free comb.	0.01 (-0.02, 0.05)	0.461	-0.01 (-0.06, 0.04)	0.671
Budesonide vs. placebo	0.00 (-0.03, 0.03)	0.997	-0.01 (-0.05, 0.04)	0.808
Formoterol vs. placebo	0.14 (0.10, 0.17)	<0.001	0.12 (0.07, 0.17)	<0.001
Symbicort HD vs. LD	0.01 (-0.03, 0.04)	0.615	0.01 (-0.04, 0.06)	0.693

Source: SHINE CSR, Section 7.2.1.2, Tables 29 and 31, p. 137 and 140
Bold Text indicates primary comparisons

In terms of the pre-specified primary comparisons, results indicate that both dosage strengths of Symbicort demonstrated a statistically significantly greater increase from baseline in post-dose FEV1 when compared with budesonide. This result was consistent when analyzed as the average of the randomized treatment period or at the end of treatment. Both dosage strengths of Symbicort demonstrated statistically significant difference in post-dose FEV1 vs. placebo when examined as the average of the randomized treatment period and at the end of treatment. These results demonstrate that formoterol makes a contribution to the efficacy of both strengths of the combination product.

Figure 14 depicts the LS mean change from baseline in post-dose FEV1 by visit. The accompanying table provides information for the number of subjects included in the analysis at each time point. Symbicort LD and HD demonstrated improvements in 1 hour post-dose FEV1 that were apparent on the day of randomization and were generally maintained over the 6-month study period.

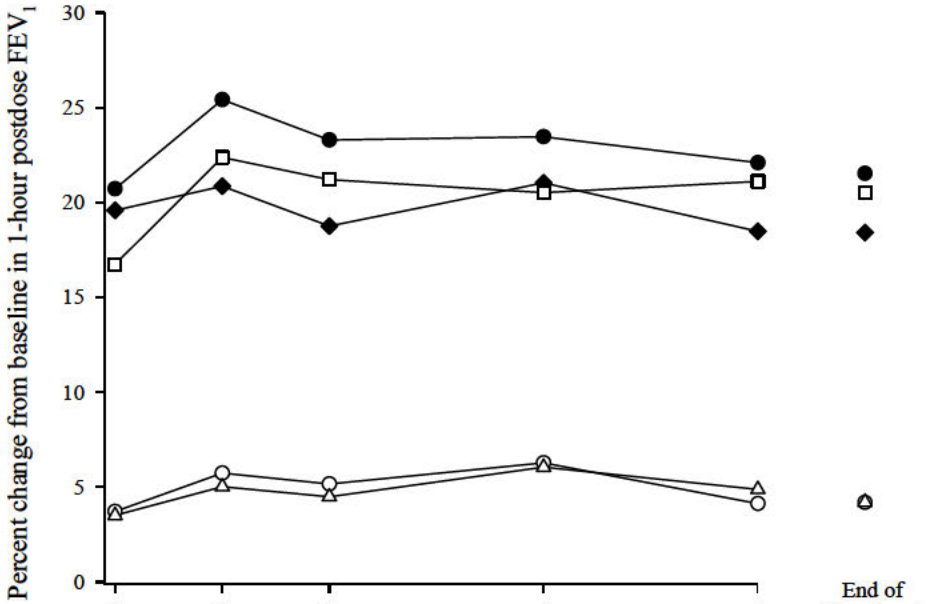
Figure 14 SHINE: LS mean change from baseline in 1-hour post-dose FEV1 by visit



Treatment group	Months				
	1	2	4	6	EOT
Symbicort HD N = 271	267	257	250	237	275
Symbicort LD N = 280	270	264	254	244	280
Free Combo N = 283	277	267	252	239	286
Budesonide N = 274	255	241	224	210	274
Formoterol N = 282	259	248	234	221	283
Placebo N = 298	262	243	238	230	299

Reviewer's comment: Of note, the although the pre-specified primary endpoint is the mean change in pre-dose and post-dose FEV1 averaged over the treatment period (as portrayed in Figure 14, (b) (4)
(see Figure 15 taken from the product label below.)

Figure 15 SHINE: Mean Percent Change from Baseline in Post-dose FEV1 Over 6 months (Figure 2, proposed product label)



	0	1	2	4	6	End of Treatment
	N	N	N	N	N	N
Symbicort 160/4.5 mcg	271	267	257	250	237	275
Budesonide 160 mcg	274	255	241	224	210	274
Formoterol 4 5 mcg	282	259	248	234	221	283
Budes 160+Form 4.5 mcg	283	277	267	252	239	286
Placebo	298	262	243	238	230	299

● SYMBICORT MDI 160/4.5 mcg, two inhalations twice daily
○ Budesonide 160 mcg, two inhalations twice daily
◆ Formoterol 4.5 mcg, two inhalations twice daily
□ Budesonide 160 mcg + Formoterol 4.5 mcg, two inhalations twice daily
△ Placebo

- Subgroup Analyses by Sex, Age, and Race

1) Pre-Dose FEV1

Similar patterns of results seen in the primary analysis were seen in the sensitivity analyses adjusting for sex and age groups. A statistically significant interaction was observed for race, particularly for black subjects, who showed a large variability across LS mean treatment effects. However, when this interaction was examined more closely, the large increase in treatment effect was noted in the free combination, budesonide, and placebo arms. For these same subjects, the primary treatment group comparison of Symbicort HD versus formoterol was equivalent to the primary analysis. Therefore, it was concluded that there was no clear evidence of a differential treatment effect across race groups.

2) 1-hour Post-Dose FEV1
Similar patterns of results seen in the primary analysis were seen in the sensitivity analyses adjusting for sex and age groups. A statistically significant interaction was observed for race, particularly for black subjects, who showed a large variability across LS mean treatment effects. Most notable was the large increase in 1-hour post-dose FEV1 for the free combination, budesonide, and placebo arms (LS means: 0.45L, 0.19L, and 0.28L, respectively), which was not consistent with primary results. For these same subjects, the primary treatment group comparison for Symbicort HD versus budesonide was 0.02L, which was also not consistent with the primary analysis. When the reason for this is further investigated, it appears that the inconsistency in the treatment effect is due to unexpected increase in the budesonide treatment group rather than a lack of effect in the Symbicort HD group, which was 0.20L. Results for subjects reporting "other" for race, show similar results to the primary analysis.

Secondary Endpoint Analyses

The Sponsor identified dyspnea, SGRQ, and COPD exacerbations as key secondary efficacy variables.

1. Dyspnea Scores

Dyspnea scores, as measured by the Breathlessness Diary, range from 0-4 with higher scores indicating more severe dyspnea. A reduction of 0.2 units has been defined as the minimally important clinical difference (MCID) based on prior validation. The primary comparison was between the Symbicort treatments and placebo. The LS mean difference between Symbicort HD and placebo averaged over the randomized treatment period was -0.16 (95% CI -0.25, -0.06, p = 0.001); Symbicort LD versus placebo yielded a LS mean difference of -0.16 (95% CI -0.26, -007, p < 0.001). Both Symbicort HD and LD demonstrated a statistically significant reduction from baseline in dyspnea scores when compared with placebo, but the pre-specified MCID was not achieved (Module 5, SHINE CSR, Table 33, p. 142). The Applicant also performed a responder analysis to identify the proportion of patients who improved by the MCID for dyspnea during randomized treatment. The odds ratio of achieving the MCID when Symbicort HD was compared to placebo was 2.30 [95% CI 1.63, 3.26, p < 0.001]; Symbicort LD versus placebo yielded an OR = 1.74 [95% CI 1.24, 2.44, p = 0.001] (Module 5, SHINE CSR, Table 35, p. 145).

Reviewer's comment: (b) (4)

2. St. George's Respiratory Questionnaire (SGRQ)

The SGRQ total score and scores for each of the 3 domains (symptoms, activity, impact) were analyzed at the end of treatment. The validated MCID for the SGRQ total score and the impact domain score has been defined as a mean change in score of 4 units. The primary comparison was between the Symbicort treatment groups and placebo. The LS mean difference between Symbicort HD and placebo in SGRQ total score change from baseline at the end of treatment was -3.12 (95% CI -5.201, -1.036, P = 0.003); Symbicort LD versus placebo yielded a LS mean difference of -2.95 (95% CI -5.011, -0.884, p = 0.005). Both Symbicort HD and LD groups demonstrated statistically significant reductions in SGRQ total scores compared with placebo, but did no achieve the pre-specified MCID of 4 units (Module 5, SHINE CSR, Table 37).

Reviewer's Comment: The Applicant has (b) (4)

3. COPD exacerbations

A COPD exacerbation was predefined as a worsening of COPD that required a course of oral steroids and/or hospitalization for treatment. Episodes of COPD worsening that were treated with parenteral steroids alone, or with antibiotics without systemic steroids or hospitalization, were not included in the definition of exacerbation, but were listed separately. The primary comparison was between Symbicort treatment groups and placebo.

The results for the primary analysis of the number of protocol-defined COPD exacerbations per subject-treatment year indicated that there were no statistically significant differences in the rate of exacerbations between treatment groups. Specifically, the rate ratio of the comparison of Symbicort HD versus placebo was 0.796 [95% CI 0.603, 1.052, p = 0.109] (Module 5, SHINE CSR, Table 41, p. 153). The rate ratio of the comparison of Symbicort LD versus placebo was 0.766 [95% CI 0.581, 1.011, p = 0.60]. Additionally, there were no differences between treatment groups for time to first exacerbation.

Reviewer's Comment: The Applicant ha (b) (4) *However, this result is not statistically significant. Further, the definition of a COPD exacerbation is based solely on treatment with oral corticosteroids or hospitalization.* (b) (4) *the results do show a numerical trend toward decrease in the defined events. In a general sense, this is supportive of the efficacy of Symbicort HD.*

Other secondary efficacy variables included serial FEV1, inspiratory capacity (IC), forced vital capacity (FVC), morning and evening PEF, COPD symptoms, and health care economics.

1. 12-hour Serial FEV1

At Visits 2, 4, and 6, FEV1 was measured pre-dose and at 5, 15, 30, 60, 120, 180, 240, 360, 480, 600, and 720 minutes post-dose in a subset of 618 subjects. The 12 hour FEV1 curves, based on mean percent change from baseline pre-dose FEV1 values are shown in Figure 16 and Figure 17.

Figure 16 SHINE: Mean percent change from baseline FEV1 over 12 hours – day of randomization

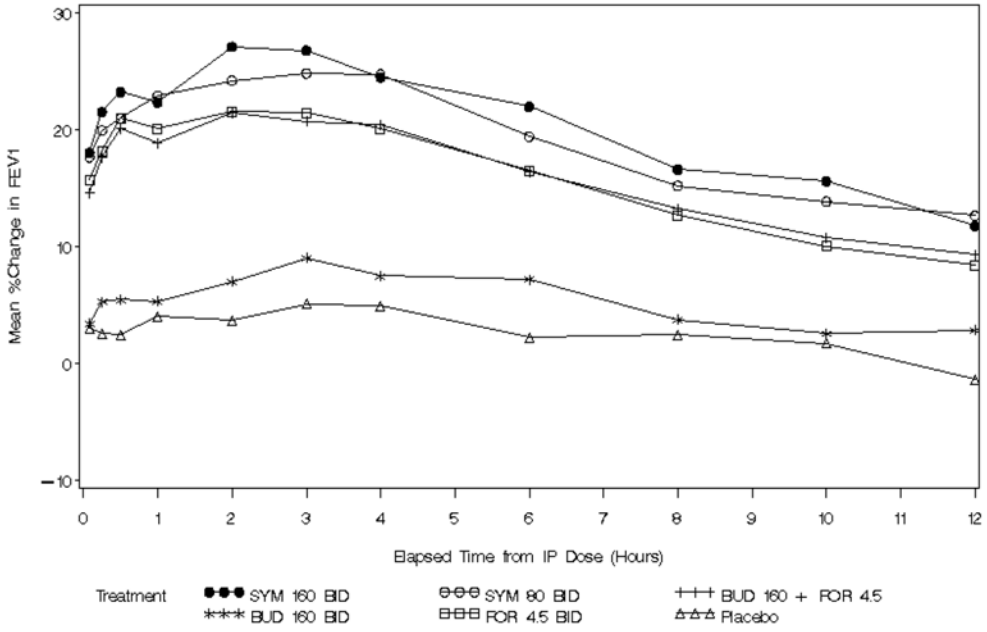
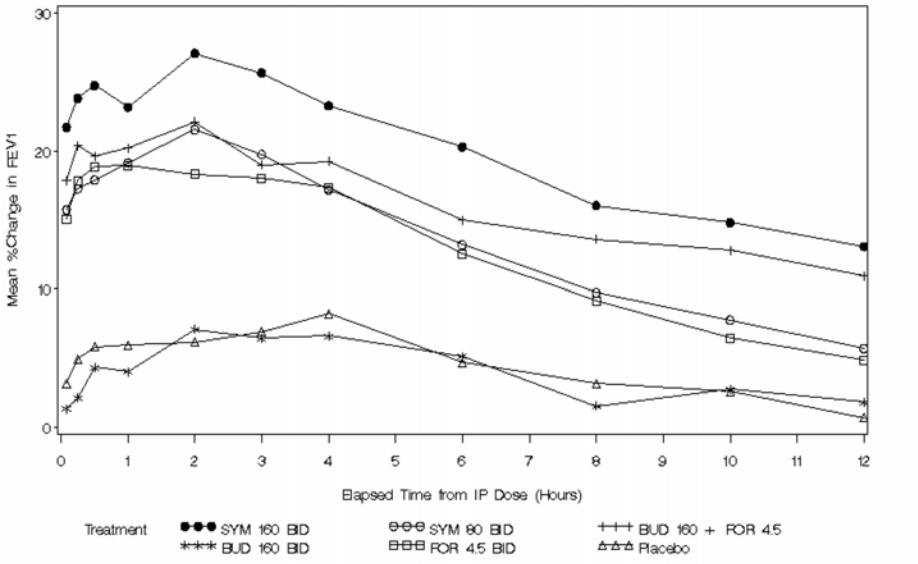


Figure 17 SHINE: Mean percent change from baseline in FEV1 over 12 hours – end of treatment



The serial FEV1 graphs above indicate that all treatment groups containing formoterol demonstrated bronchodilation at 5 minutes after dosing, compared with placebo, which reached a maximum between 2 and 3 hours, and was maintained over 12 hours. The response was present at the end of treatment as well.

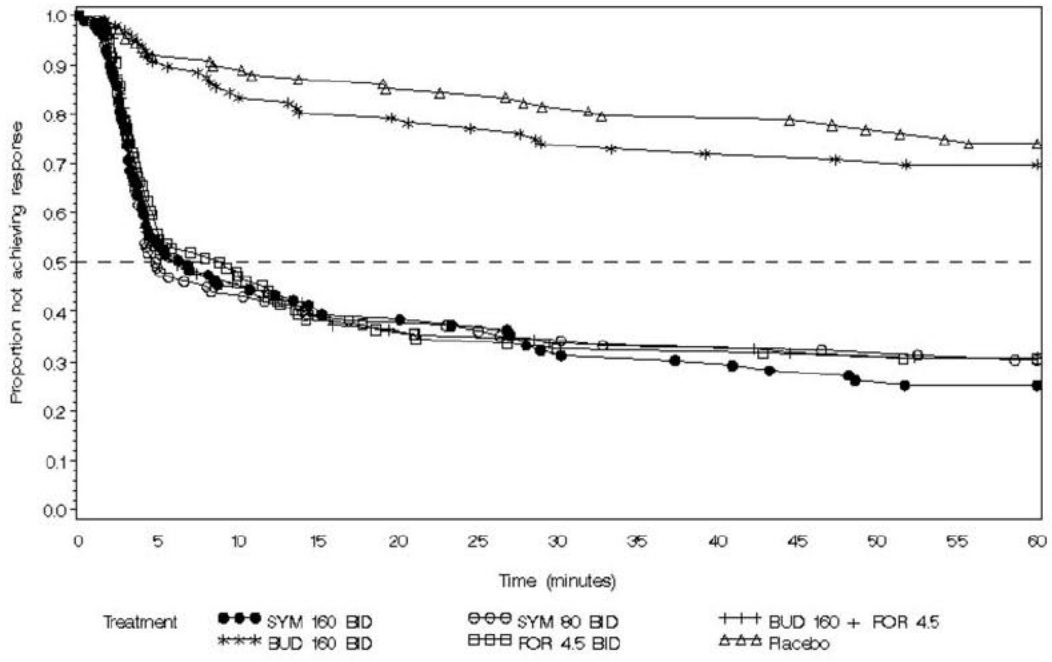
Reviewer's comment: Figures 12 and 13 are included in the product label in the clinical trials section under the new indication of COPD. Similar figures are also present in the previously approved asthma section.

a. 15% Onset of Action of Bronchodilation

"15% onset of action" is defined as the first post-dose time point at which each subject achieved a 15% improvement in FEV1 relative to baseline pre-dose FEV1. The Kaplan-Meier plots for the estimated time to 15% onset of action during the first 60 minutes post-dose on the day of randomization and at the end of treatment are shown in Figure 18 and Figure 19.

Reviewer's comment: Using the following data, the Applicant (b) (4)

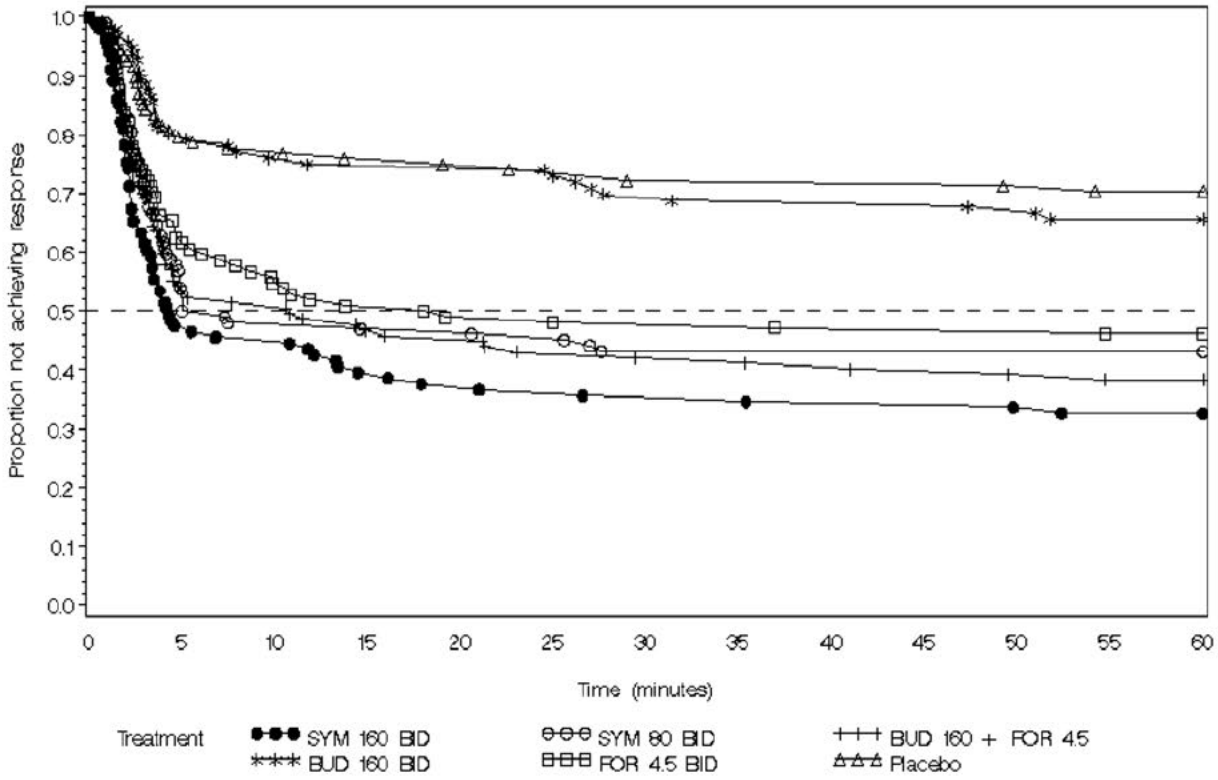
Figure 18 SHINE, Estimated time to 15% onset of action – day of randomization



On the day of randomization, the median time to 15% onset of action was 6.8 minutes for Symbicort HD, 4.9 minutes for Symbicort LD, 6.2 minutes for the free combination, and 9.0 minutes for formoterol. Median time for budesonide and placebo could not be estimated due to

the fact that few than 50% of subjects achieved a 15% improvement within 60 minutes. Both Symbicort HD and LD demonstrated a statistically significantly earlier time to 15% onset of action compared with placebo ($p < 0.001$) on the day of randomization (SHINE CSR, Tables 11.2.5.4.1.7 and 11.2.5.4.1.8).

Figure 19 SHINE: Estimate time to 15% onset of action - end of treatment



At the end of treatment, the median time to 15% onset of action for 4.3 minutes for Symbicort HD, 6.2 minutes for Symbicort LD, and 10.8 minutes for the free combination. Thus the median times for 15% onset of action for both doses of Symbicort at the end of treatment were similar to the day of randomization. Of note, formoterol showed a prolonged time to 15% onset of action (18 minutes) at the end of treatment, as compared with 9 minutes at the day of randomization.

Reviewer's comment: It is interesting that the onset of action is 3x faster in the COPD population than in the asthma population (labeled claim is 15 minutes). The reason for this is unclear, however different disease entities are known to behave differently. It is also uncertain as to why the formoterol alone arm showed a difference in 15% onset of action at the end of treatment, yet this was not seen in the combination products.

Reviewer's comment: The definition of onset of action is similar to what is used in the Sponsor's asthma program and what currently appears in the product label. (b) (4)

(b) (4)

b. Maximum FEV1

Treatment comparisons for mean maximum FEV1 on the day of randomization and at the end of treatment indicated that Symbicort HD demonstrated a statistically significant increases when compared with placebo (LS Mean = 0.15 [95% CI 0.09, 0.22, p = <0.001] that was present at then end of treatment (LS Mean = 0.12 [95% CI 0.04, 0.20, p= 0.003]). Symbicort LD did not show a significant difference for mean maximum FEV1 compared with placebo at the end of treatment, indication perhaps, of an attenuation of effect (Module 5, SHINE CSR, Tables 43 and 45, p 159-161).

2. Inspiratory Capacity (IC) – Pre- and 1-hour post-dose

During serial spirometry, both pre- and 1-hour post-dose IC were collected to measure lung hyperinflation. Treatment means and between-treatment comparisons for pre-dose IC did not show any significant difference between any of the treatment groups. Analysis of treatment means and between-treatment comparisons for post-dose IC (Module 5, SHINE CSR, Tables 11.2.4.2.2 and 11.2.4.2.3) for the treatment average indicated that both dosage strengths of demonstrated highly statistically significant increases in 1-hour post-dose IC compared with placebo (Symbicort HD: LS mean = 0.18, p<0.001; Symbicort LD 80/4.5: LS mean = 0.19, p<0.001). At the end of treatment, results for post-dose IC were similar to the day of randomization, demonstrating maintenance of effect.

3. Forced Vital Capacity (FVC) Pre- and 1-hour post-dose

Analysis of treatment means and between treatment comparisons for pre-dose FVC for the treatment average indicated that both Symbicort HD and LD demonstrated statistically significant increases in pre-dose FVC compared with placebo (HD: LS mean = 0.10, p =0.002; LD: LS mean = 0.11, p = 0.008) [Module 5, SHINE CSR, Tables 11.2.3.1.2 and 11.2.3.1.3]. The effect on pre-dose FVC was similar when analyzed at the end of treatment. Similarly, Symbicort HD and LD demonstrated statistically significant increases in post-dose FVC compared with placebo (HD: LS Mean = 0.28, p<0.001; LD: LS mean = 0.28, p< 0.001) (Module 5, SHINE CSR, Tables 11.2.3.2.2 and 11.2.3.2.3). Results for post-dose FVC at the end of treatment were similar to the day of randomization, demonstrating maintenance of effect.

4. Morning and Evening PEF

Treatment means and treatment comparisons for change in baseline averaged over the randomized treatment period are shown in Table 35 and Table 36.

Table 35 SHINE: AM and PM PEF – Treatment means

			Average Over Randomized Treatment Period	
	N	Baseline value Mean (SD)	Change from Baseline LS Mean (SEM)	95% CI
Morning PEF (L/min)				
Symbicort HD	271	(b) (4)		15.45, 23.24
Symbicort LD	278	181.30 (67.87)	16.43 (1.96)	12.60, 20.27
Free combo	282	185.00 (66.96)	18.68 (1.96)	14.84, 22.52
Budesonide 160	272	177.02 (64.58)	5.25 (1.98)	1.36, 9.15
Formoterol 4.5	281	182.73 (66.19)	9.82 (1.95)	5.99, 13.65
Placebo	291	(b) (4)		-3.31, 4.20
Evening PEF (L/min)				
Symbicort HD	270	(b) (4)		11.91, 19.81
Symbicort LD	278	191.19 (70.78)	14.48 (1.98)	10.60, 18.36
Free combo	280	195.10 (70.35)	17.17 (1.99)	13.27, 21.06
Budesonide 160	272	186.11 (65.15	3.19 (2.00)	-0.74, 7.13
Formoterol 4.5	279	192.09 (67.05)	8.13 (1.98)	4.25, 12.02
Placebo	289	(b) (4)		-3.25, 4.37
(b) (4)	(b) (4)			

Source: SHINE CSR, Section 7.2.6.1, Table 54, p. 170

Table 36 SHINE: AM and PM PEF (L/min): Primary treatment comparisons for change from baseline

Comparison	Average Of Randomized Treatment Period	
	LS Mean (SEM)	95% CI, p-value
Morning PEF (L/min)		
Symbicort HD vs. Placebo	18.91(2.61)	13.79, 24.02 ($p < 0.001$)
Symbicort LD vs. Placebo	15.99 (2.59)	10.92, 21.07 ($p < 0.001$)
Evening PEF (L/min)		
Symbicort HD vs. Placebo	15.30 (2.64)	10.12, 20.48 ($p < 0.001$)
Symbicort LD vs. Placebo	13.92 (2.62)	8.78, 19.06 ($p < 0.001$)

Source: SHINE CSR, Section 7.2.6.1, Table 55, p. 171

In terms of the primary comparisons, results indicate that both dosage strengths of Symbicort demonstrated a statistically significant change for morning and evening PEF compared with placebo, from baseline to the average during the randomized treatment period.

Reviewer's comment: (b) (4) *The magnitude of the change is much smaller than what is reported for asthma. Further, PEF is not a measure that is usually followed for COPD patients. Lastly,* (b) (4)

(b) (4)

5. Breathlessness Cough Sputum Score, Sleep Score, and Rescue Medication Use

- **Breathlessness Cough Sputum Score (BCSS):** comprised of the dyspnea, cough, and sputum scores, each rated from 0-4, with higher scores indicating a more severe manifestation of symptoms.
- **Sleep score:** is also rated on a 0-4 scale with a higher score indicating greater sleep disturbance.
  Reviewer's comment: (b) (4)
- **Rescue medication use**: is specifically referring to total daily use in puffs/day of study-provided B2-agonist rescue medication (albuterol or salbutamol).

Table 37 summarizes the treatment means and treatment comparisons for each of the aforementioned secondary efficacy variables, concentrating on the primary comparison of Symbicort HD versus placebo.

Table 37 SHINE: BCSS, Sleep Score, and Rescue Medication Use: Treatment means and primary treatment comparisons for change from baseline

Comparison	Average Of Randomized Treatment Period			
	Baseline value Mean (SD)	**Change from Baseline LS Mean (SEM) [95% CI]**	**LS Mean (SEM)**	**95% CI (p-value)**
BCSS (0-12)				
Symbicort HD [N=271]	(b) (4)	[-0.83, -0.46]		
Placebo [N = 291]		[-0.50, -0.15]		
Symbicort HD vs. Placebo			-0.32 (0.12)	-0.56, -0.08 P = 0.010
Sleep Score (0-4)				
Symbicort HD [N = 269]		[-0.35, -0.21]		
Placebo [N = 290]		[-0.22, -0.09]		
Symbicort HD vs. Placebo			-0.12 (0.05)	-0.21, -0.03 P = 0.007
Rescue Medication use (puffs/day)				
Symbicort HD [N = 269]		-1.41, -0.81]		
Placebo [N = 289]		[-0.57, 0.01]		
Symbicort HD vs. Placebo			-0.83 (0.20)	-1.22, -0.44 P < 0.001
(b) (4) (b) (4)				

Source: SHINE CSR, Section 7.2.6.2, Tables 56 and 57, p. 172-177.

The results for COPD symptoms and rescue medication use as measured by the BCSS, Sleep score, and rescue medication use averaged over the randomized treatment period indicate Symbicort HD was statistically better than placebo in terms of all variables.

Reviewer's comment: Although statistical significance was achieved, the clinical significance of these findings remains uncertain. Further, for the reasons stated above, (b) (4) *For these reasons and those stated in previous reviewer's comments, we may allow the Applicant to make a general statement regarding these findings as being supportive* (b) (4)

6. Health Economics Results

For most variables, there were no statistically significant differences seen for COPD-related resource utilization for either Symbicort HD or LD compared to placebo.

7. Pharmacokinetic Results

Two hundred thirty-eight (238) subjects underwent PK sampling over the 12 hours post-dose at the end of Month 6. AUC_{0-12}, C_{max}, and T_{max} were calculated for each subject. The following is a summary of these results. For details regarding the analysis, refer to the Biopharmaceutics Review of Dr. Partha Roy. A summary of the results is provide below:

- Generally comparable systemic exposure between Symbicort, budesonide pMDI and co-administration of budesonide pMDI and Form TBH
- A slight formulation effect for formoterol with an increase in exposure by 16-18% from Symbicort compared to co-administration of individual products.
- Budesonide appears have a small effect (~12% increase in AUC) on formoterol exposure while there was lack of any measurable effect on budesonide exposure in the presence of formoterol.
- Formoterol exposure (AUC) from Symbicort 160/4.5 mcg appears to be about 30% higher compared to formoterol TBH
- Budesonide as well as formoterol exposure (AUC) in COPD patients appear to be about 12-16% higher compared to asthma patients.

In summary, Symbicort HD showed superiority over formoterol for pre-dose FEV1, and over budesonide for post-dose FEV1. Symbicort LD failed to show the contribution of budesonide when examined in terms of pre-dose FEV1. Both dosage strengths showed superiority over placebo for each of the co-primary efficacy variables. Response to treatment was unattenuated over the 6 month randomized study period. Dyspnea scores as measured by the Breathlessness Diary, SGRQ, and COPD exacerbations were defined as key secondary endpoints. For various reasons as stated in the review, (b) (4) of these secondary endpoints are not supported, although they are generally supportive of the efficacy of Symbicort.

Additional secondary endpoints, including spirometric and non-spirometric variables were also examined. Notably, serial FEV1 testing supported the 12 hour dosing interval in COPD patients, and a median time to 15% onset of bronchodilation of approximately 6 minutes for Symbicort HD. Of the other secondary efficacy variables, although some achieved statistical significance, their clinical significance in COPD remains unclear.

Safety Assessments

Extent of Exposure

The extent of exposure in terms of duration of treatment is summarized in Table 38 below.

Table 38 SHINE: Extent of exposure

Exposure	Treatment groups					
	SYMB HD N = 277	SYMB LD N = 281	Free Comb N = 287	Budesonide N = 275	Formoterol N = 284	Placebo N = 300
Duration of randomized treatment (days)						
Mean (SD)	166 (41.29)	168.3 (37.73)	164.6 (40.27)	157.1 (51.31)	156.3 (53.22)	150 (60.15)
Median	181	181	180	181	180	180
Number (%) of subjects remaining on randomized treatment at start of each time period						
> 4 wks	268 (96.8)	276 (98.2)	282 (98.3)	261 (94.9)	265 (93.3)	271 (90.3)
> 8 wks	263 (94.9)	268 (95.4)	272 (94.8)	250 (90.9)	252 (88.7)	252 (84.0)
> 12 wks	255 (92.1)	262 (93.2)	263 (91.6)	237 (86.2)	242 (85.2)	243 (81.0)
> 16 wks	252 (91.0)	255 (90.7)	255 (88.9)	232 (84.4)	237 (83.5)	239 (79.7)
> 20 wks	244 (88.1)	250 (89.0)	247 (86.1)	219 (79.6)	232 (81.7)	235 (78.3)
> 24 wks	240 (86.6)	246 (87.5)	236 (82.2)	216 (78.5)	225 (79.2)	228 (76.0)
> 28 wks	2 (0.7)	3 (1.1)	1 (0.3)	3 (1.1)	2 (0.7)	4 (1.3)

Source: SHINE CSR, Section 8.2, Table 66, p. 201.

A total of 1704 subjects received at least 1 dose of study medication. The majority of the subjects in each treatment group received randomized treatment for at least 24 weeks and completed the planned 6 month treatment duration. Mean exposure was shortest in the placebo group (150 days) and longest in the Symbicort LD group (168 days). The percentage of subjects completing treatment was also lowest in the placebo group (76%) and highest in the two Symbicort groups (HD and LD: 87%). There were no important differences in exposure across treatment groups when analyzed by subgroups of age, race, and gender. Differences in duration of exposure between the Symbicort and placebo groups were greatest in the US due to higher rates of premature discontinuation in the placebo and monoproduct groups (SHINE CSR, Table 11.1.2.1).

Adverse Events

1. Deaths

There were 11 deaths during randomized treatment period (see Table 39): Three in the Symbicort HD group, 4 in the Symbicort LD group, 2 in the budesonide group, 1 in the formoterol group, and 1 in the placebo group. Of these deaths, 5 were reported due to cardiovascular events, 3 were due to COPD, 1 was due to both cardiovascular causes and COPD,

1 was due to cancer, and 1 was due to multiple co-morbidities. Deaths were unevenly distributed across the countries with 6 of the 11 occurring in Poland. All 4 deaths from COPD exacerbations occurred in current smokers with severe COPD at baseline. [Module 5, Shine CSR, Section 8.4.1, p. 230]

Table 39 SHINE: Deaths by treatment group and primary cause of death

Primary events leading to death*	SYMB HD N = 277	SYMB LD N= 281	BUD N= 275	FORM N= 284	Placebo N = 300
Total Deaths	3	4	2	1	1
Lung Cancer (metastatic)	1	0	0	0	0
Cardiac failure	2	1	0	1	0
COPD exacerbated	0	3	1	0	0
Cerebrovascular Accident	0	0	1	0	1

* Event grouping by reviewer
Note: There were no deaths in the Budesonide/Formoterol free combination group
Source: Module 5, SHINE CSR, Table 79, p. 231-2.

Reviewer's comment: Overall, there were relatively few deaths in this study, considering the severity of COPD in the study population and the presence of co-morbid conditions. Review of the narratives and the causes of death do not suggest a particular safety signal.

2. Serious adverse events

Serious AEs occurred in 9.4% of the overall study population, including 11.2% of the Symbicort HD group, 10.7% Symbicort LD, 9.1% free combination, 9.5% budesonide, 8.1% formoterol, and 8.3% placebo for a total of 161 patients with a SAE.

- The most common serious adverse event was COPD, occurring in 6.1% of the Symbicort HD group, 4.6% of the Symbicort LD group, 4.5% of the free combination group, 3.6% of the budesonide group, 3.9% of the formoterol group, and 4.3% of the placebo group in a total of 77 subjects.
- There were 19 serious cardiac events, including the AE terms of atrial fibrillation, congestive failure, acute myocardial infarction, angina pectoris, coronary artery disease, and myocardial ischemia. Of these events, 3 occurred in the Symbicort HD group, 3 in the Symbicort LD group, 2 in the free combination group, 5 in the budesonide group, 3 in the formoterol group, and 3 in the placebo group.
- There were 17 serious respiratory infections including AE terms of pneumonia (n=13) and other lung infections (n=4). The events are described by treatment group under "adverse events of interest" below. [Module 5, SHINE CSR, Section 8.4.2.1, Table 81, p. 240]

3. Adverse events leading to discontinuation (DAEs)

Discontinuations due to adverse events occurred in 7.8% of the overall population, including 6.9% in the Symbicort HD group, 6.8% Symbicort LD, 4.5% free combination, 9.1% budesonide, 11.3% formoterol, and 8.3% placebo, for a total of 133 patients with a DAE. The were a greater number of DAEs in the formoterol group (placebo 8.3%, formoterol, 11.3%, budesonide 9.1%, free combination 4.5%, Symbicort LD 6.8%, and Symbicort HD 6.9%). This was due to a greater number of adverse events related to COPD in the formoterol group (placebo 5%, formoterol 7.4%, budesonide 5.8%, free combination 4.5%, Symbicort LD 3.6%, and Symbicort HD 2.9%). Of note, there were 8 discontinuations due to respiratory infections, including pneumonia and other lung infections. These events are described by treatment group under "adverse events of interest" below; of note, the most discontinuations secondary to any of these respiratory tract infections were fairly evenly distributed among treatment groups. [Module 5, SHINE CSR, Section 8.4.3.1, Table 82, p. 242]

4. Overall adverse events

Adverse events (AEs) were reported in 54% of the patients: 57.4% in Symbicort HD, 52.3% in Symbicort LD, 49.5% in free combination, 57.5% in budesonide, 56.7% in formoterol, and 50.7% in placebo. COPD was the most frequently reported AE, with the highest incidence in the formoterol group. The incidence of COPD was also slightly higher in the Symbicort HD group compared to placebo. Oral candidiasis occurred with greater incidence in the budesonide and Symbicort HD groups, consistent with the known effect of inhaled steroids. Additionally, bronchitis was noted with slightly higher incidence in the higher dose budesonide arms are compared with placebo. In each treatment group, most AEs were rated as mild or moderate in intensity. The distribution of severity grading was similar across treatment groups. COPD was the only adverse event that was reported by at least 1% of the subjects all treatment groups for which the percentage of subjects with a severe event represented more than 25% of the events. Adverse events occurring in ≥ 3% of patients in any treatment group are presented in Table 40.

Table 40 SHINE: Adverse events occurring in ≥ 3% of subjects by treatment group

MedDRA System Organ Class MedDRA Preferred Term	Treatment					
	SYMB HD N (%)	SYMB LD N (%)	Bud/Form N (%)	Budesonide N (%)	Formoterol N (%)	Placebo N (%)
Total treated	277 (100.0)	281 (100.0)	287 (100.0)	275 (100.0)	284 (100.0)	300 (100.0)
Total with AE	159 (57.4)	147 (52.3)	142 (49.5)	158 (57.5)	161 (56.7)	152 (50.7)
Respiratory System Disorders (Lower)	56 (20.2)	54 (19.2)	42 (14.6)	65 (23.6)	73 (25.7)	60 (20.0)
Bronchitis	10 (3.6)	4 (1.4)	10 (3.5)	8 (2.9)	8 (2.8)	6 (2.0)
COPD	27 (13.4)	34 (12.1)	30 (10.5)	34 (12.4)	50 (17.6)	35 (11.7)
(Upper)						
Nasopharyngitis	21 (7.6)	11 (3.9)	12 (4.2)	9 (3.3)	15 (5.3)	16 (5.3)
Sinusitis	8 (2.9)	9 (3.2)	9 (3.1)	4 (1.5)	5 (1.8)	6 (2.0)
Infection and infestations	88 (31.8)	74 (26.3)	69 (24.0)	73 (26.5)	78 (27.5)	68 (22.7)
Oral Candidiasis	10 (3.6)	7 (2.5)	8 (2.8)	12 (4.4)	7 (2.5)	6 (2.0)
Gastrointestinal disorders	22 (7.9)	25 (8.9)	17 (5.9)	20 (7.3)	19 (6.7)	15 (5.0)
Diarrhea	3 (1.1)	5 (1.8)	4 (1.4)	3 (1.1)	9 (3.2)	1 (0.3)

Source: Module 5, SHINE CSR, Section 8.3.2.1, Tables 68 and 69, p. 207, 209

a) Adverse events of interest

Specific categories of AEs of interest associated with ICS or B2-agonists were evaluated by the Applicant.

ICS

- Oral candidiasis/voice effects: reported with slightly higher incidence in the budesonide containing groups versus placebo (Symbicort HD 6.9%, Symbicort LD 3.2%, free combination 3.1%, budesonide 5.5%, placebo 2.3%).
- Bone effects, diabetes control, skin effects, weight gain, ocular effects, taste effects, and adrenal suppression – reported with low and similar incidence across all treatment groups
- Pneumonia

Pneumonia-related preferred terms were evaluated due to recent findings in studies with salmeterol/fluticasone in subjects with COPD that indicated a higher rate of pneumonia in all groups receiving ICS (1-3). For pneumonia related preferred terms, no clinically important differences were seen with the overall incidence across the treatment groups ranging from 1.0% in the free combination group to 2.5% in the Symbicort LD group. There was no consistent effect in terms of dose-response for budesonide. However, when this data was added to "potential lung infections other than pneumonia", which contained preferred terms that could potentially represent lower respiratory tract infections other than pneumonia, there was a higher incidence in those groups treated with budesonide as compared with placebo. There was a numerical trend towards increased lung infections with higher doses of steroids (Symbicort HD 8.7%, Symbicort LD 5.7%). See Table 41.

Reviewer's comment: The link between ICS and lung infection is not definitive as the formoterol monotherapy arm also had a 6.7% incidence of lung infections which was numerically greater than the placebo group (4.3%). It is also of note that the Sponsor has subjects with multiple events in the same category only once in that category. This could underestimate the incidence of lung infections.

Table 41 SHINE: Subjects with Pneumonia AEs or Other Lung Infection AEs of Interest by MedDRA preferred term, during randomized treatment

MedDRA Preferred Term	Treatment					
	SYMB HD N (%)	SYMB LD N (%)	Bud/Form N (%)	Budesonide N (%)	Formoterol N (%)	Placebo N (%)
Total treated N (%)	277 (100.0)	281 (100.0)	287 (100.0)	275 (100.0)	284 (100.0)	300 (100.0)
Total AEs	**24 (8.7)**	**16 (5.7)**	**20 (7.0)**	**21 (7.6)**	**18 (6.3)**	**13 (4.3)**
Pneumonia N (%)	**3 (1.1)**	**7 (2.5)**	**3 (1.0)**	**5 (1.8)**	**5 (1.8)**	**4 (1.3)**
Pneumonia	3 (1.1)	6 (2.1)	3 (1.0)	5 (1.8)	3 (1.1)	3 (1.0)
Bronchopneumonia	0	1 (0.4)	0	0	1 (0.4)	1 (0.3)
Pneumonia pneumococcal	0	0	0	0	1 (0.4)	0
Other Lung Infections	**21 (7.6)**	**9 (3.2)**	**18 (6.3)**	**17 (6.2)**	**13 (4.6)**	**10 (3.3)**
Bronchitis	10 (3.6)	4 (1.4)	10 (3.5)	8 (2.9)	8 (2.8)	6 (2.0)
Bronchitis Acute	8 (2.9)	3 (1.1)	5 (1.7)	5 (1.8)	3 (1.1)	3 (1.0)
LRTI, bacterial	2 (0.7)	1 (0.4)	2 (0.7)	1 (0.4)	2 (0.7)	0
LRTI	1 (0.4)	0	1 (0.3)	0	0	1 (0.3)
LRTI, viral	0	0	0	2 (0.7)	0	0
Lung infection	0	0	0	1 (0.4)	0	0
Sputum purulent	0	0	0	0	1 (0.4)	0
Tracheobronchitis	0	1 (0.4)	0	0	0	0

Source: Module 5, SHINE CSR, Section 8.3.3.1, Tables 70, 72, 11.3.2.6.14, p. 210-212,

Reviewer's comment: An information request was sent to the Sponsor to resolve some perceived discrepancy in the numbers in Table 21. This may be related to how the Sponsor has only counted subjects with multiple events in the same category once in the category. The highlighted numbers in Table 21 are those in question.

In response to our information request, the Applicant has clarified that the numbers presented above are presented as the number and percentage of subjects with pneumonia or other lung infection AEs of interest, rather than the number of AEs in these categories. An individual subject could have experienced an AE in more than a single preferred term

(PT) category (for example, an AE of pneumonia, as well as AE of bronchitis). In such cases, the subject was counted for each PT. Hence in the Bud/Form group, 1 subject apparently experienced at least 1 AE in 2 PT categories.

Because subjects with multiple events in the same PT category were counted only once in that category, this reviewer also requested that the data be presented so that multiple events were counted individually in each category. The Applicant provided this data in the response dated November 25, 2008. This information is presented in Table 42.

Table 42 SHINE: Number of Pneumonia and Other lung infection AEs per Treatment Year [AE per subject treatment year]

MedDRA Preferred Term	Treatment					
	SYMB HD	SYMB LD	Bud/Form	Budesonide	Formoterol	Placebo
N = total exposure days	461222	47300	47240	43216	44380	44998
Total AEs	**27**	**18**	**22**	**25**	**20**	**15**
Pneumonia (Total)	**3**	**7**	**3**	**5**	**5**	**4**
Pneumonia	3 [0.024]	6 [0.046]	3 [0.023]	5 [0.042]	3 [0.025]	3 [0.024]
Bronchopneumonia	0	1 [0.008]	0	0	1 [0.008]	1 [0.008]
Pneumonia pneumococcal	0	0	0	0	1 [0.008]	0
Other Lung Infections (Total)	**24**	**11**	**19**	**20**	**15**	**11**
Bronchitis	10 [0.079]	5 [0.039]	10 [0.077]	10 [0.084]	9 [0.074]	7 [0.057]
Bronchitis Acute	11 [0.087]	4 [0.031]	5 [0.039]	6 [0.051]	3 [0.025]	3 [0.024]
LRTI, bacterial	2 [0.016]	1 [0.008]	2 [0.015]	1 [0.008]	2 [0.016]	0
LRTI	1 [0.008]	0	2 [0.015]	0	0	1 [0.008]
LRTI, viral	0	0	0	2 [0.017]	0	0
Lung infection	0	0	0	1 [0.008]	0	0
Sputum purulent	0	0	0	0	1 [0.008]	0
Tracheobronchitis	0	1 [0.008]	0	0	0	0

Source: Module 5, SHINE CSR, Section 8.3.3.1, Tables 70, 72, 11.3.2.6.14, p. 210-212,

Reviewer's comment (cont'd): It is notable that when events were counted rather than subjects experiencing events, the overall numbers did not change appreciably. The number of bronchitis/acute bronchitis AEs increased slightly, indicating that one or more subjects may have experienced multiple episodes of bronchitis. However, the pneumonia signal remained exactly as it was in Table 41.

Reviewer's comment: An information request was sent to the Sponsor to clarify the numbers of pneumonias and other lung infections which were SAEs and cause for discontinuation (DAEs). This reviewer wanted to ensure that although there did not

appear to be an increase in the overall incidence of pneumonias with Symbicort, that the severity of pneumonia and other lung infections was not greater in the active treatment group as well. The Applicant replied to the information request with the following tables as requested by this reviewer. From the data provided below, there were not significantly more DAEs due to either pneumonia or other lung infections when Symbicort treatment groups were compared to non-ICS treatment groups, however there were numerically more SAEs due to these adverse events of interest. This result was not seen in the 12 month study, and with such a small number of events, it is difficult to draw any firm conclusions. The number of pneumonias and other lung infections that were reported as SAEs and DAEs have been updated in the previous respective sections.

Number and % of subjects with pneumonia or other lung infections SAES during randomized treatment - SHINE

	SYMB 160	SYMB 80	Bud + form	Bud 160	Form	Placebo	Total
Pneumonia (all MedDRA PTs)	1 (0.4)	3 (1.1)	2 (0.7)	3 (1.1)	3 (1.1)	1 (0.3)	13 (0.8)
Other lung infections (all MedDRA PTs)	1 (0.4)	3 (1.1)	0	0	0	0	4 (0.2)

Number and % of subjects with DAEs due to pneumonia or other lung infection during randomized treatment – SHINE

	SYMB 160	SYMB 80	Bud + form	Bud 160	Form	Placebo	Total
Pneumonia (all MedDRA PTs)	0	0	0	1 (0.4)	1 (0.4)	1 (0.3)	3 (0.2)
Other lung infections (all MedDRA PTs)	1 (0.4)	0	1 (0.3)	1 (0.4)	1 (0.4)	1 (0.3)	5 (0.3)

B2-agonists
The incidence of cardiac-related AEs was higher in the Symbicort HD and LD groups (5.1% and 5.3%, respectively) than in the placebo group (4.0%), but was similar to that in the formoterol group (4.6%) and lower than that in the budesonide group (6.5%).

5. Subgroup analysis of adverse events

There were no clinically important differences in the incidence, types or intensities of AEs across the age, gender, and racial groups. There were no apparent differences in the overall incidence or types of AEs between current and ex-smokers other than a higher incidence of COPD AEs in current smokers than in ex-smokers among subjects in the Symbicort groups and free combination group. The overall incidence of AEs, as well as the incidence of AEs per subject treatment year was higher in the US than in the non-US region. There were clinically important differences in the incidence of overall AEs but not individual AEs, across the US and non-US regions.

Laboratory Evaluation (Hematology, Chemistry, Urinalysis)

The Applicant presented the laboratory data as mean change from baseline, shift tables, and clinically significant changes. These data were reviewed. Overall, the changes in the laboratory values throughout the study were small. There were no clinically important differences between treatment groups. Symbicort 160/4.5 mcg exhibited statistically significant (~30%) suppression of 24h-UFC levels following chronic twice daily inhalation administration in COPD patients relative to placebo.

24 hr Urinary Free Cortisol

HPA-axis assessment via measurement of 24-hour urinary free cortisol was conducted in a subset of patients in both SUN (n=179) and SHINE (n=437). See Figure 27 under SUN study for further details. Statistically significant differences (~30% suppression) by ANCOVA were seen between the Symbicort HD and placebo groups at 6 months and between Symbicort HD and formoterol at the end of treatment. A total of 4 subjects had a shift from normal at baseline to low (< 5.5 nmol/24h) at the end of treatment. The number and proportion of subjects with these shifts was evenly distributed across treatment groups. A dose-ordered response for budesonide was not observed for shifts from normal to low at 6 months or end of treatment.

ECG findings

There were no clinically important treatment group differences in mean change from baseline, shifts from baseline, or in the incidence of clinically important abnormalities for pre-dose or 1 hour post-dose QRS duration, PR interval, or heart rate. For QT, QTcB, and QTcF, there were similarly no differences.

Vital Signs/Physical Examination

The Applicant presented the vital signs (including systolic/diastolic blood pressure, heart rate, and weight) as changes in mean values over time, shift tables, and clinically significant changes. These data were reviewed. Overall, the changes in values was small, and there were no clinically important differences between treatment groups.

10.1.3 Conclusions

SHINE was a double-blind, double-dummy, randomized, parallel group, multicenter study in patients with COPD for a duration of 6 months (26 weeks). The objective of this study was to demonstrate the efficacy and safety of Symbicort for the maintenance treatment of patients with COPD compared to its mono-products and placebo.

A total of 1704 patients were randomized at 180 centers. Overall, discontinuation from the study was higher in the single ingredient treatment arms as compared with the Symbicort and free combination arms, and highest in the placebo arm. In each of the treatment arms, either adverse events or withdrawal of consent was the most likely reason for discontinuation. Of the 1704 patients randomized, 1378 patients completed the study, and a total of 326 patients discontinued

There was a greater percentage of male than female subjects consistent with the disease prevalence in the target population. Most subjects were Caucasian, with fewer than 7% non-Caucasian patients. Approximately half of the subjects were over age 65, with approximately 12% of subjects over the age of 75 years. Baseline percent predicted FEV1, post-bronchodilator percent predicted FEV1, and smoking history (pack years) were well balanced across all treatment groups. Severity classification, based on the GOLD 2006 criteria applied to post-bronchodilator FEV1 at Visit 1, indicated that approximately 80% of the study population had severe or very severe COPD, while 20% had moderate COPD at entry. In general, demographic and key baseline characteristics were similar across treatment groups and geographic regions (US vs. non-US).

The co-primary variables were change from baseline to endpoint in pre-dose FEV1, to demonstrate the anti-inflammatory contribution of budesonide, and post-dose FEV1, to demonstrate the bronchodilator contribution of formoterol, to the efficacy of the combination product, Symbicort. Each co-primary variable was calculated as an average over the randomized treatment period (primary analysis) and at the end-of-treatment. In terms of the pre-specified primary comparisons, results indicate that only Symbicort HD demonstrated a statistically significantly greater increase from baseline in pre-dose FEV1 when compared with formoterol. This result was consistent when analyzed as the average of the randomized treatment period or at the end of treatment. Symbicort LD failed to show the contribution of the inhaled corticosteroid to the efficacy of the combination product in both analyses. Both dosage strengths of Symbicort demonstrated statistically significant difference in pre-dose FEV1 vs. placebo when examined as the average of the randomized treatment period, but Symbicort LD was not statistically different from placebo at the end of treatment. In both analyses, Symbicort HD was not statistically different when compared with Symbicort LD in terms of change from baseline in pre-dose FEV1. Symbicort HD demonstrated improvements in pre-dose FEV1 that were apparent at Month 1 and were generally maintained over the 6-month study period. These results demonstrate that the higher dose of budesonide makes a contributed to the efficacy of the combination product, however the lower dose does not.

For post-dose FEV1, results indicate that both dosage strengths of Symbicort demonstrated a statistically significantly greater increase from baseline in post-dose FEV1 when compared with

budesonide. This result was consistent when analyzed as the average of the randomized treatment period or at the end of treatment. Both dosage strengths of Symbicort demonstrated statistically significant difference in post-dose FEV1 vs. placebo when examined as the average of the randomized treatment period and at the end of treatment. These results demonstrate that formoterol makes a contribution to the efficacy of both strengths of the combination product.

Dyspnea scores as measured by the Breathlessness Diary, SGRQ, and COPD exacerbations were defined as key secondary endpoints. For various reasons as stated in the review, the findings of these secondary endpoints are not supportive of the primary endpoints. Additional secondary endpoints, including spirometric and non-spirometric variables were also examined. Notably, serial FEV1 testing supported the 12 hour dosing interval in COPD patients, and a median time to 15% onset of bronchodilation of approximately 6 minutes for Symbicort HD. Of the other secondary efficacy variables, although some achieved statistical significance, their clinical significance in COPD remains unclear.

The extent of exposure was generally similar between the active treatment groups and placebo, and was satisfactory to allow for safety assessments. There were 11 deaths during the randomized treatment period, but their distribution or cause did not suggest a particular safety signal. The incidence of SAEs and DAEs were generally similar across treatment groups; the most common SAE and reason for discontinuation was COPD. The most common adverse events were bronchitis, COPD, nasopharyngitis, sinusitis, oral candidiasis, and diarrhea. Examination of adverse events of interest with B2-agonists did not reveal any new safety signals or imbalances across treatment groups. No clinically meaningful changes in laboratory findings, ECGs, vital signs, or physical examination were noted.

Pneumonia-related preferred terms were evaluated due to recent findings in studies with salmeterol/fluticasone in subjects with COPD that indicated a higher rate of pneumonia in all groups receiving ICS. For pneumonia related preferred terms, no clinically important differences were seen with the overall incidence across the treatment groups ranging from 1.0% in the free combination group to 2.5% in the Symbicort LD group. There was no consistent effect in terms of dose-response for budesonide. However, when this data was added to "potential lung infections other than pneumonia", which contained preferred terms that could potentially represent lower respiratory tract infections other than pneumonia, there was a higher incidence in those groups treated with budesonide as compared with placebo. There was a numerical trend towards increased lung infections with higher doses of steroids (Symbicort HD 8.7%, Symbicort LD 5.7%).

To summarize, "lung infections other than pneumonia" may be a new safety signal noted with Symbicort and has been added to the product label by the Sponsor. No other new safety concerns arose from the review of the data in COPD patients as compared with what has been reported in the Symbicort product label and other ICS/LABA combination products. In conclusion, the SHINE study supports the safety and efficacy of Symbicort HD BID in the treatment of patients with COPD.

10.2 Individual Study Report: Study D5899C0001 (SUN)

Protocol #:	D5899C0001 (SUN)
Title:	A 12-Month, Double-blind, Double-dummy, Randomized, Parallel group, Multicenter Efficacy & Safety Study of SYMBICORT pMDI 2 x 160/4.5 mcg bid & Symbicort pMDI 2 x 80/4.5 mcg bid Compared Formoterol TBH 2 x 4.5 mcg bid and Placebo Patients with COPD (SUN)
Study Dates:	Initiated April 4, 2005. Completed September 27, 2007.
Sites:	Total of 237 Centers: 144 centers in the U.S. 26 centers in Hungary. 26 centers in Germany. 13 centers in Denmark. 9 centers in Bulgaria. 6 centers in Greece. 6 centers in Romania. 5 centers in Mexico. 2 centers in Iceland
Investigator:	Stephen I. Rennard MD University of Nebraska Medical Center Division of Pulmonary and Critical Care Medicine

Reviewer's Comment: For the purposes of this review, the following notations will be used:

- *Symbicort HD or Symbicort 320/9 mcg will be used to denote 2 actuations of the 180/4.5 mcg device*
- *Symbicort LD or Symbicort 160/9 mcg will be used to denote 2 actuations of the 80/4.5 mcg device*
- *Formoterol 9 mcg will be used to denote 2 actuations of the 4.5 mcg Turbuhaler (TBH) device*

The protocol for Study D5899C0001 is very similar to that of D5899C0002 (See 10.1 Individual Study Report: Study D5899C0002 (SHINE). This reviewer will therefore highlight the differences and refer to the appropriate section of Study D5899C0002 when applicable.

10.2.1 Study Design/Protocol

The objective of this study was to demonstrate the efficacy and safety of Symbicort for the maintenance treatment of patients with COPD compared to formoterol and placebo.

Objectives

The **primary objectives** of this study in hierarchical order were:

- To show that Symbicort 320/9 mcg BID is effective in patients with COPD, when compared with placebo and Formoterol 9 mcg BID with regard to its effect on pre-dose FEV1 and when compared to placebo with regard to its effect on 1 hour post-dose FEV1.
- To show that Symbicort 160/9 mcg BID is effective in patients with COPD, when compared with placebo and Formoterol 9 mcg BID with regard to its effect on pre-dose FEV1 and when compared to placebo with regard to its effect on 1 hour post-dose FEV1.

Pertinent **secondary variables** measured to compare the efficacy of Symbicort HD and LD BID with placebo and formoterol included:

- Dyspnea using Breathlessness Diary
- Health-related quality of life as measured by SGRQ total score
- Number of COPD exacerbations

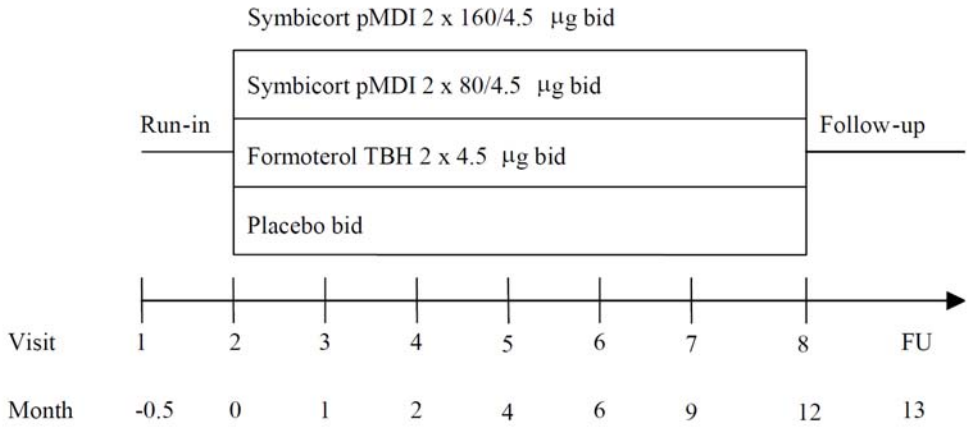
Other **secondary variables** to be measured included:
- Serial FEV1 – onset of effect and maintenance of effect at 12 hours (in a subgroup of patients)
- FVC
- Morning and evening PEF
- Inspiratory capacity (pre dose and 1 hour post-dose) (in a sub-group of patients)
- COPD symptoms (excluding dyspnea which is listed above)
    - Rescue medication use (B2 agonists)
    - Cough
    - Sputum
    - Night-time awakenings (sleep score)
- Health care utilization

Safety objectives of the study included measurement of:
- Adverse Events (AEs)
- Laboratory Evaluation (Hematology/Chemistry/Urinalysis/24 hour urinary free cortisol)
- Vital Signs
- 24 hour Holter monitoring (in a subgroup of patients)
- 12-lead ECGs
- Ophthalmologic assessment (in a subgroup of patients)
- Bone Mineral Density (BMD) (in a subgroup of patients)
- Physical Examination

Description

SUN was a double-blind, double-dummy, randomized, placebo-controlled, parallel group, multicenter study in patients with COPD, consisting of 12 month (52 weeks) of treatment, in which patients were assigned to one of four treatment arms (see Figure 20).

Figure 20 SUN: Study Design Diagram



The study consisted of an initial visit, a 2 week-run in period, 7 further visits during a 52-week treatment period and a 4-week follow-up telephone call. Prior to Visit 1, fixed dose combination therapy was to be replaced with a comparable dose of ICS monotherapy and a short-acting inhaled B2 agonist. Patients using either long-acting beta agonists or anticholinergics were to be converted to a short-acting bronchodilator of the same class. Between Visits 1 and 2, patients were allowed to continue use of inhaled steroids and/or short-acting inhaled bronchodilators. At Visit 2, treatment with ICS was to be discontinued, and all eligible patients randomized to receive one of the six study treatments listed in Figure 20. In addition, at Visit 2, all patients will also be given albuterol/salbutamol pMDI rescue medication to be used as required for the relief of bronchospasm. The study schedule is depicted in Table 43.

Table 43 SUN: Study schedule

Study plan	Run -In	Treatment							FU[a]
Month	**-0.5**	**0**	**1**	**2**	**4**	**6**	**9**	**12**	**13**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8[b]**	**FU**
Informed consent[c]	x								
Demography	x								
Medical and smoking history	x								
Inclusion/exclusion criteria	x	x							
Full physical examination	x							x	
Brief physical examination		x	x	x	x	x	x		
Vital signs	x[d]	x[e]	x	x	x	x	x	x[e]	
Clinical chemistry, hematology and urinalysis	x							x	
Pregnancy test	x							x	
24-hour urine collection[f] (I=issue, C=collect)	I	C			I	C	I	C	
ECG		x				x		x	
Holter ECG monitoring[6]	x		x						
Reversibility Test	x								
Lung function (FEV_1, FVC)	x	x[g]	x[g]	x[g]	x[g]	x[g]	x[g]	x[g]	
Serial FEV_1 and IC[f]		x	x						
Bone mineral density[f]	x							x	
Ophthalmologic assessments[f]	x							x	
Adverse events		x	x	x	x	x	x	x	x
Concomitant medication	x	x	x	x	x	x	x	x	x
SGRQ	x	x[h]	x[h]	x[h]		x[h]		x[h]	
Resource utilization		x	x	x	x	x	x	x	x
Diary card (I=issue, R = return and review)	I	I/R	I/R	I/R	I/R	I/R	I/R	R	
Dispense peak flow meter and instruct in use	x								
Randomization		x							
Study drug (D=dispense, R=return)		D		D/R	D/R	D/R	D/R	R	

a Follow-up telephone contact
b To be completed by patients that prematurely discontinue
c Signed and dated informed consent may be obtained at an information visit prior to Visit 1
d Including height
e Including weight
f Tests to be performed in a subgroup of patients
g Pre-dose and 1 hour post-dose
h SGRQ performed before all other assessments

Population

Approximately 1500 patients were to be randomized from 200 centers from the US and other countries. The patients enrolled were to be of either sex, ≥ 40 years of age with a FEV_1≤ 50% of predicted normal value pre-bronchodilator, have FEV_1/FVC <70% pre-bronchodilator, a clinical diagnosis of COPD with symptoms for ≥ 2 years, current or previous smoker with a smoking history of ≥10 pack years, score of ≥ 2 on the MMRC dyspnea scale, a total symptom score (based on breathlessness, cough and sputum) of ≥ 2 per day for at least half of the run-in period, a history of at least one COPD exacerbation requiring a course of oral steroids within 1-12 months before Visit 1, use short-acting inhaled bronchodilator (beta-agonists or anticholinergics) as rescue medication, no history of asthma, and no history of allergic rhinitis before 40 years of age.

The inclusion, exclusion, and discontinuation criteria were identical to those in the SHINE study (see Appendix 10.1, Population, p. 70).

Treatments

- Study Treatments

Table 44 SUN: Study Treatments

Treatment Group	Dosage Strength (mcg)	Dosing Regimen
Symbicort HD (budesonide/FF)	160/4.5	2 x 160/4.5 mcg BID = **320/9 mcg BID**
Symbicort LD (budesonide/FF)	80/4.5	2 x 80/4.5 mcg BID = **160/9 mcg BID**
Formoterol DPI (Oxis Turbuhaler)	4.5	2 x 4.5 mcg BID = **9 mcg BID**
Placebo pMDI + Placebo Turbuhaler	N/A	**2 x pMDI + 2 x TBH BID**

Reviewer's Comment: In general, we do not advise the use of mono-comparator in a different formulation and delivered by a different device, as is the case here with the OXIS Turbuhaler. However, in the original NDA for asthma, the Applicant has provided a PK/PD bridging study that demonstrates the comparability of the formoterol dose delivered by the OXIS TBH and Symbicort. Therefore, the use of this mono-product was accepted by the Division at the time of the original NDA review, and still remains acceptable for this program.

To maintain the double-dummy blinding of study medication, subjects randomized to active treatment delivered by a pMDI device also received placebo delivered by a TBH device, and vice versa. Rescue medications of albuterol and salbutamol were also provided.

Permitted and prohibited therapies, as well as compliance assessment are identical to those in the SHINE study (see Appendix 10.1, Treatments, p. 72).

Efficacy Assessments

Primary Efficacy Endpoints

- Pre-dose FEV1 – to assess the contribution of budesonide (ICS)
- Post-dose FEV1- to assess the contribution of formoterol (LABA)
  - Separate mean FEV1 (for both pre-dose and 1 hour post-dose measurements) was calculated for each patient for the treatment period (Visit 3 to 8) as follows:

    $$\text{Mean FEV1} = \frac{\sum \text{Available FEV1 measurements over the treatment period}}{\text{\# of available FEV1 measurements}}$$
  - The change from baseline to the mean of FEV1 was calculated for both pre-dose and 1 hour post-dose measurements:

    Change in FEV1 = Mean FEV1 – Baseline FEV1

Secondary Efficacy Endpoints

Assessment of all secondary efficacy endpoints, including SGRQ, diary card variables (PEF, rescue medication use, oral steroid use, Breathlessness Diary, Cough Score, Sputum Score, Sleep Score, hospitalization), health care economics, exacerbations, and other spirometry measures (FVC, serial FEV1, and IC) were identical to the SHINE study (see Appendix 10.1, Efficacy Assessments, p. 74). Of note, pharmacokinetic variables were not measured in the SUN study.

Safety Assessments

- **Adverse Events -** summarized by preferred term and system organ class using MedDRA. Inferential comparisons of adverse event data were not planned.
  - **Adverse Events of Interest:** Specific categories of interest potentially associated with ICS and/or B2 agonists were to be tabulated. Events representing typical and potential steroid class effects were subcategorized as:

    ICS
    - Local effects of ICS: aphonia, dysphonia, oral candidiasis, and thrush
    - Systemic steroid effects: growth, weight gain, adrenal suppression, ocular effects, skin effects, psychiatric disorder, diabetes control, thirst, taste effects, bone effects
    - Pneumonia
      - Pneumonia related terms
      - "Potential lung infections other than pneumonia" – included preferred terms that could potentially represent lower respiratory tract infections

    Reviewer's comment: It is unclear from the definition provided for "pneumonia related terms" and "potential lung infections other than pneumonia" which MedDRA preferred terms are included in these categories.

B2 Agonists

- Class effects: tremor, palpitation, tachycardia, potassium changes, glucose changes, headache, agitation, anxiety, sleep effects, etc.
- Cardiac events: all events in the cardiac system organ class (SOC) and relevant cardiac-related events from other SOCs are included

- **Vital Signs** – blood pressure, heart rate – abnormalities analyzed descriptively
- **Physical Examination**
- **12 lead ECG** – HR, PR/QT/RR intervals, QRS duration, T-wave morphology
- **Hematology** – abnormalities analyzed by descriptive statistics
- **Clinical Chemistry** – abnormalities analyzed by descriptive statistics
- **Urinalysis**
- **Urine free cortisol** – 24 hour urine collection in a subgroup of n = 150 patients.
- **Bone Mineral Density** – measured as a change from baseline to endpoint in total lumbar spine bone mineral density; change in total hip BMD was a secondary endpoint.
- **Ophthalmologic assessment** – evaluation of lenticular opacities and intraocular pressure at the beginning and end of the treatment period
- **24-hour Holter monitoring** – subgroup of 300 patients

Statistical Plan

Sample Size Determination

A sample size of in each treatment group of 400 was considered to allow 90% power to detect a reduction from 1.07 to 0.74 (about 30% reduction) in then number of exacerbations. The sample size required for exacerbations assured adequate power for the primary variable, FEV1. With a sample size of 400 per treatment group, the power to detect a 0.10 L difference in FEV1 is greater than 95%, based on an estimated standard deviation of 0.3L.
The primary and secondary efficacy analyses were identical to the SHINE study (see Appendix 10.1, Statistical Plan, p. 77). Additional safety variables to be assessed in this study include 24-hour Holter monitoring, bone mineral density, and ophthalmologic examination.

Protocol Amendments

The original protocol, dated February 14, 2005, was submitted to IND 63,394 on March 7, 2005. Subsequently, there was one amendment to the protocol in July 20, 2006. This amendment clarified that albuterol CFC was used as an alternative to albuterol HFA for study rescue medication at US study cites (local amendment).

The statistical analysis plan dated November 19, 2007 contained the following modification which were made prior to unlocking the study data, in addition to those that were identical to those in the SHINE study (see Appendix 10.1, Protocol Amendments, p. 80):

- Definition of the categorization of abnormal/normal ophthalmology exams

10.2.2 Results

Patient Disposition

A total of 1964 patients were randomized at 225 centers. Patient disposition for the SUN study is presented in Table 45. Overall, discontinuation from the study was slightly higher in the formoterol treatment arm as compared with the Symbicort arms, and highest in the placebo arm. In each of the treatment arms, either adverse events or withdrawal of consent was the most likely reason for discontinuation. Of the 1964 patients randomized, 1355 patients completed the study, and a total of 609 patients discontinued:

- 255 (13.0%) experienced adverse events
- 215 (10.9%) withdrew consent
- 51 (2.6%) for other reasons
- 46 (2.3%) were lost to follow up
- 42 (2.1%) did not meet eligibility criteria

Table 45 SUN: Patient disposition

	SYMB HD	SYMB LD	Formoterol	Placebo
Total N	494	494	495	481
Discontinuations	134 (27.1%)	143 (28.9%)	157 (31.7%)	175 (36.4%)
Not eligible	10 (2.0%)	8 (1.6%)	14 (2.8%)	10 (2.1%)
Adverse event	60 (12.1%)	65 (13.2%)	65 (13.1%)	65 (13.5%)
Withdrawal of consent	41 (8.3%)	45 (9.1%)	52 (10.5%)	77 (16.0%)
Lost to follow-up	9 (1.8%)	12 (2.4%)	12 (2.4%)	13 (2.7%)
Other	14 (2.8%)	13 (2.6%)	14 (2.8%)	10 (2.1%)

SYMB HD: Symbicort 320/9 mcg BID, SYMB LD: Symbicort 160/9 mcg BID,
Source: SUN CSR, Section 6.2, Figure 2, p. 109, Table 13, p. 110

- Protocol Deviations

The Applicant reports a total of 308 (15.7%) subjects had at least 1 protocol deviation. Most protocol deviations were minor and did not impact subject safety or efficacy assessments. The most common protocol deviations were related to use of disallowed concomitant medications [259 (13.2%) subjects] and failure to meet eligibility criteria at Visit 1 [39 (2.0%) subjects]. Overall, 31 (1.6%) subjects in the efficacy analysis set were excluded from the per-protocol analysis set (See Table 46). Three subjects were given the incorrect randomized treatment. These 3 subjects were handled on an intent-to-treat basis, but were excluded from the per-protocol analysis set. Exclusions were equally distributed across treatment groups.

Table 46 SUN: Protocol deviations				
	SYMB HD	**SYMB LD**	**Formoterol**	**Placebo**
Total N	494	494	495	481
All Deviations (%)	**82 (16.6%)**	**74 (15.0%)**	**83 (16.8%)**	**71 (14.8%)**
Use of Prohibited CMs	69 (14.0%)	64 (13.0%)	68 (13.7%)	58 (12.1%)
*Failure to Meet EC**	11 (2.2%)	10 (2.0%)	11 (2.2%)	15 (3.1%)
Excluded from PP Analysis	**6 (1.2%)**	**5 (1.0%)**	**10 (2.0%)**	**10 (2.1%)**
COPD Diagnosis < 2 years	0	0	0	1 (0.2%)
FEV1 > 50% predicted	2 (0.4%)	1 (0.2%)	6 (1.2%)	3 (0.6%)
FEV1/FVC ≥ 70%	2 (0.4%)	1 (0.2%)	1 (0.2%)	1 (0.3%)
History of Asthma	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
No exacerbations 12 months	0	0	0	1 (0.2%)
Chronic OCS use	1 (0.2%)	0	0	3 (0.6%)
TSS < 2 for run-in	0	2 (0.4%)	1 (0.2%)	2 (0.4%)
Incorrect study medication use	0	0	2 (0.4%)	0
Incorrect rescue med use	0	0	1 (0.2%)	2 (0.4%)
Incorrect xanthine use	0	0	0	1 (0.2%)
Addition to maintenance meds	0	0	0	1 (0.2%)

SYMB HD: Symbicort 320/9 mcg BID, SYMB LD: Symbicort 160/9 mcg BID, CMs: Concomitant medications, EC: Eligibility Criteria, OCS: oral corticosteroid, TSS: Total Symptom Score
Source: SUN CSR, Tables 11.1.3.3 (p. 645) and 11.1.2.5 (p. 501)
* Inability to meet EC for both Visits 1 and 2 combined

Datasets Analyzed

The Applicant has defined the following analysis sets:

- Intention-to-Treat (ITT) (N=1964): also known as the efficacy analysis set (EAS). This analysis set was considered the primary efficacy analysis set, and defined as those patients who had been randomized, received at least one dose of study drug, and contributed sufficient data for at least 1 co-primary or secondary outcome endpoint to be calculated during the randomized treatment period.
- Per Protocol (PP) (N=1933): The PP population was a subset of the ITT population including only those patients who completed the study without major detected protocol deviations.
- Safety (N=1964): This population was defined as all randomized patients who received at least one dose of study drug and from whom any data after randomization are available.
- Serial spirometry (N=491): all subjects who were randomized, received at least one dose of study medication, and had a baseline pre-dose FEV1 value and at least one post-dose FEV1 value that were from a serial spirometry procedure during the randomized treatment period.
    - 1 (0.1%) subject was excluded due to lack of sufficient data
- Urinary free cortisol (N=179): subjects who were randomized, received at least one dose of study medication, and had a baseline and on-treatment value for 24-hr urinary cortisol, urine cortisol concentration, 24-hour urinary creatinine, or urine creatinine concentration during the randomized treatment period.
    - 92 (4.7%) subjects were excluded due to lack of sufficient data.

- Holter analysis set (N = 520): subjects who were randomized, received at least 1 dose of study medication, and who had baseline and an on-treatment values for holter assessments regardless of analyzable time.
- BMD analysis set (N = 326): subjects who were randomized, received at least 1 dose of study medication, and who had baseline and an on-treatment value for BMD assessments during the randomized treatment period.
    - 221 (11.3%) subjects were excluded due to lack of sufficient data
- Ophthalmology analysis set (N = 461): subjects who were randomized, received at least 1 dose of study medication, and who had a baseline and at least 1 on-treatment value for at least 1 lenticular opacity scale (LOCSIII score) or intraocular pressure during the randomized treatment period
    - 159 (8.1%) subjects were excluded due to lack of sufficient data

(SUN CSR, Section 6.2, Table 15, pg. 116-7)

Demographics and Baseline Characteristics

- Demographics

Demographics and baseline characteristics are summarized in Table 47.

Table 47 SUN: Patient demographics				
	SYMB HD	**SYMB LD**	**Formoterol**	**Placebo**
ITT population	494	494	495	481
Male (N and %)	308 (62.3)	310 (62.8)	323 (65.3)	314 (65.3)
Race (N and %)				
Caucasian	457 (92.5)	460 (93.1)	457 (92.3)	441 (91.7)
Black	13 (2.6)	13 (2.6)	10 (2.0)	11 (2.3)
Oriental	1 (0.2)	1 (0.2)	4 (0.8)	2 (0.4)
Other	23 (4.7)	20 (4.0)	24 (4.8)	27 (5.6)
Age (years)				
Mean (SD)	63.18 (8.93)	63.58 (9.21)	62.92 (9.14)	62.88 (9.1)
Median	64	64	63	63
Range	40 to 83	42 to 89	41 to 88	40 to 84
Country (N and %)				
US	224 (45.3)	225 (45.5)	224 (45.3)	211 (43.9)
Non-US	270 (54.7)	269 (54.5)	271 (54.7)	270 (56.1)
Hungary	76 (15.4)	81 (16.4)	79 (16.0)	81 (16.8)
Germany	57 (11.5)	51 (10.3)	57 (11.5)	52 (10.8)
Romania	37 (7.5)	38 (7.7)	38 (7.7)	37 (7.7)
Bulgaria	37 (7.5)	37 (7.5)	36 (7.3)	36 (6.5)
Denmark	24 (4.9)	24 (4.9)	21 (4.2)	25 (5.2)
Mexico	23 (4.7)	20 (4.0)	22 (4.4)	24 (5.0)
Greece	10 (2.0)	12 (2.)	11 (2.2)	10 (2.1)
Iceland	6 (1.2)	6 (1.2)	7 (1.4)	5 (1.0)
Baseline % predicted FEV1 Mean (SD)	33.70 (11.89)	34.16 (10.99)	33.64 (11.39)	34.65 (10.59)
Post-BD % predicted FEV1 (N and %)				
<30%	120 (24.3)	94 (19.0)	119 (24.0)	90 (18.7)
30-50%	290 (58.7)	314 (63.6)	285 (57.6)	298 (62.0)
50-80%	84 (17.0)	85 (17.2)	89 (18.0)	91 (18.9)
≥ 80%	0	0	1 (0.2)	1 (0.2)
Missing	0	1 (0.2)	1 (0.2)	1 (0.2)
Pack Years				
Median	40.0	40.0	40.0	40.0
Min, Max	10 to 180	10 to 210	10 to 165	10 to 225

Source: SUN CSR, Table 16, Section 6.5, page 118.

There was a greater percentage of male than female subjects consistent with the disease prevalence in the target population. Most subjects were Caucasian, with fewer than 8% non-Caucasian patients. Approximately half of the subjects were over age 65, with approximately 11% of subjects over the age of 75 years. Baseline percent predicted FEV1, post-bronchodilator percent predicted FEV1, and smoking history (pack years) were well balanced across all treatment groups. Severity classification, based on the GOLD 2006 criteria applied to post-bronchodilator FEV1 at Visit 1, indicated that approximately 80% of the study population had severe or very severe COPD, while 20% had moderate COPD at entry. Severity varied somewhat across treatment groups, with approximately 30% more subjects in the most severe category in the Symbicort HD and formoterol groups. In general, demographic and key baseline characteristics were similar across treatment groups and geographic regions (US vs. non-US).

Exceptions included a higher percentage of women in the US (43.7% of the total) than in the non-US region (29.9%). In addition, a larger percentage of enrolled subjects in the US were African Americans (5.3%) compared with none in non-US countries. [Module 5, SUN CSR, Table 11.1.4.1.3, p. 720]. To summarize, treatment groups were generally balanced with respect to demographic and key baseline characteristics.

- Baseline Medical History

The study population included a representative number of subjects with co-morbid conditions, including:

- Hypertension (42%)
- Lipid profile abnormalities (22%)
- Cardiac disease (18%)
- Diabetes (11%)
- Osteoporosis (11%)
- Cataracts (5%)
- Atrial fibrillation and/or arrhythmia (4%)
- Congestive heart failure (3%)

These baseline conditions were also well-balanced across treatment groups (Module 5, SUN CSR, Table 11.1.6, p. 1011).

- Concomitant Medication Use

The most common COPD medications were inhaled short-acting anticholinergic (ipratropium bromide), systemic corticosteroids, antibiotics, mucolytics, and oxygen, used by at least 5% of subjects during randomized treatment. The most common non-COPD medications were antibiotics, platelet aggregation inhibitors (excluding heparin), diuretics, ace inhibitors, HMG CoA reductase inhibitors, proton pump inhibitors, bone mineral density medications, benzodiazepines, CYP3A4 inhibitors, cardioselective beta-blockers, anti-histamines, dihydropyridines, propionic acid derivatives, anilides, SSRIs, potassium, opiate alkaloids, organic nitrates, vitamins, H2 receptor antagonists, angiotensin II antagonists, influenza vaccines, thyroid hormones, intranasal corticosteroids, mucolytics, and acetic acid used by at least 5% of the randomized patient population. In general, use of the most common COPD medications during randomized treatment was similar across treatment groups. (Module 5, SUN CSR, Table 20, p.126)

Compliance

Study medication compliance was determined based on asking subjects twice daily as a part of diary entry whether they used their study medication. The number of "Yes" responses were used to calculate compliance in two ways. The first method was based on the number of "yes" responses to the study medication question from the diary relative to the expected number of study drug intakes based on the duration of the randomized treatment period for each subject. This method assumes that days the diary was not used were also days that the subject did not take study medication. The second method was calculated using the number of "Yes" responses to the study medication question from the diary relative to the total number of actual responses ("Yes" or "No") to the study medication question. Using both methods, study medication

compliance was ≥ 80% in more than 89% of the subjects during randomized treatment. Compliance was similar across treatment groups (SUN CSR, Table 18, p 123).

Efficacy Endpoint Outcomes

Primary Endpoint Analysis (See Primary Endpoint Analysis, p. 85, for SHINE study results)
The co-primary variables were change from baseline in pre-dose FEV1, to demonstrate the anti-inflammatory contribution of budesonide, and post-dose FEV1, to demonstrate the bronchodilator contribution of formoterol, to the efficacy of the combination product, Symbicort. Each co-primary variable was calculated as an average over the randomized treatment period (primary analysis) and at the end-of-treatment.

1. Pre-dose FEV1

Treatment means and treatment comparisons for change in baseline averaged over the randomized treatment period and at the end of treatment are shown in Table 48 and Table 49.

Table 48 SUN: Pre-dose FEV1 (L): Treatment means

			Average Of Randomized Treatment Period		End of Treatment	
	N	Baseline value Mean (SD)	Change from Baseline LS Mean (SEM)	95% CI	Change from Baseline LS Mean (SEM)	95% CI
Symbicort HD	471	1.03 (0.39)	0.10 (0.01)	0.08, 0.10	0.09 (0.02)	0.06, 0.12
Symbicort LD	479	1.04 (0.39)	0.08 (0.01)	0.06, 0.11	0.06 (0.02)	0.03, 0.10
Formoterol 4.5	465	1.03 (0.40)	0.06 (0.01)	0.04, 0.09	0.07 (0.02)	0.03, 0.10
Placebo	436	1.08 (0.42)	0.01 (0.01)	-0.02, 0.03	-0.00 (0.02)	-0.03, 0.03

Source: SUN CSR, Section 7.2.1.1, Tables 25 and 27, p. 136, 138

Table 49 SUN: Pre-dose FEV1 (L): Treatment comparisons for change from baseline

Comparison	Average Of Randomized Treatment Period		End of Treatment	
	LS Mean (95% CI)	p-value	LS Mean (95% CI)	p-value
Symbicort HD vs. placebo	0.09 (0.06, 0.12)	< 0.001	0.09 (0.06, 0.13)	< 0.001
Symbicort HD vs. formoterol	**0.04 (0.01, 0.07)**	**0.008**	**0.03 (-0.01, 0.06)**	**0.150**
Symbicort LD vs. placebo	0.07 (0.05, 0.10)	< 0.001	0.07 (0.03, 0.10)	< 0.001
Symbicort LD vs. formoterol	**0.02 (-0.01, 0.05)**	**0.161**	**-0.00 (-0.04, 0.04)**	**0.972**
Formoterol vs. placebo	0.05 (0.03, 0.08)	< 0.001	0.07 (0.03, 0.10)	< 0.001
Symbicort HD vs. LD	0.02 (-0.01, 0.05)	0.206	0.03 (-0.01, 0.06)	0.137

Source: SUN CSR, Section 7.2.2.1, Tables 26 and 28, p. 136, 138
Bold Text indicates pre-specified primary comparisons

In terms of the pre-specified primary comparisons, results indicate that only Symbicort HD demonstrated a statistically significantly greater increase from baseline in pre-dose FEV1 when compared with formoterol. However, this result was not consistent when analyzed at the end of treatment.

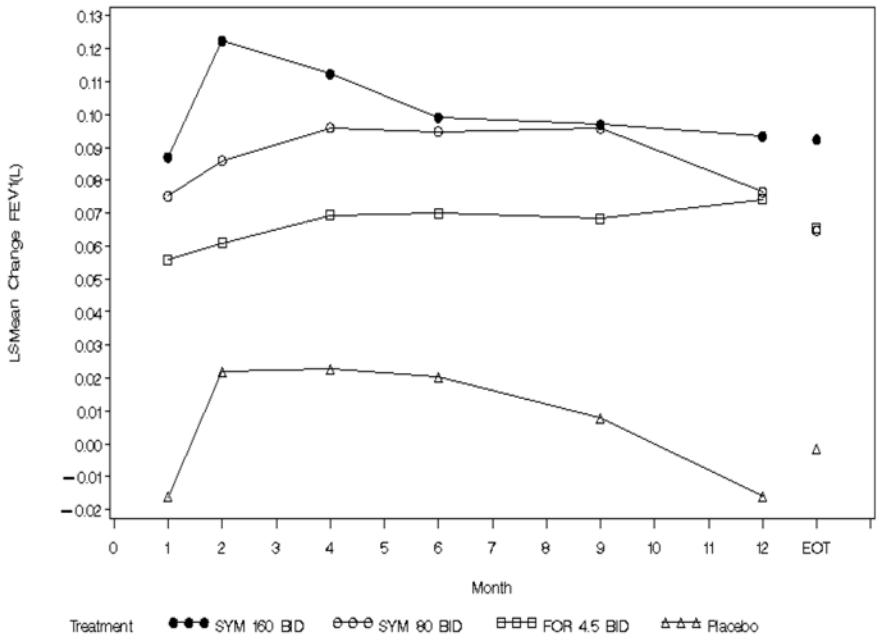
Reviewer's Comment: It is of note that the difference between Symbicort HD and formoterol, though statistically significant, was quantitatively small, approximately 40 mL, similar to what it was in the 6 month study.

Symbicort LD failed to show the contribution of the inhaled corticosteroid to the efficacy of the combination product in both analyses. Both dosage strengths of Symbicort demonstrated statistically significant difference in pre-dose FEV1 vs. placebo when examined as the average of the randomized treatment period and at the end of treatment. Symbicort HD was not statistically different when compared with Symbicort LD in terms of change from baseline in pre-dose FEV1.

Reviewer's Comment: Based on the above analysis as well as the findings from the 6 month SHINE study, the Sponsor has decided only to pursue the Symbicort high dose of 320/9 mcg BID for the COPD indication, as the lower dose failed to show the contribution of budesonide to the efficacy of the combination product.

Figure 21 depicts the LS mean change from baseline in pre-dose FEV1 by visit. The accompanying table provides information for the number of subjects included in the analysis at each time point. Symbicort HD demonstrated improvements in pre-dose FEV1 that were apparent at Month 1 and were generally maintained over the 12-month study period. Symbicort HD demonstrated a statistically significantly greater increase from baseline in pre-dose FEV1 compared with placebo, but not formoterol at the end of treatment.

Figure 21 SUN: LS Mean change from baseline in pre-dose FEV1 by visit



Treatment group	Months						
	1	2	4	6	9	12	EOT
Symbicort HD N = 494	470	451	433	408	386	361	471
Symbicort LD N = 494	474	453	418	398	369	354	479
Formoterol N = 495	462	437	403	386	362	337	465
Placebo N = 481	434	400	371	347	327	307	436

2. Post-dose FEV1

Treatment means and treatment comparisons for change in baseline averaged over the randomized treatment period and at the end of treatment are shown in Table 50 and Table 51.

Table 50 SUN: Post-dose FEV1 (L): Treatment means

			Average Of Randomized Treatment Period		End of Treatment	
	N	Baseline value Mean (SD)	Change from Baseline LS Mean (SEM)	95% CI	Change from Baseline LS Mean (SEM)	95% CI
Symbicort HD	494	1.02 (0.39)	0.21 (0.01)	0.18, 0.23	0.20 (0.02)	0.16, 0.23
Symbicort LD	494	1.04 (0.39)	0.19 (0.01)	0.16, 0.21	0.16 (0.02)	0.13, 0.20
Formoterol 4.5	495	1.03 (0.40)	0.18 (0.01)	0.15, 0.20	0.17 (0.02)	0.14, 0.20
Placebo	479	1.08 (0.42)	0.02 (0.01)	0.00, 0.05	0.01 (0.02)	-0.02, 0.04

Source: SUN CSR, Section 7.2.1.2, Tables 29 and 31, p. 140, 143

Table 51 SUN: 1-hr Post-dose FEV1 (L): Treatment comparisons for change from baseline

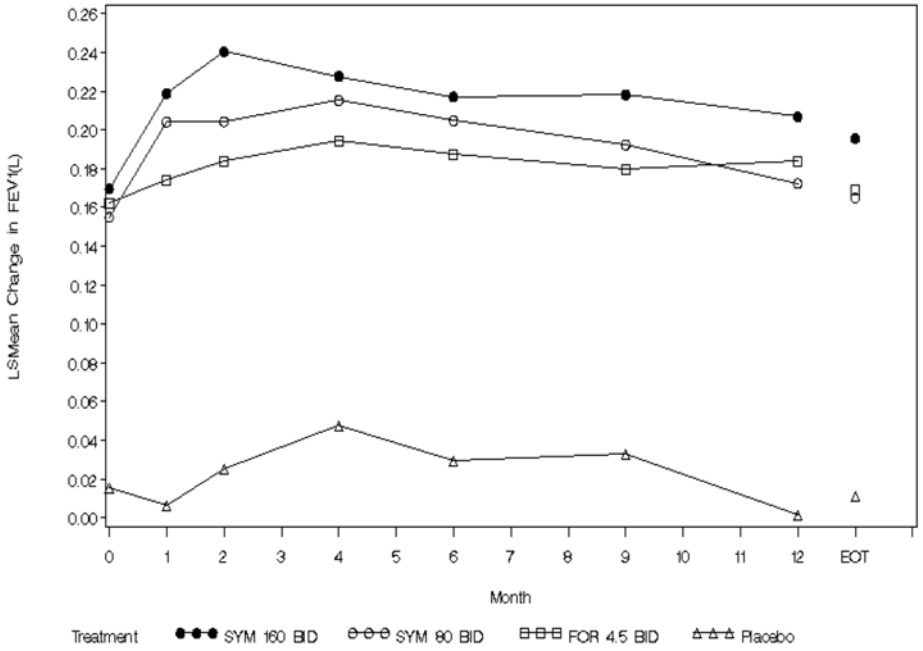
Comparison	Average Of Randomized Treatment Period		End of Treatment	
	LS Mean (95% CI)	p-value	LS Mean (95% CI)	p-value
Symbicort HD vs. placebo	**0.18 (0.16, 0.21)**	**< 0.001**	**0.18 (0.15, 0.22)**	**< 0.001**
Symbicort HD vs. formoterol	0.03 (0.00, 0.06)	0.023	0.03 (-0.01, 0.06)	0.164
Symbicort LD vs. placebo	**0.16 (0.13, 0.19)**	**< 0.001**	**0.15 (0.12, 0.19)**	**< 0.001**
Symbicort LD vs. formoterol	0.01 (-0.02, 0.04)	0.420	-0.00 (-0.04, 0.03)	0.807
Formoterol vs. placebo	0.15 (0.12, 0.18)	< 0.001	0.16 (0.12, 0.20)	< 0.001
Symbicort HD vs. LD	0.02 (-0.01, 0.05)	0.144	0.03 (-0.01, 0.07)	0.102

Source: SUN CSR, Section 7.2.1.2, Tables 30 and 32, p. 140 and 143
Bold Text indicates primary comparisons

In terms of the pre-specified primary comparisons, results indicate that both dosage strengths of Symbicort demonstrated a statistically significantly greater increase from baseline in post-dose FEV1 when compared with placebo. This result was consistent when analyzed as the average of the randomized treatment period or at the end of treatment.

Figure 22 depicts the LS mean change from baseline in post-dose FEV1 by visit. The accompanying table provides information for the number of subjects included in the analysis at each time point. Symbicort LD and HD demonstrated improvements in 1 hour post-dose FEV1 that were apparent on the day of randomization and were generally maintained over the 12-month study period.

Figure 22 SUN: LS mean change from baseline in 1-hour post-dose FEV1 by visit



Treatment group	Months						
	1	2	4	6	9	12	EOT
Symbicort HD N = 490	467	450	430	405	384	361	494
Symbicort LD N = 494	473	449	416	393	370	353	494
Formoterol N = 495	459	436	401	384	361	337	495
Placebo N = 478	428	397	368	345	323	306	479

- Subgroup Analyses by Sex, Age, and Race

1) Pre-Dose FEV1

Similar patterns of results seen in the primary analysis were seen in the sensitivity analyses adjusting for sex and age groups. A statistically significant interaction was observed for race (p=0.05), however this was deemed by the Applicant to be due to the large variability across race groups. Therefore, it was concluded that there was no clear evidence of a differential treatment effect across race groups.

2) 1-hour Post-Dose FEV1
Similar patterns of results seen in the primary analysis were seen in the sensitivity analyses adjusting for sex, age, and race groups.

Secondary Endpoint Analyses (See Secondary Endpoint Analyses, p. 92 for SHINE study results)
The Applicant identified dyspnea, SGRQ, and COPD exacerbations as key secondary efficacy variables.

1. Dyspnea Scores

Dyspnea scores, as measured by the Breathlessness Diary, range from 0-4 with higher scores indicating more severe dyspnea. A reduction of 0.2 units has been defined as the minimally important clinical difference (MCID) based on prior validation. The primary comparison was between the Symbicort treatments and placebo. The LS mean difference between Symbicort HD and placebo averaged over the randomized treatment period was -0.20 (95% CI -0.27, -0.12, $p < 0.001$); Symbicort LD versus placebo yielded a LS mean difference of -0.15 (95% CI -0.23, -0.08, $p < 0.001$). Both Symbicort HD and LD demonstrated a statistically significant reduction from baseline in dyspnea scores when compared with placebo, but the pre-specified MCID was only achieved for Symbicort HD (Module 5, SUN CSR, Table 34, p. 145). The Applicant also performed a responder analysis to identify the proportion of patients who improved by the MCID for dyspnea during randomized treatment. The odds ratio of achieving the MCID when Symbicort HD was compared to placebo was 1.88 [95% CI 1.45, 2.44, $p < 0.001$]; Symbicort LD versus placebo yielded an OR = 1.80 [95% CI 1.39, 2.33, $p < 0.001$] (Module 5, SUN CSR, Table 36, p. 147).

Reviewer's comment: The Sponsor has included a statement (b) (4) *lthough the MCID was met in this study when Symbicort HD was compared with placebo, this was not replicated in the 6-month SHINE study in which the MCID was not met, despite the statistical significance of the finding. Given that finding was not replicated, and more* (b) (4)

2. St. George's Respiratory Questionnaire (SGRQ)

The SGRQ total score and scores for each of the 3 domains (symptoms, activity, impact) were analyzed at the end of treatment. The validated MCID for the SGRQ total score and the impact domain score has been defined as a mean change in score of 4 units. The primary comparison was between the Symbicort HD treatment group and placebo. The LS mean difference between Symbicort HD and placebo in SGRQ total score change from baseline at the end of treatment was -2.39 (95% CI -4.085, -0.690, P = 0.006); Symbicort LD versus placebo yielded a LS mean difference of -3.66 (95% CI -5.351, -1.975, $p < 0.001$). Both Symbicort HD and LD groups

demonstrated statistically significant reductions in SGRQ total scores compared with placebo, but did no achieve the pre-specified MCID of 4 units (Module 5, SUN CSR, Table 38, p. 150).

Reviewer's Comment: The Applicant has not made any labeling claims based on the results of the SGRQ.

3. COPD exacerbations

A COPD exacerbation was predefined as a worsening of COPD that required a course of oral steroids and/or hospitalization for treatment. Episodes of COPD worsening that were treated with parenteral steroids alone, or with antibiotics without systemic steroids or hospitalization, were not included in the definition of exacerbation, but were listed separately. The pre-specified primary comparison was between the Symbicort treatment groups and placebo.

The results for the primary analysis of the number of protocol-defined COPD exacerbations per subject-treatment year indicate that there were statistically significant differences in the rate of exacerbations between treatment groups. Specifically, the rate ratio of the comparison of Symbicort HD versus placebo was 0.632 [95% CI 0.522, 0.765, p =< 0.001] (Module 5, SUN CSR, Table 42, p. 155). The rate ratio of the comparison of Symbicort LD versus placebo was 0.593 [95% CI 0.487, 0.722, p < 0.001]. There was no statistical difference between Symbicort treatment groups.

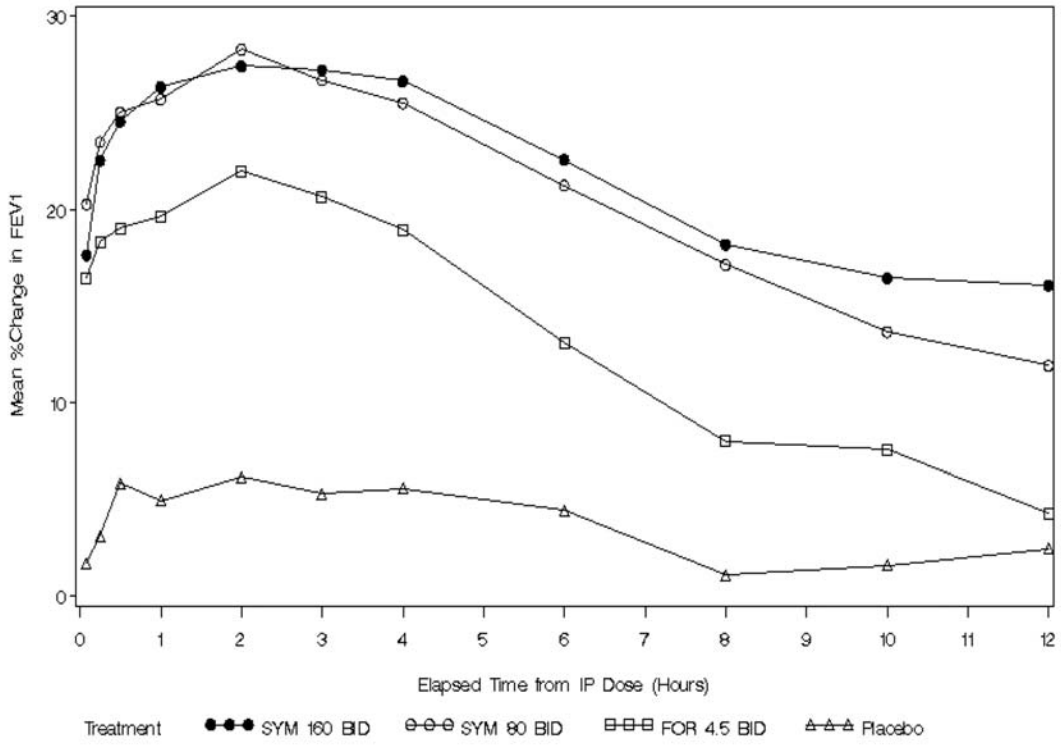
Reviewer's Comment: The Applicant has (b) (4) *It is of note that the rate ratio result in the 6 month study was not statistically significant. Further, the definition of a COPD exacerbation is based solely on treatment with oral corticosteroids or hospitalization.* (b) (4) *However, the results are generally supportive of the efficacy of Symbicort* (b) (4)

Other secondary efficacy variables included serial FEV1, inspiratory capacity (IC), forced vital capacity (FVC), morning and evening PEF, COPD symptoms, and health care economics.

2. 12-hour Serial FEV1

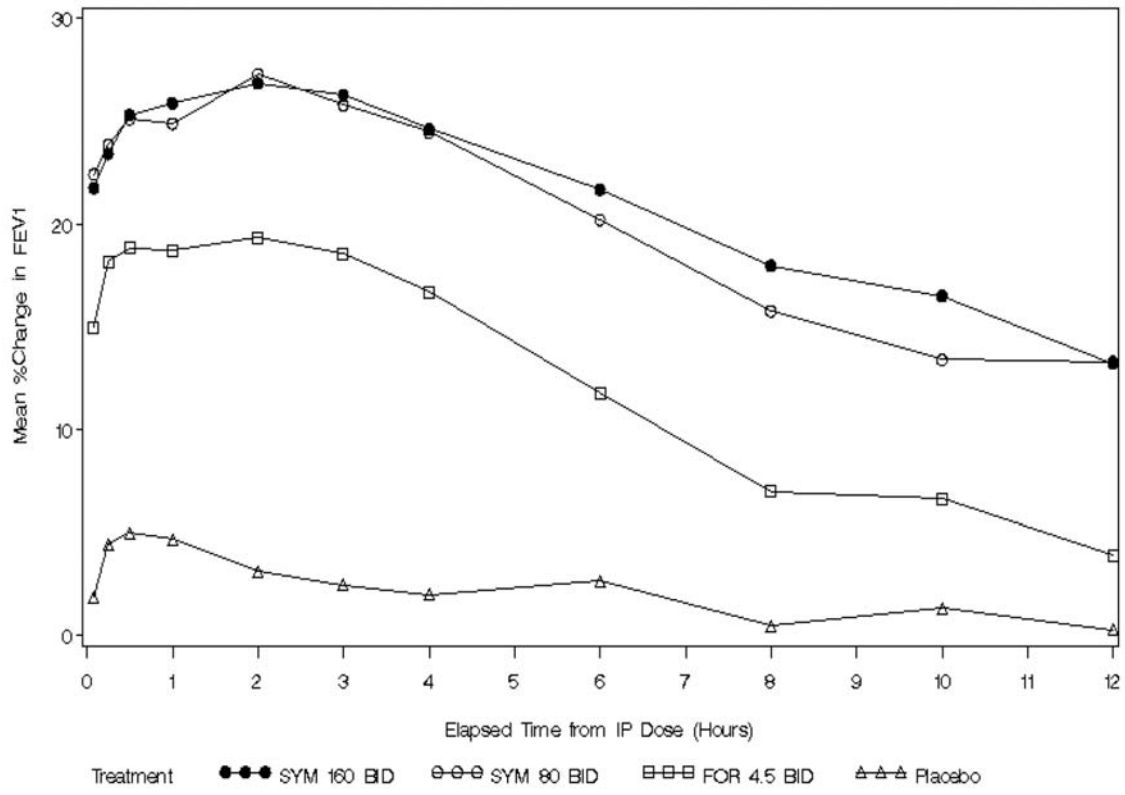
At Visits 2, 4, 6, and 8, FEV1 was measured pre-dose and at 5, 15, 30, 60, 120, 180, 240, 360, 480, 600, and 720 minutes post-dose in a subset of 419 subjects. The 12 hour FEV1 curves, based on mean percent change from baseline pre-dose FEV1 values are shown in Figure 23 and Figure 24.

Figure 23 SUN: Mean percent change from baseline FEV1 over 12 hours – day of randomization



Note: The first timepoint displayed is the 5-minute postdose timepoint.
IP Investigational product.
WV Pre-CF within-visit predose FEV_1 value carried forward extrapolation technique.
Data derived from Figure 11.2.5.2.2.3, Section 11.2.

Figure 24 SUN: Mean percent change from baseline in FEV1 over 12 hours – end of treatment



SYM 160 SYMBICORT 160/4.5 µg; SYM 80 SYMBICORT 80/4.5 µg; For 4.5 formoterol 4.5 µg; Placebo Placebo pMDI and TBH. Each treatment was administered as 2 actuations/inhalations twice daily. Note: The first timepoint displayed is the 5-minute postdose timepoint.
IP Investigational product.
LOCF Last observation carried forward; WV Pre-CF within-visit predose FEV_1 value carried forward extrapolation technique.
Data derived from Figure 11.2.5.2.10.3, Section 11.2.

The serial FEV1 graphs above indicate that both Symbicort treatment groups demonstrated bronchodilation at 5 minutes after dosing, compared with placebo, which reached a maximum between 2 and 3 hours, and was maintained over 12 hours. The response was present at the end of treatment as well.

Reviewer's comment: Figure 16 and Figure 17 (from the 6 month SHINE study) are included in the product label in the clinical trials section under the new indication of COPD. The serial 12-hour FEV1 curves in this 12 month study differ in one notable way from the 6 month study. In this study, the formoterol treatment group did not have sustained improvement in FEV1 compared to placebo over 12 hours. This is an unusual finding given the curves in the 6 month study and that formoterol is approved as a BID drug.

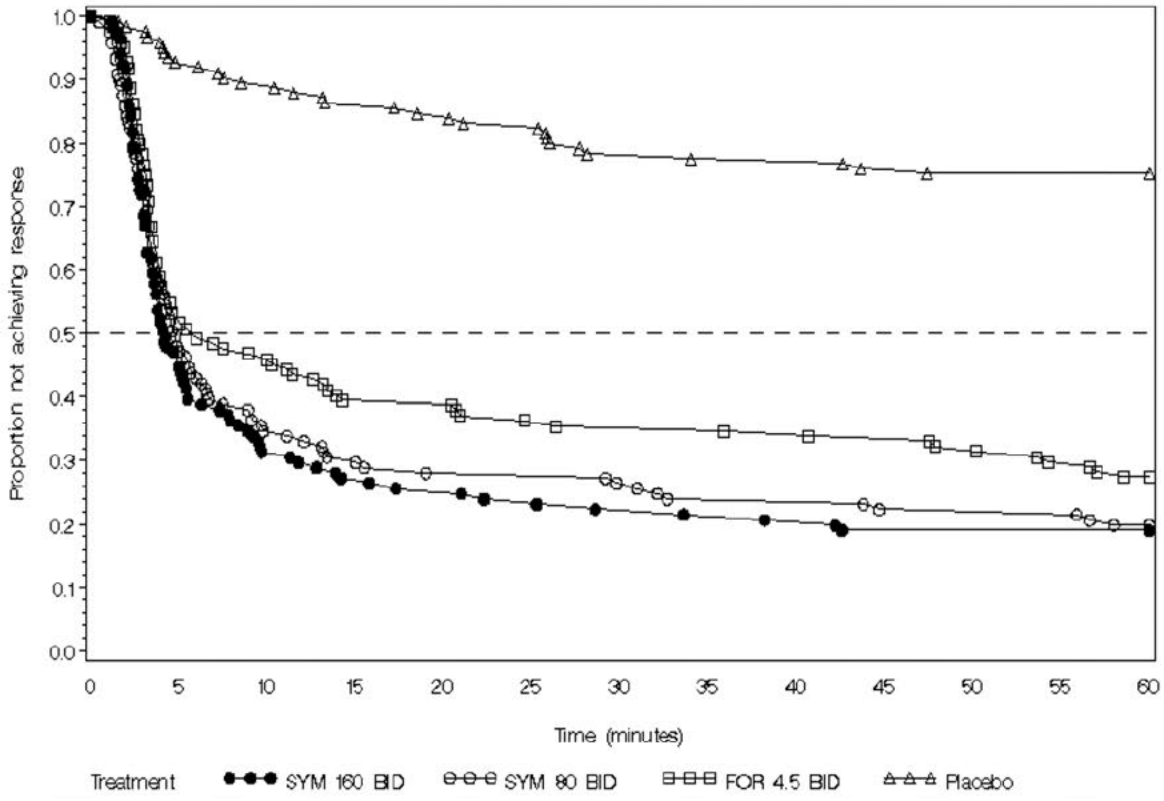
a. 15% Onset of Action of Bronchodilation

"15% onset of action" is defined as the first post-dose time point at which each subject achieved a 15% improvement in FEV1 relative to baseline pre-dose FEV1. The Kaplan-Meier plots for the estimated time to 15% onset of action during the first 60 minutes post-dose on the day of randomization and at the end of treatment are shown in Figure 25 and Figure 26.

Reviewer's comment: Using the following data, (b) (4)

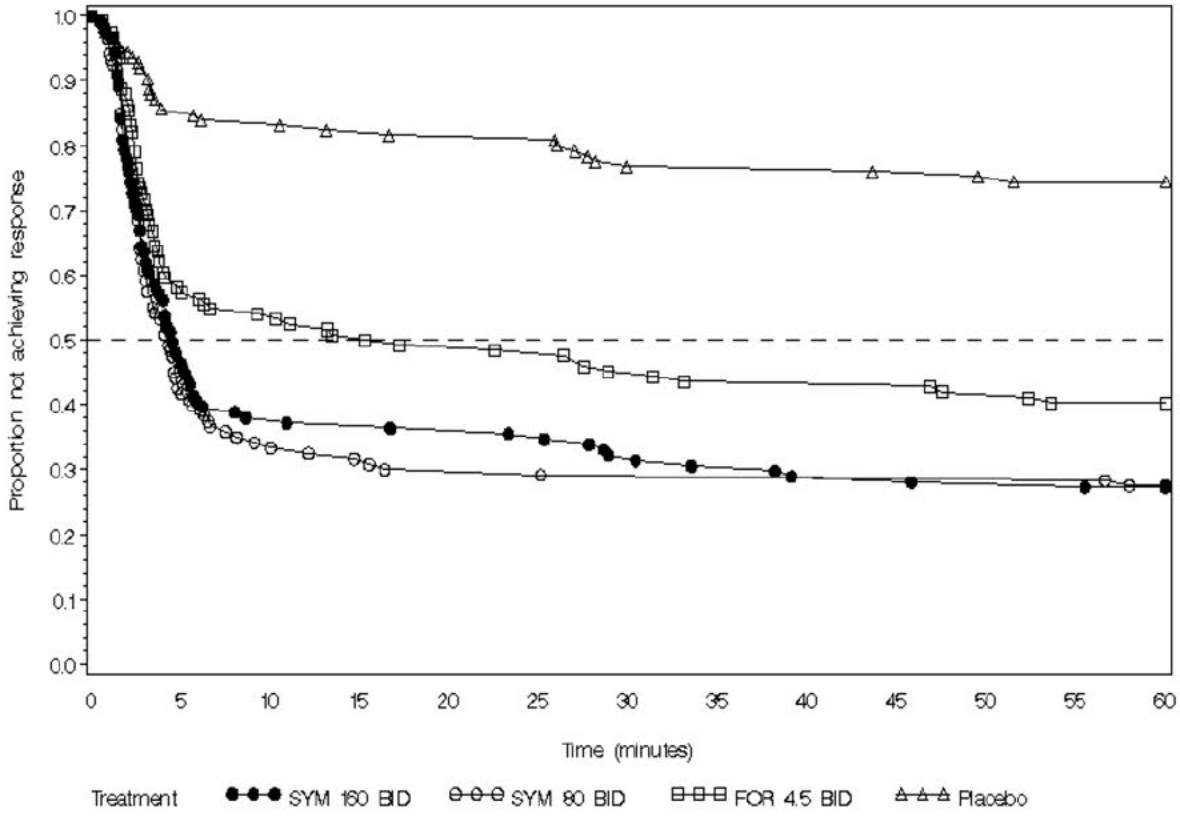
he results of the Sponsor's analysis are under review by the Division's Biometric reviewers Dr. Qian Li and Dr. Ted Guo.

Figure 25 SUN: Estimated time to 15% onset of action – day of randomization



On the day of randomization, the median time to 15% onset of action was 4.2 minutes for Symbicort HD and 4.8 minutes for Symbicort LD. Both Symbicort HD and LD demonstrated a statistically significantly earlier time to 15% onset of action compared with placebo ($p < 0.001$) on the day of randomization (SUN CSR, Tables 11.2.5.4.1.7 and 11.2.5.4.1.8).

Figure 26 SUN: Estimate time to 15% onset of action - end of treatment



At the end of treatment, the median time to 15% onset of action for 4.5 minutes for Symbicort HD and 4.3 minutes for Symbicort LD. Thus the median times for 15% onset of action for both doses of Symbicort at the end of treatment were similar to the day of randomization, and similarly statistically significant when compared with placebo. Of note, formoterol showed a prolonged time to 15% onset of action (16.3 minutes) at the end of treatment, as compared with 6 minutes at the day of randomization, but remained statistically significant when compared with placebo.

Reviewer's comment: It is interesting that the onset of action is 3x faster in the COPD population than in the asthma population (labeled claim is 15 minutes). The reason for this is unclear, however different disease entities are known to behave differently.

Reviewer's comment: The definition of onset of action is similar to what is used in the Sponsor's asthma program and what currently appears in the product label. The definition of onset of action is similar to what is used in the Sponsor's asthma program and what currently appears in the product label. (b) (4)

b. Maximum FEV1

Treatment comparisons for mean maximum FEV1 on the day of randomization and at the end of treatment indicated that Symbicort HD demonstrated a statistically significant increase when compared with placebo (LS Mean = 0.20 [95% CI 0.14, 0.25, p = <0.001] that was present at then end of treatment (LS Mean = 0.21 [95% CI 0.15, 0.28, p < 0.001]). Symbicort LD similarly demonstrated a statistically significant increased when compared with placebo on the day of randomization (LS Mean = 0.17 [95% CI 0.11, 0.22, p < 0.001] that was present at the end of treatment (LS Mean = 0.17 [95% CI 0.10, 0.24, p < 0.001]. It is of note that in the 6 months study, the lower dosage strength did not show a significant difference for mean maximum FEV1 compared with placebo at the end of treatment, indication perhaps, an attenuation of effect (Module 5, SUN CSR, Tables 44 and 46, p 163, 164).

2. Inspiratory Capacity (IC) – Pre- and 1-hour post-dose

During serial spirometry, both pre- and 1-hour post-dose IC were collected to measure lung hyperinflation. Treatment means and between-treatment comparisons for pre-dose IC did not show any significant difference between any of the treatment groups. Analysis of treatment means and between-treatment comparisons for post-dose IC (Module 5, SUN CSR, Tables 11.2.4.2.2 and 11.2.4.2.3) for the treatment average indicated that both dosage strengths of demonstrated highly statistically significant increases in 1-hour post-dose IC compared with placebo (Symbicort HD: LS mean = 0.26, p<0.001; Symbicort LD 80/4.5: LS mean = 0.25, p<0.001). At the end of treatment, results for post-dose IC were similar to the day of randomization, demonstrating maintenance of effect.

3. Forced Vital Capacity (FVC) Pre- and 1-hour post-dose

Analysis of treatment means and between treatment comparisons for pre-dose FVC for the treatment average indicated that Symbicort HD demonstrated statistically significant increases in pre-dose FVC compared with placebo (LS mean = 0.05, p =0.036), but Symbicort LD did not (LS Mean = 0.04, p = 0.069) [Module 5, SUN CSR, Tables 11.2.3.1.2 and 11.2.3.1.3]. Analysis of treatment means and treatment comparisons for pre-dose FVC at the end of treatment did not reveal results of any statistical significance. Similar to SUN study results, Symbicort HD and LD demonstrated statistically significant increases in post-dose FVC compared with placebo (HD: LS Mean = 0.24, p<0.001; LD: LS mean = 0.23, p< 0.001) (Module 5, SUN CSR, Tables 11.2.3.2.2 and 11.2.3.2.3). Results for post-dose FVC at the end of treatment were similar to the day of randomization, demonstrating maintenance of effect.

4. Morning and Evening PEF

Treatment means and treatment comparisons for change in baseline averaged over the randomized treatment period are shown in Table 52 and Table 53.

Table 52 SUN: AM and PM PEF (L/min) – Treatment means

			Average Over Randomized Treatment Period	
	N	Baseline value Mean (SD)	Change from Baseline LS Mean (SEM)	95% CI
Morning PEF (L/min)				
Symbicort HD	487	(b) (4)		17.42, 24.80
Symbicort LD	488	183.13 (62.04)	15.90 (1.88)	12.21, 19.58
Formoterol 4.5	489	184.50 (72.74)	10.54 (1.88)	6.85, 14.23
Placebo	466	(b) (4)		-1.07, 6.43
Evening PEF (L/min)				
Symbicort HD	486	(b) (4)		13.97, 21.38
Symbicort LD	484	191.83 (64.07)	13.45 (1.89)	9.74, 17.16
Formoterol 4.5	484	193.87 (74.70)	7.86 (1.89)	4.14, 11.57
Placebo	466	(b) (4)		-1.64, 5.88
(b) (4)		(b) (4)		

Source: SUN CSR, Section 7.2.6.1, Table 55, p. 173

Table 53 SUN: AM and PM PEF (L/min): Primary treatment comparisons for change from baseline

Comparison	Average Of Randomized Treatment Period	
	LS Mean (SEM)	95% CI, p-value
Morning PEF (L/min)		
Symbicort HD vs. Placebo	18.42 (2.27)	13.98, 22.88 ($p < 0.001$)
Symbicort LD vs. Placebo	13.21 (2.26)	8.77, 17.65 ($p < 0.001$)
Evening PEF (L/min)		
Symbicort HD vs. Placebo	15.56 (2.27)	11.10, 20.01 ($p < 0.001$)
Symbicort LD vs. Placebo	11.33 (2.27)	6.87, 15.78 ($p < 0.001$)

Source: SUN CSR, Section 7.2.6.1, Table 56, p. 174

In terms of the primary comparisons, results indicate that both dosage strengths of Symbicort demonstrated a statistically significant change for morning and evening PEF compared with placebo, from baseline to the average during the randomized treatment period.

Reviewer's comment: The Applicant has (b) (4)

5. Breathlessness Cough Sputum Score, Sleep Score, and Rescue Medication Use

- **Breathlessness Cough Sputum Score (BCSS):** comprised of the dyspnea, cough, and sputum scores, each rated from 0-4, with higher scores indicating a more severe manifestation of symptoms.
- **Sleep score:** is also rated on a 0-4 scale with a higher score indicating greater sleep disturbance.
  Reviewer's comment: (b) (4)
- **Rescue medication use**: is specifically referring to total daily use in puffs/day of study-provided B2-agonist rescue medication (albuterol or salbutamol).

Table 54 summarizes the treatment means and treatment comparisons for each of the aforementioned efficacy variables, concentrating on the primary comparison of Symbicort HD versus placebo.

Table 54 SUN: BCSS, Sleep Score, and Rescue Medication Use: Treatment means and primary treatment comparisons for change from baseline

Comparison	Average Of Randomized Treatment Period			
	Baseline value Mean (SD)	**Change from Baseline LS Mean (SEM) [95% CI]**	**LS Mean (SEM)**	**95% CI (p-value)**
BCSS (0-12)				
Symbicort HD [N = 489]	(b) (4)	[-1.01, -0.68]		
Placebo [N = 467]		[-0.54, -0.21]		
Symbicort HD vs. Placebo			-0.47 (0.10)	-0.66, -0.28 P < 0.001
Sleep Score (0-4)				
Symbicort HD [N = 489]		[-0.33, -0.20]		
Placebo [N = 463]		[-0.16, -0.03]		
Symbicort HD vs. Placebo			-0.17 (0.04)	-0.25, -0.10 P < 0.001
Rescue Medication use (puffs/day)				
Symbicort HD [N = 490]		[-1.26, -0.75]		
Placebo [N = 467]		[-0.12, 0.40]		
Symbicort HD vs. Placebo			-1.15 (0.16)	-1.45, -0.84 P < 0.001
(b) (4) (b) (4)				

Source: SUN CSR, Section 7.2.6.2, Tables 57 and 58, p. 175-178.

The results for COPD symptoms and rescue medication use as measured by the BCSS, Sleep score, and rescue medication use averaged over the randomized treatment period indicate Symbicort HD was statistically better than placebo in terms of all variables.

Reviewer's comment: Although statistical significance was achieved, the clinical significance of these findings remains uncertain. Further, for the reasons stated earlier, sleep disturbance in COP (b) (4) *they are generally supportive of the efficacy of Symbicort in COPD.*

6. Health Economics Results

For most variables, there were no statistically significant differences seen for COPD-related resource utilization for either Symbicort HD or LD compared to placebo. Symbicort LD compared with placebo, but not HD, did demonstrate a statistically significant reduction in the number of days of oral steroid use, number of visits to specialists, and home visits by physicians during the randomized treatment period.

Reviewer's comment: The reliability of the health economic findings is circumspect, as it was not seen with the higher dose. The Sponsor does not propose any labeling claims based on these findings.

7. Pharmacokinetic Results

Not applicable in this study.

In summary, Symbicort HD demonstrated a statistically significantly greater increase from baseline in pre-dose FEV1 compared with formoterol and placebo, with overall maintenance of effect over the 12-month treatment period. Symbicort HD also demonstrated a significant increase from baseline in 1-hour post-dose FEV1 compared with placebo. Taken together, these results demonstrate the contribution of both budesonide and formoterol to the efficacy of the combination product. Symbicort LD did not demonstrate a significant difference from formoterol for pre-dose FEV1, therefore failing to show the contribution of budesonide to the efficacy of the combination product. However, a significant difference was seen for both pre-dose and 1-hour post-dose FEV1 compared with placebo. Dyspnea scores as measured by the Breathlessness Diary, SGRQ, and COPD exacerbations were defined as key secondary endpoints. For various reasons as stated in the review, (b) (4) of these secondary endpoints are not supported, but overall, the secondary endpoints to do support the efficacy of Symbicort.

Additional secondary endpoints, including spirometric and non-spirometric variables were also examined. Notably, serial FEV1 testing supported the 12 hour dosing interval in COPD patients, and a median time to 15% onset of bronchodilation of approximately 5 minutes for Symbicort HD. Of the other secondary efficacy variables, although some achieved statistical significance, their clinical significance in COPD remains unclear.

Safety Assessments

Extent of Exposure

The extent of exposure in terms of duration of treatment is summarized in Table 55 below.

Table 55 SUN: Extent of exposure

Exposure	Treatment groups			
	SYMB HD N = 494	SYMB LD N = 494	Formoterol N = 495	Placebo N = 481
Duration of randomized treatment days				
Mean (SD)	305 (115)	299 (118)	289 (127)	270 (139)
Median	364	364	364	362
Number (%) of subjects remaining on randomized treatment at start of each time period				
> 4 wks	474 (96.0)	478 (96.8)	475 (96.0)	429 (89.2)
> 8 wks	454 (91.9)	454 (91.9)	443 (89.5)	402 (83.6)
> 12 wks	437 (88.5)	438 (88.7)	417 (84.2)	388 (80.7)
> 16 wks	434 (87.9)	426 (86.2)	407 (82.2)	379 (78.8)
> 24 wks	410 (83.0)	405 (82.0)	389 (78.6)	349 (72.6)
> 28 wks	399 (80.8)	385 (77.9)	373 (75.4)	335 (69.6)
> 36 wks	387 (78.3)	375 (75.9)	362 (73.1)	326 (67.8)
> 48 wks	373 (75.5)	359 (72.7)	344 (69.5)	307 (63.8)

Source: Sun CSR, Section 8.2, Table 63, p. 198.

A total of 1964 subjects received at least 1 dose of study medication. The majority of the subjects in each treatment group received randomized treatment for at least 48 weeks and completed the planned 12 month treatment duration. Mean exposure was shortest in the placebo group (270 days) and longest in the Symbicort HD group (305 days). The percentage of subjects completing treatment was also lowest in the placebo group (63.8%) and highest in the two Symbicort groups (HD 75.5%, LD 72.7%). There were no important differences in exposure across treatment groups when analyzed by subgroups of age, race, and gender. Across treatment groups, the mean exposure was shorter in the US (255 days) compared to the non-US regions (320 days) due to a greater discontinuation rate in the US (SUN CSR, Table 11.3.1.1).

Adverse Events

5. Deaths

There were 15 deaths during randomized treatment period (see Table 56): 3 in the Symbicort HD group, 6 in the Symbicort LD group, 2 in the formoterol group, and 4 in the placebo group. Of these deaths, 5 were reported due to cardiovascular events, 3 were due to COPD, 1 was due to both cardiovascular causes and COPD, 1 was due to cancer, and 1 was due to multiple co-morbidities. Deaths were unevenly distributed across the countries with 6 of the 11 occurring in Poland. All 4 deaths from COPD exacerbations occurred in current smokers with severe COPD at baseline. [Module 5, Shine CSR, Section 8.4.1, p. 230]

Table 56 SUN: Deaths by treatment group and primary cause of death				
Primary events leading to death*	SYMB HD N = 494	SYMB LD N= 494	FORM N= 495	Placebo N = 481
Total Deaths	**3**	**6**	**2**	**4**
Neoplasm				
Lung Cancer	1	0	0	1
Other		1	0	1
Renal Failure	1	0	0	0
Infection				0
Peritonitis	1	0	0	0
Shock	0	0	0	1
Cardiac failure		1	1	0
Respiratory				
COPD exacerbated	0	0	0	0
Pneumonia	0	1	0	0
Pulmonary Embolism	0	0	0	0
Cerebrovascular Accident	0	1	1	0
Hip Fracture	0	0	0	1
Road Traffic Accident	0	1	0	0
Unknown	0	1	0	0

* Event grouping by reviewer
Source: Module 5, SUN CSR, Table 76 p. 227-8.

Reviewer's comment: Overall, there were relatively few deaths in this study, considering the severity of COPD in the study population and the presence of co-morbid conditions. Review of the narratives and the causes of death do not suggest a particular safety signal.

6. Serious adverse events

Serious AEs occurred in 14.8% of the overall study population, including 15.6% of the Symbicort HD group, 13.6% Symbicort LD, 17.8% formoterol, and 12.1% placebo for a total of 290 patients with a SAE.

- The most common serious adverse event was COPD, occurring in 7.1% of the Symbicort HD group, 6.7% of the Symbicort LD group, 7.9% of the formoterol group, and 5.6% of the placebo group in a total of 134 subjects.
- There were 34 serious cardiac events, including the AE terms of atrial fibrillation, angina pectoris, coronary artery disease, acute myocardial infarction/myocardial infarction, cardiac failure, and congestive failure. Of these events, 6 occurred in the Symbicort HD group, 12 in the Symbicort LD group, 12 in the formoterol group, and 4 in the placebo group [SUN CSR, Section 8.4.2.1, Table 78, p. 236]
- There were 44 serious respiratory infections including AE terms of pneumonia (n = 33) and other lung infections (n = 11). These events are described by treatment group under "adverse events of interest" below; of note, there was no difference in the distribution of SAEs between Symbicort and placebo treatment groups.

7. Adverse events leading to discontinuation (DAEs)

Discontinuations due to adverse events occurred in 12.1 % of the overall population, including 11.3 % in the Symbicort HD group, 12.3% Symbicort LD, 12.3% formoterol, and 12.5% placebo, for a total of 238 patients with a DAE. The most frequently reported DAE preferred term in the total study population was COPD (5.9%, 115 patients). The incidence of COPD DAEs was highest in the formoterol group (7.3%), compared with Symbicort HD (4.0%), Symbicort LD (6.1%), and placebo (6.0%). Of note, there were 23 discontinuations due to respiratory infections, including pneumonia and other lung infections. These events are described by treatment group under "adverse events of interest" below; of note, the most discontinuations secondary to any of these respiratory tract infections occurred in the placebo group and the rest were fairly evenly distributed among treatment groups [Module 5, SUN CSR, Section 8.4.3.1, p. 238, Table 79].

8. Overall adverse events

Adverse events (AEs) were reported in 61.7% of the patients: 65.2% in Symbicort HD, 65.4% in Symbicort LD, 60.4% in formoterol, and 55.7% in placebo. There was a slight increase in the percentage of subjects with at least 1 AE or SAE in all active treatment groups compared to placebo. COPD was the most frequently reported AE, with the highest incidence in the Symbicort LD group (18.8%) and lowest in the Symbicort HD group (13.4%). The distribution of severity grading was similar across treatment groups. Adverse events occurring in ≥ 3% of patients in any treatment group are presented in Table 57.

Table 57 SUN: Adverse events occurring in ≥ 3% of subjects by treatment group

MedDRA System Organ Class MedDRA Preferred Term	Treatment			
	SYMB HD N (%)	SYMB LD N (%)	Formoterol N (%)	Placebo N (%)
Total treated	494 (100)	494 (100)	495 (100)	481 (100)
Total with AE	322 (65.2)	323 (65.4)	299 (60.4)	268 (55.7)
Respiratory System Disorders (Lower)				
Bronchitis	24 (4.9)	22 (4.5)	24 (4.8)	18 (3.7)
COPD	66 (13.4)	93 (18.8)	83 (16.8)	77 (16.0)
Pneumonia	15 (3.0)	15 (3.0)	17 (3.4)	23 (4.8)
(Upper)				
Dysphonia	16 (3.2)	6 (1.2)	1 (0.2)	4 (0.8)
Nasopharyngitis	35 (7.1)	44 (8.9)	30 (6.1)	22 (4.6)
Sinusitis	19 (3.8)	19 (3.8)	19 (3.8)	8 (1.7)
Upper respiratory tract infection (viral)	21 (4.3)	16 (3.2)	10 (2.0)	17 (3.5)
Infection and infestations				
Oral Candidiasis	36 (7.3)	21 (4.3)	2 (0.4)	8 (1.7)
Musculoskeletal				
Back Pain	18 (3.6)	5 (1.0)	14 (2.8)	11 (2.3)
Muscle Spasms	16 (3.2)	6 (1.2)	4 (0.8)	6 (1.2)

Source: Module 5, SUN CSR, Section 8.3.2.1, Tables 65 and 66, p. 203, 205
** grouping by reviewer; of note, respiratory infections have been classified by this reviewer in the respiratory SOC

a) Adverse events of interest

Specific categories of AEs of interest associated with ICS or B2-agonists were evaluated by the Applicant.

ICS

- Oral candidiasis/voice effects – overall, these local steroid class effect AEs were reported with higher incidence in the Symbicort HD (10.3%) and Symbicort LD (5.7%) groups compared with formoterol (0.6%) and the placebo groups (2.5%).
- Bone effects, diabetes control, skin effects, weight gain, ocular effects, taste effects, and adrenal suppression – reported with low and similar incidence across all treatment groups.

- Lung Infections

Pneumonia-related preferred terms were evaluated due to recent findings in studies with salmeterol/fluticasone in subjects with COPD that indicated a higher rate of pneumonia in all groups receiving ICS (1-3). For pneumonia related preferred terms (pneumonia, bronchopneumonia, lobar pneumonia, or pneumonia staphylococcal), there were 78 subjects with at least 1 event. There was no consistent effect in terms of dose-response for budesonide (See Table 58). However, when "potential lung infections other than pneumonia" (which contained preferred terms that could potentially represent lower respiratory tract infections other than pneumonia) were investigated, there was a higher

incidence in those groups treated with budesonide as compared with placebo (6.9%-8.1% vs. 6.2%). There was a numerical trend towards increased lung infections with higher doses of steroids (Symbicort HD 8.1%, Symbicort LD 6.9%) (See Table 58).

Table 58 SUN: Pneumonia AEs or Other Lung Infection AEs of Interest by MedDRA preferred term, during randomized treatment

MedDRA Preferred Term	Treatment			
	SYMB HD N (%)	SYMB LD N (%)	Formoterol N (%)	Placebo N (%)
Total treated N (%)	494 (100)	494 (100)	495 (100)	481 (100)
Total AEs	56 (11.3)	48 (9.7)	52 (10.5)	53 (11.0)
Pneumonia N (%)	**20 (4.0)**	**17 (3.4)**	**17 (3.4)**	**24 (5.0)**
Pneumonia	15 (3.0)	15 (3.0)	17 (3.4)	23 (4.8)
Bronchopneumonia	2 (0.4)	1 (0.2)	0	1 (0.2)
Lobar pneumonia	2 (0.4)	0	0	0
Pneumonia staphylococcal	1 (0.2)	1 (0.2)	0	0
Other Lung Infections	**40 (8.1)**	**34 (6.9)**	**35 (7.1)**	**30 (6.2)**
Bronchitis	24 (4.9)	22 (4.5)	24 (4.8)	18 (3.7)
LRTI, viral	6 (1.2)	7 (1.4)	5 (1.0)	3 (0.6)
LRTI, bacterial	7 (1.4)	1 (0.2)	3 (0.6)	5 (1.0)
Bronchitis, bacterial	1 (0.2)	1 (0.2)	3 (0.6)	2 (0.4)
Obstructive chronic bronchitis with acute exacerbation	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
LRTI	1 (0.2)	0	1 (0.2)	1 (0.2)
Sinobronchitis	0	1 (0.2)	1 (0.2)	0
Tracheobronchitis	0	2 (0.4)	0	1 (0.2)

Source: Module 5, SUN CSR, Section 8.3.3.1, Tables 67, 68, 11.3.2.6.14, p. 207-8, 8341

Reviewer's comment: An information request was sent to the Sponsor to resolve some apparent discrepancy in the numbers in Table 58. This may be related to how the Sponsor has only counted subjects with multiple events in the same category once in the category. The highlighted numbers in Table 58 are those in question. In response to our information request, the Applicant has clarified that the numbers presented above are presented as the number and percentage of subjects with pneumonia or other lung infection AEs of interest, rather than the number of AEs in these categories. An individual subject could have experienced an AE in more than a single preferred term (PT) category (for example, an AE of pneumonia, as well as AE of bronchitis). In such cases, the subject was counted for each PT.

Because subjects with multiple events in the same PT category were counted only once in that category, this reviewer also requested that the data be presented so that multiple events were counted individually in each category. The Applicant provided this data in the response dated November 25, 2008. This information is summarized in Table 59.

Table 59 SUN: Number of Pneumonia and Other lung infection AEs per Treatment Year [AE per subject treatment year]

MedDRA Preferred Term	Treatment			
	SYMB HD	SYMB LD	Formoterol	Placebo
N = total exposure days	150629	147665	142828	129681
Total AEs	**65**	**69**	**71**	**66**
Pneumonia (Total)	**22**	**24**	**23**	**29**
Pneumonia	17 [0.041]	22 [0.054]	23 [0.059]	28 [0.079]
Bronchopneumonia	2 [0.005]	1 [0.002]	0	1 [0.003]
Lobar pneumonia	2 [0.005]	0	0	0
Pneumonia staphylococcal	1 [0.002]	1 [0.002]	0	0
Other Lung Infections (Total)	**43**	**45**	**48**	**37**
Bronchitis	29 [0.070]	27 [0.067]	31 [0.079]	20 [0.056]
LRTI, viral	8 [0.019]	8 [0.020]	5 [0.013]	5 [0.014]
LRTI, bacterial	2 [0.005]	3 [0.007]	6 [0.015]	5 [0.014]
Bronchitis, bacterial	2 [0.005]	2 [0.005]	4 [0.010]	5 [0.014]
Obstructive chronic bronchitis with acute exacerbation	1 [0.002]	1 [0.002]	1 [0.003]	1 [0.003]
LRTI	1 [0.002]	1 [0.002]	1 [0.003]	0
Sinobronchitis	0	1 [0.002]	0	1 [0.003]
Tracheobronchitis	0	2 [0.005]	0	0

Source: Module 5, SUN CSR, Section 8.3.3.1, Tables 67, 68, 11.3.2.6.14, p. 207-8, 8341

Reviewer's comment (cont'd): It is notable that when events were counted rather than subjects experiencing events, the overall numbers did not change appreciably. The number of bronchitis/acute bronchitis AEs increased slightly, indicating that one or more subjects may have experienced multiple episodes of bronchitis. The number of pneumonias also increased slightly as compared with Table 58, however the increase was distributed equally between groups.

Reviewer's comment: An information request was sent to the Sponsor to clarify the numbers of pneumonias and other lung infections which were SAEs and cause for discontinuation (DAEs). This reviewer wanted to ensure that although there did not appear to be an increase in the overall incidence of pneumonias with Symbicort, that the severity of pneumonia and other lung infections was not greater in the active treatment group as well. The Applicant replied to the information request with the following tables as requested by this reviewer. From the data provided below, there were not significantly more SAES or DAEs due to either pneumonia or other lung infections when Symbicort treatment groups were compared to non-ICS treatment groups. The number of pneumonias and other lung infections that were reported as SAEs and DAEs have been updated in the previous respective sections.

Number and % of subjects with pneumonia or other lung infections SAES during randomized treatment - SUN

	SYMB 160	SYMB 80	Formoterol	Placebo	Total
Pneumonia (all MedDRA PTs)	8 (1.6)	5 (1.0)	8 (1.6)	12 (2.5)	33 (1.7)
Other lung infections (all MedDRA PTs)	2 (0.4)	6 (1.2)	3 (0.6)	0	11 (0.6)

Number and % of subjects with DAEs due to pneumonia or other lung infection during randomized treatment - SUN

	SYMB 160	SYMB 80	Formoterol	Placebo	Total
Pneumonia (all MedDRA PTs)	2 (0.4)	1 (0.2)	1 (0.2)	6 (1.2)	10 (0.5)
Other lung infections (all MedDRA PTs)	2 (0.4)	2 (0.4)	5 (1.0)	4 (0.8)	13 (0.7)

B2-agonists

The overall incidence of B2-agonist class effects was 7.4%, with an increase in all active treatment groups compared to placebo (Symbicort HD: 9.5%, Symbicort LD: 8.9%, formoterol: 4.5%, and placebo 4.8%).

The percentage of cardiac-related AEs was higher in all active treatment groups compared to the placebo group (7.7%, 8.5%, 7.1%, and 5.0% for Symbicort HD, Symbicort LD, formoterol, and placebo, respectively). The active treatment groups were more likely to have subjects with ≥ 1 cardiac-related AE (11.3%, 10.7%, 10.5%, and 6.9% Symbicort HD, Symbicort LD, formoterol, and placebo, respectively). The most

common preferred terms in the cardiac SOC were angina pectoris (1.2%), atrial fibrillation (1.1%), ventricular extrasystoles (0.6%), and cardiac failure (0.5%).

When the cardiac disorders were grouped under high level terms (HLT), an increase in the total percentage of subjects with supraventricular arrhythmias on Symbicort HD (2.2%) vs. placebo (0.9%) was noted.

Reviewer's comment: Arrhythmogenic potential of b2 agonists is a known cardiac effect, and overall, there are no new safety findings in this study.

5. Subgroup analysis of adverse events

There were no clinically important differences in the incidence, types or intensities of AEs across the age, gender, and racial groups. There were no apparent differences in the overall incidence or types of AEs between current and ex-smokers other than a higher incidence of COPD AEs in current smokers .The overall incidence of AEs, as well as the incidence of AEs per subject treatment year was higher in the US (64.6%) than in the non-US region (35.4%). Of note, the incidence of pneumonia AEs was higher in the non-US region (4.6%) compared with the US region (2.3%). For most other preferred terms, there were no clinically important differences in the incidences of individual AEs across regions.

Laboratory Evaluation (Hematology, Chemistry, Urinalysis)

The Applicant presented the laboratory data as mean change from baseline, shift tables, and clinically significant changes. These data were reviewed. The following non-serious AEs were reported:

- Anemia: 12 subjects (3 Symbicort HD, 7 Symbicort LD, 1 formoterol, 3 placebo)
- Hyperglycemia: 15 subjects (3 Symbicort HD, 7 Symbicort LD, 5 formoterol)
- Hypokalemia: 14 subjects (3 Symbicort HD, 8 Symbicort LD, 1 formoterol, 2 placebo)
- Hyperkalemia: 4 subjects (1 Symbicort LD, 1 formoterol, 2 placebo)

Overall, Symbicort HD did not demonstrate any clinically important changes in laboratory values compared to formoterol or placebo. The changes in hematology and clinical chemistry values, were generally minimal across all treatment groups. There were no clinically meaningful changes from baseline or differences across treatment groups at any visit. There were no meaningful treatment group differences in shifts for either standard central laboratory ranges or extended reference ranges.

HPA-axis evaluation: 24-hour urinary cortisol

HPA-axis assessment via measurement of 24-hour urinary free cortisol was conducted in a subset of patients in both SUN (n=179) and SHINE (n=437). See Figure 27.

Figure 27 Treatment means for 24-hour urinary free cortisol (nmol) at the end of treatment: combined data from SUN and SHINE

	From ANCOVA on Log-transformed values		
Treatment group (µg) comparison	LS mean treatment ratio	95% CI treatment ratio	p-value
SYMB 160/4.5 versus Plac	0.7	0.57, 0.87	0.001
SYMB 160/4.5 versus Budes 160 + Form 4.5	1.15	0.90, 1.47	0.272
SYMB 160/4.5 versus Budes 160	1.15	0.89, 1.50	0.282
SYMB 160/4.5 versus Form 4.5	0.58	0.47, 0.72	<0.001
SYMB 80/4.5 versus Plac	0.83	0.67, 1.04	0.102
SYMB 80/4.5 versus Budes 160	1.37	1.05, 1.78	0.019
SYMB 80/4.5 versus Form 4.5	0.69	0.56, 0.86	0.001
SYMB 160/4.5 versus SYMB 80/4.5	0.84	0.68, 1.04	0.110

SYMB SYMBICORT pMDI; Budes Budesonide; Form Formoterol; Plac Placebo pMDI and TBH.
Each treatment was administered as 2 actuations/inhalations twice daily.
ANCOVA Analysis of covariance; LS Mean least squares mean; CI Confidence interval; pMDI Pressurized metered-dose inhaler; TBH Turbuhaler.

Statistically significant differences (~30% suppression) by ANCOVA were seen between the Symbicort HD and placebo groups at 6 months and between Symbicort HD and formoterol at the end of treatment. A total of 4 subjects had a shift from normal at baseline to low (< 5.5 nmol/24h) at the end of treatment. The number and proportion of subjects with these shifts was evenly distributed across treatment groups. A dose-ordered response for budesonide was not observed for shifts from normal to low at 6 months or end of treatment.

Vital Signs/Physical Examination
The Applicant presented the vital signs (including systolic/diastolic blood pressure, heart rate, and weight) as changes in mean values over time, shift tables, and clinically significant changes. These data were reviewed. Overall, the changes in values was small, and there were no clinically important differences between treatment groups.

ECG findings
There were no clinically important treatment group differences in mean change from baseline, shifts from baseline, or in the incidence of clinically important abnormalities for pre-dose or 1 hour post-dose QRS duration, PR interval, or heart rate. For QT, QTcB, and QTcF, there were similarly no differences.

24-hour Holter Monitoring
A total of 520 subjects were included in the Holter monitoring subset. The data from changes in mean values across treatments, shift table results, and physician blinded review of all abnormal

Holter results were reviewed. For change in mean values across treatments, there were increases in ventricular ectopy (VE, beats/hour) and heart rate for the formoterol-containing treatment groups at Cmax. However, the differences between treatment groups was not clinically important (Symbicort HD: 15.8, Symbicort LD: 22.7, Formoterol 15.6, placebo: 5.4). The findings for supraventricular ectopy (SVE) were not consistently related to formoterol-containing treatment groups.

For VE rate, the percentage of subjects with shifts from normal at baseline to high on-treatment values was highest in the Symbicort HD group (18.6%) and lowest in the placebo group (12.2%). For SVE rate, the percentage of subjects with shifts from normal at baseline to high on-treatment values was highest for Symbicort LD (16.0%) and lowest for placebo (10.8%). For SVE, shift from normal to high was lowest in the placebo group (8.9%) and highest in the formoterol group (16.8%). For overall Holter assessment, the percentage of subjects with normal assessment at baseline who shifted to abnormal at treatment maximum was highest in the formoterol group (30.9%) and other treatment groups were similar, ranging from 23.0% to 23.7%.

The number and percentage of subjects with specific Holter findings were slightly increased in the Symbicort HD group (33, 6.7%), Symbicort LD group (39, 7.9%), and formoterol 4.5 (40, 8.1%), compared with placebo (27, 5.6%) The increase was driven by the increased supraventricular and ventricular ectopic hourly rate categories. Flags that could indicate new atrial fibrillation were infrequent and balanced across treatment groups. Overall, there was no new safety signal seen.

Bone Mineral Density

A total of 326 patients had baseline and post-baseline BMD results and were included in the BMD analysis subset. Total lumbar spine BMD was the primary variable to be analyzed, while total hip BMD was the secondary variable. Mean baseline BMD values were similar across all treatment groups for each of the spine and hip regions. Mean changes in BMD from baseline to end of treatment were very close to zero for each of the treatment groups for both spine and hip regions (mean changes ranged from –0.01 to 0.01). ANCOVA results for total spine and total hip BMD based on the end of treatment time point showed that all geometric LS Mean ratios for the pairwise treatment group comparisons were close to 1. Statistically significant differences by ANCOVA were seen between Symbicort HD and each of the other treatment groups for total lumbar spine BMD, and between Symbicort HD and formoterol 4.5 for total hip BMD. However, the geometric LS Mean ratio was either 0.99 or 0.98 for these treatment group comparisons with a 95% confidence interval upper limit of 1.00. See Table 60 and Table 61.

Reviewer's comment: The overall changes in BMD were very small and unlikely clinically significant.

Table 60 SUN: Bone Mineral Density (g/cm^2): Change in Total Lumbar and Total Hip BMD from Baseline to End of Treatment

	N	Baseline value Mean (SD)	N	Change from Baseline Mean (SD)
Total Lumbar Spine BMD (primary variable)				
Symbicort HD	87	1.01 (0.19)	83	-0.01 (0.04)
Symbicort LD	86	0.99 (0.20)	83	0.01 (0.04)
Formoterol 4.5	81	0.96 (0.16)	79	0.00 (0.04)
Placebo	66	0.97 (0.18)	66	0.01 (0.04)
Total Hip BMD (secondary variable)				
Symbicort HD	86	0.87 (0.15)	84	-0.01 (0.02)
Symbicort LD	86	0.86 (0.18)	82	0.00 (0.02)
Formoterol 4.5	80	0.85 (0.16)	76	0.00 (0.02)
Placebo	66	0.87 (0.15)	65	-0.01 (0.02)

Source: SUN CSR, Section 8.6.5, Table 99, p. 282

Table 61 SUN: Bone Mineral Density (g/cm^2): Treatment group comparisons

Comparison	End of Treatment	
	Geometric LS Mean Treatment Ratio	95% CI (p-value)
Total Lumbar Spine BMD (primary variable)		
Symbicort HD vs. Placebo	0.99	0.97, 1.00 (0.033)
Symbicort HD vs. Formoterol	0.98	0.98, 1.00 (0.037)
Symbicort LD vs. Placebo	1.00	0.99, 1.01 (0.753)
Symbicort LD vs. Formoterol	1.00	0.99, 1.02 (0.623)
Formoterol vs. Placebo	1.00	0.99, 1.01 (0.009)
Symbicort HD vs. Symbicort LD	0.98	0.97, 1.00 (0.009)
Total Hip BMD (secondary variable)		
Symbicort HD vs. Placebo	1.00	0.99, 1.01 (0.675)
Symbicort HD vs. Formoterol	0.99	0.98, 1.00 (0.012)
Symbicort LD vs. Placebo	1.00	0.99, 1.01 (0.538)
Symbicort LD vs. Formoterol	0.99	0.99, 1.00 (0.154)
Formoterol vs. Placebo	1.01	1.00, 1.02 (0.052)
Symbicort HD vs. Symbicort LD	1.00	0.99, 1.00 (0.270)

Source: SUN CSR, Section 8.6.5, Table 100, p. 283.

No subjects in any treatment group presenting with a normal BMD T-score at baseline shifted to the osteoporosis category at the end of treatment for either the hip or spine regions. There were 14 subjects who had normal BMD T-scores at baseline (spine) who shifted to the osteopenia category and 11 subjects (hip) who shifted to the osteopenia category at end of treatment, and there were no treatment group differences. Additionally, there were 3 subjects with total hip BMD T-score shifts from the osteopenia category at baseline to the osteoporosis category at the

end of treatment, and 9 subjects with total spine BMD T-score shifts from the osteopenia category at baseline to the osteoporosis category at the end of treatment. The numbers of subjects exhibiting categorical shifts were distributed similarly across the 4 treatment groups.

Bone mineral density results for total hip and total spine regions for the 12-month time point were similar to the end of treatment results presented above. Overall, across all treatment groups, bone mineral density for total hip and total spine regions for the 12 month time point were stable over the entire 1-year treatment period.

Ophthalmologic Assessments

A total of 461 patients were included in the ophthalmology analysis set. The 4 separate lenticular opacity assessments ([nuclear opalescence (NO), nuclear color (NC), cortical cataract (C), and posterior subcapsular (P)] along with intraocular pressure measurements were to be conducted at baseline, 6 months, and 12 months. Results for posterior subcapsular (P) only are presented here as the most accurate measure of lenticular opacification associated with the use of corticosteroids.

As shown in Table 62, the LS mean change from baseline to end of treatment for posterior subcapsular and intraocular pressures were small for each treatment group. The ANCOVA results in Table 63 showed a statistically significant different in the treatment group LS Mean changes from baseline for Symbicort HD vs. Symbicort LD (p = 0.022). No other treatment group comparisons were statistically significant for posterior subcapsular or intraocular pressure.

Table 62 SUN: Ophthalmology: Treatment group means of posterior subcapsular lenticular opacity grading and intraocular pressure – Change from Baseline to End of Treatment

	N	Baseline value Mean (SD)	Change from Baseline LS Mean (SE)	95% CI
Intraocular Pressure (mm Hg)				
Symbicort HD	122	15.5 (3.25)	0.48 (0.29)	-009, 1.05
Symbicort LD	105	15.3 (2.83)	0.69 (0.31)	0.09, 1.29
Formoterol 4.5	118	15.4 (2.78)	0.56 (0.29)	-0.02, 1.13
Placebo	116	15.8 (3.28)	0.58 (0.30)	-0.00, 1.16
Posterior Subcapsular				
Symbicort HD	119	0.4 (0.71)	0.18 (0.04)	0.2, 0.26
Symbicort LD	98	0.5 (0.88)	0.05 (0.04)	-0.04, 0.13
Formoterol 4.5	116	0.5 (0.82)	0.09 (0.04)	0.02, 0.17
Placebo	112	0.5 (0.78)	0.10 (0.04)	0.01, 0.18

Source: SUN CSR, Section 8.6.6, Table 102, p. 288

Table 63 SUN: Ophthalmology: Treatment group comparisons		
Comparison	**End of Treatment**	
	LS Mean (SE)	**95% CI (p-value)**
Intraocular Pressure (mm Hg)		
Symbicort HD vs. Placebo	-0.10 (0.40)	-0.9, 0.69 (0.805)
Symbicort HD vs. Formoterol	-0.07 (0.40	–0.86, 0.71 (0.852)
Symbicort LD vs. Placebo	0.11 (0.42)	–0.71, 0.93 (0.796)
Symbicort LD vs. Formoterol	0.13 (0.41)	–0.68, 0.95 (0.749)
Formoterol vs. Placebo	–0.02 (0.40)	–0.82, 0.77 (0.951)
Symbicort HD vs. Symbicort LD	–0.21 (0.41)	–1.02, 0.60 (0.615)
Posterior Subcapsular		
Symbicort HD vs. Placebo	0.08 (0.06)	–0.03, 0.19 (0.134)
Symbicort HD vs. Formoterol	0.08 (0.06)	–0.02, 0.19 (0.126)
Symbicort LD vs. Placebo	–0.05 (0.06)	–0.16, 0.07 (0.403)
Symbicort LD vs. Formoterol	–0.05 (0.06)	–0.16, 0.07 (0.408)
Formoterol vs. Placebo	0.0 (0.06)	–0.11, 0.11 (0.985)
Symbicort HD vs. Symbicort LD	0.13 (0.06)	0.02, 0.25 (0.022)
Source: SUN CSR, Section 8.6.6, Table 103, p. 289.		

In examining the shifts of individual patients from baseline to end of treatment, the percentage of patients with changes in IOP from ≥10 to ≤20 mm Hg at baseline to >20 mm Hg at the end of treatment was highest in the Symbicort HD group (11%) and lowest in the Symbicort LD groups (3%). In the Symbicort HD group, 9 of the 13 subjects had actual intraocular pressure changes of ≤ 4 mm Hg. Overall, changes from 10 to 20 mmHg, inclusive, at baseline to >20 mmHg at the end of randomized treatment in intraocular pressure considered clinically important (i.e. ≥5mmHg) were few and showed no association with a particular treatment.

There were 26 of 461 subjects (6%) with an increase in the posterior subcapsular score from baseline to the maximum value during the randomized treatment period of ≥0.7 (i.e. a worsening of 0.7 or more, a change of ≥0.7 is considered clinically important). Changes in posterior subcapsular scores of ≥0.7 from baseline to treatment maximum occurred more often in the Symbicort HD group (11 subjects, 9%), and least often in the Symbicort LD group (4 subjects, 4%). Results were similar for the end of treatment. Review of these subjects did not reveal any consistent commonalities among subjects exhibiting posterior subcapsular changes of ≥0.7.

10.2.3 Conclusions

SUN was a double-blind, double-dummy, randomized, placebo-controlled, parallel group, multicenter study in patients with COPD, consisting of 12 month (52 weeks) of treatment with Symbicort HD, Symbicort LD, formoterol, or placebo. The objective of this study was to demonstrate the efficacy and safety of Symbicort for the maintenance treatment of patients with COPD compared to formoterol and placebo.

A total of 1964 patients were randomized at 225 centers. Overall, discontinuation from the study was slightly higher in the formoterol treatment arm as compared with the Symbicort arms, and

highest in the placebo arm. In each of the treatment arms, either adverse events or withdrawal of consent was the most likely reason for discontinuation. Of the 1964 patients randomized, 1355 patients completed the study, and a total of 609 patients discontinued.

There was a greater percentage of male than female subjects consistent with the disease prevalence in the target population. Most subjects were Caucasian, with fewer than 8% non-Caucasian patients. Approximately half of the subjects were over age 65, with approximately 11% of subjects over the age of 75 years. Baseline percent predicted FEV1, post-bronchodilator percent predicted FEV1, and smoking history (pack years) were well balanced across all treatment groups. Severity classification, based on the GOLD 2006 criteria applied to post-bronchodilator FEV1 at Visit 1, indicated that approximately 80% of the study population had severe or very severe COPD, while 20% had moderate COPD at entry. Severity varied somewhat across treatment groups, with approximately 30% more subjects in the most severe category in the Symbicort HD and formoterol groups. In general, demographic and key baseline characteristics were similar across treatment groups and geographic regions (US vs. non-US).

The co-primary variables were change from baseline in pre-dose FEV1, to demonstrate the anti-inflammatory contribution of budesonide, and post-dose FEV1, to demonstrate the bronchodilator contribution of formoterol, to the efficacy of the combination product, Symbicort. Each co-primary variable was calculated as an average over the randomized treatment period (primary analysis) and at the end-of-treatment. In terms of the pre-specified primary comparisons, results indicate that only Symbicort HD demonstrated a statistically significantly greater increase from baseline in pre-dose FEV1 when compared with formoterol. However, this result was not consistent when analyzed at the end of treatment. Symbicort LD failed to show the contribution of the inhaled corticosteroid to the efficacy of the combination product in both analyses. Both dosage strengths of Symbicort demonstrated statistically significant difference in pre-dose FEV1 vs. placebo when examined as the average of the randomized treatment period and at the end of treatment. Symbicort HD was not statistically different when compared with Symbicort LD in terms of change from baseline in pre-dose FEV1. These results demonstrate that the higher dose of budesonide makes a contribution to the efficacy of the combination product, however the lower dose does not.

For post-dose FEV1, results indicate that both dosage strengths of Symbicort demonstrated a statistically significantly greater increase from baseline in post-dose FEV1 when compared with placebo. This result was consistent when analyzed as the average of the randomized treatment period or at the end of treatment. These results demonstrate that formoterol makes a contribution to the efficacy of both strengths of the combination product.

Dyspnea scores as measured by the Breathlessness Diary (BD), SGRQ, and COPD exacerbations were defined as key secondary endpoints. For various reasons as stated in the review, the findings of these secondary endpoints are not supportive of the primary endpoints. For example, the BD indicated an improvement in dyspnea in the Symbicort treatment groups versus placebo, but is not an accepted dyspnea [redacted] (b) (4) Results of the SGRQ did not meet MCID criteria for this instrument, although the differences were statistically significant. Finally, COPD exacerbations were statistically significantly reduced in the Symbicort treatment groups

in this 12 month study, however the definition of COPD exacerbations was inadequate. Additional secondary endpoints, including spirometric and non-spirometric variables, were also examined. Notably, serial FEV1 testing supported the 12 hour dosing interval in COPD patients, and a median time to 15% onset of bronchodilation of approximately 5 minutes for Symbicort HD. Of the other secondary efficacy variables, although some achieved statistical significance, their clinical significance in COPD remains unclear.

The extent of exposure was generally similar between the active treatment groups and placebo, and was satisfactory to allow for safety assessments. There were 15 deaths during the randomized treatment period, but their distribution or cause did not suggest a particular safety signal. The incidence of SAEs and DAEs were generally similar across treatment groups. The most common adverse events were COPD, bronchitis, nasopharyngitis, oral candidiasis, and upper respiratory tract infection. Examination of adverse events of interest with B2-agonists did not reveal any new safety signals or imbalances across treatment groups. No clinically meaningful changes in laboratory findings, ECGs, vital signs, or physical examination were noted.

Pneumonia-related preferred terms were evaluated due to recent findings in studies with salmeterol/fluticasone in subjects with COPD that indicated a higher rate of pneumonia in all groups receiving ICS. For pneumonia-related preferred terms, no clinically important differences were seen with the overall incidence across the treatment groups ranging from 3.4% in the Symbicort LD and formoterol groups, to 5.0% in the placebo group. There was no consistent effect in terms of dose-response for budesonide. However, when this data was added to "potential lung infections other than pneumonia", which contained preferred terms that could potentially represent lower respiratory tract infections other than pneumonia, there was a higher incidence in those groups treated with budesonide as compared with placebo (6.9%-8.1% vs. 6.2%). There was a numerical trend towards increased lung infections with higher doses of steroids (Symbicort HD 11.3%, Symbicort LD 9.7%).

Bone mineral density measurements and ophthalmologic examination were conducted in a subset of patients in this 12-month study. Overall, there were no clinically important changes in bone mineral density and ophthalmologic findings over the 12 month treatment period.

To summarize, "lung infections other than pneumonia" may be a new safety signal noted with Symbicort and has been added to the product label by the Sponsor. No other new safety concerns arose from the review of the data in COPD patients as compared with what has been previously reported in the Symbicort product label and other ICS/LABA combination products. In conclusion, the SUN study supports the safety and efficacy of Symbicort HD BID in the treatment of patients with COPD.

11 REFERENCES

1. Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. Eur Respir J 2003;22:912-9.

2. Kardos P, Wencker M, Glaab T, Vogelmeier C. Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2007;175:144-9.

3. Ernst P, Gonzalez AV, Brassard P, Suissa S. Inhaled corticosteroid use in chronic obstructive pulmonary disease and the risk of hospitalization for pneumonia. Am J Respir Crit Care Med 2007;176:162-6.

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

/s/

Banu Karimi-Shah
12/24/2008 01:19:39 PM
MEDICAL OFFICER

Sally Seymour
12/29/2008 08:21:00 AM
MEDICAL OFFICER
I concur. See my CDTL memo.

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

APPLICATION:	NDA # 21-929	**TRADE NAME:**	Symbicort Inhalation Aerosol
APPLICANT:	Astra Zeneca	**USAN NAME:**	Budesonide/Formoterol
MEDICAL OFFICER:	Banu Karimi-Shah, MD		
TEAM LEADER:	Sally Seymour, MD	**CATEGORY:**	ICS/LABA combination
REVIEW DATE:	June 12, 2008	**ROUTE:**	Oral inhalation

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
April 28, 2008		Efficacy Supplement	Electronic Submission

REVIEW SUMMARY:

This is a medical officer 45-day Filing Review of sNDA-21-929 for Symbicort. Symbicort is a fixed dose combination of the corticosteroid budesonide and the long-acting beta-agonist formoterol in a pressurized metered dose inhaler (MDI) using HFA 227 as the propellant. Symbicort is currently approved for the long-term maintenance treatment of asthma in patients 12 years of age and older.

This submission is an efficacy supplement to NDA 21-929 in which the Applicant seeks to add the indication for the (b) (4) maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. The proposed dose for the treatment of COPD patients is 320/9 mcg administered twice daily (BID) delivered via the Symbicort 160/4.5 device. The clinical development program in COPD consists of 5 studies: 2 Phase 1 bioavailability studies (SD-039-0738 and D5899C00006), 1 Phase 2 pharmacodynamic study (D5899C00748), and 2 Phase 3A efficacy and safety studies (D5899C00001 and D5899C00002). The sNDA also includes proposed revisions to the Prescribing Information and Medication Guide. The supplement is provided in eCTD format.

The submission is fileable. An audit by the Division of Scientific Investigations will not be requested. Comments will be communicated with the Sponsor in the 74-day letter.

OUTSTANDING ISSUES: **None**

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES:	____	**SAFE TO PROCEED**	____	**CLINICAL HOLD**		
NDA/SUPPLEMENTS:	X	**FILEABLE**	____	**NOT FILEABLE**		
	____	**APPROVAL**	____	**APPROVABLE**	____	**NOT APPROVABLE**
OTHER ACTION:						

I. General Information

Symbicort is a fixed dose combination of the corticosteroid budesonide and the long-acting beta-agonist formoterol in a pressurized metered dose inhaler (MDI) using HFA 227 as the propellant. Symbicort is currently approved for the long-term maintenance treatment of asthma in patients 12 years of age and older. There are two dose strengths that are currently marketed: 80/4.5 mcg (budesonide/formoterol) and 160/4.5 mcg. The approved doses for asthma patients range from 160/9 mcg administered twice daily to 320/9 mcg administered twice daily, depending on asthma severity and prior inhaled corticosteroid (ICS) use. Each of the doses is administered with two actuations of either device, respectively.

This submission is an efficacy supplement to NDA 21-929 in which the Applicant seeks to add the indication for the (b) (4) maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. The proposed dose for the treatment of COPD patients is the higher dose, 320/9 mcg BID. The clinical development program in COPD consists of 5 studies: 2 Phase 1 bioavailability studies (SD-039-0738 and D5899C00006), 1 Phase 2 pharmacodynamic study (D5899C00748), and 2 Phase 3A efficacy and safety studies (D5899C00001 and D5899C00002). The sNDA also includes proposed revisions to the Prescribing Information and Medication Guide. The supplement is provided in eCTD format.

Symbicort is not a unique drug product. Prior to the approval of Symbicort for asthma, each active ingredient was available in the United States as various single drug products. The following budesonide-containing products are approved in the United States: Rhinocort Nasal Inhaler (NDA 20-333, 2/14/1994), Pulmicort Turbuhaler (NDA 20-441, 6/24/1997), Rhinocort Aqua Nasal Spray (NDA 20-746, 10/1/1999), Pulmicort Respules (NDA 20-929, 8/8/2000, and Entocort EC (NDA 21-324, 10/2/2001). Formoterol is approved in the United States as Foradil Aerolizer (NDA 20-831, 2/16/2001) and Perforomist (NDA 22-007, 5/11/2007). The combination of budesonide and formoterol is also available in a dry powder inhaler (Symbicort Turbuhaler) outside the U.S.

II. Regulatory and Foreign Marketing History

A. Regulatory History

The sponsor originally submitted NDA 21-929 for Symbicort pMDI on September 23, 2005. This NDA was given an Approval action on July 21, 2006 in the first review cycle. An End-of-Phase 2 (EOP2) meeting was held in April 2004 to discuss the COPD development program. Key issues and recommendations from the EOP2 meeting are listed below:

- The Division suggested that a formoterol mono-comparator group be included in the 12 month study (D5899C00001) so that the combination rule could be addressed in both pivotal studies.
- The Division suggested the inclusion of a group to receive the free combination of budesonide and formoterol in the 6 month study (D5899C00002) to address pharmaceutical effects.

- Based on preliminary review of study SD-039-0729, the Division agreed with the use of the OXIS TBH (Formoterol DPI) as the formoterol mono-comparator.

The two pivotal phase 3 protocols were submitted to IND 63,394 (Serial No. 0336) in March 2005. Review of the protocols revealed that the Applicant had incorporated the Division's suggestions from the EOP2 meeting. No major recommendations were issued at that time. The Division also responded to questions in a pre-NDA briefing document in December 2007. Based on the Division's responses, the Applicant did not feel that a pre-NDA meeting was necessary.

B. Foreign Marketing History

Symbicort MDI is approved for COPD in Venezuela. No additional information regarding foreign marketing history is included in this submission.

Reviewer's Comment: An information request has been sent to the Sponsor asking for a more detailed foreign marketing history, including whether the drug has ever been withdrawn from any market.

III. Items Required for Filing

A. Necessary Elements (21 CFR 314.50)

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			

	Content Parameter	Yes	No	NA	Comment
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)1 efficacy supplement
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e*., appropriately designed dose-ranging studies)? Study Number: D5899C0001 and -0002 Study Title: SUN and SHINE Sample Size: 1964/1704 Location in submission: Module 5	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (*e.g.*, QT	X			

	Content Parameter	Yes	No	NA	Comment
	interval studies, if needed)?				
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S.			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
	population?				
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

B. Decision

The submission appears adequate from a clinical standpoint to allow for further review, and is therefore fileable.

IV. Clinical Studies

The clinical program in COPD includes five studies:

The clinical development program in COPD consists of 5 studies: 2 Phase 1 bioavailability studies (SD-039-0738 and D5899C00006), 1 Phase 2 pharmacodynamic study (D5899C00748), and 2 Phase 3A efficacy and safety studies (D5899C00001 and D5899C00002).

- 2 Phase 3 clinical efficacy and safety studies (D5899C00001 [SUN] and D5899C00002 [SHINE])

- 1 Phase 2 pharmacodynamic study (D5899C00748)
- 2 Phase 1 bioavailability studies (SD-039-0738 and D5899C00006)

The studies were conducted in accordance with Good Clinical Practices and in compliance with the World Medical Association Declaration of Helsinki concerning informed consent and the protection and rights of human subjects.

A. Pivotal Studies

Table 1: Summary of Pivotal Studies

Study #	Study Type	Design/Centers	Treatment Groups	Population[a]	Duration
D5899C0001 **(SUN)**	Efficacy/Safety	R, DB, DD, PG, PC, AC, MC Countries (# centers) US (144) Germany (26) Hungary (26) Denmark (13) Bulgaria (9) Greece (6) Romania (6) Mexico (5) Iceland (2)	SYMB 320/9 BID SYMB 160/9 BID *Formoterol 9 BID Placebo	Moderate to Severe COPD ≥ 40 years old, male or female **N = 1964**	12 months
D5899C0002 **(SHINE)**	Efficacy/Safety	R, DB, DD, PG, PC, AC, MC Countries (# centers) Czech Republic (18) Netherlands (11) Poland (30) South Africa (12) United States (123)	SYMB 320/9 BID SYMB 160/9 BID (BUD 320 + *FF 9) BID BUD 320 BID *Formoterol 9 BID Placebo	Moderate to Severe COPD ≥ 40 years old, male or female **N = 1704**	6 months

R = randomized, DB = double blind, PC = placebo controlled, AC = active controlled, MC = multicenter, DD = double dummy, PG = parallel group, SYMB = Symbicort, BUD = budesonide, FF = formoterol fumarate.

*Note: In both trials, the formoterol mono-product was delivered via the DPI formulation, the OXIS Turbuhaler.

Reviewer's Comment: In general, we do not usually advise the use of mono-comparator in a different formulation and delivered by a different device, as is the case here with the OXIS Turbuhaler. However, in the original NDA for asthma, the Applicant has provided a PK/PD bridging study that demonstrates the comparability of the formoterol dose delivered by the OXIS TBH and Symbicort. Therefore, the use of this mono-product was accepted by the Division at the time of the original NDA review, and still remains acceptable for this program.

The proposed indication was evaluated in the two clinical studies as shown above. With the exception of trial duration, the study methodology, subject populations, inclusion/exclusion criteria, efficacy assessments, primary and secondary efficacy variables, and statistical analysis were the same for both pivotal studies (See Table 1). Subjects enrolled in these trials were ≥ 40 years of age, of either sex, with a FEV1 ≤ 50% of predicted normal value pre-bronchodilator and an FEV1/FVC < 70% predicted. The patients had a diagnosis of COPD with symptoms for > 2 years and were current or previous smokers with a smoking history of ≥ 10 years.

Efficacy:

The primary efficacy endpoints in these studies were the change from baseline to treatment (mean over the treatment period) in pre-dose FEV1 and 1 hour post-dose FEV1. Key secondary endpoints included Saint George's Respiratory Questionnaire (SGRQ) total score, Breathlessness Diary Score, and number of exacerbations.

A summary of the primary efficacy endpoints as analyzed by the Sponsor are presented in Table 2 below.

Table 2 Treatment Comparisons for Change From Baseline Averaged Over the Randomized Treatment Period

	Pre-Dose FEV1 (L)		Post-Dose FEV1 (L)	
	Study 0001 12 months	**Study 0002 6 months**	**Study 0001 12 months**	**Study 0002 6 months**
Symbicort LD vs. placebo	0.07 (0.05, 0.10)	0.05 (0.02, 0.09)	**0.16 (0.13, 0.19)**	0.16 (0.13, 0.20)
Symbicort HD vs. placebo	0.09 (0.06, 0.12)	0.08 (0.04, 0.11)	**0.18 (0.16, 0.21)**	0.17 (0.14, 0.20)
Symbicort LD vs. budesonide		0.06 (0.02, 0.09)		**0.16 (0.13, 0.20)**
Symbicort HD vs. budesonide		0.08 (0.04, 0.11)		**0.17 (0.14, 0.21)**
Symbicort LD vs. formoterol	**0.02 (-0.01, 0.05)**	**0.02 (-0.02, 0.05)**	0.01 (-0.02, 0.04)	0.03 (-0.01, 0.06)
Symbicort HD vs. formoterol	**0.04 (0.01, 0.07)**	**0.04 (0.00, 0.07)**	0.03 (0.00, 0.06)	0.04 (0.00, 0.07)
Symbicort HD vs. free comb.		0.01 (-0.02, 0.05)		0.01 (-0.02, 0.05)
Budesonide HD vs. placebo		0.00 (-0.04, 0.03)		0.00 (-0.03, 0.03)
Formoterol vs. placebo	0.05 (0.03, 0.08)	0.04 (0.00, 0.07)	0.15 (0.12, 0.18)	0.14 (0.10, 0.17)

- Symbicort HD (320/9 mcg BID) – delivered as 2 puffs from the 160/4.5 mcg device
- Symbicort LD (160/9 mcg BID) - delivered as 2 puffs from the 80/4.5 mcg device
- **Bolded text indicated the primary comparisons for each efficacy variable**

1) Pre-Dose FEV1 (L)

This primary efficacy endpoint was defined as the change from baseline to treatment (mean over the treatment period) in pre-dose FEV1. The primary comparison in this analysis was between Symbicort and formoterol, to address the contribution of budesonide, the inhaled corticosteroid.

Pertinent results for pre-dose FEV1 comparisons from baseline averaged over the randomized treatment period for both Studies 0001 and 0002 indicated the following:

- Symbicort HD demonstrated a statistically significantly greater increase from baseline in pre-dose FEV1 compared with formoterol and placebo in both studies, thus demonstrating the contribution of the budesonide component.
- Symbicort LD did not demonstrate a significant increase from baseline in pre-dose FEV1 compared to formoterol, and therefore failed to show the contribution of the budesonide component.
- Budesonide as a mono-product did not demonstrate a statistically significant difference from baseline in pre-dose FEV1 compared with placebo in Study 0002.

Reviewer's Comment: Based on the above analysis, the Sponsor has decided only to pursue the high dose of 320/9 mcg BID for the COPD indication, as the lower dose failed to show the contribution of budesonide when the combination was compared with formoterol in both studies.

Reviewer's Comment: In this reviewer's preliminary look at the sponsor's data, it appears that there is a discrepancy in the primary efficacy variables if the effect is analyzed at the end of treatment. Although the pre-specified analysis was as stated above, the average over the treatment period, the sponsor has also conducted an analysis of the primary endpoints at the end of treatment (EOT). In this analysis, the Sponsor found that the comparison of Symbicort HD with formoterol at EOT DID NOT demonstrate the contribution of the budesonide component as measured by pre-dose FEV1. The fact that both analyses do not yield the same result raises some concern, and will be a review issue.

Reviewer's Comment: It is of note that budesonide did not beat placebo in terms of pre-dose FEV1 in either study. Generally, the validity of the mono-comparators depends upon their ability to be better than placebo, thereby allowing for a comparison with the combination product to show the contribution of the other component. However, in this case, steroids are not known to have a robust response in COPD, so it is difficult to interpret these data in the general sense. This will be a review issue.

2) Post-Dose FEV1

This primary efficacy endpoint was defined as the change from baseline to treatment (mean over the treatment period) in FEV1 one hour post-dose. The primary comparison in this analysis was between Symbicort and budesonide, to address the contribution of formoterol, the LABA. In Study 0001, the primary comparison was between Symbicort and placebo, as there was no budesonide arm included in this study.

Pertinent results for post-dose FEV1 comparisons from baseline averaged over the randomized treatment period for both Studies 0001 and 0002 indicated the following:

- Symbicort LD and HD demonstrated a statistically significant increase from baseline in 1-hour post-dose FEV1 compared with budesonide in Study 0002, and compared with placebo in both studies, thus demonstrating the contribution of formoterol to the improvement in post-dose lung function.

Safety:

The safety data was collected in the two pivotal phase 3 studies. The clinical program complied with recommendations for exposure in the ICH guidelines for evaluation of long-term safety. The program included standard safety assessments generally performed in the

development of a new drug product (i.e. adverse events, serious adverse events, hematology, chemistry, urinalysis) as well as assessments of cardiac safety (centrally read 12-lead ECGs and 24 hour Holter monitoring), effects on the HPA axis, and assessment of bone mineral density and ophthalmology measures. No new safety signals were identified by the Applicant.

Reviewer's comment: Given our knowledge regarding other ICS/LABA programs, it will be important to address the incidence of respiratory infections with Symbicort HD during the course of the review.

B. Supportive Studies

Table 3: Summary of Supportive Studies

Study #	Study Type	Design	Treatment Groups	Population	Duration
SD-039-0738	Phase 1 Comparative bioavailability study	OL, R, 2 way XO, SC	SYMB MDI 8 x 160/4.5 mcg BUD MDI 8 x 160 mcg + OXIS TBH 8 x 4.5 mcg	Adults with COPD N = 30	SD
D5899C00006	Phase 1 Comparative bioavailability	COPD: OL, R, 2 way XO, SC Asthma: OL, SC	COPD: SYMB MDI 12 x 80/4.5 mcg BUD 12 x 80 mcg + OXIS TBH 12 x 4.5 mcg Asthma: SYMB MDI 12 x 80/4.5 mcg	Adults with COPD and asthma N = 26 COPD patients N = 26 asthma patients	SD
D589900748	Phase 2 PD study to examine FEV1 5 minutes post-dose	DB, DD, 4 way XO, 4 visits, MC	SYMB MDI 2 x 160/4.5 mcg Sal/Flu 2 x 25/250 mcg Salbutamol 2 x 100 mcg Placebo MDI x 2	Adults with COPD N = 90	SD x 4 visits

R = randomized, DB = double blind, EB = evaluator blind, OL = open label, MC = multicenter, SC = single center, // = parallel group, CO = crossover

Reviewer's Comment: The supportive studies do not contribute to labeling claims or the primary efficacy outcomes. They will be reviewed as needed by the Division's Biopharmaceutics Reviewer, Dr. Partha Roy.

V. DSI Review / Audit

At this time, a DSI audit is not planned. Symbicort Inhalation Aerosol is an approved drug product for the treatment of asthma and the ICS/LABA combination is a known effective combination for the treatment of COPD. In addition, investigators that had significant financial interest in the Applicant enrolled relatively few subjects in the trials. This would preclude them from having the ability to alter the outcomes of the pivotal studies. The Biometrics reviewer has analyzed the data and has found no treatment by site interaction. As a result, no DSI audit will be requested.

VI. Brief Review of Proposed Labeling

Draft labeling in the new structured product label format is included in the electronic submission. The label has been amended to include the newly proposed indication in COPD. The Clinical Studies section of the proposed label includes data on improvement in both primary and secondary efficacy endpoints with the proposed dose of 320/9 mcg BID. In the Clinical Studies section, the Applicant has also made (b) (4) A detailed label review will be performed later in the course of review of this efficacy supplement.

Reviewer's Comment: The (b) (4) *is based on a PRO instrument whose development does not meet with the rigorous criteria required by the Agency's PRO guidance document.* (b) (4)

hese comments will be conveyed to the Applicant in the 74-day letter.

Reviewer's Comment: The newly revised Advair product label will serve as the reference label as we review/re-write the Symbicort label.

VII. Timeline for Review

Milestone	Target Date for Completion
Stamp Date	April 29, 2008
Filing Date	June 27, 2008
74th Day	July 11, 2008
Mid-Cycle Meeting	September 30, 2008
Label Review	November 11, 2008
Wrap-up Meeting	December 10, 2008
Primary Reviews	December 17, 2008
Draft CDTL Memo	January 10, 2009
Labeling Tcon with Applicant	December 16, 2008
Secondary Reviews	January 16, 2009
PDUFA Due Date	February 27, 2009

VIII. Summary

This is a medical officer 45-day Filing Review of sNDA-21-929 for Symbicort. Symbicort is a fixed dose combination of the corticosteroid budesonide and the long-acting beta-agonist formoterol in a pressurized metered dose inhaler (MDI) using HFA 227 as the propellant. Symbicort is currently approved for the long-term maintenance treatment of asthma in patients 12 years of age and older.

This submission is an efficacy supplement to NDA 21-929 in which the Applicant seeks to add the indication for the (b) (4) maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. The proposed dose for the treatment of COPD patients is 320/9 mcg administered twice daily (BID) delivered via the Symbicort 160/4.5 device. The clinical development program in COPD consists of 5 studies: 2 Phase 1 bioavailability studies (SD-039-0738 and D5899C00006), 1 Phase 2 pharmacodynamic study (D5899C00748), and 2 Phase 3A efficacy and safety studies (D5899C00001 and D5899C00002). The sNDA also includes proposed revisions to the Prescribing Information and Medication Guide. The supplement is provided in eCTD format.

The submission is fileable. An audit by the Division of Scientific Investigations will not be requested. Comments will be communicated with the Sponsor in the 74-day letter.

IX. Comments to the Sponsor

1. We note (b) (4) It is unlikely that your PRO was developed and validated as outlined in our guidance document. In addition, dyspnea is quite complex and assessment with a single question regarding breathlessness is questionable. (b) (4)

2. We note (b) (4) our definition of a COPD exacerbation is based solely on treatment with oral corticosteroids or hospitalization (b) (4)

Reviewed by:
Banu Karimi-Shah, M.D.
Medical Officer, Division of Pulmonary and Allergy Products

Sally Seymour, M.D.
Medical Team Leader, Division of Pulmonary and Allergy Products

---

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

/s/

Banu Karimi-Shah
6/17/2008 11:34:31 AM
MEDICAL OFFICER

Sally Seymour
6/20/2008 02:59:12 PM
MEDICAL OFFICER
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21–929/S012

CHEMISTRY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
OFFICE OF NEW DRUG QUALITY ASSESSMENT

POST-MARKETING EVALUATION
CMC ASSESSMENT FORM

APPLICANT: ASTRAZENECA	**NDA NUMBER:** 021929	**DOC TYPE:** SE1	**SEQ NUMBER:** 012	**SUBMISSION TYPE:** ORIGINAL
PROPRIETARY NAME: SYMBICORT		**ESTABLISHED NAME:** BUDESONIDE/ FORMOTEROL		
DOSAGE FORM: AER	**STRENGTH/POTENCY:** 80/4.5 & 160/4.5 MCG		**PHARMACOLOGICAL CATEGORY:**	
LETTER DATE: 4/28/2008	**STAMP DATE:** 4/29/2008	**PDUFA GOAL DATE:** 2/28/2009	**SUBMISSION (CHECK ONE)** FIRM: ☐ CBE-0 ☐ CBE-30 ☐ PA ☐ AR ☐ SR FINAL: PA	
DIVISION IV **BRANCH: VII**	**OND DIVISION:** 570	**MANAGED BY:** OND	**PAL:** Raghavachari	
			MEDIA SUBMISSION: Electronic	
SUPPLEMENT PROVIDES FOR: Revisions to the Prescribing Information and Medication Guide for drug product.				
BUNDLED: No				
CHANGE CATEGORY: Efficacy Supplement				
LABELING INVOLVED: Yes - Both PI & Label	**PAT:** No	**COMPARABILITY PROTOCOL:** No	**PHASE 4 COMMITMENT:**	
REVIEW PATH: 6 - OND Multi-Discipline Review				
CONSULTS:				

JUSTIFICATION/COMMENTS: 10/20/2008 - RAGHAVACHARI - Review: This efficacy supplement proposes for the addition of (b) (4) maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)including bronchitis and emphysema as an indication. This proposal is supported by clinical studies conducted under IND 63,394. Based on this the applicant has requested categorical exclusion from the need to prepare an environmental assessment in accordance with 21 CFR 25.31 (a) or (b). The applicant states that to the best of their knowledge, no extraordinary circumstances exist relative to this action. The labeling portion was also reviewed which was submitted in the PLR form. There were no CMC related changes in the proposed package insert labeling in the PLR format. The requested categorical exclusion may be granted.

Suggested labeling changes are attached in the Review Notes.

PAL ACTION: PA (Path-6)

BRANCH CHIEF: James D. Vidra

COMMENTS:

From CMC point of view this supplement is recommended for approval with the suggested labeling changes.

BRANCH CHIEF ACTION: Recommends approval from CMC perspective.

REVIEWER: Ramesh

REVIEWER ACTION:

From CMC perspective this supplement is recommended for approval.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

Ramesh Raghavachari
12/18/2008 11:56:32 AM
CHEMIST

Jim Vidra
12/18/2008 12:59:02 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21–929/S012

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-929 SE1-012**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**4/29/2008**
PRODUCT:	**Symbicort (budesonide/formoterol fumarate dihydrate)**
INTENDED CLINICAL POPULATION:	**Chronic Obstructive Pulmonary Disease Patients**
SPONSOR:	**AstraZeneca Pharmaceuticals** **1800 Concord Pike** **P.O. Box 8355** **Wilmington, DE 19803-8355**
DOCUMENTS REVIEWED:	**Electronic Submission**
REVIEW DIVISION:	**Division of Pulmonary and Allergy Drug Products (HFD-570)**
PHARM/TOX REVIEWER:	**Timothy W. Robison, Ph.D.**
PHARM/TOX SUPERVISOR:	**Luqi Pei, Ph.D.**
DIVISION DIRECTOR:	**Badrul Chowdhury, M.D., Ph.D.**
PROJECT MANAGER:	**Colette Jackson**

Date of review submission to Division File System (DFS): November 4, 2008

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

From a nonclinical pharmacology and toxicology standpoint, the application is recommended for approval.

B. Recommendation for nonclinical studies

None.

C. Recommendations on labeling

Edits were made to the nonclinical sections of the proposed labeling to conform the Draft Guidance for Industry "Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements" (January 2006) while the content of the original and approved product labeling was retained. The proposed labeling was based on the approval date of October 23, 2007. The edits included creation of new headings and rearrangement of the text accordingly. Compared to the approved labeling, the new headings included Sections 8.1, 10, 13.1 and 13.2. The recommended labeling, edits to the proposed labeling, and rationales and clarifications for these and other edits can be found in the Labeling Review of the document (next page).

II. Summary of nonclinical findings

Not applicable. No new nonclinical information was submitted. All nonclinical information was cross-referenced to the original Symbicort MDI NDA. See the Pharmacology Toxicology Review and Evaluation of NDA 21-929 submitted to the Division File System on May 22, 2006.

Labeling Review

For nonclinical sections, the content of the original product labeling was retained; however, it was rearranged to conform the Draft Guidance for Industry "Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements" (January 2006). Recent labeling for ADVAIR™ was used to assist in this process. In the sections for budesonide, the reviewer attempted to retain the content in the labeling used for Pulmicort Respules.

In Section 8.1, for use during pregnancy, findings in nonclinical reproductive toxicology studies were described in relation to multiples of the maximum recommended human daily inhalation dose. Nonclinical doses were not provided in Section 8.1; however, they were provided in Section 13.2. Further, more details of nonclinical reproductive toxicology studies were provided in Section 13.2. The Animal Pharmacology section was moved to Section 13.2. Section 10 was created for the Overdosage information.

As noted in the Pharmacology Toxicology Review and Evaluation of NDA 21-929 submitted to the Division File System on May 22, 2006, exposure margins for formoterol were based upon mcg/m^2 comparisons rather than AUC comparisons due to concerns regarding the sponsor's methods for measuring plasma concentrations of formoterol.

This is the first labeling review of budesonide and formoterol, alone or in combination, in compliance with the new labeling format. The sponsor created most of the headings, but additional headings (e.g., 13.2 Animal Toxicology and/or Pharmacology) were necessary.

Recommended labeling has been inserted below.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

Timothy Robison
11/4/2008 03:41:36 PM
PHARMACOLOGIST

Luqi Pei
11/5/2008 08:16:47 AM
PHARMACOLOGIST
I concur.

NDA Pharmacology Fileability Check List

NDA No: 21-929/S-012

Date of submission: April 28, 2008

Date of Fileability meeting: June 9, 2008

Information to Sponsor Yes ( ) No (X)

Date of check list: July 10, 2008

(1) On its face, is the Pharm/Tox section of the NDA organized in a manner to allow substantive review? Yes ( ) No ( ) NA (X)
Pharm/Tox studies were not provided in this supplement. The review will reference studies provided in the original NDA 21-929 submission dated September 23, 2005.

(2) On its face, is the Pharm/Tox section of the NDA legible for review?
Yes ( ) No ( ) NA (X)
Pharm/Tox studies were not provided in this supplement. The review will reference studies provided in the original NDA 21-929 submission dated September 23, 2005.

(3) Are final reports of all required and requested preclinical studies submitted in this NDA? Yes ( ) No ( ) NA (X)
Pharm/Tox studies were not provided in this supplement. The review will reference studies provided in the original NDA 21-929 submission dated September 23, 2005.

	Yes	No	NA
Pharmacology	( )	( )	(X)
ADME	( )	( )	(X)
Toxicology (duration, route of administration and species specified)			
acute	( )	( )	(X)
subchronic and chronic studies	( )	( )	(X)
reproductive studies	( )	( )	(X)
carcinogenicity studies	( )	( )	(X)
mutagenicity studies	( )	( )	(X)
special studies	( )	( )	(X)
others	( )	( )	(X)

(4) If the formulation to be marketed is different from the formulation used in the toxicology studies, is repeating or bridging the studies necessary? Yes ( ) No (X) NA ( )

If no, state why not?
The same formulation was used in 3-month bridging toxicology studies with rats and dogs as compared to the to be marketed product.

If yes, has the applicant made an appropriate effort to repeat the studies using the to be marketed product, to bridge the studies or to explain why such repetition or bridging should not be required? Yes (X) No ( ) NA ( )

The sponsor conducted single dose and 3-month bridging studies in rats and dogs using the to be marketed formulation produced from a pilot scale batch.

(5) Are the proposed preclinical labeling sections (carcinogenesis, mutagenesis and impairment of fertility, pregnancy category and overdosage) appropriate (including human dose multiples expressed in either mg/m^2 or comparative systemic exposure levels) and in accordance with 201.57? Yes (X) No ( ).

(6) Has the applicant submitted all special studies/data requested by the Division prior to the submission including but not limited to pre-NDA discussion? Yes (X) No ( ) NA ( )

(7) On its face, does the route of administration used in the pivotal toxicity studies appear to be the same as the intended clinical route? Yes (X) No ( ) NA ( )

If not, has the applicant submitted a rationale to justify the alternative route?
Yes ( ) No ( ) NA

(8) Has the applicant submitted a statement(s) that all of the toxicity studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? Yes ( ) No ( ) NA (X)

(9) Has the applicant submitted any studies or data to address any impurity or extractable issues (if any)? Yes (X) No ( ) NA ( )

(10) Are there any outstanding preclinical issues? Yes ( ) No (X)
If yes, identify those below.

(11) From a preclinical perspective, is this NDA fileable? Yes (X) No ( )

If no, state below why it is not.

(12) Should any additional information/data be requested? Yes ( ) No (X)

NDA Planning Timeline

NDA No.: 21-929/S-012

Date of planning timeline: July 10, 2008

PDUFA Due Date: February 27, 2009

Projected review completion date: Shortly after the midcycle meeting

		Milestone Dates
Pharmacology and ADME		Completed
Toxicology		
General toxicity studies		Completed
Carcinogenicity studies and mutagenicity studies		Completed
a. Statistical consult request for CA studies		Completed
b. Submission of CA studies for CAC concurrence		Completed
Reproductive studies		Completed
Special studies and Others		Completed
Labeling	Approximately	Nov. 1, 2008

Signatures (optional):

Reviewer Signature _____
Timothy W. Robison, Ph.D.

cc:
NDA 21-929, HFD-570 Division Files
JacksonC, HFD-570
RobisonT, HFD-570

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

/s/

Timothy Robison
7/10/2008 02:30:23 PM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21–929/S012

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation
Clinical Studies

NDA/Serial Number:	sNDA 21929/S12
Drug Name:	SYMBICORT
Indication(s):	Proposed indication is (b) (4) maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema for patients (b) (4) For patients with COPD the recommended dose is Symbicort 160/4.5 two inhalations twice daily.
Applicant:	AstraZeneca
Date(s):	Applicant's submission date: 4/28/2008
Review Priority:	Standard
Biometrics Division:	Biometrics Division 2
Statistical Reviewer:	Ted Guo, Ph.D., Biometrics Division 2
Concurring Reviewers:	Qian Li, Sc. D., Team Leader, Biometrics Division 2
Medical Division:	Division of Pulmonary and Allergy Products (ODE II)
Clinical Team:	Banu Karimi-Shah, M.D., Medical Officer (ODE II)
Project Manager:	Colette Jackson (ODE II)
Keywords:	NDA review, clinical studies

1/14/2009

Table of Contents

List of Tables

List of Figures

Executive Summary

SYMBICORT (a combination of budesonide and formoterol), delivered via pMDI, was previously approved for the long-term maintenance treatment of asthma in patients 12 years of age and older. This sNDA 21-929 was submitted on 4/28/2008 to seek an approval of indication for the (b) (4) maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema in patients (b) (4).

This submission studied two dose regimens of SYMBICORT pMDI. They are 160/4.5 μg (160 μg budesonide and 4.5 μg formoterol) 2 inhalations bid and 80/4.5 μg (80 μg budesonide and 4.5 μg formoterol) 2 inhalations bid. The proposed dose for COPD is 160/4.5 μg 2 inhalations bid.

The sponsor submitted 5 studies: 2 Phase 1 bioavailability studies (SD-039-0738 and D5899C00006), 1 Phase 2 pharmacodynamic study (D5899C00748), and 2 Phase 3A efficacy and safety studies (D5899C00001-SUN and D5899C00002-SHINE, referred to as Studies SUN and SHINE in this review). The statistical evaluation for this sNDA includes the two phase 3 studies.

The results of the statistical evaluation are summarized as follows:

- The co-primary efficacy variables for efficacy evaluation are predose and 1-hour postdose FEV_1. Both Studies SUN and SHINE showed that Symbicort 160/4.5 satisfy the combination rules for efficacy evaluation. That is, Symbicort 160/4.5 had statistically significantly greater improvement compared with formoterol 4.5 μg in predose FEV_1 and greater improvement compared with placebo in 1-hour postdose FEV_1. However, both studies showed that the contribution of budesonide in Symbicort in predose was only about 40 ml better than formoterol. Budesonide's contribution was also seen in 1-hour postdose FEV_1, about 30 ml better than formoterol. Such small extra benefit raised a concern on whether the additional treatment benefit of the combination therapy in comparison to the formoterol mono-therapy is clinically meaningful in COPD patients. The 80/4.5 dosing regimen of Symbicort failed to satisfy the combination rule in both studies because of smaller treatment effect.
- Three key secondary efficacy variables were evaluated in the two phase 3 studies. They are the number of COPD exacerbations, total SGRQ score, and dyspnea score. Based on Studies SUN and SHINE, Symbicort 160/4.5 bid showed statistically significantly better improvement of dyspnea compared to placebo. However, the dyspnea diary was not accepted as a valid measurement for breathlessness according to the clinical review team. The definition of COPD exacerbation was considered inadequate by the clinical review team. In addition only Study SUN showed statistical significance in reducing the rate of exacerbation in comparison to placebo. The

reduction in SGRQ score in Symbicort 160/4.5, although statistically significantly greater than placebo, did not reach the clinically important difference defined to be 4 scales compared with placebo in either study.

- Onset of action was defined as the first time FEV1 reached 15% above baseline after the first dose and assessed in the two phase 3 studies in a subset of patients based on the serial FEV_1 spirometry over 12-hour period on Day 1. The median onset time was shown to be 5 minutes and 15 minutes in Studies SUN and SHINE, respectively.
- The overall dropout rates in the two studies were about 30% in Study SUN and 19% in Study SHINE. The higher dropout rate in Study SUN was due to the longer study duration in comparison to Study SHINE. In both studies, the placebo groups had the highest dropout rates, about 37% and 26% in Studies SUN and SHINE, respectively. The two Symbicort 160/4.5 dosing regimens had about 10% less dropout rates than the placebo groups in both studies. In both studies, the dropout rates in US sites were alarmingly high, 44% in Study SUN and 29% in Study SHINE. In both studies, US sites enrolled above 40% of all the patients. Although subgroup analyses suggested that treatment differences in US and non-US regions are similar, the robustness of the efficacy is a concern due to the high dropout rate.
- In the two Phase 3 studies, testing procedures were placed in the protocols to protect type I error. These procedures placed in each individual study are not useful in efficacy evaluation when evidence is assessed collectively from both studies. For the purpose of evaluating the efficacy of Symbicort, we look at analyses of both dosing regimens of Symbicort from both studies for both the primary and secondary endpoints. The evidence collectively indicates that Symbicort, as a combination production, provides additional benefit compared with the monotherapies, and the add-on benefit reaches statistically significance for Symbicort 160/4.5, although it is not clear if the size of the extra-benefit is clinically meaningful. Such evaluation can properly control the error rate of wrongly approving an ineffective drug, as well as identify relatively optimal dosing regimen among studied dosing regimens. Once the efficacy of the drug is established, (b) (4) from the secondary endpoints should depend upon the clinical importance of the secondary endpoints and the evidence obtained from both studies.
- Adverse reactions: Consistently demonstrated in Studies SUN and SHINE and using MedDRA preferred terms, the most frequent AEs -- defined as the occurrences in 3% and more of the patients and were more common in Symbicort 160/4.5 group than in placebo group -- including: COPD, nasopharyngitis, oral candidiasis, bronchitis, sinusitis, viral upper respiratory tract infection.

Introduction

Overview

The sponsor submitted 2 Phase 3 efficacy and safety studies: SUN (D5899C00001) and SHINE (D5899C00002) to seek approval for [redacted] (b) (4) maintenance treatment of COPD. The studies were randomized, double-blind, double-dummy, placebo-controlled, parallel group studies designed to assess the efficacy and safety of Symbicort 160/4.5 and 80/4.5 in patients 40+ years of age with COPD.

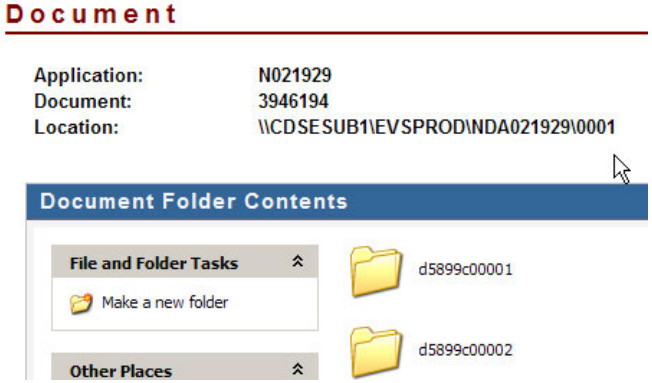
Scope of Statistical Review

In this report the statistical evaluations of efficacy and safety are based on Studies SUN and SHINE.

Data Sources

The sponsor submitted its electronic study reports and data sets to the Agency's Electronic Document Room (See the following snapshot for location).

Figure 1 Data path



The data submitted in SAS v.5 transport format were converted to SAS v.9 data for statistical analyses.

Statistical Evaluation

Study SUN (D5899C00001)

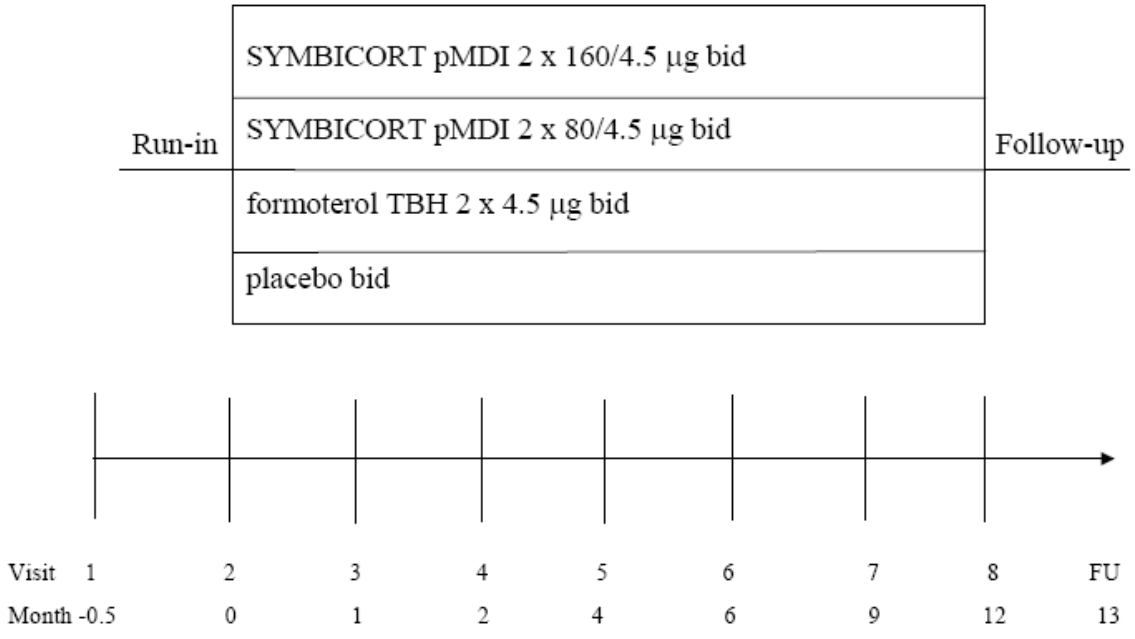
Evaluation of Efficacy

Study Designs and Endpoints

Study SUN was a 12-month double-blind, double-dummy, randomized, parallel group, multicenter efficacy & safety study of Symbicort pMDI 2 x 160/4.5 µg bid and 2 x 80/4.5 µg bid, in comparison with formoterol TBH 2 x 4.5 µg bid and placebo in patients with COPD. The study enrolled its first patient on 4/4/2005 and finished for the last patient on 9/27/2007. The study was conducted in 9 countries including the US, Bulgaria, Denmark, Germany, Greece, Hungary, Iceland, Mexico, and Romania. A total of 225 centers participated in the study.

Figure 2 shows the study flow chart. The time between the screening Visit 1 and the randomization Visit 2 was a placebo run-in period. The 12 months of randomized treatments ended at Visit 8.

Figure 2 Study flow chart (SUN)



Blinding

To maintain the double-dummy blinding of study medication, patients randomized to active treatment delivered by a pMDI device (Symbicort pMDI) also received placebo delivered by a TBH device; and subjects randomized to active treatment delivered by a TBH device (formoterol) also received placebo delivered by a pMDI device. Subjects randomized to placebo received placebo pMDI plus placebo TBH.

The co-primary efficacy variables were:

- Predose FEV_1: It was used to demonstrate the anti-inflammatory effect of Symbicort, largely contributed by the budesonide component. It was expected that Symbicort would be statistically more efficacious than placebo and formoterol alone in this variable.
- One-hour postdose FEV_1: It was used to demonstrate the bronchodilatory effect of Symbicort. It was expected that Symbicort would be statistically more efficacious than placebo.

Baseline, same for both predose and one-hour postdose FEV_1, was defined as the last available predose FEV_1 value measured prior to the first dose of randomized treatment. The analyses of the co-primary efficacy variables were based on the change from baseline to the average of the randomized treatment period.

The key secondary efficacy variables included:

1. **Dyspnea** from the Breathlessness Diary data. Patients were asked daily to evaluate their breathlessness on a 5-point Likert-type scale, ranging from 0 to 4, with higher scores indicating a more severe manifestation of the symptom. The analysis of dyspnea was based on the change from baseline to the average score over the randomized treatment period (with no imputation for missing data). The baseline was defined as the mean score of the last 10 days of the run-in period, excluding Day 1.
2. **SGRQ** total score. The SGRQ consists of 3 domains: symptoms, activities, and impacts. Together, they comprise the total SGRQ score. The analysis of total SGRQ was based on the change from baseline to the end of the treatment period. The baseline was defined as the last assessment prior to the first dose of randomized treatment.
3. **Number of exacerbations**. A COPD exacerbation was defined as worsening of COPD that required a course of oral steroids for treatment and/or hospitalization. The use of oral steroids and hospitalizations was recorded in the diary card by the subject during the randomized treatment period. Note that in the calculation of the number of COPD exacerbations, the sponsor used two methods to measure the treatment period. Method 1: the randomized treatment period was determined as the first dose of randomized treatment to one day after the last dose; Method 2: The randomized treatment period extended from the first dose of randomized

treatment to the last day of assessment for exacerbations, regardless of study completion. The sponsor used Method 2 for the treatment period for the primary analysis of the secondary efficacy variables.

The above descriptions of the key secondary variables were used for the primary analysis of the secondary efficacy variables.

The sponsor also performed other analyses, for example, the by-visit analyses of SGRQ. Variations of these three key secondary efficacy variables were also analyzed by the sponsor, but they were not considered as "primary [analyses of the secondary efficacy variables]."

Other efficacy variables worth mentioning were based on 12-hour serial FEV_1:

1. **Time to 15% improvement in FEV_1 during 12-hour serial spirometry.** On the day of randomization (Visit 2), estimated time to 15% improvement was defined as the interpolated first timepoint within the first 60 minutes after dosing at which the first increase in FEV_1 of 15% from baseline was reached (referred to as "onset of effect"). If a subject did not show a 15% improvement within 60 minutes, the data for the time to onset of effect analysis was censored at 60 minutes. If a subject discontinued serial spirometry before showing an improvement, the subject was censored at the last available timepoint. Each subject was categorized as improving within ≤5 minutes, ≤15 minutes, ≤30 minutes, ≤60 minutes, or as showing no improvement. The 15% improvement in FEV1 at the other serial spirometry visits was also calculated in the same fashion.
2. **Time to 12% improvement in FEV_1 during 12-hour serial spirometry** (Similarly defined as the one for 15% improvement)

The 12-hour serial FEV_1 at Visits 6 and 8 were measured predose, postdose at 5 (±1), 15 (±2), 30(±3), 60 (±5), 120 (±10), 180 (±10), 240 (±10), 360 (±10), 480 (±10), 600 (±10), and 720(±10) minutes in a subset of patients.

Analysis Patient Populations

Safety set: The safety analysis set included all randomized subjects who took at least 1 dose of randomized study medication and from whom any data after randomization were available.

ITT (Intention-to-Treat) population: The efficacy analysis set (EAS), referred to as the Intention-to-Treat population in the protocol, was considered the primary efficacy analysis set, consisted of all subjects who were randomized, received at least 1 dose of randomized study medication, and contributed sufficient data for at least 1 co-primary or secondary efficacy outcome endpoint to be calculated (including baselines if applicable) during the randomized treatment period.

PP (per-protocol): The PP set was based on the efficacy analysis set, excluding all data or partial data for subjects with protocol deviations (5.7.3.5 Per-protocol analysis set, study report SUN)

Serial spirometry analysis set: The serial spirometry analysis set consisted of a subset of patients who were randomized, received at least 1 dose of randomized study medication, and had a baseline predose FEV_1 value and at least 1 postdose FEV_1 value that were from a serial spirometry procedure during the randomized treatment period.

Analysis of Patients Accountability

There were 1964 randomized patients. All were included in the safety population and ITT population, among which there were 1672 PP patients. A total of 292 patients had major protocol violations. A total of 261 patients were classified as "partial data PP." The above count for the PP patients did not include these "partial data PP" as PP. If they were counted as PP, the number of PP patients would be 1933, and there would be 31 patients with major protocol violations (This counting method was used by the sponsor). In addition, note that 491 patients had data for the serial spirometry analysis that determines the onset-of-action.

Table 1 Patients withdrawn by country (SUN)

		Country									Total
		Bulgaria	Denmark	Germany	Greece	Hungary	Iceland	Mexico	Romania	US	
Dropping out? (1=Yes)	Reason for dropping out										
0	n/a	124	61	165	34	261	18	76	121	495	1355
1	Adverse Event	10	12	23	3	22	4	2	11	168	255
	Eligibility Criteria not Fulfilled	0	2	3	0	1	0	1	1	34	42
	Other	1	4	4	0	5	0	0	5	32	51
	Subject Lost to Follow-up	1	0	2	0	4	0	4	1	34	46
	Subject not Willing to Continue Study	10	15	20	6	24	2	6	11	121	215
Total		146	94	217	43	317	24	89	150	884	1964

Source: Data set disp00a

Table 2 Patients withdrawn by treatment (SUN)

Reason for dropping out	Treatment								Total	
	SYM 160 BID		SYM 80 BID		FOR 4.5 BID		Placebo			
	N	%	N	%	N	%	N	%	N	%
(Stayed in study)	360	72.9	351	71.1	338	68.3	306	63.6	1355	69.0
Adverse Event	60	12.1	65	13.2	65	13.1	65	13.5	255	13.0
Eligibility Criteria not Fulfilled	10	2.0	8	1.6	14	2.8	10	2.1	42	2.1
Subject Lost to Follow-up	9	1.8	12	2.4	12	2.4	13	2.7	46	2.3
Subject not Willing to Continue Study	41	8.3	45	9.1	52	10.5	77	16.0	215	10.9
Other	14	2.8	13	2.6	14	2.8	10	2.1	51	2.6
Total	494	100.0	494	100.0	495	100.0	481	100.0	1964	100.0

Source: Data set disp00a

Among the dropouts, the main reasons for early withdrawal were “adverse event” (13%) and “not willing to continue” (11%).

Patient Distributions of Demographic and Baseline Characteristics

As shown in Table 3, below, the US made up the majority of the centers (134 out of 225) among 9 participating countries. There were 884 randomized patients in the US centers.

Table 3 Numbers of centers and patients by country (SUN)

Country	#Centers	#Patients
Bulgaria	9	146
Denmark	12	94
Germany	25	217
Greece	6	43
Hungary	26	317
Iceland	2	24
Mexico	5	89
Romania	6	150
US	134	884

Source: Data set demo

Table 4 and 5 below, show the numbers and percentages of patients by treatment and sex/race. It appears that there were about twice as many males as females. Also, whites were predominant.

Table 4 Number of patients by sex (SUN)

Sex	SYM 160 BID		SYM 80 BID		FOR 4.5 BID		Placebo		Total	
	N	%	N	%	N	%	N	%	N	%
Female	186	37.7	184	37.2	172	34.7	167	34.7	709	36.1
Male	308	62.3	310	62.8	323	65.3	314	65.3	1255	63.9
Total	494	100.0	494	100.0	495	100.0	481	100.0	1964	100.0

Source: Data set demo

Table 5 Number of patients by race (SUN)

Race	SYM 160 BID		SYM 80 BID		FOR 4.5 BID		Placebo		Total	
	N	%	N	%	N	%	N	%	N	%
Black	13	2.6	13	2.6	10	2.0	11	2.3	47	2.4
White	457	92.5	460	93.1	457	92.3	441	91.7	1815	92.4
Asian	1	0.2	1	0.2	4	0.8	2	0.4	8	0.4
Other	23	4.7	20	4.0	24	4.8	27	5.6	94	4.8
Total	494	100.0	494	100.0	495	100.0	481	100.0	1964	100.0

Source: Data set demo

Table 6 shows that patients' were similar across the treatment groups in age distribution.

Table 6 Distribution of patients' age by treatment (SUN)

	#Patients	Median	Mean	Std	Min	Max
SYM 160 BID	494	64	63	9	40	83
SYM 80 BID	494	64	64	9	42	89
FOR 4.5 BID	495	63	63	9	41	88
Placebo	481	63	63	9	40	84
Total	1,964	63	63	9	40	89

Source: Data set demo

Statistical Methodology

Statistical analysis

The sponsor performed an ANCOVA of the changes in predose FEV_1 and in 1-hr postdose FEV_1 from baseline to the average over the double blind treatment period. The ANCOVA model included treatment and country as fixed effects and baseline FEV_1 as a covariate. The baseline FEV_1 was defined as the last FEV_1 measurement prior to the first dose of randomized treatment. The sponsor's approach is reasonable. The same method was used in my statistical evaluation.

Missing data handling

For the primary analysis, the average of all available observations of predose FEV_1 (or 1-hr postdose FEV_1) during the randomized treatment period without imputation of missing data was calculated. The change from baseline to this average FEV_1 was the primary efficacy variable. For the by-visit analyses, LOCF was used. Missing baseline was never carried forward.

Efficacy Results

Primary analysis based on predose FEV_1

The change in **predose FEV_1** from baseline to the randomization-period average was used to demonstrate the anti-inflammatory effect of Symbicort, contributed by the budesonide component.

Table 7 LS-Means and 95% CIs of change from baseline in predose FEV_1 (SUN)

Treatment	LS-Mean	Lower CL	Upper CL
SYM 160 BID	0.10	0.08	0.12
SYM 80 BID	0.08	0.06	0.11
FOR 4.5 BID	0.06	0.04	0.09
Placebo	0.01	-0.02	0.03

Source: Data set pftpre01b

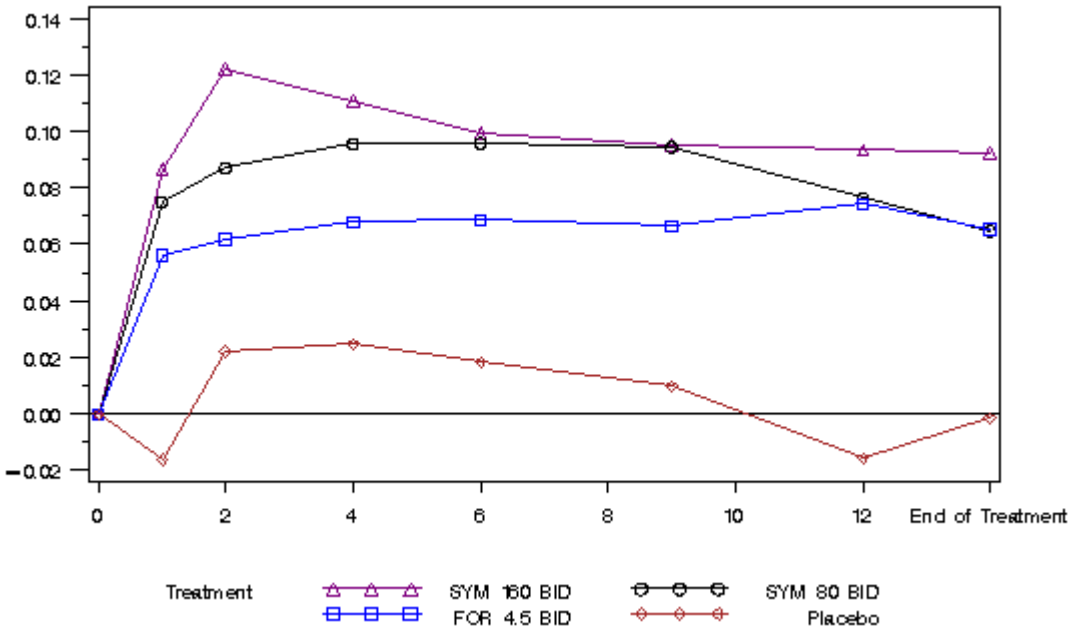
The efficacy results based on predose FEV_1 are shown in Table 8. The numbers in bold face represent the primary analysis. Symbicort 160/4.5 demonstrated a statistical superiority to formoterol 4.5 (P=0.008), but Symbicort 80/4.5 did not (P=0.16) do so. In the following tables, I created a column, Test Seq. No., indicating the protocol-specified hypothesis testing sequence. An overall conclusion is summarized following all the analyses of the primary efficacy variables.

Table 8 Comparisons for change from baseline in predose FEV_1 (SUN)

Treatment	Comparator	Difference	P Value	Lower CL	Upper CL
SYM 160 BID	**FOR 4.5 BID**	**0.04**	**0.0080**	**0.01**	**0.07**
SYM 160 BID	**Placebo**	**0.09**	**0.0000**	**0.06**	**0.12**
SYM 80 BID	**FOR 4.5 BID**	**0.02**	**0.1608**	**-0.01**	**0.05**
SYM 80 BID	**Placebo**	**0.07**	**0.0000**	**0.05**	**0.10**
FOR 4.5 BID	Placebo	0.05	0.0002	0.03	0.08
SYM 160 BID	SYM 80 BID	0.02	0.2062	-0.01	0.05

Source: Data set pftpre01b

Figure 3 LS-mean change from baseline in predose FEV_1 (SUN)



Source: Data set pftpre01a

The above graph was created using an ANCOVA model including effects of treatment and country with baseline FEV_1 as a covariate.

Primary analysis based on 1-hr postdose FEV_1

The change in **1-hr postdose FEV_1** from baseline to the randomization-period average was used to demonstrate the bronchodilatory effect of Symbicort, contributed by the formoterol component. The efficacy results are shown in Table 9 and Table 10

Table 9 LS-Means and 95% CIs of change from baseline in 1-hr postdose FEV_1 (SUN)

TREATMENT	LS-Mean	Lower CL	Upper CL
SYM 160 BID	0.21	0.18	0.23
SYM 80 BID	0.19	0.16	0.21
FOR 4.5 BID	0.18	0.15	0.20
Placebo	0.02	0.00	0.05

Source: Data set pft1hr01b

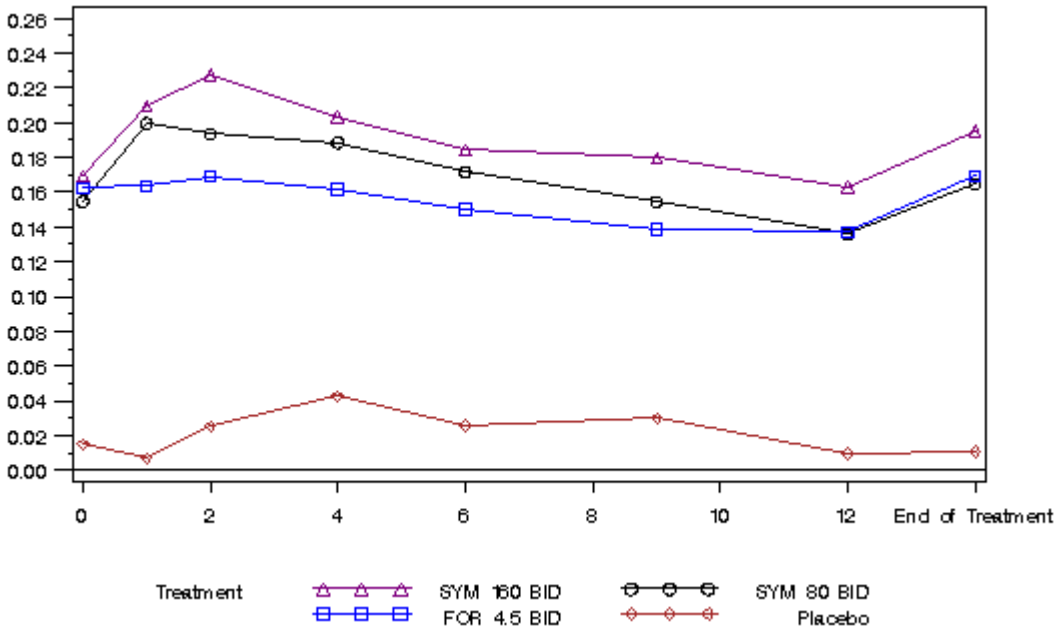
.

Table 10 Comparisons for change from baseline in 1-hr postdose FEV_1 (SUN)

Treatment	Comparator	Difference	P Value	Lower CL	Upper CL
SYM 160 BID	FOR 4.5 BID	0.03	0.0233	0.00	0.06
SYM 160 BID	**Placebo**	**0.18**	**0.0000**	**0.16**	**0.21**
SYM 80 BID	FOR 4.5 BID	0.01	0.4201	-0.02	0.04
SYM 80 BID	**Placebo**	**0.16**	**0.0000**	**0.13**	**0.19**
FOR 4.5 BID	Placebo	0.15	0.0000	0.12	0.18
SYM 160 BID	SYM 80 BID	0.02	0.1438	-0.01	0.05

Source: Data set pft1hr01b

Figure 4 LS-mean change from baseline in 1-hr postdose FEV1 (SUN)



Source: Data set pft1hr01a

The above graph was created using an ANCOVA model including effects of treatment and country with baseline FEV_1 as a covariate.

In conclusion, the superiority of Symbicort 160/4.5 bid was supported by the data. However, the superiority of Symbicort at 80/4.5 dose level was not shown.

Analyses of 3 key secondary efficacy variables

Analysis of dyspnea (breathlessness)

The analysis of dyspnea was based on the change in dyspnea score from baseline to entire randomized period by comparing Symbicort and placebo. The comparisons are based on an ANCOVA model including treatment and country as fixed factors and baseline score as a covariate. Table 11 shows the raw means, std., LS-means, and 95% CIs. Table 12 shows the comparisons between the Symbicort doses and placebo.

Table 11 Means, Std, and CI of dyspnea scores (SUN)

Treatment	#Patients	Baseline mean	Baseline std	Postbaseline mean	Postbaseline std	Change mean	Change std	Change LS-mean	Change lower CL	Change upper CL
SYM 160 BID	489	2.16	0.67	1.79	0.76	-0.37	0.67	-0.36	-0.43	-0.30
SYM 80 BID	488	2.15	0.71	1.83	0.76	-0.33	0.66	-0.33	-0.39	-0.26
FOR 4.5 BID	489	2.15	0.68	1.86	0.75	-0.29	0.62	-0.28	-0.35	-0.22
Placebo	467	2.11	0.71	1.95	0.75	-0.16	0.65	-0.17	-0.23	-0.11

Source: Data set Dyspnea01a, disp00 (Based on non-missing change from baseline in dyspnea score in the ITT population)

Table 12 Analysis of dyspnea: Treatment comparisons (SUN)

Treatment	Comparator	LS-Mean Difference	P Value	Lower CL	Upper CL
SYM 160 BID	SYM 80 BID	-0.04	0.3103	-0.11	0.04
SYM 160 BID	FOR 4.5 BID	-0.08	0.0367	-0.16	-0.00
SYM 160 BID	**Placebo**	**-0.19**	**<0.001**	**-0.27**	**-0.12**
SYM 80 BID	FOR 4.5 BID	-0.04	0.2827	-0.12	0.03
SYM 80 BID	Placebo	-0.15	<0.001	-0.23	-0.08
FOR 4.5 BID	Placebo	-0.11	0.0035	-0.19	-0.04

Source: Data set Dyspnea01a, disp00 (Based on non-missing change from baseline in dyspnea score in the ITT population)

Analysis of SGRQ

The analysis of SGRQ was based on the change in total SGRQ score from baseline to the end of treatment by comparing Symbicort and placebo. The comparisons are based on an ANCOVA model including treatment and country as fixed factors and baseline score as a covariate. The MID for the total SGRQ score is defined as a mean reduction in score of 4. Table 13 shows the raw means, std., LS-means, and 95% CIs. Table 14 shows the comparisons between the Symbicort doses and placebo.

Table 13 Means, Std, and CI of total SGRQ scores (SUN)

Treatment	#Patients	Baseline mean	Baseline std	Postbaseline mean	Postbaseline std	Change mean	Change std	Change LS-mean	Change lower CL	Change upper CL
SYM 160 BID	442	54.64	17.43	50.78	18.36	-3.86	13.48	-3.56	-4.99	-2.14
SYM 80 BID	453	55.65	16.74	50.40	18.63	-5.25	13.72	-4.84	-6.26	-3.42
FOR 4.5 BID	446	55.13	16.37	52.24	18.88	-2.88	13.31	-2.50	-3.92	-1.09
Placebo	408	54.65	16.07	53.17	17.24	-1.49	12.65	-1.18	-2.63	0.28

Source: Data set Sgrq00a, disp00 (Based on non-missing change from baseline in total SGRQ score in the ITT population)

Table 14 Analysis of SGRQ: Treatment comparisons (SUN)

Treatment	Comparator	LS-Mean Difference	P Value	Lower CL	Upper CL
SYM 160 BID	SYM 80 BID	1.28	0.1304	-0.38	2.93
SYM 160 BID	FOR 4.5 BID	-1.06	0.2111	-2.72	0.60
SYM 160 BID	**Placebo**	**-2.39**	**0.0059**	**-4.08**	**-0.69**
SYM 80 BID	FOR 4.5 BID	-2.33	0.0056	-3.98	-0.68
SYM 80 BID	Placebo	-3.66	0.0000	-5.35	-1.97
FOR 4.5 BID	Placebo	-1.33	0.1240	-3.02	0.36

Source: Data set Sgrq00a, disp00 (Based on non-missing change from baseline in total SGRQ score in the ITT population)

Note that the absolute value of the LS-mean difference is smaller than the pre-specified MID. Therefore, the claim for significant improvement in SGRQ cannot be established.

Analysis of COPD exacerbation

A COPD exacerbation was defined as worsening of COPD that required a course of oral steroids for treatment and/or hospitalization. For the primary analysis of COPD

exacerbation, only exacerbations occurred during the randomized period were included. This was based on the number of exacerbations defined as the number of exacerbations per subject-treatment year (The sponsor did not specifically define the term of "subject-treatment year" anywhere in either the protocol or the study report). However, the sponsor employed the Poisson regression model, adjusted for country and randomization time period. The time period was defined as the day of the first dose of a randomized treatment to the final assessment day of the COPD exacerbations at Visit 8. If the patient did not complete the study at Visit 8, the last available data of COPD exacerbation assessment from CRF were used.

The sponsor had a second way of defining the treatment period: The treatment period was defined as the first dose of randomized treatment to one day after the last dose, inclusive. I analyzed the number of COPD exacerbation using the treatment period thus defined as a sensitivity analysis.

There were 1,964 patients in total included in the data set for COPD exacerbation analysis. The number of patients with or without COPD exacerbations by treatment and number of COPD exacerbations is shown in Table 15. The overall picture suggests that there were fewer patients COPD exacerbations in the Symbicort groups than in the formoterol and placebo groups.

Table 15 Number of patients with COPD exacerbations (SUN)

#COPD exacerbations	Treatment				
	SYM 160 BID	SYM 80 BID	FOR 4.5 BID	Placebo	Overall
0	345	335	320	305	1305
1	91	104	96	96	387
2	32	42	43	44	161
3	14	8	21	16	59
4	7	5	6	10	28
5	4		5	4	13
6			3	3	6
7			1	1	2
8				1	1
9	1				1
12				1	1
Overall	494	494	495	481	1964

Source: Data set _exac01, disp00

Table 16 shows the number of COPD exacerbations (rather than the number of patients with COPD exacerbations as shown in Table 15, above)

Table 16 Number COPD exacerbations (SUN)

Treatment	#Patients	#CDPD exacerbations
SYM 160 BID	494	254
SYM 80 BID	494	232
FOR 4.5 BID	495	319
Placebo	481	337
Overall	1964	1142

Source: Data set _exac01, disp00

Results from the analysis the number of COPD exacerbations is demonstrated in Table 17 and Table 18. Symbicort groups demonstrated a statistically significant reduction in the rate of COPD exacerbations compared with placebo.

Table 17 Analysis of LS-mean rate of COPD exacerbations (SUN)

Treatment	LS-Mean rate	Lower 95% CL	Upper 95% CL
SYM 160	0.564	0.476	0.668
SYM 80	0.529	0.444	0.631
FOR 4.5	0.750	0.640	0.878
Placebo	0.892	0.766	1.038

Source: Data set _exac01, disp00

Table 18 Comparisons between Symbicort groups and placebo (SUN)

Difference	LS-mean diff	Lower 95% CL for diff	Upper 95% CL for diff	P-value for diff
SYM 160 BID-Placebo	**0.6318**	**0.5216**	**0.7652**	**<.0001**
SYM 80 BID-Placebo	0.5932	0.4872	0.7223	<.0001

Source: Data set _exac01, disp00

Analysis of onset-of-action

The analysis of onset-of-action was based on a subset of patients who had serial PFT data where FEV_1 values over time. Table 19 shows the number of patients who had serial FEV_1 data by treatment and country. There were 492 patients in total available for the analysis of onset-of-action. I found that these 492 patients came from US (420 out of 884 US's ITT patients) and Germany (72 out of 217 Germany's ITT patients).

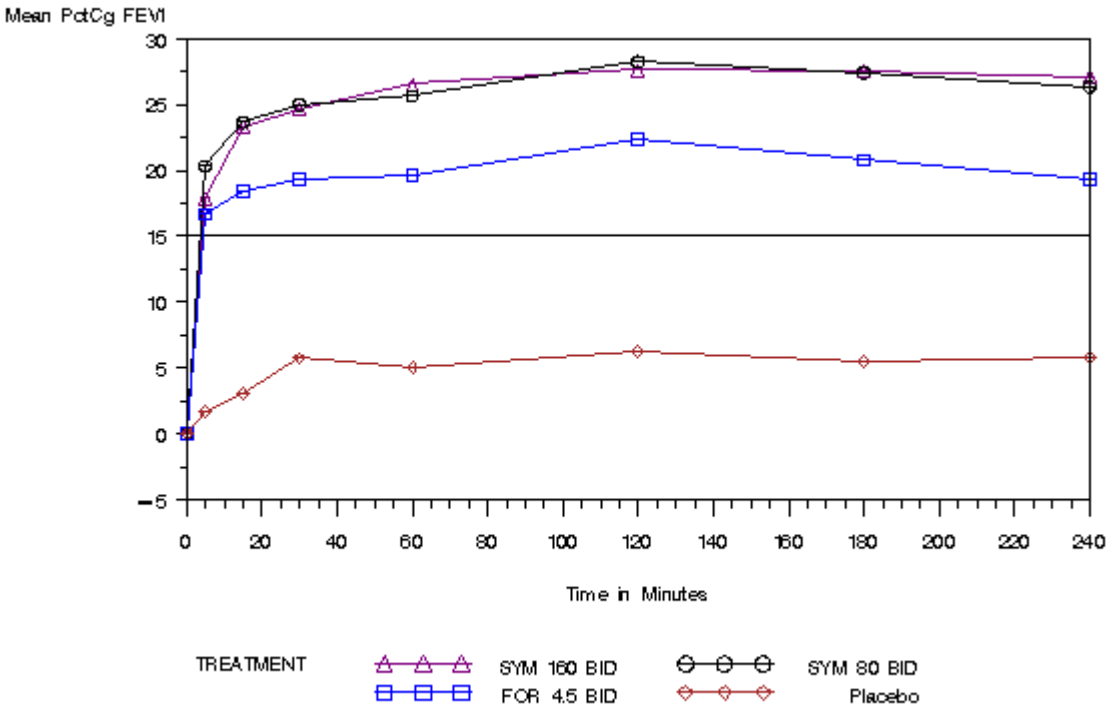
Table 19 Number of patients reported in onset-of-action data set (SUN)

Treatment	Germany	US
SYM 160 BID	18	103
SYM 80 BID	18	103
FOR 4.5 BID	18	106
Placebo	18	108
Overall	72	420

Source: Data set pftsr01a

Figure 5 depicts the mean percent change in FEV_1 from baseline to 4 hours at the day of randomization. Note that the onset-of-action is defined as the median time to a 15% increase in FEV_1. My analysis confirmed that the onset-of-action was established at 5 minutes for this study. From Figure 5, it can be seen that the maximum improvement in FEV_1 occurred at approximately 2 hours postdose.

Figure 5 Mean percent change in FEV_1 from baseline to 4 hours postdose (SUN)



Source: Data set pftsr01a

Evaluation of Safety

The safety evaluation includes listing AEs reported by the sponsor using MedDRA's preferred terms and organ class terms. A complete account of the AEs can be found in the Appendix. An analysis using pooled AE data from SUN and SHINE can be found in the Section, Comments on Labeling.

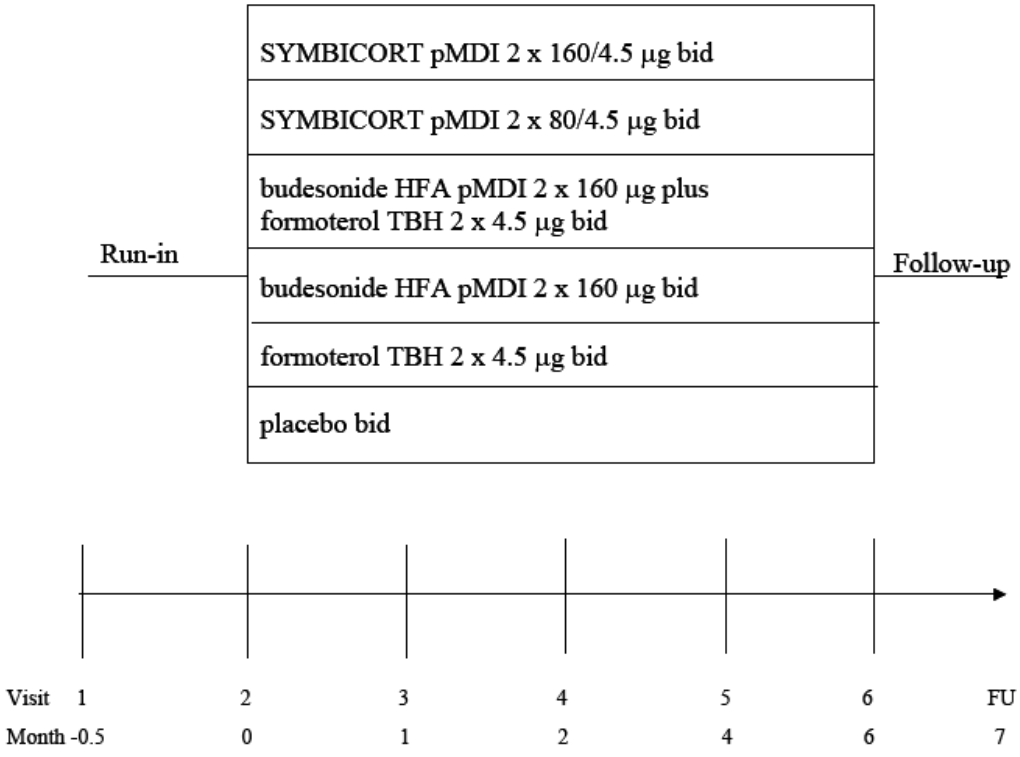
Study SHINE (D5899C00002)

Evaluation of Efficacy

Study Designs and Endpoints

Study SHINE was a 6-month double-blind, double-dummy, randomized, parallel group, multicenter efficacy & safety study of Symbicort pMDI 2 x 160/4.5 µg bid and 2 x 80/4.5 µg bid, in comparison with formoterol TBH 2 x 4.5 µg bid, free combination of formoterol 4.5 µg and budesonide 160 µg, and placebo in patients with COPD. The study enrolled its first patient on 4/4/2005 and finished for the last patient on 12/28/2006. The study was conducted in 5 countries including the US, Czech Republic, Netherlands, Poland, and South Africa. A total of 194 centers participated in the study. The rest of the study design is similar to that in Study SUN.

Figure 6 - Study flow chart (SHINE)



Analysis of Patients Accountability

There were 1704 randomized patients. All were included in the safety population, among which there were 1697 ITT patients. Among which there were 1504 PP patients. Note that the sponsor classified 172 patients as "partial-data PP." No explanation could be found for "partial-data PP" in the study report. A total of 21 patients had major protocol violations.

Table 20 Number of ITT and PP patients (SHINE)

	PP population			Total
	No	Partial data*	Yes	
ITT population				
No	7	0	0	7
Yes	21	172	1504	1697
Total	28	172	1504	1704

Source: Data set disp00a
*: The sponsor indicated that these patients pertain to "partial-data PP." No explanation could be found for "partial-data PP" in the study report. If they were counted as PP, then the number of PP patients would be 1676.

Table 21 Number of patients with pft serial data in ITT population (SHINE)

	Patients with Pft Serial data		Total
	No	Yes	
PP Population			
No	9	12	21
Partial data	118	54	172
Yes	952	552	1504
Total	1079	618	1697

Source: Data set ITT group in disp00a
There were 618 ITT patients with pft serial data.

Table 22 Patients withdrawn by country (SHINE)

		Country					
		Czech Republic	Netherlands	Poland	South Africa	US	Total
Dropping out? (1=Yes)	Reason for dropping out	244	62	440	118	514	1378
0							
1	n/a	0	0	1	0	0	1
	Adverse Event	13	26	23	4	77	143
	Eligibility Criteria not Fulfilled	1	0	7	1	8	17
	Other	1	1	9	2	40	53
	Subject Lost to Follow-up	1	0	0	0	24	25
	Subject not Willing to Continue Study	6	3	17	4	57	87
Total		266	92	497	129	720	1704

Source: Data set disp00a

Table 23 Patients withdrawn by treatment (SHINE)

Reason for dropping out	Treatment												Total	
	SYM 160 BID		SYM 80 BID		BUD 160+?FOR 4.5		BUD 160 BID		FOR 4.5 BID		Placebo			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
(Stayed in study)	238	85.9	243	86.5	239	83.3	213	77.5	223	78.5	223	74.3	1379	80.9
Adverse Event	21	7.6	20	7.1	14	4.9	26	9.5	34	12.0	28	9.3	143	8.4
Eligibility Criteria not Fulfilled	3	1.1	1	0.4	4	1.4	2	0.7	4	1.4	3	1.0	17	1.0
Subject Lost to Follow-up	4	1.4	3	1.1	6	2.1	4	1.5	1	0.4	7	2.3	25	1.5
Subject not Willing to Continue Study	6	2.2	8	2.8	14	4.9	20	7.3	12	4.2	27	9.0	87	5.1
Other	5	1.8	6	2.1	10	3.5	10	3.6	10	3.5	12	4.0	53	3.1
Total	277	100.0	281	100.0	287	100.0	275	100.0	284	100.0	300	100.0	1704	100.0

Source: Data set disp00a

Among the dropouts, the main reasons for early withdrawal were "adverse event" (8%) and "not willing to continue" (5%).

Patient Distributions of Demographic and Baseline Characteristics

As shown in Table 24, below, the US made up the majority of the centers (109 out of 180) among 5 participating countries. There were 720 randomized patients in the US centers.

Table 24 Numbers of centers and patients by country (SHINE)

Country	#Centers	#Patients
Czech Republic	18	266
Netherlands	11	92
Poland	30	497
South Africa	12	129
US	109	720

Source: Data set demo

Table 25 and Table 26 show the numbers and percentages of patients by treatment and sex/race. It appears that there were about twice as many males as females. Also, whites were predominant.

Table 25 Number of patients by sex (SHINE)

	SYM 160 BID		SYM 80 BID		BUD 160+FOR 4.5		BUD 160 BID		FOR 4.5 BID		Placebo		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Female	89	32.1	100	35.6	74	25.8	89	32.4	98	34.5	93	31.0	543	31.9
Male	188	67.9	181	64.4	213	74.2	186	67.6	186	65.5	207	69.0	1161	68.1
Total	277	100.0	281	100.0	287	100.0	275	100.0	284	100.0	300	100.0	1704	100.0

Source: Data set demo

Table 26 Number of patients by race (SHINE)

	SYM 160 BID		SYM 80 BID		BUD 160+FOR 4.5		BUD 160 BID		FOR 4.5 BID		Placebo		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Black	9	3.2	14	5.0	14	4.9	8	2.9	11	3.9	8	2.7	64	3.8
whites	261	94.2	262	93.2	264	92.0	259	94.2	262	92.3	284	94.7	1592	93.4
Asian	0	0	0	0	2	0.7	1	0.4	2	0.7	1	0.3	6	0.4
Other	7	2.5	5	1.8	7	2.4	7	2.5	9	3.2	7	2.3	42	2.5
Total	277	100.0	281	100.0	287	100.0	275	100.0	284	100.0	300	100.0	1704	100.0

Source: Data set demo

Table 27 shows that patients' were similar across the treatment groups in age distribution.

Table 27 Distribution of patients' age by treatment (SHINE)

Treatment	#Patients	Median	Mean	Std	Min	Max
SYM 160 BID	277	63	63	9	41	86
SYM 80 BID	281	63	64	9	40	90
BUD 160+FOR 4.5	287	64	64	9	40	84
BUD 160 BID	275	63	63	9	40	90
FOR 4.5 BID	284	64	64	10	42	89
Placebo	300	63	63	10	40	86
Total	1704	64	63	9	40	90

Source: Data set demo

Statistical analysis

The sponsor performed an ANCOVA of the changes in predose FEV_1 and in 1-hr postdose FEV_1 from baseline to the average of the double blind treatment period. The ANCOVA model included treatment and country as fixed effects and baseline FEV_1 as a covariate. The baseline FEV_1 was defined as the last FEV_1 measurement prior to the first dose of randomized treatment. The sponsor's approach is reasonable. I used the same approach in my statistical evaluation.

Missing data handling

For the primary analysis, the average of all available observations of predose FEV_1 (or 1-hr postdose FEV_1) during the randomized treatment period without imputation of missing data was calculated. The change from baseline to this average FEV_1 was the primary efficacy variable. For the by-visit analyses, LOCF was used. Missing baseline was never carried forward.

Efficacy Results

Primary analysis based on predose FEV_1

The change in **predose FEV_1** from baseline to the randomization-period average was used to demonstrate the anti-inflammatory effect of Symbicort, contributed by the budesonide component.

Table 28 LS-Means and 95% CIs of change from baseline in predose FEV_1 (SHINE)

Treatment	N	LS-Mean	Lower CL	Upper CL
SYM 160 BID	266	0.08	0.06	0.11
SYM 80 BID	275	0.06	0.03	0.08
BUD 160+FOR 4.5	279	0.07	0.04	0.09
BUD 160 BID	265	0.00	-0.02	0.03
FOR 4.5 BID	263	0.04	0.02	0.07
Placebo	270	0.01	-0.02	0.03

Source: Data set pftpre01b

The efficacy results are shown in Table 29. The numbers in bold face represent the primary analysis. Symbicort 160/4.5 demonstrated a statistical superiority to formoterol (P=0.03), but Symbicort 80/4.5 did not (P=0.33). Note that the free combination of formoterol 4.5 μg and budesonide 160 μg ("BUD 160+FOR 4.5") did not show the superiority to formoterol (P=0.12). In addition, budesonide did not show the significance when comparing with placebo (P=0.9).

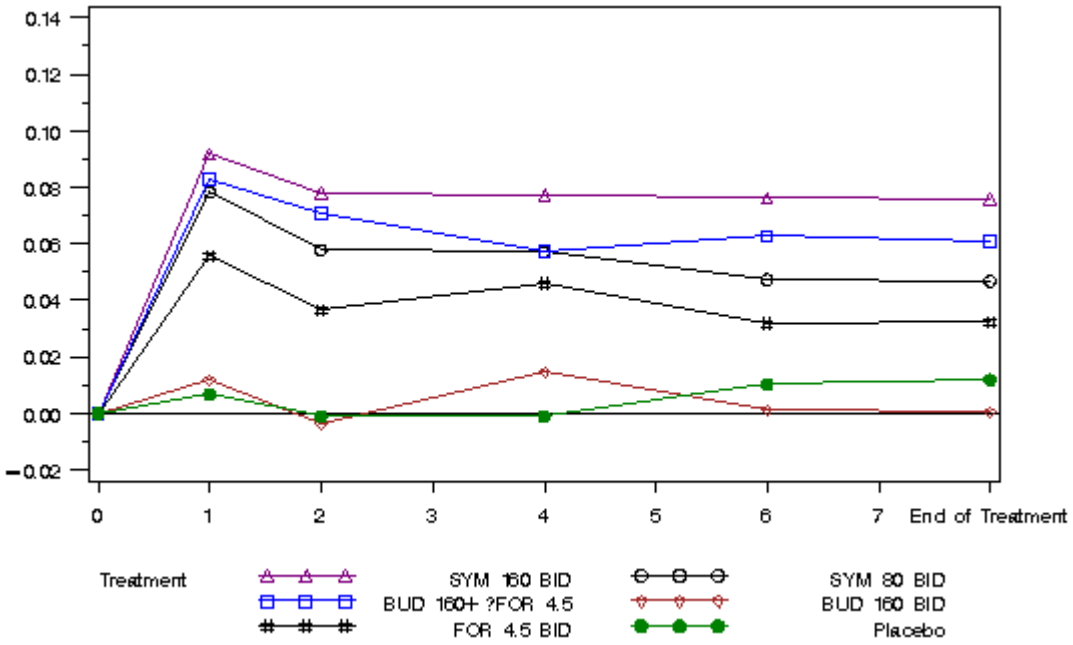
Table 29 Comparisons for change from baseline in predose FEV_1 (SHINE)

Treatment	N	Comparator	Difference	P Value	Lower CL	Upper CL
SYM 160 BID	266	SYM 80 BID	0.02	0.1980	-0.01	0.06
SYM 160 BID	266	BUD 160+FOR 4.5	0.01	0.4787	-0.02	0.05
SYM 160 BID	266	BUD 160 BID	0.08	0.0000	0.04	0.11
SYM 160 BID	**266**	**FOR 4.5 BID**	**0.04**	**0.0258**	**0.00**	**0.07**
SYM 160 BID	266	Placebo	0.08	0.0000	0.04	0.11
SYM 80 BID	275	BUD 160+FOR 4.5	-0.01	0.5559	-0.04	0.02
SYM 80 BID	275	BUD 160 BID	0.06	0.0015	0.02	0.09
SYM 80 BID	**275**	**FOR 4.5 BID**	**0.02**	**0.3346**	**-0.02**	**0.05**
SYM 80 BID	275	Placebo	0.05	0.0021	0.02	0.09

Treatment	N	Comparator	Difference	P Value	Lower CL	Upper CL
BUD 160+FOR 4.5	279	BUD 160 BID	0.07	0.0002	0.03	0.10
BUD 160+FOR 4.5	279	FOR 4.5 BID	0.03	0.1212	-0.01	0.06
BUD 160+FOR 4.5	279	Placebo	0.06	0.0002	0.03	0.10
BUD 160 BID	265	FOR 4.5 BID	-0.04	0.0280	-0.07	-0.00
BUD 160 BID	265	Placebo	-0.00	0.9016	-0.04	0.03
FOR 4.5 BID	263	Placebo	0.04	0.0375	0.00	0.07

Source: Data set pftpre01b

Figure 7 LS-mean change from baseline in predose FEV1 (SHINE)



Source: Data set pftpre01a

The above graph was created using an ANCOVA model including factors of treatment and country with baseline FEV_1 as a covariate.

Primary analysis based on 1-hr postdose FEV_1

The change in **1-hr postdose FEV_1** from baseline to the randomization-period average was used to demonstrate the bronchodilatory effect of Symbicort, contributed by the formoterol component.

Table 30 LS-Means and 95% CIs of change from baseline in 1-hr postdose FEV_1 (SHINE)

Treatment	N	LS-Mean	Lower CL	Upper CL
SYM 160 BID	275	0.20	0.18	0.23
SYM 80 BID	280	0.19	0.17	0.22
BUD 160+FOR 4.5	286	0.19	0.16	0.21
BUD 160 BID	274	0.03	0.01	0.06
FOR 4.5 BID	283	0.17	0.14	0.19
Placebo	299	0.03	0.01	0.06

Source: Data set pft1hr01b

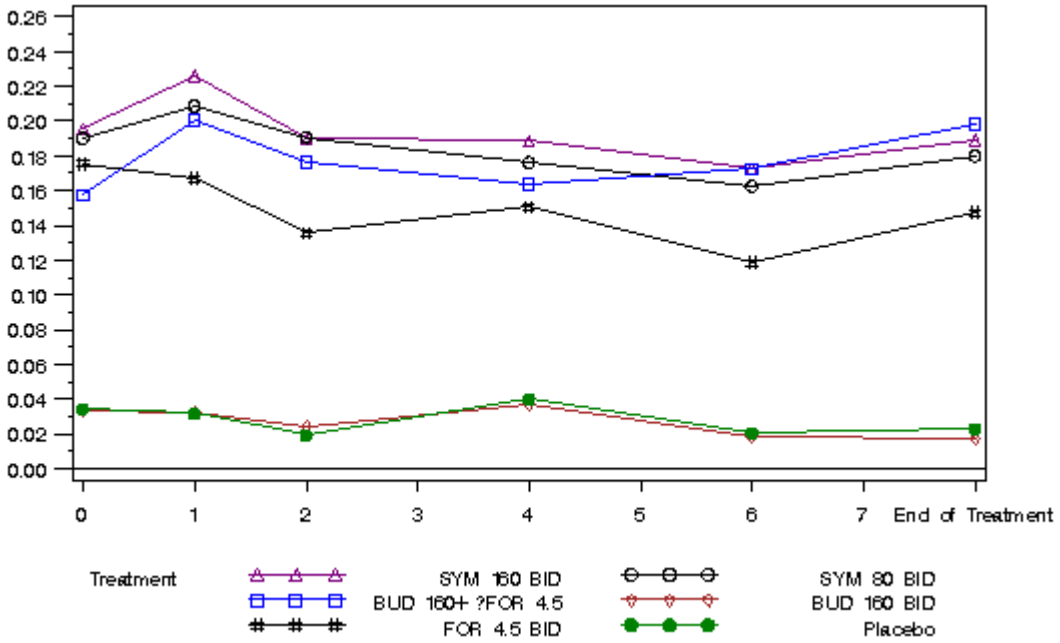
The efficacy results are shown in Table 31. Symbicort at 160/4.5 and 80 demonstrated a statistical superiority to budesonide (P≈0), demonstrating a significant bronchodilatory effect from formoterol. Note that the free combination of formoterol 4.5 μg and budesonide 160 μg ("BUD 160+FOR 4.5") demonstrated the superiority to budesonide (P≈0). In addition, budesonide showed the significance when comparing with placebo (P≈0).

Table 31 Comparisons for change from baseline in 1-hr postdose FEV_1 (SHINE)

Treatment	N	Comparator	Difference	P Value	Lower CL	Upper CL
SYM 160 BID	275	SYM 80 BID	0.01	0.6154	-0.03	0.04
SYM 160 BID	275	BUD 160+FOR 4.5	0.01	0.4612	-0.02	0.05
SYM 160 BID	**275**	**BUD 160 BID**	**0.17**	**0.0000**	**0.14**	**0.21**
SYM 160 BID	275	FOR 4.5 BID	0.04	0.0386	0.00	0.07
SYM 160 BID	275	Placebo	0.17	0.0000	0.14	0.20
SYM 80 BID	280	BUD 160+FOR 4.5	0.00	0.8158	-0.03	0.04
SYM 80 BID	**280**	**BUD 160 BID**	**0.16**	**0.0000**	**0.13**	**0.20**
SYM 80 BID	280	FOR 4.5 BID	0.03	0.1158	-0.01	0.06
SYM 80 BID	280	Placebo	0.16	0.0000	0.13	0.20
BUD 160+FOR 4.5	286	BUD 160 BID	0.16	0.0000	0.13	0.19
BUD 160+FOR 4.5	286	FOR 4.5 BID	0.02	0.1779	-0.01	0.06
BUD 160+FOR 4.5	286	Placebo	0.16	0.0000	0.13	0.19
BUD 160 BID	274	FOR 4.5 BID	-0.14	0.0000	-0.17	-0.10
BUD 160 BID	274	Placebo	0.00	0.9970	-0.03	0.03
FOR 4.5 BID	283	Placebo	0.14	0.0000	0.10	0.17

Source: Data set pft1hr01b

Figure 8 LS-mean change from baseline in 1-hr postdose FEV1 (SHINE)



Source: Data set pftpre01a

The above graph was created using an ANCOVA model including factors treatment and country with baseline FEV_1 as a covariate.

In conclusion, the superiority of Symbicort 160/4.5 bid was supported by the data. However, the superiority of Symbicort at 80/4.5 dose level was not shown.

Analyses of 3 key secondary efficacy variables

According to the sponsor's protocol, Symbicort 80/4.5 failed to consistently demonstrate its efficacy. This report includes results of the 3 key secondary efficacy variables for Symbicort 160/4.5 alone.

Analysis of dyspnea (breathlessness)

The analysis of dyspnea was based on the change in dyspnea score from baseline to entire randomized period by comparing Symbicort and placebo. The comparisons are based on an ANCOVA model including treatment and country as fixed factors and baseline score as a covariate. Table 32 shows the raw means, std., LS-means, and 95% CIs. Table 33 shows the comparisons between the Symbicort doses and placebo.

Table 32 Means, Std, and CI of dyspnea scores (SHINE)

Treatment	#Patients	Baseline mean	Baseline std	Postbaseline mean	Postbaseline std	Change mean	Change std	Change LS-mean	Change lower CL	Change upper CL
SYM 160 BID	271	2.14	0.68	1.81	0.73	-0.33	0.58	-0.34	-0.41	-0.26
SYM 80 BID	279	2.02	0.71	1.73	0.73	-0.29	0.64	-0.34	-0.42	-0.27
BUD 160+FOR 4.5	282	2.20	0.68	1.80	0.77	-0.40	0.71	-0.39	-0.46	-0.31
BUD 160 BID	272	2.15	0.70	1.94	0.71	-0.21	0.67	-0.21	-0.28	-0.14
FOR 4.5 BID	280	2.13	0.69	1.90	0.73	-0.23	0.65	-0.24	-0.31	-0.17
Placebo	291	2.02	0.72	1.90	0.75	-0.13	0.59	-0.18	-0.25	-0.11

Source: Data set Dyspnea01a, disp00 (Based on non-missing change from baseline in dyspnea score in the ITT population)

Table 33 Analysis of dyspnea: Treatment comparisons (SHINE)

Treatment	Comparator	LS-Mean Difference	P Value	Lower CL	Upper CL
SYM 160 BID	SYM 80 BID	0.01	0.9011	-0.09	0.10
SYM 160 BID	BUD 160+FOR 4.5	0.05	0.3139	-0.05	0.15
SYM 160 BID	BUD 160 BID	-0.13	0.0117	-0.22	-0.03
SYM 160 BID	FOR 4.5 BID	-0.10	0.0455	-0.20	-0.00
SYM 160 BID	**Placebo**	**-0.16**	**0.0011**	**-0.26**	**-0.06**
SYM 80 BID	BUD 160+FOR 4.5	0.04	0.3752	-0.05	0.14
SYM 80 BID	BUD 160 BID	-0.13	0.0078	-0.23	-0.03
SYM 80 BID	FOR 4.5 BID	-0.11	0.0325	-0.20	-0.01
SYM 80 BID	Placebo	-0.17	0.0006	-0.26	-0.07
BUD 160+FOR 4.5	BUD 160 BID	-0.18	0.0004	-0.27	-0.08
BUD 160+FOR 4.5	FOR 4.5 BID	-0.15	0.0024	-0.24	-0.05
BUD 160+FOR 4.5	Placebo	-0.21	0.0000	-0.31	-0.12
BUD 160 BID	FOR 4.5 BID	0.03	0.5884	-0.07	0.12
BUD 160 BID	Placebo	-0.04	0.4724	-0.13	0.06
FOR 4.5 BID	Placebo	-0.06	0.2026	-0.16	0.03

Source: Data set Dyspnea01a, disp00 (Based on non-missing change from baseline in dyspnea score in the ITT population)

Analysis of SGRQ

The analysis of SGRQ was based on the change in total SGRQ score from baseline to the end of treatment by comparing Symbicort and placebo. The comparisons are based on an ANCOVA model including treatment and country as fixed factors and baseline score as a covariate. The MID for the total SGRQ score is defined as a mean reduction in score of 4. Table 34 shows the raw means, std., LS-means, and 95% CIs. Table 35 shows the comparisons between the Symbicort doses and placebo.

Table 34 Means, Std, and CI of total SGRQ scores (SHINE)

Treatment	#Patients	Baseline mean	Baseline std	Postbaseline mean	Postbaseline std	Change mean	Change std	Change LS-mean	Change lower CL	Change upper CL
SYM 160 BID	253	56.53	15.75	52.21	18.49	-4.32	12.17	-5.16	-6.73	-3.59
SYM 80 BID	262	55.47	16.32	51.58	18.87	-3.89	11.90	-4.99	-6.53	-3.46
BUD 160+FOR 4.5	263	56.69	16.43	52.24	18.75	-4.46	14.28	-5.25	-6.79	-3.71
BUD 160 BID	243	56.08	16.92	54.33	18.39	-1.75	13.15	-2.74	-4.34	-1.15
FOR 4.5 BID	248	53.77	16.03	52.54	17.44	-1.24	11.35	-2.60	-4.18	-1.01
Placebo	254	55.60	17.03	54.57	18.49	-1.02	12.41	-2.04	-3.60	-0.49

Source: Data set Sgrq00a, disp00 (Based on non-missing change from baseline in total SGRQ score in the ITT population)

Table 35 Analysis of SGRQ: Treatment comparisons (SHINE)

Treatment	Comparator	LS-Mean Difference	P Value	Lower CL	Upper CL
SYM 160 BID	SYM 80 BID	-0.17	0.8708	-2.24	1.89
SYM 160 BID	BUD 160+FOR 4.5	0.09	0.9333	-1.98	2.15
SYM 160 BID	BUD 160 BID	-2.42	0.0244	-4.52	-0.31
SYM 160 BID	FOR 4.5 BID	-2.56	0.0165	-4.66	-0.47
SYM 160 BID	**Placebo**	**-3.12**	**0.0034**	**-5.20**	**-1.04**
SYM 80 BID	BUD 160+FOR 4.5	0.26	0.8036	-1.79	2.31
SYM 80 BID	BUD 160 BID	-2.25	0.0349	-4.33	-0.16
SYM 80 BID	FOR 4.5 BID	-2.39	0.0240	-4.47	-0.32
SYM 80 BID	Placebo	-2.95	0.0052	-5.01	-0.88
BUD 160+FOR 4.5	BUD 160 BID	-2.51	0.0186	-4.59	-0.42

Treatment	Comparator	LS-Mean Difference	P Value	Lower CL	Upper CL
BUD 160+FOR 4.5	FOR 4.5 BID	-2.65	0.0124	-4.73	-0.58
BUD 160+FOR 4.5	Placebo	-3.21	0.0023	-5.27	-1.14
BUD 160 BID	FOR 4.5 BID	-0.15	0.8925	-2.26	1.97
BUD 160 BID	Placebo	-0.70	0.5139	-2.80	1.40
FOR 4.5 BID	Placebo	-0.55	0.6036	-2.65	1.54

Source: Data set Sgrq00a, disp00 (Based on non-missing change from baseline in total SGRQ score in the ITT population)

Note that the absolute value of the LS-mean difference is smaller than the pre-specified MID. Therefore, the claim for significant improvement in SGRQ cannot be established.

Analysis of COPD exacerbation

A COPD exacerbation was defined as worsening of COPD that required a course of oral steroids for treatment and/or hospitalization. For the primary analysis of COPD exacerbation, only exacerbations occurred during the randomized period were included. This was based on the number of exacerbations defined as the number of exacerbations per subject-treatment year (The sponsor did not specifically define the term of "subject-treatment year" anywhere in either the protocol or the study report). However, the sponsor employed the Poisson regression model, adjusted for country and randomization time period. The time period was defined as the day of the first dose of a randomized treatment to the final assessment day of the COPD exacerbations at Visit 6. If the patient did not complete the study at Visit 6, the last available data of COPD exacerbation assessment from CRF were used.

The sponsor had a second way of defining the treatment period: The treatment period was defined as the first dose of randomized treatment to one day after the last dose, inclusive. I analyzed the number of COPD exacerbation using the treatment period thus defined as a sensitivity analysis.

There were 1,697 patients in total included in the data set for COPD exacerbation analysis. The number of patients with or without COPD exacerbations by treatment and number of COPD exacerbations is shown in Table 36.

Table 36 Number of patients with COPD exacerbations (SHINE)

#COPD exacerbations	Treatment						
	SYM 160 BID	SYM 80 BID	BUD 160+FOR 4.5	BUD 160 BID	FOR 4.5 BID	Placebo	Overall
0	209	209	225	206	205	223	1277
1	42	55	48	48	54	52	299
2	21	8	9	17	15	13	83
3	1	5	3	3	5	5	22
4	1	2			2	2	7
5	1	1	1		2	3	8
6						1	1
Overall	275	280	286	274	283	299	1697

Source: Data set _exac01, disp00

Table 37 shows the number of COPD exacerbations (rather than the number of patients with COPD exacerbations as shown in Table 36, above)

Table 37 Number COPD exacerbations (SHINE)

Treatment	#Patients	#CDPD exacerbations
SYM 160 BID	275	96
SYM 80 BID	280	99
BUD 160+FOR 4.5	286	80
BUD 160 BID	274	91
FOR 4.5 BID	283	117
Placebo	299	122
Overall	1697	605

Source: Data set _exac01, disp00

Results from the analysis the number of COPD exacerbations is demonstrated in Table 38 and Table 39. Symbicort groups did not demonstrate statistically significant reduction in the rate of COPD exacerbations, compared with placebo.

Table 38 Analysis of LS-mean rate of COPD exacerbations (SHINE)

Treatment	LS-Mean rate	Lower 95% CL	Upper 95% CL
SYM 160	0.884	0.714	1.095
SYM 80	0.851	0.688	1.052
BUD 160+FOR 4.5	0.710	0.562	0.896
BUD 160	0.882	0.707	1.102
FOR 4.5	1.098	0.901	1.338
Placebo	1.110	0.917	1.344

Source: Data set _exac01, disp00

Table 39 Comparisons between Symbicort groups and placebo (SHINE)

Difference	LS-mean diff	Lower 95% CL for diff	Upper 95% CL for diff	P-value for diff
SYM 160 BID vs. Placebo	**0.7965**	**0.6032**	**1.0517**	**0.1086**
SYM 80 BID vs. Placebo	0.7663	0.5808	1.0109	0.0597

Source: Data set _exac01, disp00

Analysis of onset-of-action

The analysis of onset-of-action was based on a subset of serial PFT data where FEV_1 values over time were reported. Table 40 shows the number of patients in the serial FEV_1 data set. There were 616 patients in total available for the analysis of onset-of-action. I found that these 616 patients came from US (330), Poland (238), Netherlands (20) and Czech Republic (28). The sponsor did not explain for such a low availability of patients with serial FEV_1.

Table 40 Number of patients reported in onset-of-action data set (SHINE)

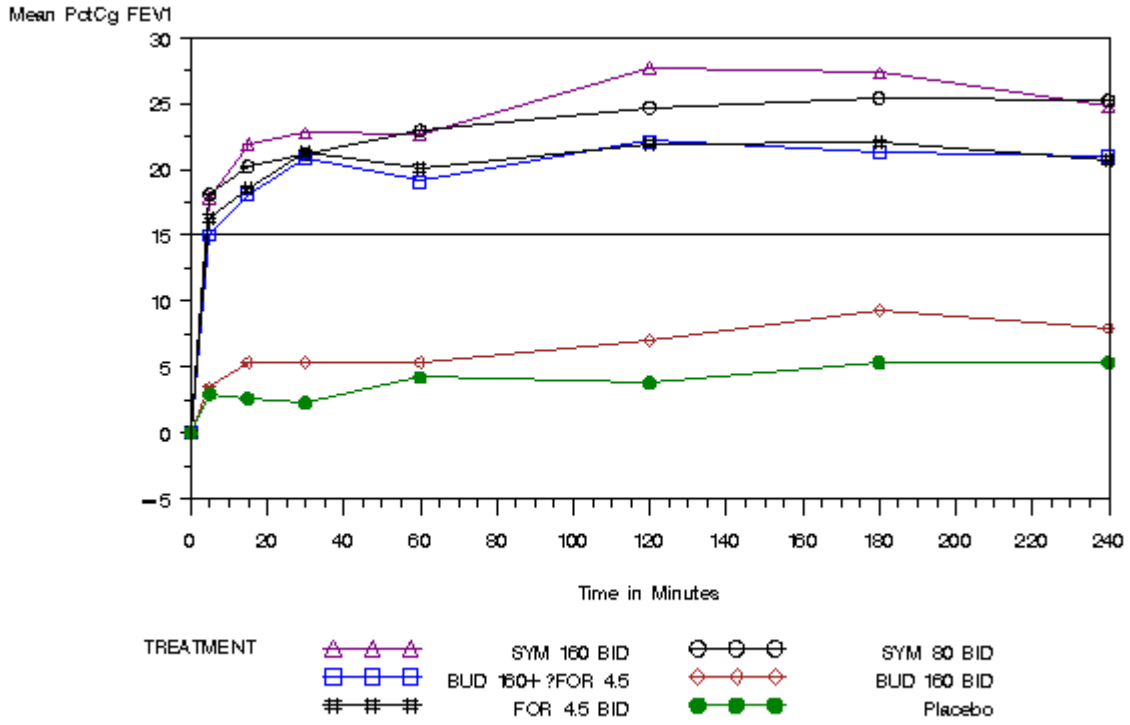
Treatment	Czech Republic	Netherlands	Poland	US
SYM 160 BID	4	2	40	53
SYM 80 BID	2	6	41	53
BUD 160+FOR 4.5	6	3	40	58
BUD 160 BID	5	3	36	52
FOR 4.5 BID	6	1	39	58
Placebo	5	5	42	56
Overall	28	20	238	330

Source: Data set pftsr01a

Figure 9 depicts the mean percent change in FEV_1 from baseline to 4 hours at the day of randomization. Note that the onset-of-action is defined as the median time to a 15%

increase in FEV_1. My analysis concluded that the onset-of-action was established at 15 minutes. From Figure 9, the maximum improvement in FEV_1 occurred at approximately 2 hours postdose. These findings were based on a data set including 616 available patients with serial spirometry data.

Figure 9 Mean percent change in FEV_1 from baseline to 4 hours postdose (SHINE)



Source: Data set pftsr01a

Evaluation of Safety

The safety evaluation includes listing AEs reported by the sponsor using MedDRA's preferred terms and organ class terms. A complete account of the AEs can be found in the Appendix. An analysis using pooled AE data from SUN and SHINE can be found in the Section, Comments on Labeling.

Findings in Special/Subgroup Populations

Selected subgroup analyses were performed for exploratory purposes. The following analyses include analyses of predose and 1-hr postdose FEV_1 by country, sex, race, and age group (65 years of age as the cut point). The analyses were done using an ANCOVA including a fix effect of treatment and using baseline FEV_1 as a covariate. Note that for the following analyses, only the comparisons between Symbicort 160/4.5 bid and its protocol-specified comparators are reported. Also, the p-values are not used for formal statistical interpretations.

Study SUN

Analysis by Country

Analysis of change from baseline in predose FEV_1 by country - **Table 41**, below
Analysis of change from baseline in 1-hr postdose FEV_1 by country - **Table 42**, below

Analysis by Sex

Analysis of change from baseline in predose FEV_1 by sex - **Table 43**, below
Analysis of change from baseline in 1-hr postdose FEV_1 by sex - **Table 44**, below

Analysis by Race

Analysis of change from baseline in predose FEV_1 by race - **Table 45**, below
Analysis of change from baseline in 1-hr postdose FEV_1 by race - **Table 46**, below

Analysis by Age Group

Analysis of change from baseline in predose FEV_1 by age group - **Table 47**, below
Analysis of change from baseline in 1-hr postdose FEV_1 by age group - **Table 48**, below

Study SHINE

Analysis by Country

Analysis of change from baseline in predose FEV_1 by country - **Table 49**, below
Analysis of change from baseline in 1-hr postdose FEV_1 by country - **Table 50**, below

Analysis by Sex

Analysis of change from baseline in predose FEV_1 by sex - **Table 51**, below
Analysis of change from baseline in 1-hr postdose FEV_1 by sex - **Table 52**, below

Analysis by Race

Analysis of change from baseline in predose FEV_1 by race - **Table 53**, below
Analysis of change from baseline in 1-hr postdose FEV_1 by race - **Table 54**, below

Analysis by Age Group

Analysis of change from baseline in predose FEV_1 by age group - **Table 55**, below
Analysis of change from baseline in 1-hr postdose FEV_1 by age group - **Table 56**, below

Table 41 Analysis of change from baseline in predose FEV_1 by country (SUN)
[back]

Country	Treatment	N_Trt	Comparator	N_Cmp	Difference	95% Lower CL	95% Upper CL	P-Value
US	SYM 160 BID	206	FOR 4.5 BID	199	0.04	-0.00	0.07	0.0680
[Non-US]	SYM 160 BID	265	FOR 4.5 BID	266	0.04	0.00	0.08	0.0498

Table 42 Analysis of change from baseline in 1-hr postdose FEV_1 by country (SUN)
[back]

Country	Treatment	N_Trt	Comparator	N_Cmp	Difference	95% Lower CL	95% Upper CL	P-Value
US	SYM 160 BID	224	Placebo	209	0.20	0.16	0.23	0.0000
[Non-US]	SYM 160 BID	270	Placebo	270	0.17	0.13	0.21	0.0000

Table 43 Analysis of change from baseline in predose FEV_1 by sex (SUN)
[back]

Sex	Treatment	N_Trt	Comparator	N_Cmp	Difference	95% Lower CL	95% Upper CL	P-Value
Female	SYM 160 BID	176	FOR 4.5 BID	160	0.06	0.01	0.10	0.0124
Male	SYM 160 BID	295	FOR 4.5 BID	305	0.03	-0.01	0.06	0.1449

Table 44 Analysis of change from baseline in 1-hr postdose FEV_1 by sex (SUN)
[back]

Sex	Treatment	N_Trt	Comparator	N_Cmp	Difference	95% Lower CL	95% Upper CL	P-Value
Female	SYM 160 BID	186	Placebo	167	0.19	0.14	0.23	0.0000
Male	SYM 160 BID	308	Placebo	312	0.18	0.14	0.22	0.0000

Table 45 Analysis of change from baseline in predose FEV_1 by race (SUN)
[back]

Race	Treatment	N_Trt	Comparator	N_Cmp	Difference	95% Lower CL	95% Upper CL	P-Value
White	SYM 160 BID	435	FOR 4.5 BID	429	0.03	-0.00	0.05	0.0648
[Non-White]	SYM 160 BID	36	FOR 4.5 BID	36	0.21	0.07	0.35	0.0041

Table 46 Analysis of change from baseline in 1-hr postdose FEV_1 by race (SUN)
[back]

Race	Treatment	N_Trt	Comparator	N_Cmp	Difference	95% Lower CL	95% Upper CL	P-Value
White	SYM 160 BID	457	Placebo	439	0.17	0.14	0.20	0.0000
[Non-White]	SYM 160 BID	37	Placebo	40	0.32	0.19	0.45	0.0000

Table 47 Analysis of change from baseline in predose FEV_1 by age group (SUN)
[back]

Age Group	Treatment	N_Trt	Comparator	N_Cmp	Difference	95% Lower CL	95% Upper CL	P-Value
65+	SYM 160 BID	213	FOR 4.5 BID	199	0.04	0.00	0.07	0.0429
<65	SYM 160 BID	258	FOR 4.5 BID	266	0.04	-0.00	0.08	0.0502

Table 48 Analysis of change from baseline in 1-hr postdose FEV_1 by age group (SUN)
[back]

Age Group	Treatment	N_Trt	Comparator	N_Cmp	Difference	95% Lower CL	95% Upper CL	P-Value
65+	SYM 160 BID	228	Placebo	206	0.15	0.11	0.18	0.0000
<65	SYM 160 BID	266	Placebo	273	0.22	0.17	0.26	0.0000

[Back to subgroup analysis]

Table 49 Analysis of change from baseline in predose FEV_1 by country (SHINE)
[back]

Country	Treatment	N_Trt	Comparator	N_Cmp	Difference	95% Lower CL	95% Upper CL	P-Value
US	SYM 160 BID	111	FOR 4.5 BID	107	0.06	0.01	0.12	0.0308
[Non-US]	SYM 160 BID	155	FOR 4.5 BID	156	0.02	-0.02	0.06	0.2922

Table 50 Analysis of change from baseline in 1-hr postdose FEV_1 by country (SHINE)
[back]

Country	Treatment	N_Trt	Comparator	N_Cmp	Difference	95% Lower CL	95% Upper CL	P-Value
US	SYM 160 BID	114	BUD 160 BID	112	0.16	0.11	0.22	0.0000
[Non-US]	SYM 160 BID	161	BUD 160 BID	162	0.17	0.13	0.22	0.0000

Table 51 Analysis of change from baseline in predose FEV_1 by sex (SHINE)
[back]

Sex	Treatment	N_Trt	Comparator	N_Cmp	Difference	95% Lower CL	95% Upper CL	P-Value
Female	SYM 160 BID	87	FOR 4.5 BID	91	0.06	0.01	0.11	0.0230
Male	SYM 160 BID	179	FOR 4.5 BID	172	0.03	-0.01	0.07	0.1892

Table 52 Analysis of change from baseline in 1-hr postdose FEV_1 by sex (SHINE)
[back]

Sex	Treatment	N_Trt	Comparator	N_Cmp	Difference	95% Lower CL	95% Upper CL	P-Value
Female	SYM 160 BID	89	FOR 4.5 BID	89	0.15	0.10	0.20	0.0000
Male	SYM 160 BID	186	FOR 4.5 BID	185	0.18	0.14	0.23	0.0000

Table 53 Analysis of change from baseline in predose FEV_1 by race (SHINE)
[back]

Race	Treatment	N_Trt	Comparator	N_Cmp	Difference	95% Lower CL	95% Upper CL	P-Value
White	SYM 160 BID	251	FOR 4.5 BID	244	0.04	0.00	0.07	0.0398
[Non-White]	SYM 160 BID	15	FOR 4.5 BID	19	0.09	-0.11	0.28	0.3845

Table 54 Analysis of change from baseline in 1-hr postdose FEV_1 by race (SHINE)
[back]

Race	Treatment	N_Trt	Comparator	N_Cmp	Difference	95% Lower CL	95% Upper CL	P-Value
White	SYM 160 BID	259	BUD 160 BID	258	0.17	0.14	0.21	0.0000
[Non-White]	SYM 160 BID	16	BUD 160 BID	16	0.11	-0.09	0.31	0.2666

Table 55 Analysis of change from baseline in predose FEV_1 by age group (SHINE)
[back]

Age Group	Treatment	N_Trt	Comparator	N_Cmp	Difference	95% Lower CL	95% Upper CL	P-Value
65+	SYM 160 BID	114	FOR 4.5 BID	127	0.04	-0.00	0.08	0.0617
<65	SYM 160 BID	152	FOR 4.5 BID	136	0.03	-0.02	0.09	0.1993

Table 56 Analysis of change from baseline in 1-hr postdose FEV_1 by age group (SHINE)
[back]

Age Group	Treatment	N_Trt	Comparator	N_Cmp	Difference	95% Lower CL	95% Upper CL	P-Value
65+	SYM 160 BID	120	BUD 160 BID	120	0.16	0.12	0.21	0.0000
<65	SYM 160 BID	155	BUD 160 BID	154	0.18	0.13	0.23	0.0000

[Back to subgroup analysis]

Conclusions and Recommendations

The effectiveness of Symbicort 160/4.5 mcg twice daily in the treatment of COPD was demonstrated based on Studies SUN and SHINE. Therefore, I recommend the approval of Symbicort at this dose level, but I do not recommend the approval of Symbicort at 80/4.5 μg twice daily.

Comments on Labeling

Clinical Studies

I evaluated Section 14 CLINICAL STUDIES of the proposed label, in particular, Section 14.1 Chronic Obstructive Pulmonary Disease (COPD). Major comments are listed in the following points:

- Section 14.1 of the label deals with the claims for COPD based on Studies 1 (SHINE) and 2 (SUN). Nearly all the numbers were verified and confirmed to be

correct using the sponsor's data. In the second paragraph of Sec. 14, the total number of patients in both studies should be corrected to exclude the 7 non-ITT patients. The correct number of patients should be 3661.

- The analyses of the co-primary efficacy variables were based on the absolute change in pre-dose and 1-hour post dose FEV_1 from baseline to the average of the double-blind treatment period. However, the graphs and statements in the proposed label used the **percent change** instead. Modify the label so that it is consistent with the analyses of the primary efficacy variables.
- If the time of onset-of-action for the COPD indication needs to be included in the label, the median time to a 15% increase from baseline in FEV_1 at the day of randomization is 15 minutes rather than 5 minutes in the proposed label. This number is based on Study SHINE.

Adverse Reactions

The proposed label included a table reporting the adverse reactions for the COPD trials, SUN and SHINE, for "all adverse events that occurred at an incidence of ≥3% in the SYMBICORT group and more commonly than in the placebo group (See Section 6.3 Clinical Trials Experience, and Table 45, below)."

Table 57 Sponsor's Table 2: Adverse events occurring at an incidence of ≥3% and more commonly than placebo in the SYMBICORT group: pooled data from two double-blind, placebo-controlled clinical COPD trials

Table 2 **Adverse events occurring at an incidence of ≥ 3% and more commonly than placebo in the SYMBICORT group: pooled data from two double-blind, placebo-controlled clinical COPD trials**

Treatment*	**SYMBICORT**	**Budesonide**	**Formoterol**	**Placebo**
	160/4.5 mcg	**160 mcg**	**4.5 mcg**	
	N = 771	**N = 275**	**N = 779**	**N = 781**
Adverse Event	%	%	**%**	%
Nasopharyngitis	7.3	3.3	5.8	4.9
Oral candidiasis	6.0	4.4	1.2	1.8
Bronchitis	5.4	4.7	4.5	3.5
Sinusitis	3.5	1.5	3.1	1.8
Upper respiratory tract infection viral	3.5	1.8	3.6	2.7
Average Duration of Exposure (days)	**255.2**	**157.1**	**240.3**	**223.7**

I verified Table 57 using the sponsor data. The numbers and percentages in Table 58 represent patients in the safety group with AEs in 3% or more of the patients in the safety group. There are small differences in percentages. However, the AE findings are consistent when comparing Table 57 and Table 58. Although the sponsor's Table 2

(Table 45, this report) of the label does not include the number of patients for the AEs, but the percentages presented appear to be reasonable.

Table 58 Analysis of AEs using the sponsor's AE data by pooling Studies SUN AND SHINE

AEs presented using preferred terms	Treatment									
	SYM 160 BID		SYM 80 BID		BUD 160 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%	N	%
Number of patients	771		775		275		779		781	
(No AE)	279	36.19	287	37.03	113	41.09	302	38.77	337	43.15
COPD	116	15.05	137	17.68	37	13.45	147	18.87	125	16.01
NASOPHARYNGITIS	57	**7.39**	61	7.87	11	**4.00**	46	**5.91**	39	**4.99**
ORAL CANDIDIASIS	50	**6.49**	31	4.00	13	**4.73**	9	**1.16**	18	**2.30**
BRONCHITIS	34	**4.41**	28	3.61	10	**3.64**	35	**4.49**	28	**3.59**
PNEUMONIA	27	3.50	25	3.23	6	2.18	25	3.21	30	3.84
SINUSITIS	30	**3.89**	29	3.74	4	**1.45**	27	**3.47**	16	**2.05**
VIRAL UPPER RESPIRATORY TRACT INFECTION	28	**3.63**	31	4.00	5	**1.82**	28	**3.59**	21	**2.69**

Appendix

Complete AE findings reported from SUN and SHINE

Table 59 AE Reported using MedDRA preferred terms (SUN)

AEs presented as: AEPTTXT; Group totals: 494,494,495,481	Treatment SYM 160 BID		SYM 80 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%
(No AE)	166	33.60	163	33.00	185	37.37	201	41.79
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	74	14.98	95	19.23	89	17.98	83	17.26
NASOPHARYNGITIS	36	7.29	48	9.72	31	6.26	22	4.57
BRONCHITIS	24	4.86	23	4.66	26	5.25	20	4.16
PNEUMONIA	21	4.25	17	3.44	20	4.04	26	5.41
VIRAL UPPER RESPIRATORY TRACT INFECTION	21	4.25	24	4.86	22	4.44	17	3.53
ORAL CANDIDIASIS	38	7.69	23	4.66	2	0.40	11	2.29
SINUSITIS	21	4.25	20	4.05	21	4.24	9	1.87
BACK PAIN	18	3.64	9	1.82	19	3.84	12	2.49
HYPERTENSION	14	2.83	10	2.02	18	3.64	11	2.29
HEADACHE	13	2.63	15	3.04	10	2.02	12	2.49
UPPER RESPIRATORY TRACT INFECTION BACTERIAL	14	2.83	17	3.44	10	2.02	6	1.25
OEDEMA PERIPHERAL	12	2.43	9	1.82	13	2.63	11	2.29
MUSCLE SPASMS	16	3.24	16	3.24	5	1.01	7	1.46
DYSPNOEA	9	1.82	12	2.43	7	1.41	14	2.91
DIARRHOEA	12	2.43	11	2.23	8	1.62	10	2.08
PHARYNGITIS	9	1.82	13	2.63	8	1.62	9	1.87
NAUSEA	9	1.82	9	1.82	9	1.82	6	1.25
COUGH	9	1.82	8	1.62	10	2.02	3	0.62
MUSCULOSKELETAL CHEST PAIN	7	1.42	8	1.62	8	1.62	7	1.46
DIZZINESS	8	1.62	7	1.42	9	1.82	5	1.04
PHARYNGOLARYNGEAL PAIN	12	2.43	5	1.01	4	0.81	8	1.66
ANXIETY	8	1.62	10	2.02	7	1.41	3	0.62
DYSPHONIA	16	3.24	6	1.21	1	0.20	4	0.83
URINARY TRACT INFECTION	11	2.23	4	0.81	5	1.01	7	1.46
ANGINA PECTORIS	6	1.21	6	1.21	9	1.82	5	1.04
ATRIAL FIBRILLATION	6	1.21	13	2.63	4	0.81	2	0.42
INSOMNIA	4	0.81	9	1.82	6	1.21	5	1.04

AEs presented as: AEPTTXT; Group totals: 494,494,495,481	Treatment SYM 160 BID		SYM 80 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%
LOWER RESPIRATORY TRACT INFECTION VIRAL	6	1.21	7	1.42	5	1.01	3	0.62
ARTHRALGIA	4	0.81	3	0.61	9	1.82	4	0.83
FATIGUE	4	0.81	3	0.61	8	1.62	5	1.04
GASTROOESOPHAGEAL REFLUX DISEASE	7	1.42	5	1.01	5	1.01		
OSTEOPOROSIS	5	1.01	2	0.40	3	0.61	7	1.46
PAIN IN EXTREMITY	3	0.61	5	1.01	4	0.81	5	1.04
CONSTIPATION	2	0.40	3	0.61	6	1.21	5	1.04
INFLUENZA	4	0.81	4	0.81	3	0.61	5	1.04
LOWER RESPIRATORY TRACT INFECTION BACTERIAL	7	1.42	1	0.20	3	0.61	5	1.04
PYREXIA	5	1.01	2	0.40	3	0.61	6	1.25
UPPER RESPIRATORY TRACT INFECTION	3	0.61	4	0.81	8	1.62	1	0.21
DIABETES MELLITUS	3	0.61	6	1.21	4	0.81	2	0.42
ABDOMINAL PAIN UPPER	5	1.01	3	0.61	5	1.01	1	0.21
DYSPEPSIA	3	0.61	5	1.01	4	0.81	2	0.42
GASTROENTERITIS VIRAL	3	0.61	3	0.61	3	0.61	5	1.04
NASAL CONGESTION	4	0.81	2	0.40	5	1.01	3	0.62
ACUTE SINUSITIS	3	0.61	3	0.61	5	1.01	2	0.42
C-REACTIVE PROTEIN INCREASED	1	0.20	5	1.01	4	0.81	3	0.62
GASTRITIS	3	0.61	3	0.61	4	0.81	3	0.62
HAEMOPTYSIS	3	0.61	6	1.21	2	0.40	2	0.42
HERPES ZOSTER	3	0.61	1	0.20	7	1.41	2	0.42
MUSCULOSKELETAL PAIN	3	0.61	3	0.61	5	1.01	2	0.42
MYALGIA	4	0.81	3	0.61	4	0.81	2	0.42
NON-CARDIAC CHEST PAIN	2	0.40	2	0.40	5	1.01	4	0.83
TACHYCARDIA	2	0.40	5	1.01	4	0.81	2	0.42
VENTRICULAR EXTRASYSTOLES	4	0.81	3	0.61	3	0.61	3	0.62
VIRAL INFECTION	3	0.61	4	0.81	2	0.40	4	0.83
WHEEZING	4	0.81	3	0.61	4	0.81	2	0.42
ANAEMIA	3	0.61	5	1.01	2	0.40	2	0.42
CARDIAC FAILURE CONGESTIVE	3	0.61	6	1.21	2	0.40	1	0.21
EPISTAXIS	2	0.40	4	0.81	4	0.81	2	0.42
HYPOKALAEMIA	2	0.40	7	1.42	1	0.20	2	0.42
CARDIAC FAILURE	3	0.61	2	0.40	5	1.01	1	0.21
CATARACT	1	0.20	5	1.01	2	0.40	3	0.62
CONTUSION	2	0.40	3	0.61	5	1.01	1	0.21
LARYNGITIS	3	0.61	3	0.61	3	0.61	2	0.42
RHINITIS	4	0.81	1	0.20	2	0.40	4	0.83
RHINORRHOEA	4	0.81	1	0.20	2	0.40	4	0.83
VERTIGO	4	0.81	4	0.81	3	0.61		
WEIGHT DECREASED	7	1.42	1	0.20	1	0.20	2	0.42
BLOOD PRESSURE INCREASED	4	0.81	1	0.20	4	0.81	1	0.21
CYSTITIS	2	0.40	3	0.61	2	0.40	3	0.62
DEPRESSION	3	0.61	2	0.40	4	0.81	1	0.21
GOUT	3	0.61			6	1.21	1	0.21

AEs presented as: AEPTTXT; Group totals: 494,494,495,481	Treatment SYM 160 BID		SYM 80 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%
HYPERGLYCAEMIA	2	0.40	4	0.81	4	0.81		
OSTEOARTHRITIS	4	0.81	4	0.81			2	0.42
VENTRICULAR TACHYCARDIA	3	0.61	4	0.81	2	0.40	1	0.21
DECREASED APPETITE	2	0.40	1	0.20	3	0.61	3	0.62
GASTROENTERITIS	2	0.40	4	0.81	2	0.40	1	0.21
HAEMATURIA	2	0.40	3	0.61	3	0.61	1	0.21
MUSCLE STRAIN	3	0.61	2	0.40	2	0.40	2	0.42
RHONCHI	1	0.20	3	0.61	2	0.40	3	0.62
TOOTH ABSCESS	1	0.20	1	0.20	3	0.61	4	0.83
TOOTH INFECTION	4	0.81	3	0.61	1	0.20	1	0.21
ATRIOVENTRICULAR BLOCK FIRST DEGREE	2	0.40	3	0.61	2	0.40	1	0.21
BRONCHITIS BACTERIAL	1	0.20	2	0.40	3	0.61	2	0.42
BRONCHOPNEUMONIA	2	0.40	3	0.61	1	0.20	2	0.42
CORONARY ARTERY DISEASE	1	0.20	3	0.61	2	0.40	2	0.42
DYSURIA	2	0.40	4	0.81	1	0.20	1	0.21
FUNGAL SKIN INFECTION	4	0.81			2	0.40	2	0.42
OTITIS MEDIA	1	0.20	3	0.61	2	0.40	2	0.42
SINUS CONGESTION	3	0.61	1	0.20	3	0.61	1	0.21
AORTIC ANEURYSM			3	0.61	3	0.61	1	0.21
ASTHENIA	1	0.20	2	0.40	3	0.61	1	0.21
CHOLELITHIASIS	1	0.20			3	0.61	3	0.62
CONJUNCTIVITIS	2	0.40	2	0.40	3	0.61		
DERMATITIS CONTACT	2	0.40	2	0.40	2	0.40	1	0.21
EAR INFECTION			1	0.20	3	0.61	3	0.62
HYPERLIPIDAEMIA	1	0.20	2	0.40	2	0.40	2	0.42
HYPOTENSION			3	0.61	2	0.40	2	0.42
MYOCARDIAL INFARCTION			4	0.81	1	0.20	2	0.42
NECK PAIN	1	0.20	1	0.20	5	1.01		
RESPIRATORY FAILURE	1	0.20	3	0.61	2	0.40	1	0.21
SEASONAL ALLERGY	2	0.40	3	0.61			2	0.42
TOOTHACHE			4	0.81	3	0.61		
VISION BLURRED	2	0.40	2	0.40	1	0.20	2	0.42
VOMITING	1	0.20	1	0.20	4	0.81	1	0.21
ABDOMINAL PAIN	2	0.40	3	0.61			1	0.21
BLOOD GLUCOSE INCREASED	1	0.20	1	0.20	3	0.61	1	0.21
CEREBROVASCULAR ACCIDENT	2	0.40	1	0.20	2	0.40	1	0.21
DEHYDRATION	3	0.61	1	0.20	1	0.20	1	0.21
HYPERCHOLESTEROLAEMIA	2	0.40	1	0.20	1	0.20	2	0.42
RALES	2	0.40	3	0.61	1	0.20		
RASH	1	0.20	1	0.20	3	0.61	1	0.21
RASH MACULO-PAPULAR	1	0.20	2	0.40	3	0.61		
SLEEP APNOEA SYNDROME	1	0.20	2	0.40	2	0.40	1	0.21
TENDONITIS	1	0.20	2	0.40	3	0.61		
URTICARIA			3	0.61	1	0.20	2	0.42
ACUTE MYOCARDIAL INFARCTION	2	0.40	1	0.20	2	0.40		

AEs presented as: AEPTTXT; Group totals: 494,494,495,481	Treatment SYM 160 BID		SYM 80 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%
ARTERIOSCLEROSIS	2	0.40	1	0.20	2	0.40		
BENIGN PROSTATIC HYPERPLASIA			5	1.01				
BREATH SOUNDS ABNORMAL	2	0.40	1	0.20			2	0.42
BUNDLE BRANCH BLOCK LEFT	2	0.40	1	0.20	1	0.20	1	0.21
DERMATITIS			3	0.61			2	0.42
DRY MOUTH	1	0.20	1	0.20	2	0.40	1	0.21
EAR PAIN	1	0.20			2	0.40	2	0.42
ECZEMA	1	0.20	3	0.61	1	0.20		
ERYTHEMA	2	0.40	2	0.40			1	0.21
HIATUS HERNIA	1	0.20	1	0.20	3	0.61		
HYPOAESTHESIA	1	0.20	2	0.40	1	0.20	1	0.21
INCREASED UPPER AIRWAY SECRETION	3	0.61	2	0.40				
INTERVERTEBRAL DISC PROTRUSION	2	0.40	1	0.20	2	0.40		
LUNG NEOPLASM	2	0.40	3	0.61				
LYMPHADENOPATHY	2	0.40	1	0.20	1	0.20	1	0.21
OTITIS EXTERNA	2	0.40	1	0.20			2	0.42
PLEURISY	2	0.40	1	0.20	2	0.40		
PULMONARY EMBOLISM	2	0.40	2	0.40			1	0.21
PULMONARY HYPERTENSION	2	0.40	1	0.20	1	0.20	1	0.21
RHINITIS ALLERGIC	2	0.40	1	0.20	1	0.20	1	0.21
RIB FRACTURE	1	0.20	2	0.40	1	0.20	1	0.21
SINUS TACHYCARDIA	1	0.20	2	0.40	2	0.40		
SUPRAVENTRICULAR EXTRASYSTOLES	1	0.20	2	0.40	1	0.20	1	0.21
TRACHEITIS	2	0.40	2	0.40	1	0.20		
WEIGHT INCREASED	1	0.20	1	0.20	2	0.40	1	0.21
ABDOMINAL DISTENSION	1	0.20	1	0.20	1	0.20	1	0.21
ABDOMINAL HERNIA	2	0.40	1	0.20	1	0.20		
BASAL CELL CARCINOMA	3	0.61					1	0.21
BLADDER CANCER	2	0.40			2	0.40		
CARPAL TUNNEL SYNDROME	1	0.20			3	0.61		
CELLULITIS					1	0.20	3	0.62
CHEST DISCOMFORT			1	0.20	3	0.61		
COLONIC POLYP	2	0.40			1	0.20	1	0.21
DENTAL CARIES	3	0.61			1	0.20		
DIVERTICULITIS	1	0.20	2	0.40	1	0.20		
HYPOXIA			2	0.40	2	0.40		
INTERVERTEBRAL DISC DEGENERATION			2	0.40	1	0.20	1	0.21
LUNG NEOPLASM MALIGNANT	1	0.20	2	0.40			1	0.21
MIGRAINE	2	0.40			2	0.40		
OBSTRUCTIVE CHRONIC BRONCHITIS WITH ACUTE EXACERBATION	1	0.20	1	0.20	1	0.20	1	0.21
PALPITATIONS	3	0.61	1	0.20				
PHARYNGEAL ERYTHEMA	1	0.20			1	0.20	2	0.42
PITTING OEDEMA	1	0.20	1	0.20	2	0.40		
PSORIASIS			1	0.20	2	0.40	1	0.21

AEs presented as: AEPTTXT; Group totals: 494,494,495,481	Treatment SYM 160 BID		SYM 80 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%
RESTLESS LEGS SYNDROME	2	0.40			1	0.20	1	0.21
SKIN LACERATION	3	0.61	1	0.20				
SKIN LESION	1	0.20	2	0.40			1	0.21
SOMNOLENCE					4	0.81		
SPINAL OSTEOARTHRITIS			2	0.40			2	0.42
TREMOR	4	0.81						
URINARY INCONTINENCE	1	0.20			1	0.20	2	0.42
VISUAL DISTURBANCE	2	0.40	1	0.20			1	0.21
ABDOMINAL DISCOMFORT			1	0.20	1	0.20	1	0.21
ACUTE RESPIRATORY FAILURE	1	0.20	1	0.20			1	0.21
ARRHYTHMIA	1	0.20			2	0.40		
ATRIAL FLUTTER	1	0.20	1	0.20	1	0.20		
BACK INJURY	2	0.40					1	0.21
BONE PAIN			2	0.40	1	0.20		
BRONCHITIS CHRONIC	1	0.20			1	0.20	1	0.21
BUNDLE BRANCH BLOCK RIGHT	2	0.40	1	0.20				
COR PULMONALE	1	0.20			1	0.20	1	0.21
DEATH	1	0.20	1	0.20			1	0.21
DERMATITIS ALLERGIC	1	0.20	1	0.20			1	0.21
DRUG HYPERSENSITIVITY	1	0.20	1	0.20			1	0.21
DRY THROAT	2	0.40	1	0.20				
DYSPHAGIA			1	0.20	2	0.40		
EYE IRRITATION	1	0.20			1	0.20	1	0.21
EYE PAIN			1	0.20	1	0.20	1	0.21
FALL			1	0.20	1	0.20	1	0.21
FOOT FRACTURE	1	0.20	1	0.20			1	0.21
GASTROINTESTINAL INFECTION			1	0.20	2	0.40		
GINGIVITIS	1	0.20			1	0.20	1	0.21
GLAUCOMA	2	0.40	1	0.20				
HORDEOLUM	3	0.61						
HYPERHIDROSIS	1	0.20			2	0.40		
HYPERKALAEMIA			1	0.20	1	0.20	1	0.21
HYPERURICAEMIA	2	0.40	1	0.20				
HYPONATRAEMIA	2	0.40	1	0.20				
HYPOTHYROIDISM	1	0.20			1	0.20	1	0.21
INGUINAL HERNIA			3	0.61				
LOWER RESPIRATORY TRACT INFECTION	1	0.20	1	0.20	1	0.20		
LUNG SQUAMOUS CELL CARCINOMA STAGE UNSPECIFIED	2	0.40					1	0.21
MALAISE	1	0.20	1	0.20	1	0.20		
MYOCARDIAL ISCHAEMIA	1	0.20	1	0.20	1	0.20		
NASAL OEDEMA	2	0.40	1	0.20				
NERVOUSNESS	1	0.20			1	0.20	1	0.21
ONYCHOMYCOSIS	1	0.20	1	0.20	1	0.20		
ORAL FUNGAL INFECTION	2	0.40					1	0.21

AEs presented as: AEPTTXT; Group totals: 494,494,495,481	Treatment SYM 160 BID		SYM 80 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%
ORAL MUCOSAL BLISTERING	1	0.20					2	0.42
PAIN IN JAW	2	0.40					1	0.21
PHARYNGITIS STREPTOCOCCAL			2	0.40	1	0.20		
PLEURAL EFFUSION	1	0.20	1	0.20	1	0.20		
PLEURITIC PAIN	1	0.20			2	0.40		
POLLAKIURIA	1	0.20			2	0.40		
PROLONGED EXPIRATION			1	0.20			2	0.42
PROSTATIC SPECIFIC ANTIGEN INCREASED			2	0.40	1	0.20		
PROTEINURIA			3	0.61				
PRURITUS	1	0.20					2	0.42
PULMONARY CONGESTION							3	0.62
RADIUS FRACTURE	1	0.20	1	0.20			1	0.21
REFLUX OESOPHAGITIS			2	0.40	1	0.20		
RENAL CYST	1	0.20	1	0.20	1	0.20		
RENAL DISORDER	2	0.40	1	0.20				
RENAL FAILURE	3	0.61						
RENAL PAIN	1	0.20	2	0.40				
RHINITIS SEASONAL			1	0.20	2	0.40		
ROTATOR CUFF SYNDROME	1	0.20	1	0.20			1	0.21
SCIATICA	2	0.40	1	0.20				
SINUS HEADACHE	1	0.20	1	0.20	1	0.20		
STOMATITIS	1	0.20					2	0.42
SYNCOPE	2	0.40	1	0.20				
THROAT IRRITATION	1	0.20			1	0.20	1	0.21
UMBILICAL HERNIA	1	0.20			2	0.40		
VULVOVAGINAL MYCOTIC INFECTION	1	0.20			1	0.20	1	0.21
WOUND			1	0.20	1	0.20	1	0.21
ABDOMINAL PAIN LOWER	1	0.20			1	0.20		
ACUTE CORONARY SYNDROME	1	0.20					1	0.21
ACUTE TONSILLITIS	1	0.20					1	0.21
ANGINA UNSTABLE			1	0.20	1	0.20		
APPENDICITIS	1	0.20	1	0.20				
ARTERIAL OCCLUSIVE DISEASE	1	0.20			1	0.20		
ARTHRITIS	1	0.20			1	0.20		
ASPIRATION	1	0.20	1	0.20				
ATELECTASIS	1	0.20	1	0.20				
ATRIAL TACHYCARDIA			1	0.20			1	0.21
ATRIOVENTRICULAR BLOCK COMPLETE	1	0.20	1	0.20				
BLEPHARITIS	1	0.20	1	0.20				
BLOOD CHOLESTEROL INCREASED					1	0.20	1	0.21
BLOOD CREATININE INCREASED			1	0.20	1	0.20		
BLOOD POTASSIUM DECREASED	1	0.20	1	0.20				
BLOOD POTASSIUM INCREASED					1	0.20	1	0.21
BLOOD URINE PRESENT	1	0.20	1	0.20				
BREAST MASS			1	0.20	1	0.20		

AEs presented as: AEPTTXT; Group totals: 494,494,495,481	Treatment SYM 160 BID		SYM 80 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%
BREAST PAIN	1	0.20			1	0.20		
BRONCHOSPASM			1	0.20	1	0.20		
BURNING SENSATION							2	0.42
BURSITIS	1	0.20					1	0.21
CARDIAC DISCOMFORT	1	0.20	1	0.20				
CARDIAC MURMUR					1	0.20	1	0.21
CAROTID ARTERY STENOSIS	1	0.20	1	0.20				
CERUMEN IMPACTION					1	0.20	1	0.21
CHEST PAIN	1	0.20	1	0.20				
CHILLS	1	0.20					1	0.21
CHOLECYSTITIS	1	0.20			1	0.20		
CONFUSIONAL STATE	1	0.20			1	0.20		
CONJUNCTIVAL HYPERAEMIA			1	0.20	1	0.20		
CONVULSION			2	0.40				
CORONARY ARTERY OCCLUSION			2	0.40				
COSTOCHONDRITIS	1	0.20			1	0.20		
DERMAL CYST	1	0.20					1	0.21
DIVERTICULUM	1	0.20			1	0.20		
DRY EYE	2	0.40						
DYSLIPIDAEMIA	1	0.20	1	0.20				
ECCHYMOSIS					2	0.40		
ELECTROCARDIOGRAM ABNORMAL			1	0.20	1	0.20		
ELECTROCARDIOGRAM QT CORRECTED INTERVAL PROLONGED	1	0.20	1	0.20				
ELECTROCARDIOGRAM QT PROLONGED	1	0.20			1	0.20		
ELECTROCARDIOGRAM T WAVE ABNORMAL					2	0.40		
EPIDIDYMITIS	1	0.20					1	0.21
ERYSIPELAS			2	0.40				
EUSTACHIAN TUBE DYSFUNCTION			2	0.40				
EXCORIATION	1	0.20	1	0.20				
EXOSTOSIS			1	0.20			1	0.21
EYE HAEMORRHAGE			2	0.40				
EYE INJURY	1	0.20	1	0.20				
EYE PRURITUS	1	0.20			1	0.20		
EYELID OEDEMA	1	0.20					1	0.21
FACIAL BONES FRACTURE	1	0.20					1	0.21
FAECES DISCOLOURED					2	0.40		
FEELING COLD	1	0.20					1	0.21
FOOD POISONING			1	0.20	1	0.20		
FUNGAL INFECTION			1	0.20	1	0.20		
GASTROINTESTINAL HYPERMOTILITY	1	0.20			1	0.20		
GASTROINTESTINAL HYPOMOTILITY	1	0.20	1	0.20				
GLOSSODYNIA					1	0.20	1	0.21
HAEMATOCHEZIA	1	0.20	1	0.20				
HAEMOGLOBIN DECREASED	1	0.20	1	0.20				

AEs presented as: AEPTTXT; Group totals: 494,494,495,481	Treatment SYM 160 BID		SYM 80 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%
HAEMORRHOIDS			1	0.20			1	0.21
HEPATIC CYST	2	0.40						
HIP FRACTURE			1	0.20			1	0.21
HYPOGLYCAEMIA			2	0.40				
HYPOPHARYNGEAL CANCER			1	0.20	1	0.20		
HYPOREFLEXIA	1	0.20	1	0.20				
ILEUS			2	0.40				
INFECTED SEBACEOUS CYST	1	0.20	1	0.20				
INTERCOSTAL NEURALGIA	1	0.20			1	0.20		
INTERSTITIAL LUNG DISEASE	2	0.40						
INTESTINAL OBSTRUCTION	1	0.20			1	0.20		
IRRITABILITY					2	0.40		
JOINT SWELLING	1	0.20			1	0.20		
LABYRINTHITIS	1	0.20	1	0.20				
LEUKOCYTOSIS			1	0.20	1	0.20		
LIMB INJURY					2	0.40		
LOBAR PNEUMONIA	2	0.40						
LUNG ADENOCARCINOMA					2	0.40		
MACULAR DEGENERATION					1	0.20	1	0.21
MALNUTRITION			2	0.40				
MEDICAL DEVICE SITE REACTION			1	0.20	1	0.20		
MOUTH INJURY			1	0.20	1	0.20		
MUSCLE TIGHTNESS	1	0.20			1	0.20		
MUSCULAR WEAKNESS					1	0.20	1	0.21
NAIL TINEA	1	0.20			1	0.20		
NASAL DRYNESS			1	0.20	1	0.20		
NASAL POLYPS	2	0.40						
NASAL SEPTUM DEVIATION			1	0.20	1	0.20		
NECK MASS	1	0.20	1	0.20				
NEPHROLITHIASIS			2	0.40				
NEURALGIA			1	0.20	1	0.20		
NIGHTMARE			1	0.20			1	0.21
NOCTURIA					2	0.40		
OESOPHAGITIS	1	0.20			1	0.20		
ORAL PAIN	1	0.20			1	0.20		
OROPHARYNGEAL CANDIDIASIS	1	0.20	1	0.20				
OSTEOMYELITIS	1	0.20			1	0.20		
OSTEOPENIA					1	0.20	1	0.21
PAIN OF SKIN	1	0.20	1	0.20				
PANCREATITIS					2	0.40		
PARANASAL SINUS HYPERSECRETION	2	0.40						
PARONYCHIA	2	0.40						
PHLEBITIS	1	0.20	1	0.20				
PNEUMONIA STAPHYLOCOCCAL	1	0.20	1	0.20				
PNEUMOTHORAX	1	0.20					1	0.21

AEs presented as: AEPTTXT; Group totals: 494,494,495,481	Treatment SYM 160 BID		SYM 80 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%
POOR QUALITY SLEEP			1	0.20	1	0.20		
POSTNASAL DRIP	1	0.20			1	0.20		
RASH MACULAR	1	0.20					1	0.21
RECTAL POLYP	1	0.20			1	0.20		
SICK SINUS SYNDROME					1	0.20	1	0.21
SINOBRONCHITIS			1	0.20			1	0.21
SINUS BRADYCARDIA	1	0.20					1	0.21
SLEEP DISORDER	1	0.20	1	0.20				
SMALL INTESTINAL OBSTRUCTION			1	0.20	1	0.20		
SNEEZING	1	0.20					1	0.21
STAPHYLOCOCCAL INFECTION	2	0.40						
STOMACH DISCOMFORT					1	0.20	1	0.21
SUBCUTANEOUS ABSCESS	1	0.20					1	0.21
SYNOVIAL CYST			1	0.20			1	0.21
TACHYARRHYTHMIA			1	0.20			1	0.21
TENDON RUPTURE	1	0.20			1	0.20		
TONSILLITIS	1	0.20	1	0.20				
TOOTH DISORDER			2	0.40				
TOOTH FRACTURE	1	0.20	1	0.20				
TRACHEOBRONCHITIS			2	0.40				
TRANSIENT ISCHAEMIC ATTACK	1	0.20					1	0.21
TRANSITIONAL CELL CARCINOMA					1	0.20	1	0.21
TUBERCULOSIS	1	0.20			1	0.20		
TYMPANIC MEMBRANE PERFORATION			1	0.20	1	0.20		
URINARY HESITATION					2	0.40		
URINARY RETENTION							2	0.42
URINARY TRACT OBSTRUCTION	1	0.20			1	0.20		
VAGINAL INFECTION					1	0.20	1	0.21
VITAMIN D DEFICIENCY	1	0.20					1	0.21
WRIST FRACTURE	1	0.20					1	0.21
ABDOMINAL MASS	1	0.20						
ABSCESS					1	0.20		
ABSCESS OF EYELID	1	0.20						
ACARODERMATITIS	1	0.20						
ACROCHORDON	1	0.20						
ACTINIC KERATOSIS	1	0.20						
ADRENAL ADENOMA							1	0.21
ADRENOCORTICAL INSUFFICIENCY ACUTE					1	0.20		
AGEUSIA	1	0.20						
ALCOHOL POISONING	1	0.20						
ALLERGIC PHARYNGITIS					1	0.20		
ALOPECIA	1	0.20						
AMNESIA							1	0.21
ANEURYSM							1	0.21
ANGIOEDEMA					1	0.20		

AEs presented as: AEPTTXT; Group totals: 494,494,495,481	Treatment SYM 160 BID		SYM 80 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%
ANKLE FRACTURE							1	0.21
ANKYLOSING SPONDYLITIS					1	0.20		
AORTIC VALVE INCOMPETENCE			1	0.20				
APHONIA	1	0.20						
ARRHYTHMIA SUPRAVENTRICULAR	1	0.20						
ARTERIAL DISORDER	1	0.20						
ARTERIOSPASM CORONARY							1	0.21
ARTHROPOD BITE	1	0.20						
ASCITES	1	0.20						
ASTHMA					1	0.20		
ATRIOVENTRICULAR BLOCK					1	0.20		
ATRIOVENTRICULAR BLOCK SECOND DEGREE					1	0.20		
AURICULAR SWELLING			1	0.20				
BENIGN BREAST NEOPLASM					1	0.20		
BENIGN LUNG NEOPLASM					1	0.20		
BENIGN NEOPLASM OF SKIN	1	0.20						
BLADDER NEOPLASM					1	0.20		
BLEPHAROSPASM					1	0.20		
BLISTER	1	0.20						
BLOOD ALKALINE PHOSPHATASE INCREASED	1	0.20						
BLOOD CREATINE PHOSPHOKINASE ABNORMAL					1	0.20		
BLOOD CREATINE PHOSPHOKINASE INCREASED	1	0.20						
BLOOD GLUCOSE ABNORMAL			1	0.20				
BOWEL MOVEMENT IRREGULARITY					1	0.20		
BRADYCARDIA			1	0.20				
BRAIN CONTUSION					1	0.20		
BREAST CANCER					1	0.20		
BREAST CANCER IN SITU							1	0.21
BREAST MICROCALCIFICATION							1	0.21
BRONCHIAL CARCINOMA					1	0.20		
BRONCHIAL NEOPLASM	1	0.20						
BRONCHIAL OBSTRUCTION							1	0.21
BRONCHIAL SECRETION RETENTION							1	0.21
BUNDLE BRANCH BLOCK					1	0.20		
CARCINOMA IN SITU OF BLADDER							1	0.21
CARDIAC ARREST							1	0.21
CARDIAC DISORDER	1	0.20						
CARDIO-RESPIRATORY ARREST					1	0.20		
CARDIOMEGALY			1	0.20				
CARDIOMYOPATHY			1	0.20				
CAROTID ARTERIOSCLEROSIS			1	0.20				
CAROTID ARTERY DISEASE	1	0.20						
CAROTID ARTERY OCCLUSION							1	0.21
CAROTID BRUIT	1	0.20						
CEREBRAL INFARCTION	1	0.20						

AEs presented as: AEPTTXT; Group totals: 494,494,495,481	Treatment SYM 160 BID		SYM 80 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%
CEREBRAL ISCHAEMIA					1	0.20		
CEREBROVASCULAR INSUFFICIENCY	1	0.20						
CERVICAL VERTEBRAL FRACTURE			1	0.20				
CERVICOBRACHIAL SYNDROME							1	0.21
CHEILITIS							1	0.21
CHEST INJURY							1	0.21
CHOLANGIOLITIS							1	0.21
CHOLECYSTITIS ACUTE							1	0.21
CHOLECYSTITIS CHRONIC							1	0.21
COLITIS ISCHAEMIC			1	0.20				
COLON ADENOMA					1	0.20		
COLON CANCER			1	0.20				
COLONIC STENOSIS			1	0.20				
COLORECTAL CANCER METASTATIC			1	0.20				
COMA HEPATIC					1	0.20		
COMPLETED SUICIDE					1	0.20		
COMPRESSION FRACTURE							1	0.21
CONCUSSION							1	0.21
CONGESTIVE CARDIOMYOPATHY							1	0.21
CONJUNCTIVAL ABRASION	1	0.20						
CONJUNCTIVAL HAEMORRHAGE			1	0.20				
CONJUNCTIVITIS ALLERGIC	1	0.20						
CONJUNCTIVITIS BACTERIAL	1	0.20						
CONJUNCTIVITIS INFECTIVE							1	0.21
COORDINATION ABNORMAL	1	0.20						
CORNEAL LESION			1	0.20				
CORONARY ARTERY THROMBOSIS	1	0.20						
CORTISOL FREE URINE INCREASED					1	0.20		
CROHN'S DISEASE	1	0.20						
CYANOSIS	1	0.20						
CYSTITIS NONINFECTIVE			1	0.20				
CYTOLYTIC HEPATITIS					1	0.20		
DEEP VEIN THROMBOSIS	1	0.20						
DERMATITIS BULLOUS							1	0.21
DERMATITIS PSORIASIFORM					1	0.20		
DIABETES MELLITUS NON-INSULIN-DEPENDENT	1	0.20						
DIABETIC NEUROPATHY							1	0.21
DIPLOPIA							1	0.21
DIVERTICULUM INTESTINAL							1	0.21
DIZZINESS POSTURAL	1	0.20						
DRUG INTOLERANCE			1	0.20				
DUODENAL ULCER			1	0.20				
DUODENAL ULCER HAEMORRHAGE					1	0.20		
DUODENITIS	1	0.20						
DYSGEUSIA			1	0.20				

AEs presented as: AEPTTXT; Group totals: 494,494,495,481	Treatment SYM 160 BID		SYM 80 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%
DYSKINESIA							1	0.21
DYSPNOEA PAROXYSMAL NOCTURNAL							1	0.21
EAR INJURY					1	0.20		
ECTROPION	1	0.20						
ECZEMA ASTEATOTIC	1	0.20						
ELECTROCARDIOGRAM ST SEGMENT DEPRESSION	1	0.20						
ELECTROCARDIOGRAM T WAVE AMPLITUDE DECREASED					1	0.20		
ELECTROCARDIOGRAM T WAVE INVERSION							1	0.21
ENDOMETRIAL HYPERTROPHY					1	0.20		
ENTERITIS					1	0.20		
ENTEROCOLITIS							1	0.21
EPICONDYLITIS					1	0.20		
ERECTILE DYSFUNCTION					1	0.20		
ERYTHEMA OF EYELID	1	0.20						
ESSENTIAL HYPERTENSION			1	0.20				
EXCESSIVE EYE BLINKING	1	0.20						
EXPOSURE TO TOXIC AGENT							1	0.21
EXTERNAL EAR DISORDER			1	0.20				
EXTRAOCULAR MUSCLE PARESIS							1	0.21
EYE INFECTION					1	0.20		
EYELID DISORDER	1	0.20						
FAECAL INCONTINENCE	1	0.20						
FAT TISSUE INCREASED	1	0.20						
FEELING JITTERY					1	0.20		
FEMORAL HERNIA							1	0.21
FEMUR FRACTURE			1	0.20				
FLANK PAIN	1	0.20						
FLATULENCE			1	0.20				
FLUID RETENTION					1	0.20		
FOOD ALLERGY			1	0.20				
FOREIGN BODY ASPIRATION			1	0.20				
FUNGAL OESOPHAGITIS			1	0.20				
FURUNCLE			1	0.20				
GAMMA-GLUTAMYLTRANSFERASE INCREASED	1	0.20						
GASTRIC POLYPS			1	0.20				
GASTRIC ULCER			1	0.20				
GASTRIC ULCER HAEMORRHAGE	1	0.20						
GASTRITIS VIRAL	1	0.20						
GASTRODUODENITIS							1	0.21
GASTROINTESTINAL DISORDER	1	0.20						
GASTROINTESTINAL PAIN	1	0.20						
GASTROOESOPHAGITIS	1	0.20						
GENERAL PHYSICAL CONDITION ABNORMAL					1	0.20		
GENERALISED OEDEMA	1	0.20						

AEs presented as: AEPTTXT; Group totals: 494,494,495,481	Treatment SYM 160 BID		SYM 80 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%
GINGIVAL INFECTION					1	0.20		
GINGIVAL PAIN							1	0.21
GLOSSITIS	1	0.20						
GLUCOSE URINE							1	0.21
GOUTY ARTHRITIS					1	0.20		
GROIN PAIN							1	0.21
HAEMANGIOMA	1	0.20						
HAEMATOCRIT DECREASED	1	0.20						
HAEMATOCRIT INCREASED							1	0.21
HAEMORRHAGE URINARY TRACT	1	0.20						
HALLUCINATION					1	0.20		
HEAD INJURY	1	0.20						
HEAT RASH	1	0.20						
HELICOBACTER INFECTION							1	0.21
HEMIANOPIA HOMONYMOUS	1	0.20						
HEPATIC CIRRHOSIS					1	0.20		
HEPATIC NEOPLASM MALIGNANT					1	0.20		
HEPATITIS C			1	0.20				
HERNIA PAIN			1	0.20				
HERPES SIMPLEX	1	0.20						
HERPES ZOSTER OPHTHALMIC	1	0.20						
HUMERUS FRACTURE			1	0.20				
HYDROCELE					1	0.20		
HYPERCALCAEMIA	1	0.20						
HYPERNATRAEMIA			1	0.20				
HYPERSENSITIVITY			1	0.20				
HYPERTENSIVE ENCEPHALOPATHY							1	0.21
HYPERTHYROIDISM							1	0.21
HYPERTONIC BLADDER							1	0.21
HYPERTROPHY	1	0.20						
HYPERVENTILATION							1	0.21
HYPOACUSIS							1	0.21
HYPOCALCAEMIA			1	0.20				
HYPOXIC ENCEPHALOPATHY	1	0.20						
ILEUS PARALYTIC			1	0.20				
IMPETIGO							1	0.21
INCREASED BRONCHIAL SECRETION			1	0.20				
INFECTED BUNION					1	0.20		
INFECTED SKIN ULCER	1	0.20						
INFLUENZA LIKE ILLNESS					1	0.20		
INGROWING NAIL	1	0.20						
INGUINAL HERNIA, OBSTRUCTIVE					1	0.20		
INJECTION SITE PAIN			1	0.20				
INTENTIONAL OVERDOSE			1	0.20				
INTERNATIONAL NORMALISED RATIO					1	0.20		

AEs presented as: AEPTTXT; Group totals: 494,494,495,481	Treatment SYM 160 BID		SYM 80 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%
FLUCTUATION								
INTERNATIONAL NORMALISED RATIO INCREASED			1	0.20				
INTERVERTEBRAL DISC DISORDER	1	0.20						
INTERVERTEBRAL DISC SPACE NARROWING					1	0.20		
INTESTINAL HAEMORRHAGE	1	0.20						
INTRACRANIAL ANEURYSM			1	0.20				
INTRAOCULAR PRESSURE INCREASED							1	0.21
IRITIS			1	0.20				
IRON DEFICIENCY ANAEMIA							1	0.21
IRRITABLE BOWEL SYNDROME					1	0.20		
ISCHAEMIC CARDIOMYOPATHY			1	0.20				
JAW DISORDER	1	0.20						
JAW FRACTURE	1	0.20						
JOINT EFFUSION	1	0.20						
JOINT INJURY							1	0.21
JOINT SPRAIN							1	0.21
LARYNGEAL DISORDER	1	0.20						
LEFT VENTRICULAR DYSFUNCTION			1	0.20				
LEFT VENTRICULAR FAILURE					1	0.20		
LEIOMYOSARCOMA							1	0.21
LETHARGY							1	0.21
LEUKOPENIA			1	0.20				
LICHEN SCLEROSUS							1	0.21
LIP BLISTER			1	0.20				
LIP PAIN	1	0.20						
LOCALISED INFECTION	1	0.20						
LOCALISED INTRAABDOMINAL FLUID COLLECTION	1	0.20						
LOSS OF CONSCIOUSNESS					1	0.20		
LOWER EXTREMITY MASS							1	0.21
LUMBAR RADICULOPATHY	1	0.20						
LUMBAR VERTEBRAL FRACTURE	1	0.20						
LUNG ABSCESS					1	0.20		
LUNG CARCINOMA CELL TYPE UNSPECIFIED RECURRENT	1	0.20						
LUNG DISORDER			1	0.20				
LUNG INFILTRATION							1	0.21
LYMPHADENITIS	1	0.20						
MALIGNANT NEOPLASM OF EYELID			1	0.20				
MASS	1	0.20						
MEMORY IMPAIRMENT	1	0.20						
MENINGIOMA			1	0.20				
MENISCUS LESION			1	0.20				
METASTATIC NEOPLASM			1	0.20				
MIDDLE EAR INFLAMMATION							1	0.21

AEs presented as: AEPTTXT; Group totals: 494,494,495,481	Treatment SYM 160 BID		SYM 80 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%
MITRAL VALVE INCOMPETENCE							1	0.21
MULTI-ORGAN FAILURE	1	0.20						
MUSCLE SPASTICITY			1	0.20				
MUSCULOSKELETAL DISCOMFORT			1	0.20				
MYOSITIS							1	0.21
NAIL DISORDER	1	0.20						
NASAL DISORDER			1	0.20				
NASAL MUCOSAL DISORDER							1	0.21
NASOPHARYNGEAL DISORDER	1	0.20						
NECK INJURY			1	0.20				
NEPHRITIS	1	0.20						
NEUROPATHY					1	0.20		
NON-SMALL CELL LUNG CANCER							1	0.21
NON-SMALL CELL LUNG CANCER METASTATIC					1	0.20		
OCCULT BLOOD POSITIVE					1	0.20		
OCULAR HYPERTENSION					1	0.20		
OEDEMA	1	0.20						
OESOPHAGEAL STENOSIS					1	0.20		
OPHTHALMOPLEGIA	1	0.20						
ORAL HERPES			1	0.20				
ORAL SOFT TISSUE DISORDER							1	0.21
ORAL VIRAL INFECTION	1	0.20						
OSTEOPOROTIC FRACTURE	1	0.20						
OTITIS MEDIA CHRONIC					1	0.20		
OVARIAN CYST					1	0.20		
OXYGEN SATURATION DECREASED			1	0.20				
PAIN							1	0.21
PALATAL DISORDER							1	0.21
PARAESTHESIA			1	0.20				
PARKINSON'S DISEASE			1	0.20				
PAROTID ABSCESS							1	0.21
PERIARTHRITIS							1	0.21
PERICARDIAL EFFUSION			1	0.20				
PERIODIC LIMB MOVEMENT DISORDER			1	0.20				
PERITONITIS	1	0.20						
PERONEAL NERVE PALSY					1	0.20		
PHARYNGOESOPHAGEAL DIVERTICULUM	1	0.20						
PHARYNGOTONSILLITIS					1	0.20		
PHONOPHOBIA							1	0.21
PHOTOPHOBIA							1	0.21
PITYRIASIS			1	0.20				
PLATELET COUNT DECREASED	1	0.20						
PLATELET COUNT INCREASED	1	0.20						
PODAGRA					1	0.20		
POLYCYTHAEMIA					1	0.20		

AEs presented as: AEPTTXT; Group totals: 494,494,495,481	Treatment SYM 160 BID		SYM 80 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%
POST PROCEDURAL COMPLICATION			1	0.20				
POST PROCEDURAL HAEMORRHAGE							1	0.21
POSTOPERATIVE WOUND INFECTION			1	0.20				
PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA					1	0.20		
PROCEDURAL HEADACHE					1	0.20		
PROCEDURAL PAIN	1	0.20						
PRODUCTIVE COUGH					1	0.20		
PROSTATE CANCER	1	0.20						
PROSTATE INFECTION					1	0.20		
PROSTATIC ADENOMA	1	0.20						
PROSTATITIS	1	0.20						
PRURITUS ANI			1	0.20				
PRURITUS GENITAL							1	0.21
PULMONARY MASS					1	0.20		
PULMONARY VALVE INCOMPETENCE			1	0.20				
PULSE ABSENT			1	0.20				
PYURIA					1	0.20		
RASH PRURITIC							1	0.21
RASH PUSTULAR	1	0.20						
RED BLOOD CELL COUNT INCREASED							1	0.21
RENAL CELL CARCINOMA STAGE UNSPECIFIED							1	0.21
RENAL FAILURE ACUTE			1	0.20				
RENAL FAILURE CHRONIC			1	0.20				
RESPIRATORY TRACT CONGESTION	1	0.20						
RESPIRATORY TRACT INFECTION VIRAL							1	0.21
RESTLESSNESS			1	0.20				
RETINAL ANEURYSM							1	0.21
RETINAL DETACHMENT					1	0.20		
RETINAL VEIN OCCLUSION			1	0.20				
RHABDOMYOLYSIS							1	0.21
RHINITIS PERENNIAL					1	0.20		
RHINOTRACHEITIS	1	0.20						
ROAD TRAFFIC ACCIDENT			1	0.20				
ROSACEA	1	0.20						
SACROILIITIS			1	0.20				
SALIVARY GLAND MASS	1	0.20						
SALPINGITIS					1	0.20		
SCAPULA FRACTURE							1	0.21
SCLERAL HAEMORRHAGE					1	0.20		
SCOTOMA	1	0.20						
SCRATCH							1	0.21
SEPSIS			1	0.20				
SHOCK							1	0.21
SILENT MYOCARDIAL INFARCTION							1	0.21

AEs presented as: AEPTTXT; Group totals: 494,494,495,481	Treatment SYM 160 BID		SYM 80 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%
SINUS DISORDER							1	0.21
SKELETAL INJURY							1	0.21
SKIN CANDIDA	1	0.20						
SKIN DISCOLOURATION	1	0.20						
SKIN INJURY			1	0.20				
SKIN NODULE			1	0.20				
SKIN PAPILLOMA					1	0.20		
SKIN ULCER					1	0.20		
SMALL CELL LUNG CANCER METASTATIC	1	0.20						
SPINAL COMPRESSION FRACTURE							1	0.21
SPUTUM DISCOLOURED	1	0.20						
STERNAL FRACTURE	1	0.20						
STRESS URINARY INCONTINENCE					1	0.20		
SUBCUTANEOUS NODULE							1	0.21
SUBDURAL HAEMATOMA							1	0.21
SUICIDE ATTEMPT			1	0.20				
SUNBURN			1	0.20				
SUPRAVENTRICULAR TACHYCARDIA	1	0.20						
SWELLING FACE			1	0.20				
TENSION HEADACHE			1	0.20				
THERMAL BURN			1	0.20				
THROMBOPHLEBITIS							1	0.21
THYROID ADENOMA	1	0.20						
THYROID NEOPLASM							1	0.21
TINEA INFECTION					1	0.20		
TINEA PEDIS			1	0.20				
TINNITUS			1	0.20				
TOE DEFORMITY	1	0.20						
TONGUE BLISTERING	1	0.20						
TONGUE ERUPTION			1	0.20				
TONGUE INJURY					1	0.20		
TONGUE OEDEMA					1	0.20		
TONGUE ULCERATION	1	0.20						
TONSILLAR HYPERTROPHY			1	0.20				
TROPONIN INCREASED			1	0.20				
ULCERATIVE KERATITIS			1	0.20				
ULNAR NERVE INJURY	1	0.20						
UPPER LIMB FRACTURE	1	0.20						
URETHRAL INTRINSIC SPHINCTER DEFICIENCY							1	0.21
URETHRITIS			1	0.20				
URINARY TRACT DISORDER			1	0.20				
URINARY TRACT INFLAMMATION			1	0.20				
UROSEPSIS	1	0.20						
VAGINAL HAEMORRHAGE	1	0.20						
VAGINITIS BACTERIAL							1	0.21

AEs presented as: AEPTTXT; Group totals: 494,494,495,481	Treatment SYM 160 BID		SYM 80 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%
VARICOPHLEBITIS					1	0.20		
VASOMOTOR RHINITIS			1	0.20				
VENOUS THROMBOSIS LIMB					1	0.20		
VERTEBROBASILAR INSUFFICIENCY					1	0.20		
VERTIGO POSITIONAL			1	0.20				
WOLFF-PARKINSON-WHITE SYNDROME							1	0.21
WOUND DEHISCENCE			1	0.20				

Source: Data set aeana

[Back]

Table 60 AE Reported using MedDRA organ class terms (SUN)
[Back]

AEs presented as: AESOCTXT; Group totals: 494,494,495,481	Treatment SYM 160 BID		SYM 80 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%
INFECTIONS AND INFESTATIONS	201	40.69	209	42.31	164	33.13	142	29.52
(No AE)	166	33.60	163	33.00	185	37.37	201	41.79
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	135	27.33	140	28.34	132	26.67	129	26.82
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	66	13.36	53	10.73	62	12.53	49	10.19
GASTROINTESTINAL DISORDERS	69	13.97	58	11.74	62	12.53	38	7.90
CARDIAC DISORDERS	49	9.92	50	10.12	42	8.48	29	6.03
NERVOUS SYSTEM DISORDERS	42	8.50	35	7.09	35	7.07	26	5.41
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	33	6.68	25	5.06	37	7.47	30	6.24
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	25	5.06	27	5.47	17	3.43	20	4.16
METABOLISM AND NUTRITION DISORDERS	24	4.86	22	4.45	24	4.85	15	3.12
INVESTIGATIONS	23	4.66	19	3.85	25	5.05	15	3.12
VASCULAR DISORDERS	20	4.05	18	3.64	27	5.45	16	3.33
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	22	4.45	23	4.66	17	3.43	14	2.91
EYE DISORDERS	21	4.25	21	4.25	15	3.03	10	2.08
PSYCHIATRIC DISORDERS	17	3.44	21	4.25	17	3.43	8	1.66
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	17	3.44	11	2.23	16	3.23	10	2.08
RENAL AND URINARY DISORDERS	16	3.24	16	3.24	14	2.83	7	1.46
EAR AND LABYRINTH DISORDERS	5	1.01	10	2.02	7	1.41	4	0.83
BLOOD AND LYMPHATIC SYSTEM DISORDERS	6	1.21	8	1.62	5	1.01	4	0.83
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	4	0.81	6	1.21	4	0.81	3	0.62
HEPATOBILIARY DISORDERS	4	0.81			6	1.21	4	0.83
IMMUNE SYSTEM DISORDERS	3	0.61	6	1.21			3	0.62
ENDOCRINE DISORDERS	1	0.20			2	0.40	2	0.42
CONGENITAL, FAMILIAL AND GENETIC DISORDERS					1	0.20	1	0.21

Source: Data set aeana

[Back]

Table 61 AE Reported using MedDRA preferred terms (SHINE)

[Back]

AEs presented as: AEPTTXT; Group totals: 277,281,287,275,284,300	Treatment											
	SYM 160 BID		SYM 80 BID		BUD 160+FOR 4.5		BUD 160 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%	N	%	N	%
(No AE)	113	40.79	124	44.13	132	45.99	113	41.09	117	41.20	136	45.33
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	42	15.16	42	14.95	35	12.20	37	13.45	58	20.42	42	14.00
NASOPHARYNGITIS	21	7.58	13	4.63	16	5.57	11	4.00	15	5.28	17	5.67
ORAL CANDIDIASIS	12	4.33	8	2.85	8	2.79	13	4.73	7	2.46	7	2.33
BRONCHITIS	10	3.61	5	1.78	10	3.48	10	3.64	9	3.17	8	2.67
HEADACHE	7	2.53	9	3.20	5	1.74	10	3.64	7	2.46	6	2.00
SINUSITIS	9	3.25	9	3.20	9	3.14	4	1.45	6	2.11	7	2.33
PNEUMONIA	6	2.17	8	2.85	6	2.09	6	2.18	5	1.76	4	1.33
VIRAL UPPER RESPIRATORY TRACT INFECTION	7	2.53	7	2.49	5	1.74	5	1.82	6	2.11	4	1.33
DYSPNOEA	5	1.81	6	2.14	3	1.05	6	2.18	6	2.11	7	2.33
DIARRHOEA	4	1.44	5	1.78	8	2.79	4	1.45	10	3.52	1	0.33
BRONCHITIS ACUTE	8	2.89	4	1.42	5	1.74	6	2.18	4	1.41	3	1.00
PHARYNGOLARYNGEAL PAIN	6	2.17	2	0.71	2	0.70	7	2.55	9	3.17	4	1.33
HYPERTENSION	2	0.72	7	2.49	8	2.79	6	2.18	2	0.70	4	1.33
UPPER RESPIRATORY TRACT INFECTION BACTERIAL	3	1.08	4	1.42	3	1.05	6	2.18	5	1.76	7	2.33
INFLUENZA	6	2.17	7	2.49	3	1.05	5	1.82	4	1.41	2	0.67
NAUSEA	7	2.53	3	1.07	3	1.05	2	0.73	6	2.11	6	2.00
OEDEMA PERIPHERAL	2	0.72	5	1.78	5	1.74	6	2.18	5	1.76	4	1.33
INSOMNIA	2	0.72	7	2.49	2	0.70	6	2.18	3	1.06	6	2.00
URINARY TRACT INFECTION	4	1.44	5	1.78	4	1.39	6	2.18	3	1.06	4	1.33
VIRAL INFECTION	5	1.81	4	1.42	5	1.74	3	1.09	5	1.76	4	1.33
BACK PAIN	4	1.44	7	2.49	7	2.44	1	0.36	5	1.76	1	0.33
COUGH	3	1.08	4	1.42	2	0.70	2	0.73	6	2.11	8	2.67
PHARYNGITIS	4	1.44	5	1.78	1	0.35	5	1.82	3	1.06	4	1.33
DIABETES MELLITUS	1	0.36	4	1.42	2	0.70	2	0.73	7	2.46	2	0.67
ANXIETY	3	1.08	4	1.42	2	0.70	2	0.73	3	1.06	2	0.67
ARTHRALGIA	3	1.08	5	1.78	3	1.05	1	0.36	2	0.70	2	0.67
DIZZINESS	3	1.08	4	1.42	2	0.70	3	1.09	3	1.06	1	0.33
DYSPEPSIA	4	1.44	3	1.07	2	0.70	4	1.45	2	0.70	1	0.33
DYSPHONIA	6	2.17	1	0.36	1	0.35	4	1.45	3	1.06	1	0.33
MUSCLE SPASMS	3	1.08	2	0.71	3	1.05	3	1.09	4	1.41	1	0.33
MUSCULOSKELETAL CHEST PAIN	2	0.72	2	0.71	3	1.05	2	0.73	3	1.06	4	1.33
ATRIAL FIBRILLATION	2	0.72	4	1.42			2	0.73	4	1.41	3	1.00
WHEEZING	3	1.08	1	0.36	2	0.70	4	1.45	3	1.06		
NASAL CONGESTION	1	0.36	1	0.36	2	0.70	1	0.36	3	1.06	4	1.33
ABDOMINAL PAIN	2	0.72	1	0.36	2	0.70	4	1.45	1	0.35	1	0.33
CONSTIPATION	2	0.72	3	1.07	3	1.05	1	0.36	1	0.35	1	0.33
FATIGUE	1	0.36	3	1.07	1	0.35	4	1.45			2	0.67

AEs presented as: AEPTTXT; Group totals: 277,281,287,275,284,300	Treatment											
	SYM 160 BID		SYM 80 BID		BUD 160+FOR 4.5		BUD 160 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%	N	%	N	%
RHINITIS	3	1.08	1	0.36	2	0.70	2	0.73	1	0.35	2	0.67
UPPER RESPIRATORY TRACT INFECTION	1	0.36	3	1.07	2	0.70			4	1.41	1	0.33
VERTIGO			3	1.07	2	0.70	1	0.36	5	1.76		
CONTUSION	3	1.08	2	0.71	2	0.70			1	0.35	2	0.67
PALPITATIONS	3	1.08	1	0.36			1	0.36	2	0.70	3	1.00
PRODUCTIVE COUGH	4	1.44	1	0.36	1	0.35	1	0.36	1	0.35	2	0.67
VOMITING	3	1.08	2	0.71	3	1.05	1	0.36			1	0.33
ANAEMIA	4	1.44	3	1.07			1	0.36	1	0.35		
EPISTAXIS	1	0.36	1	0.36	1	0.35	2	0.73	4	1.41		
RHINORRHOEA	2	0.72	2	0.71			3	1.09			2	0.67
ANGINA PECTORIS	1	0.36			3	1.05	1	0.36	2	0.70	1	0.33
CARDIAC FAILURE CONGESTIVE	1	0.36	1	0.36			4	1.45	1	0.35	1	0.33
DRY MOUTH	3	1.08	1	0.36	2	0.70	1	0.36	1	0.35		
GASTROOESOPHAGEAL REFLUX DISEASE			2	0.71	2	0.70	1	0.36	1	0.35	2	0.67
HYPOKALAEMIA	1	0.36	1	0.36	1	0.35	2	0.73	1	0.35	2	0.67
LOWER RESPIRATORY TRACT INFECTION BACTERIAL	2	0.72	1	0.36	2	0.70	1	0.36	2	0.70		
MYALGIA	5	1.81							3	1.06		
BENIGN PROSTATIC HYPERPLASIA	1	0.36			2	0.70	2	0.73			2	0.67
BLOOD PRESSURE INCREASED	2	0.72	2	0.71	1	0.35	2	0.73				
DEPRESSION	3	1.08	2	0.71			1	0.36	1	0.35		
HAEMORRHOIDS	3	1.08	2	0.71							2	0.67
PYREXIA	1	0.36	2	0.71	2	0.70	1	0.36			1	0.33
TOOTH ABSCESS	2	0.72	2	0.71					2	0.70	1	0.33
ABDOMINAL PAIN UPPER	2	0.72	1	0.36	2	0.70	1	0.36				
CONJUNCTIVITIS	2	0.72	1	0.36			2	0.73			1	0.33
CORONARY ARTERY DISEASE	1	0.36	1	0.36			1	0.36	2	0.70	1	0.33
GASTRITIS			1	0.36			3	1.09	1	0.35	1	0.33
GOUT					2	0.70	1	0.36	3	1.06		
HAEMOPTYSIS			2	0.71	1	0.35	1	0.36	1	0.35	1	0.33
HEPATIC STEATOSIS	1	0.36			3	1.05	1	0.36	1	0.35		
HERPES ZOSTER	1	0.36					3	1.09	1	0.35	1	0.33
LARYNGITIS	3	1.08	1	0.36					1	0.35	1	0.33
MYOCARDIAL ISCHAEMIA	1	0.36	1	0.36	2	0.70					2	0.67
PAIN IN EXTREMITY	1	0.36			1	0.35	1	0.36	1	0.35	2	0.67
PHARYNGEAL ERYTHEMA			3	1.07	1	0.35	1	0.36	1	0.35		
TREMOR	1	0.36	3	1.07	1	0.35	1	0.36				
WEIGHT INCREASED			1	0.36	2	0.70	1	0.36			2	0.67
ASTHENIA			1	0.36	1	0.35	1	0.36	1	0.35	1	0.33
BRONCHOPNEUMONIA			2	0.71					1	0.35	2	0.67
CEREBROVASCULAR ACCIDENT			1	0.36	1	0.35	1	0.36	1	0.35	1	0.33
CYSTITIS	1	0.36			1	0.35	2	0.73	1	0.35		
HYPERGLYCAEMIA	1	0.36					1	0.36	1	0.35	2	0.67

AEs presented as: AEPTTXT; Group totals: 277,281,287,275,284,300	Treatment											
	SYM 160 BID		SYM 80 BID		BUD 160+FOR 4.5		BUD 160 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%	N	%	N	%
HYPOXIA	1	0.36	1	0.36	1	0.35	1	0.36	1	0.35		
INCREASED UPPER AIRWAY SECRETION	1	0.36	1	0.36			1	0.36			2	0.67
MUSCULOSKELETAL PAIN	2	0.72							1	0.35	2	0.67
NON-CARDIAC CHEST PAIN	1	0.36	1	0.36					1	0.35	2	0.67
OSTEOARTHRITIS	1	0.36			2	0.70	1	0.36	1	0.35		
RHINITIS ALLERGIC	1	0.36	1	0.36	1	0.35	2	0.73				
RIB FRACTURE	1	0.36	1	0.36	1	0.35	1	0.36			1	0.33
CELLULITIS	1	0.36			1	0.35			2	0.70		
DIABETES MELLITUS NON-INSULIN-DEPENDENT					1	0.35			1	0.35	2	0.67
GASTROENTERITIS	1	0.36			2	0.70			1	0.35		
GASTROENTERITIS VIRAL	1	0.36			1	0.35	1	0.36			1	0.33
NECK PAIN	1	0.36	1	0.36	1	0.35	1	0.36				
OTITIS EXTERNA			1	0.36	1	0.35			1	0.35	1	0.33
PROSTATE CANCER	1	0.36	2	0.71							1	0.33
PRURITUS	1	0.36	1	0.36					1	0.35	1	0.33
SEASONAL ALLERGY	1	0.36			1	0.35	1	0.36	1	0.35		
SINUS CONGESTION			1	0.36					1	0.35	2	0.67
SLEEP DISORDER			1	0.36	1	0.35			1	0.35	1	0.33
SPINAL OSTEOARTHRITIS	1	0.36	1	0.36			1	0.36			1	0.33
TACHYCARDIA			2	0.71	2	0.70						
TOOTHACHE	1	0.36							2	0.70	1	0.33
AORTIC ANEURYSM	1	0.36	1	0.36			1	0.36				
ARRHYTHMIA			2	0.71	1	0.35						
ARTHRITIS							2	0.73	1	0.35		
ARTHROPOD BITE							1	0.36	1	0.35	1	0.33
ATRIOVENTRICULAR BLOCK FIRST DEGREE					1	0.35			1	0.35	1	0.33
BLOOD GLUCOSE INCREASED					1	0.35			1	0.35	1	0.33
BONE PAIN	1	0.36							1	0.35	1	0.33
BREATH SOUNDS ABNORMAL			1	0.36					2	0.70		
BRONCHOSPASM	1	0.36			1	0.35			1	0.35		
CHEST PAIN	1	0.36			1	0.35	1	0.36				
CHOLELITHIASIS	1	0.36					2	0.73				
DECREASED APPETITE					1	0.35			1	0.35	1	0.33
DENTAL CARIES			1	0.36			1	0.36			1	0.33
DERMATITIS ALLERGIC	1	0.36					1	0.36	1	0.35		
DERMATITIS CONTACT					1	0.35			1	0.35	1	0.33
DIVERTICULUM	1	0.36	1	0.36							1	0.33
DRUG HYPERSENSITIVITY			1	0.36	1	0.35					1	0.33
DRY THROAT			1	0.36	1	0.35			1	0.35		
DYSGEUSIA					1	0.35			2	0.70		
EAR PAIN	1	0.36			1	0.35			1	0.35		
ERYTHEMA			2	0.71			1	0.36				

AEs presented as: AEPTTXT; Group totals: 277,281,287,275,284,300	Treatment											
	SYM 160 BID		SYM 80 BID		BUD 160+FOR 4.5		BUD 160 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%	N	%	N	%
GAMMA-GLUTAMYLTRANSFERASE INCREASED			2	0.71			1	0.36				
HAEMATURIA	1	0.36	2	0.71								
HERPES SIMPLEX	1	0.36							2	0.70		
HYPERCHOLESTEROLAEMIA	1	0.36	1	0.36	1	0.35						
HYPOAESTHESIA	1	0.36					1	0.36	1	0.35		
HYPOTENSION					1	0.35			1	0.35	1	0.33
INFLAMMATION	2	0.72							1	0.35		
JOINT SPRAIN			2	0.71					1	0.35		
LIVER FUNCTION TEST ABNORMAL			1	0.36					1	0.35	1	0.33
LOWER RESPIRATORY TRACT INFECTION	1	0.36			1	0.35					1	0.33
MYOCARDIAL INFARCTION			1	0.36					1	0.35	1	0.33
OSTEOPOROSIS	1	0.36	1	0.36			1	0.36				
OTITIS MEDIA	1	0.36	1	0.36	1	0.35						
PROCEDURAL PAIN			1	0.36							2	0.67
PROSTATITIS	1	0.36			1	0.35					1	0.33
RASH MACULO-PAPULAR					1	0.35			1	0.35	1	0.33
RESPIRATORY FAILURE			1	0.36	1	0.35			1	0.35		
SCIATICA	1	0.36	2	0.71								
SUPRAVENTRICULAR EXTRASYSTOLES					1	0.35			1	0.35	1	0.33
SYNCOPE							1	0.36			2	0.67
THROAT IRRITATION					1	0.35			2	0.70		
TRACHEITIS	1	0.36					1	0.36			1	0.33
URINARY RETENTION	1	0.36	1	0.36			1	0.36				
VENTRICULAR EXTRASYSTOLES					1	0.35	1	0.36	1	0.35		
WEIGHT DECREASED			1	0.36			2	0.73				
WOUND	1	0.36	1	0.36					1	0.35		
ABDOMINAL TENDERNESS	1	0.36									1	0.33
ACUTE MYOCARDIAL INFARCTION			1	0.36			1	0.36				
ACUTE SINUSITIS			1	0.36					1	0.35		
AGITATION									1	0.35	1	0.33
ALCOHOLISM					1	0.35	1	0.36				
ALOPECIA							2	0.73				
BASAL CELL CARCINOMA											2	0.67
BLADDER CANCER	1	0.36	1	0.36								
BUNDLE BRANCH BLOCK LEFT					1	0.35			1	0.35		
BURSITIS							2	0.73				
CATARACT							1	0.36			1	0.33
CEREBRAL ISCHAEMIA	1	0.36									1	0.33
CHEST DISCOMFORT					2	0.70						

AEs presented as: AEPTTXT; Group totals: 277,281,287,275,284,300	Treatment											
	SYM 160 BID		SYM 80 BID		BUD 160+FOR 4.5		BUD 160 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%	N	%	N	%
CHOLECYSTITIS ACUTE					1	0.35					1	0.33
CONFUSIONAL STATE	1	0.36					1	0.36				
DEHYDRATION	1	0.36							1	0.35		
DUODENAL ULCER			1	0.36							1	0.33
DYSURIA					1	0.35	1	0.36				
EAR CONGESTION			1	0.36			1	0.36				
ECZEMA	1	0.36									1	0.33
ELECTROCARDIOGRAM T WAVE INVERSION									1	0.35	1	0.33
EPICONDYLITIS			1	0.36					1	0.35		
EXCORIATION	1	0.36					1	0.36				
FACIAL BONES FRACTURE	1	0.36							1	0.35		
FALL									2	0.70		
FLATULENCE									1	0.35	1	0.33
FURUNCLE			1	0.36	1	0.35						
GINGIVAL INFECTION							1	0.36	1	0.35		
HAEMATOCHEZIA					1	0.35	1	0.36				
HEART RATE IRREGULAR					2	0.70						
HEPATOMEGALY					1	0.35	1	0.36				
HUMERUS FRACTURE	1	0.36	1	0.36								
HYPERCHLORHYDRIA					2	0.70						
HYPERLIPIDAEMIA			1	0.36					1	0.35		
HYPERURICAEMIA									1	0.35	1	0.33
HYPOGLYCAEMIA			1	0.36			1	0.36				
HYPONATRAEMIA							1	0.36	1	0.35		
INCREASED APPETITE	1	0.36			1	0.35						
INTERVERTEBRAL DISC DEGENERATION							1	0.36	1	0.35		
INTERVERTEBRAL DISC DISORDER			1	0.36	1	0.35						
INTERVERTEBRAL DISC PROTRUSION			1	0.36							1	0.33
IRRITABILITY			1	0.36					1	0.35		
JOINT SWELLING							1	0.36	1	0.35		
LARYNGOPHARYNGITIS	1	0.36	1	0.36								
LOWER LIMB FRACTURE							1	0.36	1	0.35		
LOWER RESPIRATORY TRACT INFECTION VIRAL							2	0.73				
LUNG ADENOCARCINOMA	1	0.36					1	0.36				
LUNG SQUAMOUS CELL CARCINOMA STAGE UNSPECIFIED			1	0.36	1	0.35						
MALAISE					1	0.35			1	0.35		
MIGRAINE	1	0.36									1	0.33
MITRAL VALVE INCOMPETENCE					2	0.70						
MUSCLE TIGHTNESS	1	0.36	1	0.36								

AEs presented as: AEPTTXT; Group totals: 277,281,287,275,284,300	Treatment											
	SYM 160 BID		SYM 80 BID		BUD 160+FOR 4.5		BUD 160 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%	N	%	N	%
MUSCULOSKELETAL STIFFNESS			1	0.36	1	0.35						
NEPHROLITHIASIS			1	0.36							1	0.33
NEUROSIS					1	0.35			1	0.35		
OBESITY			1	0.36			1	0.36				
ORAL FUNGAL INFECTION	2	0.72										
ORAL PAIN			1	0.36							1	0.33
OROPHARYNGEAL CANDIDIASIS	1	0.36	1	0.36								
PAIN					1	0.35	1	0.36				
PHARYNGEAL CANDIDIASIS	2	0.72										
PNEUMOTHORAX							2	0.73				
POSTNASAL DRIP			1	0.36			1	0.36				
PROTEINURIA					1	0.35	1	0.36				
PSORIASIS							1	0.36			1	0.33
RALES			1	0.36							1	0.33
RASH					1	0.35			1	0.35		
RECTAL HAEMORRHAGE			1	0.36	1	0.35						
RESTLESS LEGS SYNDROME							1	0.36	1	0.35		
SKIN LACERATION					1	0.35					1	0.33
SOFT TISSUE INJURY			1	0.36			1	0.36				
SPINAL DISORDER											2	0.67
STOMACH DISCOMFORT					1	0.35			1	0.35		
STOMATITIS			1	0.36							1	0.33
TENDONITIS					1	0.35			1	0.35		
THERMAL BURN							1	0.36	1	0.35		
THROMBOPHLEBITIS							1	0.36			1	0.33
TOOTH INFECTION	2	0.72										
TOOTH INJURY					1	0.35			1	0.35		
VAGINAL INFECTION					1	0.35	1	0.36				
VENTRICULAR FIBRILLATION			1	0.36					1	0.35		
VIRAL RHINITIS							1	0.36	1	0.35		
VISUAL ACUITY REDUCED	1	0.36									1	0.33
WHITE BLOOD CELL COUNT INCREASED					1	0.35					1	0.33
ABDOMINAL DISCOMFORT	1	0.36										
ABDOMINAL DISTENSION	1	0.36										
ABDOMINAL STRANGULATED HERNIA			1	0.36								
ABSCESS LIMB					1	0.35						
ACNE							1	0.36				
ACUTE CORONARY SYNDROME									1	0.35		
ALANINE AMINOTRANSFERASE INCREASED									1	0.35		
ALLERGY TO CHEMICALS					1	0.35						
AMNESIA					1	0.35						
AMYOTROPHIC LATERAL			1	0.36								

AEs presented as: AEPTTXT; Group totals: 277,281,287,275,284,300	Treatment											
	SYM 160 BID		SYM 80 BID		BUD 160+FOR 4.5		BUD 160 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%	N	%	N	%
SCLEROSIS												
ANGINA UNSTABLE					1	0.35						
ANIMAL BITE							1	0.36				
AORTIC ARTERIOSCLEROSIS											1	0.33
APHASIA											1	0.33
APHONIA	1	0.36										
APHTHOUS STOMATITIS							1	0.36				
APPENDICEAL ABSCESS							1	0.36				
ARTHRITIS INFECTIVE							1	0.36				
ARTHROPOD STING			1	0.36								
ATRIAL TACHYCARDIA							1	0.36				
ATROPHIC VULVOVAGINITIS									1	0.35		
BILIARY COLIC							1	0.36				
BLADDER DISORDER			1	0.36								
BLADDER SPASM											1	0.33
BLEPHARITIS									1	0.35		
BLISTER					1	0.35						
BLOOD CREATINE PHOSPHOKINASE INCREASED									1	0.35		
BLOOD POTASSIUM DECREASED					1	0.35						
BLOOD PRESSURE SYSTOLIC INCREASED							1	0.36				
BLOOD URINE							1	0.36				
BREAST CANCER METASTATIC											1	0.33
BREAST MASS			1	0.36								
BREAST MICROCALCIFICATION					1	0.35						
BREAST PAIN			1	0.36								
BREATH SOUNDS									1	0.35		
BRONCHIAL CARCINOMA											1	0.33
BURNS SECOND DEGREE			1	0.36								
CARDIAC ARREST			1	0.36								
CARDIAC DISCOMFORT									1	0.35		
CARDIAC FAILURE	1	0.36										
CARDIAC MURMUR			1	0.36								
CARDIOMYOPATHY											1	0.33
CARDIOMYOPATHY ALCOHOLIC											1	0.33
CARDIOPULMONARY FAILURE	1	0.36										
CARDIOVASCULAR DISORDER					1	0.35						
CARDIOVASCULAR INSUFFICIENCY					1	0.35						
CAROTID ARTERY STENOSIS											1	0.33
CEREBROVASCULAR SPASM											1	0.33
CERUMEN IMPACTION											1	0.33
CHALAZION					1	0.35						
CHILLBLAINS					1	0.35						

AEs presented as: AEPTTXT; Group totals: 277,281,287,275,284,300	Treatment											
	SYM 160 BID		SYM 80 BID		BUD 160+FOR 4.5		BUD 160 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%	N	%	N	%
CHILLS											1	0.33
CHOLECYSTITIS	1	0.36										
CHRONIC SINUSITIS	1	0.36										
COLITIS ISCHAEMIC									1	0.35		
COLITIS ULCERATIVE									1	0.35		
COLON ADENOMA	1	0.36										
CONJUNCTIVAL HAEMORRHAGE	1	0.36										
CONJUNCTIVITIS ALLERGIC									1	0.35		
CONJUNCTIVITIS INFECTIVE											1	0.33
COR PULMONALE									1	0.35		
COR PULMONALE CHRONIC							1	0.36				
CORTISOL FREE URINE DECREASED					1	0.35						
CREPITATIONS							1	0.36				
DEAFNESS					1	0.35						
DEPRESSED LEVEL OF CONSCIOUSNESS											1	0.33
DEPRESSED MOOD											1	0.33
DERMATITIS					1	0.35						
DERMATITIS ATOPIC											1	0.33
DIVERTICULITIS									1	0.35		
DIZZINESS POSTURAL							1	0.36				
DRY EYE									1	0.35		
DRY SKIN											1	0.33
DYSTONIA									1	0.35		
EAR INFECTION											1	0.33
ELECTROCARDIOGRAM ST SEGMENT ELEVATION	1	0.36										
ENTERITIS					1	0.35						
ENTEROCOLITIS	1	0.36										
EPIDIDYMITIS											1	0.33
EPIGLOTTITIS							1	0.36				
ERYSIPELAS							1	0.36				
ERYTHEMA NODOSUM											1	0.33
ESCHERICHIA URINARY TRACT INFECTION											1	0.33
ESSENTIAL HYPERTENSION											1	0.33
EXSANGUINATION					1	0.35						
EXTRASYSTOLES			1	0.36								
EYE IRRITATION			1	0.36								
EYE PRURITUS							1	0.36				
EYE SWELLING									1	0.35		
FACIAL PALSY					1	0.35						
FACIAL SPASM											1	0.33
FEELING ABNORMAL							1	0.36				

AEs presented as: AEPTTXT; Group totals: 277,281,287,275,284,300	Treatment											
	SYM 160 BID		SYM 80 BID		BUD 160+FOR 4.5		BUD 160 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%	N	%	N	%
FEMORAL ARTERIAL STENOSIS			1	0.36								
FEMORAL ARTERY OCCLUSION			1	0.36								
FLUID RETENTION			1	0.36								
FOOD POISONING							1	0.36				
FOOT FRACTURE											1	0.33
FOREIGN BODY IN EYE											1	0.33
GASTRIC ULCER			1	0.36								
GASTRIC ULCER HELICOBACTER							1	0.36				
GASTROINTESTINAL FUNGAL INFECTION							1	0.36				
GASTROINTESTINAL HAEMORRHAGE			1	0.36								
GASTROINTESTINAL INFECTION			1	0.36								
GASTROINTESTINAL INFLAMMATION					1	0.35						
GASTROINTESTINAL PAIN			1	0.36								
GINGIVAL DISORDER											1	0.33
GINGIVITIS									1	0.35		
GLYCOSURIA											1	0.33
GOITRE	1	0.36										
GOUTY ARTHRITIS			1	0.36								
GROIN PAIN									1	0.35		
HAEMATOMA							1	0.36				
HALLUCINATION							1	0.36				
HAND FRACTURE											1	0.33
HEAD INJURY									1	0.35		
HEAT EXHAUSTION					1	0.35						
HEAT RASH											1	0.33
HEPATIC ENZYME INCREASED											1	0.33
HEPATITIS ALCOHOLIC					1	0.35						
HEPATOCELLULAR DAMAGE			1	0.36								
HERNIA			1	0.36								
HERPES OPHTHALMIC									1	0.35		
HIATUS HERNIA							1	0.36				
HIP FRACTURE	1	0.36										
HOT FLUSH									1	0.35		
HYPERAESTHESIA	1	0.36										
HYPERHIDROSIS			1	0.36								
HYPERKALAEMIA					1	0.35						
HYPERNATRAEMIA			1	0.36								
HYPERSENSITIVITY					1	0.35						
HYPERTHYROIDISM			1	0.36								
HYPERTONIC BLADDER			1	0.36								
HYPERTRIGLYCERIDAEMIA									1	0.35		
HYPOTHYROIDISM							1	0.36				

AEs presented as: AEPTTXT; Group totals: 277,281,287,275,284,300	Treatment											
	SYM 160 BID		SYM 80 BID		BUD 160+FOR 4.5		BUD 160 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%	N	%	N	%
HYPOVENTILATION											1	0.33
INGUINAL HERNIA	1	0.36										
INTERCOSTAL NEURALGIA			1	0.36								
INTERMITTENT CLAUDICATION									1	0.35		
INTERVERTEBRAL DISCITIS					1	0.35						
INTRACRANIAL ANEURYSM	1	0.36										
INTRAOCULAR PRESSURE INCREASED	1	0.36										
IRON DEFICIENCY ANAEMIA			1	0.36								
JOINT DISLOCATION							1	0.36				
JOINT INJURY									1	0.35		
JOINT STIFFNESS					1	0.35						
KETONURIA					1	0.35						
LACRIMATION INCREASED									1	0.35		
LEUKOCYTOSIS			1	0.36								
LIMB INJURY							1	0.36				
LIP DRY									1	0.35		
LIVER DISORDER											1	0.33
LOBAR PNEUMONIA	1	0.36										
LUNG CANCER METASTATIC	1	0.36										
LUNG INFECTION							1	0.36				
LUNG NEOPLASM							1	0.36				
LUNG NEOPLASM MALIGNANT					1	0.35						
MAJOR DEPRESSION			1	0.36								
MASTOID DISORDER							1	0.36				
MASTOIDITIS							1	0.36				
MENINGIOMA							1	0.36				
MENISCUS LESION	1	0.36										
MITRAL VALVE PROLAPSE					1	0.35						
MOTION SICKNESS					1	0.35						
MUSCLE INJURY											1	0.33
MUSCLE SPASTICITY									1	0.35		
MUSCLE STRAIN											1	0.33
MUSCULAR WEAKNESS	1	0.36										
MUSCULOSKELETAL DISCOMFORT									1	0.35		
NASAL SEPTUM PERFORATION											1	0.33
NECK MASS									1	0.35		
NERVE ROOT LESION	1	0.36										
NEURALGIA					1	0.35						
NEURITIS					1	0.35						
NEUROPATHY PERIPHERAL									1	0.35		
NEUTROPHIL COUNT INCREASED					1	0.35						
NIGHT SWEATS					1	0.35						
NODULE											1	0.33

AEs presented as: AEPTTXT; Group totals: 277,281,287,275,284,300	Treatment											
	SYM 160 BID		SYM 80 BID		BUD 160+FOR 4.5		BUD 160 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%	N	%	N	%
NON-HODGKIN'S LYMPHOMA	1	0.36										
NON-SMALL CELL LUNG CANCER			1	0.36								
NON-SMALL CELL LUNG CANCER STAGE IV					1	0.35						
OEDEMA											1	0.33
OESOPHAGEAL CANDIDIASIS							1	0.36				
OESOPHAGEAL ULCER							1	0.36				
OESOPHAGITIS							1	0.36				
OSTEOMYELITIS									1	0.35		
OSTEOPENIA							1	0.36				
OTITIS MEDIA ACUTE			1	0.36								
PANIC ATTACK									1	0.35		
PARAESTHESIA											1	0.33
PARONYCHIA					1	0.35						
PAROTITIS			1	0.36								
PELVIC FRACTURE											1	0.33
PEPTIC ULCER	1	0.36										
PERIPHERAL EMBOLISM	1	0.36										
PERIPHERAL VASCULAR DISORDER							1	0.36				
PERITONITIS											1	0.33
PLEURAL EFFUSION							1	0.36				
PLEURITIC PAIN							1	0.36				
PNEUMONIA PNEUMOCOCCAL									1	0.35		
POLLAKIURIA											1	0.33
POST HERPETIC NEURALGIA											1	0.33
POST PROCEDURAL COMPLICATION					1	0.35						
POSTOPERATIVE ILEUS					1	0.35						
PRESYNCOPE									1	0.35		
PROSTATIC ADENOMA					1	0.35						
PULMONARY CONGESTION									1	0.35		
PULMONARY OEDEMA	1	0.36										
PYELOCYSTITIS			1	0.36								
PYELONEPHRITIS			1	0.36								
RADICULAR PAIN	1	0.36										
RASH MACULAR									1	0.35		
RASH PRURITIC							1	0.36				
RENAL CELL CARCINOMA STAGE UNSPECIFIED					1	0.35						
RENAL CYST					1	0.35						
RENAL FAILURE ACUTE					1	0.35						
RENAL FAILURE CHRONIC							1	0.36				
RESPIRATION ABNORMAL									1	0.35		
RESPIRATORY DISORDER	1	0.36										

AEs presented as: AEPTTXT; Group totals: 277,281,287,275,284,300	Treatment											
	SYM 160 BID		SYM 80 BID		BUD 160+FOR 4.5		BUD 160 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%	N	%	N	%
RHEUMATOID ARTHRITIS	1	0.36										
RIGHT VENTRICULAR FAILURE											1	0.33
ROAD TRAFFIC ACCIDENT											1	0.33
SCHISTOSOMIASIS					1	0.35						
SCLERAL HAEMORRHAGE											1	0.33
SCLERODERMA									1	0.35		
SENSITIVITY OF TEETH									1	0.35		
SEPSIS											1	0.33
SEPTIC SHOCK									1	0.35		
SHOCK	1	0.36										
SINUS BRADYCARDIA	1	0.36										
SKELETAL INJURY									1	0.35		
SKIN LESION					1	0.35						
SKIN NODULE					1	0.35						
SNEEZING											1	0.33
SOMNOLENCE			1	0.36								
SPINAL COMPRESSION FRACTURE					1	0.35						
SPLENOMEGALY					1	0.35						
SPUTUM PURULENT									1	0.35		
SUBARACHNOID HAEMORRHAGE											1	0.33
SUBCUTANEOUS EMPHYSEMA							1	0.36				
SUDDEN DEATH											1	0.33
SWELLING FACE							1	0.36				
THROMBOCYTOPENIA							1	0.36				
THYROID CYST							1	0.36				
THYROID NEOPLASM					1	0.35						
THYROIDITIS SUBACUTE			1	0.36								
TIBIA FRACTURE							1	0.36				
TINEA PEDIS									1	0.35		
TINNITUS									1	0.35		
TONGUE COATED	1	0.36										
TONSIL CANCER	1	0.36										
TONSILLITIS							1	0.36				
TOOTH DISORDER									1	0.35		
TOOTH FRACTURE									1	0.35		
TOOTH LOSS			1	0.36								
TRACHEOBRONCHITIS			1	0.36								
TUBERCULOSIS							1	0.36				
UPPER LIMB FRACTURE	1	0.36										
UPPER RESPIRATORY TRACT CONGESTION			1	0.36								
URTICARIA							1	0.36				
VAGINAL CANDIDIASIS	1	0.36										
VAGUS NERVE DISORDER											1	0.33

AEs presented as: AEPTTXT; Group totals: 277,281,287,275,284,300	Treatment									
	SYM 160 BID		SYM 80 BID		BUD 160+FOR 4.5		BUD 160 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%	N	%	N	%
VASCULAR CALCIFICATION					1	0.35						
VASOMOTOR RHINITIS					1	0.35						
VENOUS INSUFFICIENCY									1	0.35		
VENTRICULAR HYPERTROPHY					1	0.35						
VISION BLURRED									1	0.35		
VISUAL DISTURBANCE			1	0.36								
WOUND DEHISCENCE					1	0.35						
WOUND INFECTION					1	0.35						
WOUND SEPSIS									1	0.35		
WRIST FRACTURE					1	0.35						

Source: Data set aeana

[Back]

Table 62 AE Reported using MedDRA organ class terms (SHINE)
[Back]

AEs presented as: AESOCTXT; Group totals: 277,281,287,275,284,300	Treatment											
	SYM 160 BID		SYM 80 BID		BUD 160+FOR 4.5		BUD 160 BID		FOR 4.5 BID		Placebo	
	N	%	N	%	N	%	N	%	N	%	N	%
(No AE)	113	40.79	124	44.13	132	45.99	113	41.09	117	41.20	136	45.33
INFECTIONS AND INFESTATIONS	93	33.57	85	30.25	80	27.87	79	28.73	83	29.23	74	24.67
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	61	22.02	64	22.78	48	16.72	71	25.82	87	30.63	68	22.67
GASTROINTESTINAL DISORDERS	26	9.39	28	9.96	26	9.06	24	8.73	23	8.10	20	6.67
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	27	9.75	22	7.83	23	8.01	17	6.18	25	8.80	15	5.00
NERVOUS SYSTEM DISORDERS	18	6.50	18	6.41	12	4.18	18	6.55	15	5.28	16	5.33
CARDIAC DISORDERS	12	4.33	14	4.98	13	4.53	12	4.36	16	5.63	13	4.33
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	8	2.89	14	4.98	14	4.88	16	5.82	10	3.52	13	4.33
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	11	3.97	11	3.91	10	3.48	9	3.27	13	4.58	12	4.00
PSYCHIATRIC DISORDERS	9	3.25	14	4.98	7	2.44	10	3.64	10	3.52	10	3.33
METABOLISM AND NUTRITION DISORDERS	6	2.17	10	3.56	9	3.14	9	3.27	17	5.99	8	2.67
VASCULAR DISORDERS	4	1.44	9	3.20	11	3.83	10	3.64	6	2.11	8	2.67
INVESTIGATIONS	4	1.44	9	3.20	9	3.14	8	2.91	8	2.82	7	2.33
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3	1.08	4	1.42	7	2.44	10	3.64	6	2.11	9	3.00
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	7	2.53	4	1.42	6	2.09	3	1.09			5	1.67
EYE DISORDERS	4	1.44	3	1.07	1	0.35	4	1.45	6	2.11	4	1.33
EAR AND LABYRINTH DISORDERS	1	0.36	4	1.42	5	1.74	3	1.09	7	2.46	1	0.33
RENAL AND URINARY DISORDERS	1	0.36	4	1.42	4	1.39	4	1.45			4	1.33
HEPATOBILIARY DISORDERS	3	1.08	1	0.36	4	1.39	4	1.45	1	0.35	2	0.67
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	2	0.72	2	0.71	4	1.39	2	0.73	1	0.35	3	1.00
BLOOD AND LYMPHATIC SYSTEM DISORDERS	4	1.44	4	1.42	1	0.35	2	0.73	1	0.35		
IMMUNE SYSTEM DISORDERS	1	0.36	1	0.36	4	1.39	1	0.36	1	0.35	1	0.33
ENDOCRINE DISORDERS	1	0.36	2	0.71			2	0.73				

Source: Data set aeana

[Back]

--END OF DOCUMENT--

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

/s/

Ted Guo
1/14/2009 02:00:47 PM
BIOMETRICS
Statistical review

Qian Li
1/14/2009 02:37:05 PM
BIOMETRICS

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

Statistician's Filling Review of Clinical Studies

NDA/Serial Number:	NDA 21-929
Drug Name:	SYMBICORT (pMDI, 160/4.5μg and 80/4.5μg) administered as two puffs twice daily
Indication(s):	SYMBICORT is proposed to be indicated for the long-term maintenance treatment of asthma in patients 12 years of age and beyond, and for the (b) (4) maintenance treatment of COPD including chronic bronchitis and emphysema in patients (b) (4)
Applicant:	AstraZeneca
Date(s):	Applicant's letter date: 4/28/2008
Review Priority:	Standard
Biometrics Division:	Biometrics Division 2
Statistical Reviewer:	Ted Guo, Ph.D., Biometrics Division 2
Concurring Reviewers:	Qian Li, Sc. D., Team Leader, Biometrics Division 2
Medical Division:	Division of Pulmonary and Allergy Products (ODE II)
Clinical Team:	Banu Karimi-Shah, MD, Medical Officers (ODE II)
Project Manager:	Colette Jackson (ODE II)
Keywords:	NDA review, clinical studies
Last Modified:	6/24/2008

The sponsor submitted two phase-3 clinical studies: D5899C00001 (SUN) and D5899C00002 (SHINE) for the purpose of assessing the efficacy and safety of SYMBICORT for the maintain treatment of COPD. Overall, the study reports of these two studies include materials that are sufficient for the statistical evaluations of efficacy and safety.

However, the following issue deserves careful examination. For both Studies SUN and SHINE, the sponsor did not include all randomized patients in its serial pft data sets named PFTSR00 and PFTSR01 for establishing onset-of-effect (usually called onset-of-action). In the study protocols and study reports, the sponsor did indicate that the assessment of onset-of-effect was determined based on a subset of the patients. No justifications were easily located in the contents of the study reports. (b) (4)

Therefore, (b) (4) should this be the case, further **explain** how the subset was selected. **Inform** us whether the complete set of serial pft data have ever been obtained and are currently available. The sponsor is expected to submit the full data set for our evaluation.

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

/s/

Ted Guo
6/24/2008 01:20:05 PM
BIOMETRICS

Qian Li
8/4/2008 11:21:34 AM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21–929/S012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	21-929 SE1 012
Type:	Efficacy Supplement
Brand Name:	Symbicort® pMDI
Generic Name:	Budesonide/Formoterol
Drug Class:	Inhaled Corticosteroid/LABA combo
Indication:	Approved: long-term maintenance treatment of asthma in patients ≥12 years. Proposed additional indications: COPD with chronic bronchitis and emphysema
Dosage Form:	Inhalation Aerosol
Strength:	160/4.5 mcg per inhalation
Route of Administration:	Oral Inhalation
Dosing regimen:	2 inhalations bid (b) (4)
Applicant:	Astra Zeneca
OCP Division:	DCP2
Clinical Division:	DPAP (OND-570)
Submission Date:	April 28, 2008
Reviewer:	Partha Roy, Ph.D.
Team Leader (Acting):	Wei Qiu, Ph. D.

TABLE OF CONTENTS

1 Executive Summary

1.1 Background

Symbicort pMDI is a combination inhaled product containing budesonide and formoterol fumarate dihydrate (hereafter referred to as formoterol). Budesonide is a potent topical glucocorticosteroid and formoterol is a long-acting β2-agonist (LABA). Symbicort pMDI is administered by oral inhalation. Symbicort pMDI received approval from the FDA on 21 July 2006 for the long-term maintenance treatment of asthma in patients 12 years of age and older.

The objective of this sNDA is to provide data supporting an indication for the (b) (4) maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema. Two formulation strengths of Symbicort pMDI were evaluated in the COPD clinical development program: 80/4.5 mcg per actuation and160/4.5 mcg per actuation, each administered as 2 actuations per dose. These strengths correspond to doses of 160/9 mcg, and 320/9 mcg, respectively, each administered on a bid regimen. However, the sponsor is only seeking approval of the higher strength (160/4.5 mcg with daily dose of 640/18 mcg) in the COPD patient population.

The formulation of Symbicort pMDI used in the COPD clinical development program is identical to the commercially available product and also to that used in the asthma program. As a result of the extensive characterization of the PK of Symbicort pMDI in the asthma clinical program, the clinical pharmacology plan specific to the COPD indication was limited in scope.

The primary objective of the clinical pharmacology program in this supplement was to provide data on the PK profile of budesonide and formoterol delivered via Symbicort pMDI in subjects with COPD. This was achieved through extensive 12-hour post-dose plasma PK sampling in a subset of patients during the Phase 3 efficacy and safety study (D5899C00002 – SHINE). An assessment of PK of budesonide and formoterol was also obtained in a Phase I relative BA study (study D5899C00006). An additional goal was to evaluate the formulation effect, i.e. relative systemic bioavailability (BA) of budesonide and formoterol in patients with COPD when given as either Symbicort pMDI compared to coadministration of the monoproducts used as active comparators in the Phase III safety/efficacy studies. Study D5899C00006 also included a group of asthma patients who received a single dose of Symbicort pMDI in order to compare the bioavailability in COPD patients with asthma patients for which the product is already marketed.

In addition, HPA-axis assessment [24-hour urinary free cortisol (24h-UFC)] was conducted in a subgroup of patients in both the Phase 3 studies (D5899C00001 [SUN] and D5899C00002 [SHINE]) following administration of Symbicort pMDI.

1.2 Recommendation

The Office of Clinical Pharmacology /Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed NDA 21-929 SE1 012 submitted on April 28, 2008 and finds it acceptable provided that a mutually satisfactory agreement can be reached between the sponsor and the agency regarding the language in the package insert. The Clinical Pharmacology Optional Intra-Divisional Briefing was held on December 03, 2008 with the following attendees: Drs. Suresh Doddapenani (DCP 2 Deputy Director), Wei Qiu (Acting Team Leader, Pulmonary Team), Banu Karimi-Shah (Medical Reviewer), Lydia Gilbert-Mclean (DPAP Deputy Director and Medical Team Leader) and other OCP reviewers.

1.3 Comments to the Medical Team

- Budesonide exposure from Symbicort pMDI is comparable to that from budesonide pMDI alone and coadministration of monoproducts i.e. budesonide pMDI and formoterol via a dry powder inhaler (OXIS Turbuhaler, OXIS TBH, Form TBH).

- Formoterol exposure (AUC) from Symbicort160/4.5 mcg was consistently about 16-18% higher compared to individual products administered together, indicating a slight formulation effect.

- Budesonide appears to have a small effect (~12% increase in AUC) on formoterol exposure while on the other hand there was lack of any measurable effect on budesonide exposure in the presence of formoterol.

- Formoterol exposure (AUC) from Symbicort 160/4.5 mcg was about 30% higher compared to the formoterol monoproduct OXIS TBH 4.5 mg, which appears to be the consequence of summation of a small drug-drug interaction effect and a small formulation effect.

- Budesonide as well as formoterol systemic exposure (AUC) in COPD patients appear to be about 12-16% higher compared to asthma patients.

- Two actuations of Symbicort pMDI 160/4.5 mcg exhibited statistically significant (~30%) suppression of 24h-UFC levels following chronic twice daily inhalation administration in COPD patients relative to placebo.

1.4 Summary of Clinical Pharmacology Findings

Formulation Effect

Formulation effect was initially evaluated in an open-label, randomized, 2-way crossover study (D5899C00006) that determined the relative bioavailability (BA) of budesonide and formoterol when administered as Symbicort pMDI versus the monoproducts administered concurrently in subjects with COPD. Twenty-six (26) male and female

subjects with COPD (mean age 53 years) participated in the study. The two orally inhaled treatments were 1) Symbicort pMDI (80/4.5 μg x 12 actuations, total dose 960/54 μg), and 2) budesonide pMDI (80 μg x 12 actuations, total dose 960 μg) plus OXIS TBH (4.5 μg x 12 inhalations, total dose 54 μg).

Study D5899C00002 (SHINE) was the pivotal safety and efficacy study which included PK assessments during steady-state administration of Symbicort pMDI and the monoproducts. The doses tested in this study were the proposed clinical doses of 2 inhalations twice daily in a parallel group design.

Despite the differences in study designs, the results of the two studies were quite similar with respect to the relative bioavailability between Symbicort pMDI and the monoproducts. As shown in Table 1, in the single-dose study, systemic exposure of budesonide was found to be nearly identical between the treatment arms while the steady state comparison showed slightly higher exposure to budesonide (8-12%) from Symbicort® compared to two monoproducts administered together.

Table 1. Relative bioavailability comparisons of budesonide from Symbicort pMDI vs. individual components coadministered (BUD pMDI + Oxis TBH): Geometric Mean Plasma PK measures and ratios with 90% Confidence Intervals

PK Parameters	Symbicort®** *960/54 mcg – SD study* *320/9 mcg – SS study*	Budesonide + Formoterol *960+54 mcg – SD study* *320+9 mcg – SS study*	Symbicort® vs. Budesonide +Formoterol [Ratio (90% CI)]
Study D5899C00006 (Single-Dose) N = 26 COPD patients			
AUC_{inf} (nmol.hr/L)	14.08	14.49	0.97 (0.91-1.04)
C_{max} (nmol/L)	3.30	3.18	1.04 (0.94-1.15)
T_{max}* (hr)	0.5 (15-240)	0.5 (15-242)	
Study SHINE (Steady-State) N = 238 COPD patients in PK sub-set			
AUC_{0-12h} (nmol.hr/L)	7.24	6.72	1.08 (0.85-1.36)
C_{max} (nmol/L)	1.71	1.48	1.12 (0.90-1.49)
T_{max}* (hr)	0.67 (0.15-4.0)	0.67(0.117-12.117)	

*Median (range); **For SHINE study, n = 53 (Symbicort pMDI arm) n = 56 (Budesonide+Formoterol arm)

For formoterol, Table 2 shows higher exposure (18-22%) from Symbicort compared to two monoproducts coadministered. This has been confirmed from the comparative PK data from the SHINE study where about 12-16% higher exposure of formoterol was observed with Symbicort® compared to two drugs given together.

Table 2. Relative bioavailability comparisons of formoterol from SYMBICORT pMDI vs. individual components coadministered (BUD pMDI + Oxis TBH): Geometric Mean Plasma PK measures and ratios with 90% Confidence Intervals

PK Parameters	Symbicort®** *960/54 mcg – SD study* *320/9 mcg – SS study*	Budesonide + Formoterol *960+54 mcg – SD study* *320+9 mcg – SS study*	Symbicort® vs. Budesonide +Formoterol [Ratio (90% CI)]
Study D5899C00006 (Single-Dose) N = 26 COPD patients			
AUC_{inf} (pmol.hr/L)	945	801	1.18 (1.08-1.28)
C_{max} (pmol/L)	167	137	1.22 (1.03-1.44)
T_{max}* (hr)	0.25 (0.25-2)	0.25 (0.25-2)	
Study SHINE (Steady-State) N = 238 COPD patients			
AUC_{0-12h} (pmol.hr/L)	172.50	148.37	1.16 (0.95-1.42)
C_{max} (pmol/L)	30.99	27.63	1.12 (0.92-1.36)
T_{max}* (hr)	1.0 (0.17-12.0)	0.183 (0.12-6.1)	

*Median (range); ** For SHINE study, n = 53 (Symbicort® arm) n = 54 (Budesonide+Formoterol arm)

These results indicate a lack of any appreciable formulation effect for budesonide while demonstrating a small formulation effect for formoterol when delivered through the pMDI device.

Drug-Drug Interaction

Evaluation of drug-drug interaction came from the pharmacokinetic data from SHINE study. Systemic exposure of budesonide and formoterol from two individual drugs administered together compared to single ingredient administered alone, reflect the impact of drug-drug interaction on the systemic exposure of these drugs when combined together. As shown in SHINE study (Table 3), budesonide did have a small effect on formoterol exposure while there was lack of any measurable effect on budesonide exposure in the presence of formoterol. Formoterol AUC was shown to be 12% greater in combination (budesonide 160 mcg and formoterol 4.5 mcg) compared to formoterol 4.5 mcg alone while formoterol C_{max} remained unchanged between the two treatment arms. For Budesonide, both C_{max} and AUC remained nearly identical between the combination and budesonide alone.

Table 3. Relative bioavailability comparisons (multiple-dose) of budesonide and formoterol from individual components coadministerd vs. monoproduct (budesonide or formoterol): Geometric Mean Plasma PK measures and ratios with 90% Confidence Intervals

Budesonide			
PK Parameters	Budesonide 160 + Formoterol 4.5 (n = 56)	Budesonide 160 (n = 37)	(Budesonide 160 + Formoterol 4.5) vs. Budesonide 160 [Ratio (90% CI)]
$AUC_{0\text{-}12h}$ (nmol.hr/L)	6.72	6.49	1.03 (0.8-1.34)
C_{max} (nmol/L)	1.48	1.54	0.96 (0.73-1.27)
T_{max}* (hr)	0.67 (0.12-12.12)	0.67 (0.13-5.85)	
Formoterol			
PK Parameters	Budesonide 160 + Formoterol 4.5 (n = 54)	Formoterol 4.5 (n = 45)	(Budesonide 160 + Formoterol 4.5) vs. Formoterol 4.5 [Ratio (90% CI)]
$AUC_{0\text{-}12h}$ (pmol.hr/L)	148.4	132.6	1.12 (0.90-1.38)
C_{max} (pmol/L)	27.63	27.45	1.0 (0.82-1.23)
T_{max}* (hr)	0.18 (0.12-6.07)	0.3 (0.13-4.07)	

*Median (range);

Comparisons of systemic exposure of budesonide and formoterol from Symbicort with individual monoproducts administered alone reflect the sum of formulation and drug-drug interaction effects. As shown in Table 4, about 11-12% higher systemic exposure for budesonide (AUC as well as C_{max}) was observed with Symbicort compared to budesonide alone administration. This is similar to 8-12% formulation effect seen with budesonide (Table 1), confirming a lack of drug-drug interaction effect beyond a small formulation effect.

For formoterol, about 30% and 13% higher $AUC_{0\text{-}12h}$ and C_{max}, respectively, was observed with Symbicort compared to formoterol alone administration. As indicated in Tables 2 and 4, it appears that the increase in formoterol exposure (AUC) in the presence of budesonide is slightly greater than that can be accounted for by the formulation effect (30% vs. 16%), indicating a small drug-drug interaction effect based on AUC. On the other hand, 13% formoterol C_{max} increase (Table 3) from Symbicort is in line with about 12% increase seen due to the formulation effect (Table 2), suggesting no drug-drug interaction with respect to C_{max}.

Table 4. Relative bioavailability comparisons of budesonide and formoterol from SYMBICORT pMDI vs. monoproduct (budesonide or formoterol): Geometric Mean Plasma PK measures and ratios with 90% Confidence Intervals

Budesonide			
PK Parameters	Symbicort® 160/4.5 (n = 53)	Budesonide 160 (n = 37)	Symbicort® 160/4.5 vs. Budesonide 160 [Ratio (90% CI)]
$AUC_{0\text{-}12h}$ (nmol.hr/L)	7.24	6.49	1.12 (0.86-1.45)
C_{max} (nmol/L)	1.71	1.54	1.11 (0.84-1.47)
T_{max}* (hr)	0.67 (0.15-4.0)	0.67 (0.13-5.85)	
Formoterol			
PK Parameters	Symbicort® 160/4.5 (n = 53)	Formoterol 4.5 (n = 45)	Symbicort® 160/4.5 vs. Formoterol 4.5 [Ratio (90% CI)]
$AUC_{0\text{-}12h}$ (pmol.hr/L)	172.50	132.6	1.30 (1.05-1.61)
C_{max} (pmol/L)	30.99	27.45	1.13 (0.92-1.38)
T_{max}* (hr)	1.0 (0.17-12.0)	0.3 (0.13-4.07)	

*Median (range);

Systemic exposure in COPD vs Asthma patients

Results from the statistical analyses of pharmacokinetic parameters for budesonide in COPD vs. asthma patients are summarized in Table 5. Mean $AUC_{0\text{-}\infty}$ and $AUC_{0\text{-}t}$ were 12% higher whereas mean C_{max} was 10% lower in COPD patients compared with asthma patients. Mean $T_{1/2}$, median T_{max} and mean MRT were all longer in COPD patients than in asthma patients.

Table 5. Pharmacokinetic parameters for budesonide in COPD vs. Asthma patients

parameter	COPD patients Symbicort 960/54 µg		Asthma patients Symbicort 960/54 µg		COPD patients vs. Asthma patients[2]	
	mean	90% conf.lim.	mean	90% conf.lim.	mean	90% conf.lim.
$AUC_{0\text{-}\infty}$ (nmol/L·h)	14.08	12.65 - 15.66	12.52	11.26 - 13.93	1.12	0.97 - 1.31
$AUC_{0\text{-}t}$ (nmol/L·h)	13.90	12.48 - 15.49	12.39	11.12 - 13.80	1.12	0.96 - 1.31
MRT (h)	5.67	5.30 - 6.05	4.71	4.33 - 5.09	0.96	0.43 - 1.49
$t_{1/2}$ (h)	5.27	4.88 - 5.69	4.57	4.23 - 4.93	1.15	1.04 - 1.29
t_{max} (min)[1]	30	15 - 240	15	15 - 45		
C_{max} (nmol/L)	3.30	2.89 - 3.78	3.66	3.20 - 4.19	0.90	0.75 - 1.09

1. Median and range.
2. Ratios for AUC $_{0\text{-}\infty}$, $AUC_{0\text{-}t}$, C_{max} and $t_{1/2}$, difference for MRT

Results from the statistical analyses of pharmacokinetic parameters for formoterol in COPD vs. asthma patients are summarized in Table 6. Following Symbicort administration, mean C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ were all higher (12-16%) in COPD patients compared to asthma patients. Mean $T_{1/2}$ and MRT estimates for formoterol were

longer in COPD patients than in asthma patients while T_{max} remained unchanged between the two patient populations.

Table 6. Pharmacokinetic parameters for formoterol in COPD vs. Asthma patients

parameter	COPD patients Symbicort 960/54 µg		Asthma patients Symbicort 960/54 µg		COPD patients vs. Asthma patients [2]	
	mean	90% conf.lim.	mean	90% conf.lim.	mean	90% conf.lim.
$AUC_{0-\infty}$ (pmol/L·h)	945	834 - 1070	819	723 - 928	1.15	0.97 - 1.38
AUC_{0-t} (pmol/L·h)	846	742 - 965	729	639 - 831	1.16	0.96 - 1.40
MRT (h)	11.60	10.38 - 12.81	10.33	9.11 - 11.55	1.27	-0.45 - 2.99
$t_{1/2}$ (h)	9.23	8.17 - 10.42	8.72	7.72 - 9.84	1.06	0.89 - 1.26
t_{max} (min)[1]	15	15 - 120	15	15 - 120		
C_{max} (pmol/L)	167	142 - 196	149	127 - 175	1.12	0.89 - 1.41

1. Median and range.
2. Ratios for AUC $_{0-\infty}$, AUC_{0-t}, C_{max} and $t_{1/2}$, difference for MRT

HPA axis assessment

HPA-axis function in COPD patients was assessed by measuring 24-hour urinary free cortisol (24h-UFC) in a subgroup of subjects in both SUN (179 subjects) and SHINE (437 subjects) studies. In both studies, 24-hour urine specimens were collected at baseline (prior to randomization), at Month 6 (SUN and SHINE), and at Month 12 (SUN). Urine samples were analyzed for urinary free cortisol and creatinine. Creatinine levels were measured to adjust for variations in urine volume by expressing results as the 24-hour urinary cortisol/creatinine ratio.

Urinary free cortisol and cortisol:creatinine ratio were analyzed using a multiplicative ANCOVA. The multiplicative ANCOVA model involved the natural logarithm of the values on treatment, adjusting for the factors of the natural logarithm of the baseline value, country, and treatment group.

Following high-level conclusions can be drawn from the combined 24h-UFC data collected from the two Phase 3 studies (SUN and SHINE):

1. Both higher and lower strengths of Symbicort pMDI exhibited measurable suppression of 24h-UFC levels following chronic twice daily inhalation administration in COPD patients relative to placebo. While the cortisol suppression of 30% from Symbicort pMDI 160/4.5 mcg was statistically significant (p=0.001), 17% suppression from Symbicort pMDI 80/4.5 mcg did not achieve statistical significance (p=0.102). This suggests a dose-dependent response in the budesonide dose range of 160 to 320 mcg following twice daily administration.
2. Symbicort pMDI 160/4.5 exhibited comparable cortisol suppression to Budesonide 160 mcg alone treatment or free combination of budesonide 160 mcg and formoterol 4.5 mcg.

3. Visual inspection of the cortisol suppression data from Symbicort pMDI plotted against budesonide steady-state systemic exposure data (C_{max} and AUC_{0-12h}) revealed completely random distribution and therefore failed to reveal any apparent trend towards an exposure-response relationship. Therefore, exploration of PK/PD relationship was not pursued further.

2 QUESTION BASED REVIEW

2.1 General Attributes/Background

2.1.1 What are the highlights of the formulation and the Product/Device?

Symbicort 80/4.5 mcg and Symbicort 160/4.5 mcg each contain micronized budesonide and micronized formoterol fumarate dehydrate in a pressurized metered dose inhaler (pMDI) containing either 60 or 120 actuations for oral inhalation only. Budesonide is a potent topical glucocorticosteroid and formoterol is a long-acting β2-agonist (LABA) with a rapid onset of action.

Symbicort pMDI also contains the non-ozone-depleting hydrofluoroalkane (HFA) propellant, HFA-227, the suspending agent polyvinylpyrrolidone (PVP) K25, and the lubricant polyethylene glycol (PEG) 1000. Symbicort pMDI received approval from the FDA on 21 July 2006 for the long-term maintenance treatment of asthma in patients 12 years of age and older. Two formulation strengths of Symbicort pMDI were evaluated in the COPD clinical development program: 80/4.5 mcg per actuation and 160/4.5 mcg per actuation, each administered as 2 actuations per dose. These strengths correspond to doses of 160/9 mcg, and 320/9 mcg, respectively, each administered on a twice daily regimen.

Budesonide is approved in the US for the treatment of asthma, allergic rhinitis, and Crohn's disease. Formoterol is available in the US as Foradil® Aerolizer® (Novartis) for the maintenance treatment of asthma and COPD. Formoterol is also available outside the US in the form of OXIS® TURBUHALER® (TBH), which has been on the market since 1996 and is approved in 79 countries as of 17 June 2007. The OXIS TBH was used as an active formoterol comparator in the pivotal safety and efficacy studies (SUN and SHINE) in the COPD development program. The formulation of Symbicort pMDI used in the COPD clinical development program is identical to the commercially available product and also to that used in the asthma program.

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

Symbicort pMDI contains budesonide and formoterol fumarate dehydrate in a pressurized metered dose inhaler (pMDI). Budesonide is a potent topical glucocorticosteroid and formoterol is a long-acting β_2-agonist (LABA) with a rapid onset of action.

Current treatment options for COPD patients primarily include bronchodilators (short-acting and long-acting β_2-agonists, anticholinergics and xanthines) and inhaled corticosteroids (ICS), many of which are taken in combination such as ADVAIR DISKUS, a combination of an ICS (fluticasone propionate) and a long-acting β_2-agonist (salmeterol) in a dry powder inhaler. Literature data suggest that LABAs improve lung function, reduce symptoms such as dyspnea, decrease the need for rescue medication, and improve exercise tolerance and health-related quality of life (HRQL) in patients with COPD. Treatment with an ICS such as budesonide or fluticasone has shown benefit to patients with COPD through improvements in symptoms and HRQL, and decreased frequency of exacerbation. Therefore, treatment of severe COPD with the combination of a LABA and an ICS is now a well-established and accepted part of current clinical practice.

In the current submission, the applicant is seeking the following indication for Symbicort pMDI: (b) (4) maintenance treatment of airflow obstruction in patients with COPD including chronic bronchitis and emphysema. This is in addition to the asthma indication for which it was already approved in 2006.

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

The proposed route of administration is by oral inhalation.

For COPD patients, the proposed dose is Symbicort 160/4.5, two inhalations twice daily for a total daily dose of Budesonide/Formoterol 640/18 mcg.

For asthma patients, Symbicort pMDI is already approved with the following dosage recommendations.

ASTHMA PATIENTS 12 YEARS AND OLDER

Previous ICS Dose	*Recommended Starting Dose*
Medium to high	160/4.5 mcg, 2 inhalations bid
Low to medium	80/4.5 mcg, 2 inhalations bid
None	Depending on asthma severity: 160/4.5 mcg or 80/4.5 mcg, 2 inhalations bid

2.2 General Clinical Pharmacology

2.2.1 What clinical studies were submitted in this NDA?

The Symbicort pMDI COPD clinical program consisted of 2 Phase 1 relative bioavailability (BA) studies (SD-039-0738 and D5899C00006), 1 Phase 2 pharmacodynamic (PD) study (D5899C00748), and 2 Phase 3 confirmatory efficacy and safety studies (D5899C00002 [SUN] and D5899C00002 [SHINE]). In addition, study SHINE involved an extensive 12-hour PK blood sampling in a sub-set of COPD patients. The data from the Phase 1 study SD-039-0738 were considered unreliable due to some

technical issues and hence will not be included in any further discussion in this review. Study D5899C00006 is considered the definitive relative BA study. Study D5899C00748 was designed to evaluate onset of bronchodilation in COPD patients within the first 180 minutes. Refer to medical officer's review for a review of this study.

The Phase 1 program was designed with the primary goal to evaluate the relative BA of budesonide and formoterol in COPD patients when given as either Symbicort MDI or as a combination of the monoproducts used as active comparators in the Phase 3 safety/efficacy studies, i.e., budesonide pMDI and OXIS TBH. Formulation effect in COPD patients, if any, can be evaluated by this comparison. A secondary goal was to compare the bioavailability of budesonide and formoterol from Symbicort pMDI in patients with COPD versus patients with asthma.

The PK analysis in SHINE study was designed to assess the systemic exposure to budesonide and formoterol following administration of Symbicort pMDI 80/4.5 μg, Symbicort pMDI 160/4.5 μg, budesonide HFA pMDI 160 μg and OXIS TBH 4.5 μg (when taken together and separately), each administered as 2 inhalations bid, by measuring plasma concentrations over 12 hours at steady state. This allows for the evaluation of drug-drug interaction as well as formulation effect at steady state for both the active drugs.

Bioequivalence studies were not considered necessary within this development program since there have been no changes to the formulation used in the COPD program from the approved product.

2.2.2 What are the PK characteristics of budesonide and formoterol when delivered via Symbicort pMDI?

The single-dose mean plasma concentration-time profiles of budesonide (960 mcg) and formoterol (54 mcg) are shown in Figures 1 and 2, respectively. Mean plasma concentrations of budesonide were found to be similar after administration of Symbicort and budesonide plus formoterol in COPD patients. Mean plasma concentrations of formoterol were found to be slightly higher after Symbicort compared to budesonide plus formoterol in COPD patients. The plasma half-life of budesonide was calculated to be 5.3 hours following single-dose inhalation administration of Symbicort 960/54 mcg (12 inhalations of 80/4.5 mcg). The plasma half-life of formoterol was calculated to be 9.2 hours following single-dose inhalation administration of Symbicort 960/54 mcg (12 inhalations of 80/4.5 mcg).

Figure 1. Mean plasma concentration-time profile of budesonide after single dose (960 mcg) inhalation administration

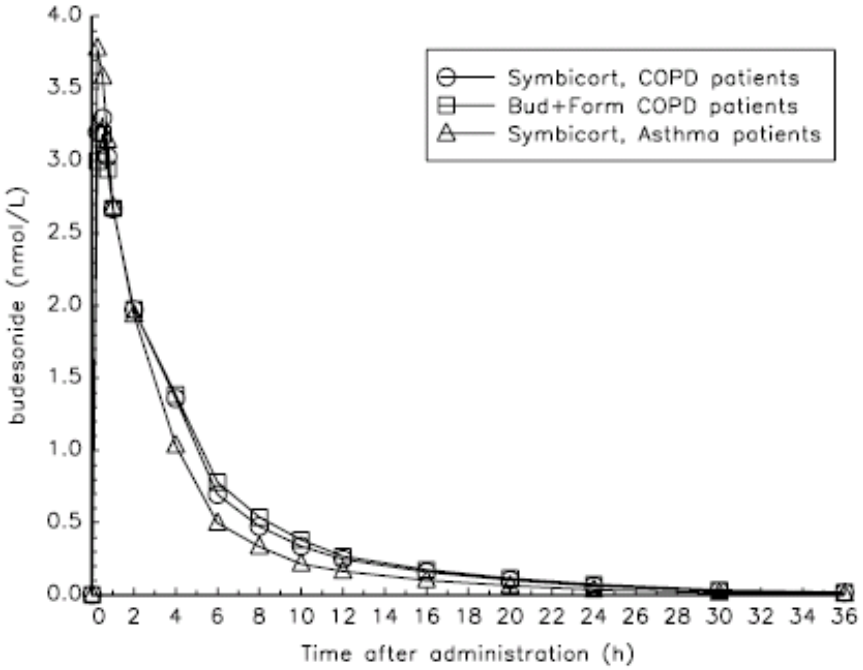
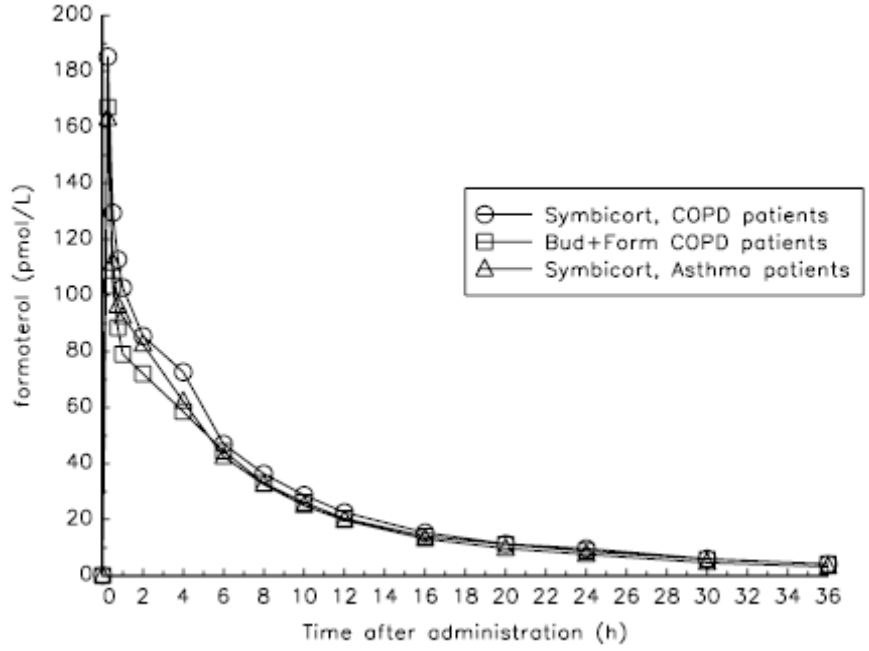


Figure 2. Mean plasma concentration-time profile of formoterol after single dose (54 mcg) inhalation administration



The steady-state mean plasma concentration-time profiles of budesonide (320 mcg bid) and formoterol (9 mcg bid) are shown in Figures 3 and 4, respectively. While budesonide profiles from Symbicort 160/4.5 mcg, Budesonide plus formoterol 160/4.5 mcg and Budesonide 160 mcg alone appear generally similar, the profile from Symbicort 80/4.5

mcg containing half the dose indicates a lower budesonide systemic exposure, as expected (Figure 3). Following administration of the same dose of formoterol from Symbicort 160/4.5 mcg and 80/4.5 mcg, formoterol plasma concentration-time profiles indicate similar systemic exposure. However, the same dose of formoterol from formoterol 4.5 mcg alone and budesonide 160 mcg plus formoterol 4.5 mcg resulted in slightly lower exposure compared to Symbicort treatments as indicated by the formoterol profiles (Figure 4).

Figure 3. Mean plasma concentration-time profile of budesonide after multiple dose (320 mcg twice daily) inhalation administration

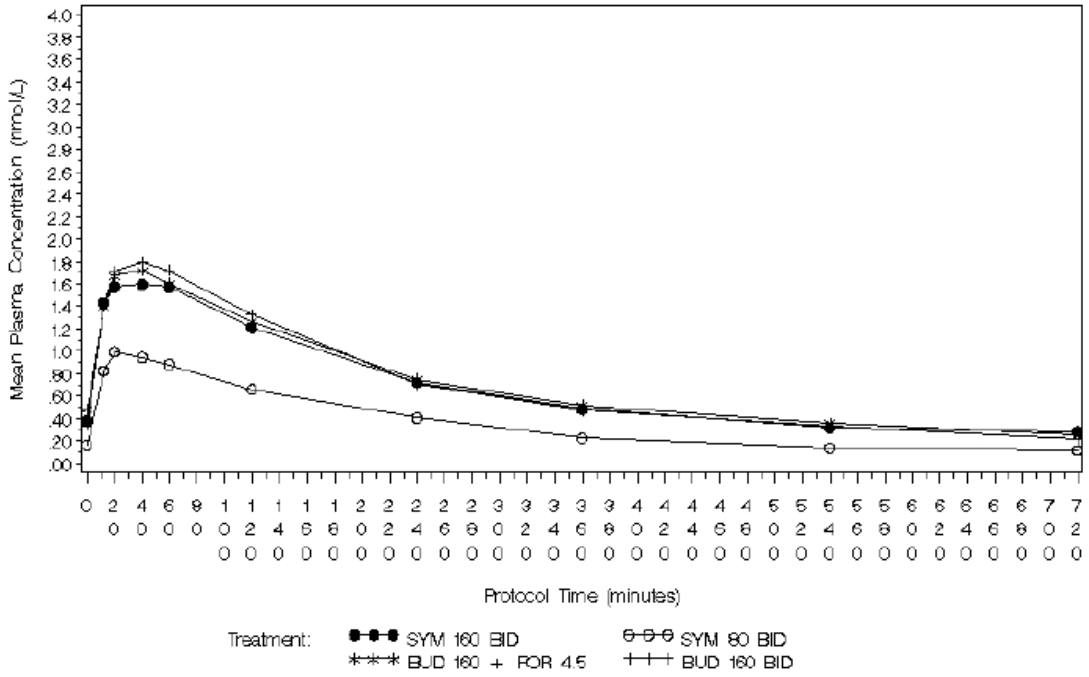
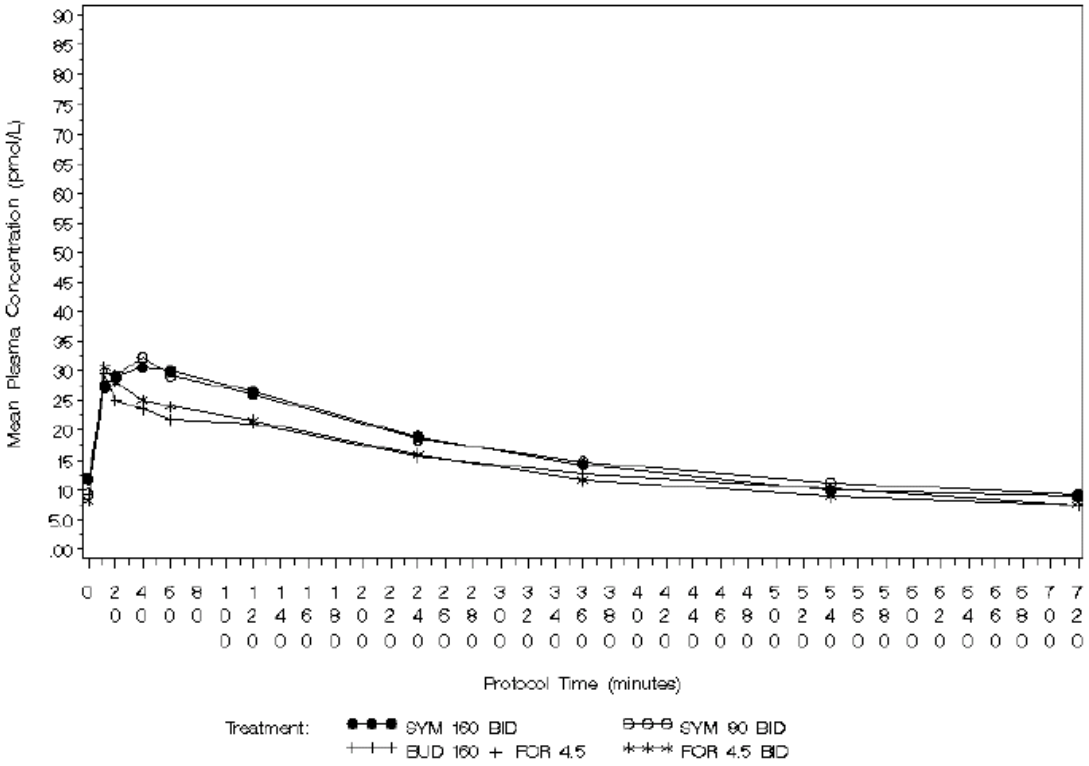


Figure 4. Mean plasma concentration-time profile of formoterol after multiple dose (9 mcg twice daily) inhalation administration



Budesonide systemic exposure increased dose proportionally following multiple-dose administration of 160 mcg to 320 mcg twice daily as evident from dose-corrected $AUC_{0\text{-}12h}$ and C_{max} values listed in Table 7. For budesonide, T_{max} occurred at 20 to 40 minutes post-dose after both single and multiple dose administration. For formoterol, T_{max} occurred at 15 minutes following single dose administration but was between 40 and 60 minutes at steady-state in the SHINE study. This delayed T_{max} under steady-state is a significant deviation from the historical data included in the asthma label. Although PK sampling between the two studies was not identical, sampling was carried out for earlier timepoints of 10 and 20 minutes post-dose in the SHINE study, therefore this observation could not be blamed on the frequency of PK blood sampling immediately after dosing in the SHINE study.

As has been known from the approved Symbicort pMDI label for asthma and also consistent with the half-life values of the two drugs, budesonide and formoterol are expected to accumulate following multiple-dose twice daily administration. Based on half-life estimates from the single-dose study, formoterol was expected to accumulate more than budesonide. As shown in Tables 7 and 8, cross-study comparison of dose corrected $AUC_{0\text{-}12h}$ and C_{max} values for budesonide showed an accumulation of approximately 1.55, generally consistent with its half-life estimate of 5.3 hours, while for formoterol, the data indicated a lack of any appreciable accumulation contrary to the half-life estimate of 9.2 hours. Caution should be exercised in interpreting this data

particularly due to lack of dose-proportionality information at supra-therapeutic dose of budesonide/formoterol 960/54 mcg.

Table 7. Single and multiple-dose Budesonide PK parameters for Symbicort pMDI in COPD patients

Duration	Study	Dose	Geometric mean AUC_{0-12h} (nmol.h/L)	Dose-corrected AUC_{0-12h}	Geometric mean C_{max} (nmol/L)	Dose-corrected C_{max}	Median T_{max}
Single-Dose	D5899C00006	960	13.9	14.5	3.3	3.4	30
Multiple-Dose	SHINE	160	3.4	21.3	0.9	5.6	20
		320	7.2	22.5	1.7	5.3	40

Table 8. Single and multiple-dose Formoterol PK parameters for Symbicort pMDI in COPD patients

Duration	Study	Dose	Geometric mean AUC_{0-12h} (pmol.h/L)	Dose-corrected AUC_{0-12h}	Geometric mean C_{max} (pmol/L)	Dose-corrected C_{max}	Median T_{max}
Single-Dose	D5899C00006	54	846	15.7	167	3.1	15
Multiple-Dose	SHINE	9[a]	153	17.0	30	3.3	40
		9[b]	173	19.2	31	3.4	60

[a]Symbicort pMDI 2 x 80/4.5 mcg
[b]Symbicort pMDI 2 x 160/4.5 mcg

2.2.3 What efficacy and safety information contribute to the assessment of clinical pharmacology study data?

The primary efficacy variable in the pivotal efficacy studies was the change from baseline in average pre-dose and 1-hour post-dose FEV_1 (forced expiratory volume in one second) over the treatment period. Since systemic absorption of inhaled drugs is the result of pulmonary and gastrointestinal absorption, and because there is uncertainty about the site of absorption along the respiratory tract/airways, plasma concentrations cannot be correlated to efficacy (FEV1).

One of the major systemic side effects of therapeutic corticosteroids is the suppression of endogenous cortisol production. In the case of topical corticosteroid therapy such as in the lungs, the goal has always been to minimize the systemic contribution by the absorbed corticosteroids in favor of primarily local effects. In this case, the suppression of endogenous cortisol release (HPA-axis function) assessed by cortisol concentration measurements (plasma and/or urine) is a suitable marker to quantify the degree of systemic steroid burden of a drug in the target patient population.

2.2.4 What are the results of the assessment of HPA-axis function following administration of Symbicort pMDI in COPD patients?

HPA-axis function in COPD patients was assessed by measuring 24-hour urinary free cortisol (24h-UFC) in a subgroup of subjects in both SUN (179 subjects) and SHINE (437 subjects). In both studies, 24-hour urine specimens were collected at baseline (prior to randomization), at Month 6 (SUN and SHINE), and at Month 12 (SUN). Urine samples were analyzed for urinary free cortisol and creatinine. Creatinine levels were measured to adjust for variations in urine volume by expressing results as the 24-hour urinary cortisol/creatinine ratio.

Urinary free cortisol and cortisol:creatinine ratio were analyzed using a multiplicative ANCOVA. The multiplicative ANCOVA model involved the natural logarithm of the values on treatment, adjusting for the factors of the natural logarithm of the baseline value, country, and treatment group. LS means and LS mean treatment differences (with their associated 95% confidence intervals), and p-value were reported. The LS means and 95% CI bounds were exponentiated to transform the LS treatment means to LS geometric means and the LS mean treatment difference and confidence intervals for the difference to treatment ratios. All analyses of 24-hr urine free cortisol and cortisol:creatinine ratio were repeated in two separate sensitivity analyses after excluding data for factors that may have affected the urinary cortisol analysis including urine sample collection deviation (Sensitivity Analysis I) and prior corticosteroid use or stopping intranasal steroid use (Sensitivity Analysis II).

SUN study

This was a randomized, double-blind, double-dummy, parallel-group, multi-center study in patients with COPD, consisting of 12 months (52 weeks) of treatment with Symbicort pMDI 2x 160/4.5 µg bid, Symbicort pMDI 2x 80/4.5 µg bid, formoterol TBH 2x 4.5 µg bid, or placebo bid. Table 9 depicts the results of the 24-hour urinary free cortisol as well as urinary cortisol:creatinine ratio at 6 months and end of treatment for all the treatment groups.

Table 9 presents the treatment comparisons at 6 months and end of treatment (~12 months) period for corresponding estimates of mean treatment ratios from the multiplicative ANCOVA for 24-hour urinary cortisol.

Table 9. Treatment means for 24-hr urinary free cortisol (nmol/24 hr) as well as urinary cortisol/creatinine ratios (nmol/mmol) at 6 months and at end of treatment.

Trt group (mcg)/ Timepoint[a]	N	Baseline GeoMean Cortisol	Baseline GeoMean Cortisol: Creatinine	Results at timepoint			
				GeoMean Cortisol	GeoMean Cortisol: Creatinine	Geo LS Mean[b] Cortisol	Geo LS Mean[b] Cortisol: Creatinine
SYM 160/4.5							
6 months	48	48.68	5.13	33.54	3.59	35.13	3.61
End of Trt	48	48.68	5.13	34.32	4.11	36.66	4.14
SYM 80/4.5							
6 months	44	43.74	4.53	41.62	4.73	45.65	4.98
End of Trt	47	43.73	4.43	40.84	4.40	44.91	4.67
FORM 4.5							
6 months	38	47.72	4.81	50.55	5.37	51.62	5.42
End of Trt	38	47.72	4.81	53.20	5.66	55.15	5.71
Placebo							
6 months	45	36.58	3.70	45.75	4.92	53.45	5.55
End of Trt	45	36.58	3.70	46.11	5.36	52.60	6.00

[a] Only subjects with both a baseline and an end-of-treatment value are included. Baseline=Last observed value before first dose of randomized treatment; End of treatment=Last observed value during the treatment period (LOCF).
b Geometric LS mean is derived from the exponentiated LS mean from ANCOVA on log-transformed values.

Table 10. Treatment comparisons for 24-hr urinary free cortisol (nmol/24h) at 6 months and at end of treatment.

ANCOVA of log-transformed values			
Treatment comparisons (mcg)a	**LS Mean ratio[a]**	**95% CI**	**p-value**
6 months			
SYM 160/4.5 vs. Plac	0.66	0.44 – 0.97	0.035
SYM 160/4.5 vs. FORM 4.5	0.68	0.45 – 1.02	0.063
SYM 80/4.5 vs. Plac	0.85	0.57 – 1.27	0.434
SYM 80/4.5 vs. FORM 4.5	0.88	0.58 – 1.14	0.559
SYM 160/4.5 vs. SYM 80/4.5	0.77	0.64 – 1.46	0.186
End of treatment			
SYM 160/4.5 vs. Plac	0.70	0.48 – 1.02	0.064
SYM 160/4.5 vs. FORM 4.5	0.66	0.45 – 0.99	0.044
SYM 80/4.5 vs. Plac	0.85	0.58 – 1.25	0.416
SYM 80/4.5 vs. FORM 4.5	0.81	0.55 – 1.21	0.311
SYM 160/4.5 vs. SYM 80/4.5	0.82	0.56 – 1.19	0.287

[a] LS mean treatment ratio is derived by exponentiating the LS mean treatment difference from ANCOVA (analysis of covariance) on log transformed values.

The results from this study can be summarized as follows:

1. The baseline geometric mean values in the placebo group were lower compared to the other treatment groups for both urinary cortisol as well as cortisol:creatinine ratio. The geometric LS mean values at 6 months and the end of treatment were

lower in both Symbicort pMDI groups compared to formoterol 4.5 and placebo (Table 9). A dose-dependent numerical decrease in cortisol value was observed with budesonide doses of 80 and 160 mcg from Symbicort pMDI (Tables 9 and 10).

2. Statistically significant differences were seen between the Symbicort pMDI 160/4.5 and placebo groups at 6 months and between Symbicort pMDI 160/4.5 and formoterol 4.5 groups at end of treatment. No other group comparisons were statistically significant (Table 10).
3. Findings for cortisol/creatinine ratio comparisons between treatment groups were generally consistent with the findings for 24-hour urinary cortisol.

For 24-hour urinary cortisol, the number of subjects with shifts from normal to low (using criteria used by (b) (4) of <5.5 nmol/24 hr) was generally low across treatment groups. At end of treatment among patients normal at baseline, 1 out of 43 patients in the Symbicort 80/4.5 mcg group, 2 out of 28 patients in the formoterol 4.5 mcg group, and 1 out of 40 patients in the placebo group shifted from normal to low. None out of 41 patients in the Symbicort 160/4.5 mcg group shifted from normal to low.

SHINE study

This was a randomized, double-dummy, parallel-group, multi-center study in patients with COPD, consisting of 6 months (26 weeks) of treatment with Symbicort pMDI 160/ 4.5, Symbicort pMDI 80/4.5, budesonide 160, formoterol 4.5, budesonide pMDI 160 mcg and formoterol TBH 4.5 mcg administered together, or placebo.

Table 11 depicts the results of the 24-hour urinary free cortisol as well as urinary cortisol:creatinine ratio at 6 months and end of treatment for all the treatment groups. Table 12 presents the treatment comparisons at 6 months and end of treatment period for corresponding estimates of mean treatment ratios from the multiplicative ANCOVA for 24-hour urinary cortisol.

Table 11. Treatment means for 24-hr urinary free cortisol (nmol/24 hr) as well as urinary cortisol/creatinine ratios (nmol/mmol) at 6 months and at end of treatment.

Trt group (mcg)/ Timepoint[a]	N	Baseline GeoMean Cortisol	Baseline GeoMean Cortisol: Creatinine	Results at timepoint			
				GeoMean Cortisol	GeoMean Cortisol: Creatinine	Geo LS Mean[b] Cortisol	Geo LS Mean[b] Cortisol: Creatinine
SYM 160/4.5							
6 months	75	54.21	5.17	37.29	3.78	44.94	4.33
End of Trt	78	52.61	5.06	37.71	3.79	46.35	4.40
SYM 80/4.5							
6 months	71	63.26	6.10	48.36	4.63	53.83	4.90
End of Trt	73	61.43	5.93	46.58	4.48	52.76	4.73
BUD 160 + FORM 4.5							
6 months	75	51.34	5.08	33.32	3.67	40.84	4.22
End of Trt	75	51.34	5.08	33.32	3.67	40.69	4.21
BUD 160							
6 months	63	55.38	5.29	35.53	3.79	40.45	4.17
End of Trt	63	55.38	5.29	35.53	3.79	40.34	4.15
FORM 4.5							
6 months	76	54.18	5.37	70.75	6.58	83.82	7.28
End of Trt	78	55.12	5.43	71.19	6.63	83.67	7.29
Placebo							
6 months	68	59.32	5.72	55.69	5.33	63.24	5.69
End of Trt	69	60.10	5.93	55.81	5.35	62.90	5.64

[a] Only subjects with both a baseline and an end-of-treatment value are included. Baseline=Last observed value before first dose of randomized treatment; End of treatment=Last observed value during the treatment period (LOCF).

b Geometric LS mean is derived from the exponentiated LS mean from ANCOVA on log-transformed values.

Table 12. Treatment comparisons for 24-hr urinary free cortisol (nmol/24h) at 6 months and at end of treatment.

ANCOVA of log-transformed values			
Treatment comparisons (mcg)a	**LS Mean ratio[a]**	**95% CI**	**p-value**
6 months			
SYM 160/4.5 vs. Plac	0.71	0.54 – 0.93	0.012
SYM 160/4.5 vs. BUD 160	1.11	0.85 – 1.46	0.448
SYM 160/4.5 vs. FORM 4.5	0.54	0.41 – 0.69	<0.001
SYM 160/4.5 vs. BUD 160 + FORM 4.5	1.10	0.85 – 1.43	0.470
SYM 80/4.5 vs. Plac	0.85	0.65 – 1.11	0.241
SYM 80/4.5 vs. BUD 160	1.33	1.01 – 1.75	0.043
SYM 80/4.5 vs. FORM 4.5	0.64	0.49 – 0.84	0.001
SYM 160/4.5 vs. SYM 80/4.5	0.83	0.64 – 1.09	0.179
BUD 160 vs. Plac	0.64	0.48 – 0.84	0.002
End of treatment			
SYM 160/4.5 vs. Plac	0.74	0.57 – 0.96	0.023
SYM 160/4.5 vs. BUD 160	1.15	0.88 – 1.50	0.312
SYM 160/4.5 vs. FORM 4.5	0.55	0.43 – 0.71	<0.001
SYM 160/4.5 vs. BUD 160 + FORM 4.5	1.14	0.88 – 1.47	0.320
SYM 80/4.5 vs. Plac	0.84	0.64 – 1.09	0.195
SYM 80/4.5 vs. BUD 160	1.31	0.99 – 1.72	0.055
SYM 80/4.5 vs. FORM 4.5	0.63	0.49 – 0.82	<0.001
SYM 160/4.5 vs. SYM 80/4.5	0.88	0.68 – 1.14	0.326
BUD 160 vs. Plac	0.64	0.49 – 0.85	0.002

[a] LS mean treatment ratio is derived by exponentiating the LS mean treatment difference from ANCOVA (analysis of covariance) on log transformed values.

The results from this study can be summarized as follows:

1. The baseline geometric mean values in the Symbicort pMDI 80/4.5 and placebo groups were marginally higher compared to the other treatment groups for both urinary cortisol as well as cortisol:creatinine ratio.
2. Geometric LS mean values for the formoterol 4.5 and placebo groups were the only groups in which the 24-hour urinary cortisol values increased at Month 6 and end of treatment relative to baseline. The geometric LS mean values at 6 months and the end of treatment were lower in all budesonide containing treatment groups compared to formoterol 4.5 and placebo (Table 11). A dose-dependent numerical decrease in cortisol value was observed with budesonide doses of 80 and 160 mcg from Symbicort pMDI (Tables 11 and 12).
3. Statistically significant differences were seen between all budesonide-containing treatment groups versus placebo or formoterol 4.5 groups, except between Symbicort pMDI 80/4.5 versus placebo. Differences between budesonide-containing groups were all estimated to be not significant at 6 months and end of treatment (Table 12).

4. Findings for cortisol/creatinine ratio comparisons between treatment groups were generally consistent with the findings for 24-hour urinary cortisol (Tables 11 and 12).

For 24-hour urinary cortisol, the number of subjects with shifts from normal to low (<5.5 nmol/24 hr) was generally few across treatment groups. At end of treatment among patients normal at baseline, 4 out of 68 patients in the Symbicort 160/4.5 mcg group, 3 out of 64 patients in the Budesonide 160+Formoterol 4.5 mcg group, 2 out of 53 patients in the Budesonide 160 mcg group and 1 out of 56 patients in the placebo group shifted from normal to low. None out of 60 patients in the Symbicort 80/4.5 mcg group and none out of 56 patients in the Formoterol 4.5 mcg group shifted from normal to low.

Overall assessment of HPA-axis function

Urinary free cortisol at baseline and at the end of treatment (~6 months for SUN and 12 months for SHINE studies), and treatment comparison results, are summarized in Tables 13 and 14.

Table 13. Treatment means for 24-hour urinary cortisol (nmol) at baseline and at the end of randomized treatment: combined data from SUN and SHINE studies

			End of treatment	
		Baseline value	Observed value	Multiplicative ANCOVA
Treatment group (µg)	N	Geometric mean	Geometric mean	Adjusted geometric mean
SYMB 160/4.5	126	51.07	36.38	44.92
SYMB 80/4.5	120	53.78	44.24	53.37
Budes 160 + Form 4.5	75	51.34	33.32	39.16
Budes 160	63	55.38	35.53	38.93
Form 4.5	116	52.58	64.71	76.82
Plac	114	49.41	51.76	63.99

SYMB SYMBICORT pMDI; Budes Budesonide; Form Formoterol; Plac Placebo pMDI and TBH.
Each treatment was administered as 2 actuations/inhalations twice daily.
ANCOVA Analysis of covariance; EOT End of treatment; pMDI Pressurized metered-dose inhaler; TBH Turbuhaler.
Data derived from Table 2.3.4.2.2, ISS Section in Module 5.3.5.3.

Table 14. Treatment comparisons for 24-hour urinary cortisol at the end of randomized treatment: combined data from SUN and SHINE studies

	From ANCOVA on Log-transformed values		
Treatment group (μg) comparison	LS mean treatment ratio	95% CI treatment ratio	p-value
SYMB 160/4.5 versus Plac	0.7	0.57, 0.87	0.001
SYMB 160/4.5 versus Budes 160 + Form 4.5	1.15	0.90, 1.47	0.272
SYMB 160/4.5 versus Budes 160	1.15	0.89, 1.50	0.282
SYMB 160/4.5 versus Form 4.5	0.58	0.47, 0.72	<0.001
SYMB 80/4.5 versus Plac	0.83	0.67, 1.04	0.102
SYMB 80/4.5 versus Budes 160	1.37	1.05, 1.78	0.019
SYMB 80/4.5 versus Form 4.5	0.69	0.56, 0.86	0.001
SYMB 160/4.5 versus SYMB 80/4.5	0.84	0.68, 1.04	0.110

SYMB SYMBICORT pMDI; Budes Budesonide; Form Formoterol; Plac Placebo pMDI and TBH.
Each treatment was administered as 2 actuations/inhalations twice daily.
ANCOVA Analysis of covariance; LS Mean least squares mean; CI Confidence interval; pMDI Pressurized metered-dose inhaler; TBH Turbuhaler.
Data derived from Table 2.3.4.2.2, Module 5.3.5.3.

The following broad conclusions can be drawn from the individual and combined results from the two Phase 3 studies (SUN and SHINE studies):

1. Treatment group comparisons at the end of treatment show evidence of lower mean 24-hour urinary free cortisol values following chronic administration (≥6 months) of Symbicort pMDI relative to placebo.
2. Repeated twice daily administration of Symbicort pMDI 160/4.5 mcg and Symbicort pMDI 80/4.5 mcg in COPD patients caused about 30% and 17% decrease in 24-hour urinary free cortisol level, respectively. As expected, these data suggest a dose-dependent response across budesonide doses of 80 and 160 mcg after multiple-dose administration.
3. Symbicort pMDI 160/4.5 exhibited comparable cortisol suppression to Budesonide 160 mcg alone treatment or free combination of budesonide 160 mcg and formoterol 4.5 mcg.

2.2.5 What are the characteristics of the dose/systemic exposure-response relationships for safety?

The majority of subjects who underwent PK testing also had urinary cortisol measurements in the SHINE study. Figures 5 and 6 present plots of change (%) of 24-hour urinary cortisol at end of Symbiort pMDI 160/4.5 mcg and Symbiort pMDI 80/4.5 mcg treatment from baseline versus plasma budesonide exposure, measured by AUC_{0-12} and C_{max}, respectively. Visual inspection of these plots indicated a lack of any apparent trend in distribution of inter-individual cortisol suppression data with budesonide systemic exposue (AUC_{0-12} and C_{max}). Although not shown here, similar lack of any obvious PK/PD relationship was also apparent within each of the other budesonide treatment groups (Budesonide 160 mcg and concomitant administration of Budesonide

160 mcg and Formoterol 4.5 mcg). Therefore, no additional statistical analysis of this relationship was performed.

Figure 5. Individual percentage change of 24hr-urinary cortisol at end of treatment (Symbicort pMDI 160/4.5 or 80/4.5 mcg twice daily for approximately 6 months) from baseline versus measure of systemic exposure ($AUC_{0\text{-}12h}$)

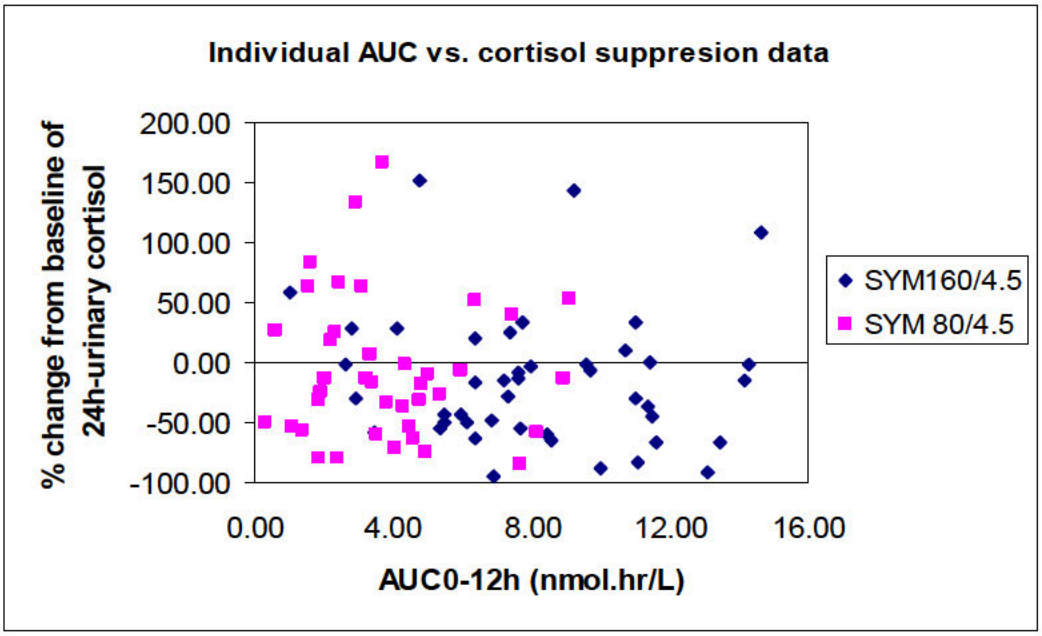
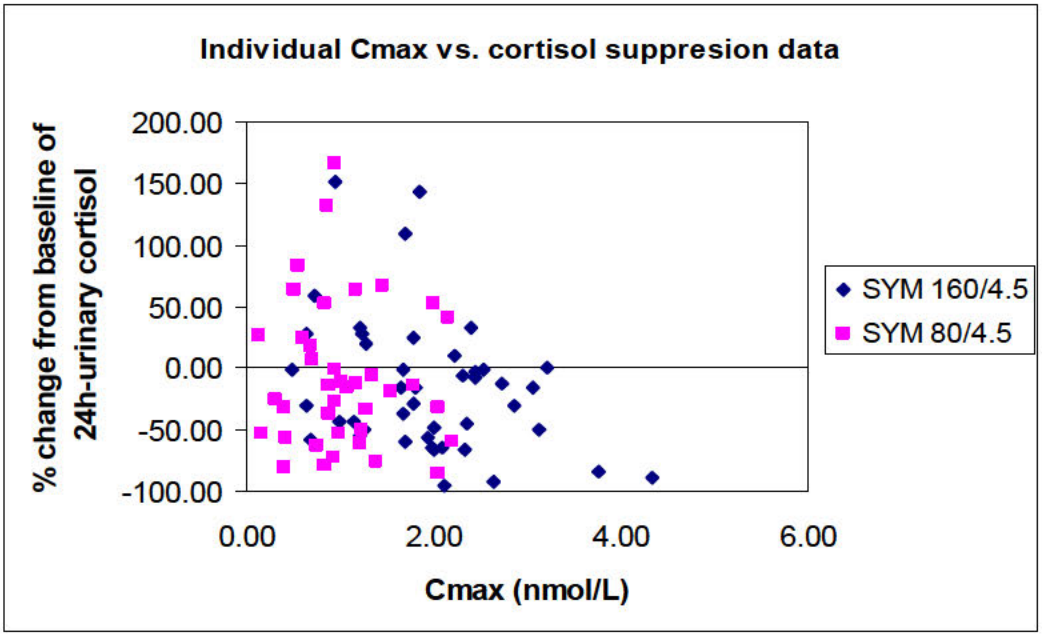


Figure 6. Individual percentage change of 24hr-urinary cortisol at end of treatment (Symbicort pMDI 160/4.5 or 80/4.5 mcg twice daily for approximately 6 months) from baseline versus measure of systemic exposure (Cmax)



2.3 Extrinsic Factors

2.3.1 Does the presence of budesonide affect the PK of formoterol and vice versa?

Evaluation of drug-drug interaction came from the pharmacokinetic data from SHINE study. In this study, the COPD patients were randomly assigned to the following six treatments: 1) Symbicort 160/4.5 mcg, 2) Symbicort 80/4.5 mcg, 3) Budesonide 160 mcg, 4) Formoterol 4.5 mcg, 5) Budesonide and formoterol administered together, and 6) placebo. Systemic exposure of budesonide and formoterol from treatment 5 compared to treatments 3 and 4, respectively; reflect the impact of drug-drug interaction on the systemic exposure of these drugs. As shown in Table 15, budesonide exhibited a small effect on formoterol exposure while there was lack of any measurable effect on budesonide exposure in the presence of formoterol. Formoterol AUC was 12% greater in combination (budesonide 160 mcg and formoterol 4.5 mcg) compared to formoterol 4.5 mcg alone while formoterol C_{max} remained unchanged between the two treatment arms. For Budesonide, both C_{max} and AUC remained nearly identical between the combination and budesonide alone.

Table 15. Relative bioavailability comparisons of budesonide and formoterol from individual components coadministerd vs. monoproduct (budesonide or formoterol): Geometric Mean Plasma PK measures and ratios with 90% Confidence Intervals

Budesonide			
PK Parameters	Budesonide 160 + Formoterol 4.5 (n = 56)	Budesonide 160 (n = 37)	(Budesonide 160 + Formoterol 4.5) vs. Budesonide 160 [Ratio (90% CI)]
$AUC_{0\text{-}12h}$ (nmol.hr/L)	6.72	6.49	1.03 (0.8-1.34)
C_{max} (nmol/L)	1.48	1.54	0.96 (0.73-1.27)
T_{max}* (hr)	0.67 (0.12-12.12)	0.67 (0.13-5.85)	
Formoterol			
PK Parameters	Budesonide 160 + Formoterol 4.5 (n = 54)	Formoterol 4.5 (n = 45)	(Budesonide 160 + Formoterol 4.5) vs. Formoterol 4.5 [Ratio (90% CI)]
$AUC_{0\text{-}12h}$ (nmol.hr/L)	148.4	132.6	1.12 (0.90-1.38)
C_{max} (nmol/L)	27.63	27.45	1.0 (0.82-1.23)
T_{max}* (hr)	0.18 (0.12-6.07)	0.3 (0.13-4.07)	

*Median (range);

Comparisons of systemic exposure of budesonide and formoterol from Symbicort with individual monoproducts administered alone reflect the sum of formulation and drug-drug interaction effects. As shown in Table 16, about 11-12% higher systemic exposure (AUC as well as C_{max}) was observed with Symbicort compared to budesonide alone

administration. This is similar to 8-12% formulation effect seen with budesonide (Table 1), indicating a lack of drug-drug interaction effect thereby confirming the earlier results.

For formoterol, about 30% and 13% higher AUC_{0-12h} and C_{max}, respectively, was observed with Symbicort 160/4.5 compared to formoterol 4.5 alone administration (Table 16). As indicated in Tables 16 and 20, it appears that the increase in formoterol exposure (AUC) in the presence of budesonide is slightly greater than that can be accounted for by the formulation effect (30% vs. 16%), indicating a small drug-drug interaction effect based on AUC. On the other hand, 13% formoterol C_{max} increase (Table 16) from Symbicort 160/4.5 is in line with about 12% increase seen due to the formulation effect (Table 20), suggesting no drug-drug interaction with respect to C_{max}.

Table 16. Relative bioavailability comparisons of budesonide and formoterol from Symbicort pMDI vs. monoproduct (budesonide or formoterol): Geometric Mean Plasma PK measures and ratios with 90% Confidence Intervals

Budesonide			
PK Parameters	Symbicort® 160/4.5 (n = 53)	Budesonide 160 (n = 37)	Symbicort® 160/4.5 vs. Budesonide 160 [Ratio (90% CI)]
AUC_{0-12h} (nmol.hr/L)	7.24	6.49	1.12 (0.86-1.45)
C_{max} (nmol/L)	1.71	1.54	1.11 (0.84-1.47)
T_{max}* (hr)	0.67 (0.15-4.0)	0.67 (0.13-5.85)	
Formoterol			
PK Parameters	Symbicort® 160/4.5 (n = 53)	Formoterol 4.5 (n = 45)	Symbicort® 160/4.5 vs. Formoterol 4.5 [Ratio (90% CI)]
AUC_{0-12h} (pmol.hr/L)	172.50	132.6	1.30 (1.05-1.61)
C_{max} (pmol/L)	30.99	27.45	1.13 (0.92-1.38)
T_{max}* (hr)	1.0 (0.17-12.0)	0.3 (0.13-4.07)	

*Median (range);

2.3.2 Is the systemic exposure of budesonide and formoterol in COPD patients comparable to that in asthma patients?

The relative bioavailability study D5899C00006 also included an open-label group of subjects with moderate asthma to determine the pharmacokinetics of a single dose of Symbicort pMDI (960/54 μg). Twenty-six (26) asthma and 26 COPD patients participated in the study. Results from the statistical analyses of pharmacokinetic parameters for budesonide in COPD vs. asthma patients are summarized in Table 17. Mean $AUC_{0-\infty}$ and AUC_{0-t} were 12% higher whereas mean C_{max} was 10% lower in COPD patients compared with asthma patients. Mean $T_{1/2}$, median T_{max} and mean MRT were all longer in COPD patients than in asthma patients.

Table 17. Pharmacokinetic parameters for budesonide in COPD vs. Asthma patients

parameter	COPD patients Symbicort 960/54 µg		Asthma patients Symbicort 960/54 µg		COPD patients vs. Asthma patients[2]	
	mean	90% conf.lim.	mean	90% conf.lim.	mean	90% conf.lim.
$AUC_{0-\infty}$ (nmol/L·h)	14.08	12.65 - 15.66	12.52	11.26 - 13.93	1.12	0.97 - 1.31
AUC_{0-t} (nmol/L·h)	13.90	12.48 - 15.49	12.39	11.12 - 13.80	1.12	0.96 - 1.31
MRT (h)	5.67	5.30 - 6.05	4.71	4.33 - 5.09	0.96	0.43 - 1.49
$t_{1/2}$ (h)	5.27	4.88 - 5.69	4.57	4.23 - 4.93	1.15	1.04 - 1.29
t_{max} (min)[1]	30	15 - 240	15	15 - 45		
C_{max} (nmol/L)	3.30	2.89 - 3.78	3.66	3.20 - 4.19	0.90	0.75 - 1.09

1. Median and range.
2. Ratios for AUC $_{0-\infty}$, AUC_{0-t}, C_{max} and $t_{1/2}$, difference for MRT

Results from the statistical analyses of pharmacokinetic parameters for formoterol in COPD vs. asthma patients are summarized in Table 18. Following Symbicort pMDI administration, mean C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were all higher (12-16%) in COPD patients compared to asthma patients. Mean $T_{1/2}$ and MRT estimates for formoterol were longer in COPD patients than in asthma patients while T_{max} remained unchanged between the two patient populations.

Table 18. Pharmacokinetic parameters for formoterol in COPD vs. Asthma patients

parameter	COPD patients Symbicort 960/54 µg		Asthma patients Symbicort 960/54 µg		COPD patients vs. Asthma patients [2]	
	mean	90% conf.lim.	mean	90% conf.lim.	mean	90% conf.lim.
$AUC_{0-\infty}$ (pmol/L·h)	945	834 - 1070	819	723 - 928	1.15	0.97 - 1.38
AUC_{0-t} (pmol/L·h)	846	742 - 965	729	639 - 831	1.16	0.96 - 1.40
MRT (h)	11.60	10.38 - 12.81	10.33	9.11 - 11.55	1.27	-0.45 - 2.99
$t_{1/2}$ (h)	9.23	8.17 - 10.42	8.72	7.72 - 9.84	1.06	0.89 - 1.26
t_{max} (min)[1]	15	15 - 120	15	15 - 120		
C_{max} (pmol/L)	167	142 - 196	149	127 - 175	1.12	0.89 - 1.41

1. Median and range.
2. Ratios for AUC $_{0-\infty}$, AUC_{0-t}, C_{max} and $t_{1/2}$, difference for MRT

2.4 General Biopharmaceutics

2.4.1 Is there any formulation effect due to the inhalation administration of budesonide and formoterol via Symbicort pMDI device in COPD patients?

Formulation effect was initially evaluated in an open-label, single-dose, 2-way crossover study (D5899C00006) that determined the relative bioavailability (BA) of budesonide and formoterol when administered as Symbicort pMDI versus the monoproducts administered concurrently in subjects with COPD. Twenty-six (26) male and female

subjects with COPD (mean age 53 years) participated in the study. The two orally inhaled treatments were 1) Symbicort pMDI (80/4.5 µg x 12 actuations, total dose 960/54 µg), and 2) budesonide pMDI (80 µg x 12 actuations, total dose 960 µg) plus Formoterol TBH (4.5 µg x 12 inhalations, total dose 54 µg).

Study D5899C00002 (SHINE) was the pivotal safety and efficacy study which included PK assessments during steady-state administration of Symbicort pMDI and the monoproducts co-administered in COPD patients. The doses tested in this study were the clinical doses of 2 inhalations twice daily for both treatments in a parallel group design.

Despite the differences in study designs, the results of the two studies were quite similar with respect to the relative bioavailability between Symbicort pMDI and the coadministration of monoproducts. As shown in Figure 7 and Table 19, in the single-dose study, systemic exposure of budesonide was found to be nearly identical between the treatment arms while the steady state comparison (Table 19) showed slightly higher exposure to budesonide (8-12%) from Symbicort compared to two monoproducts administered together.

Figure 7. Individual and mean AUC (left panel) and Cmax (right panel) values for budesonide (total dose: 960 mcg) following single-dose inhalation administration of Symbicort pMDI (12 x 80/4.5 mcg) and Budesonide pMDI (12 x 80 mcg) plus Formoterol TBH (12 x 4.5 mcg)

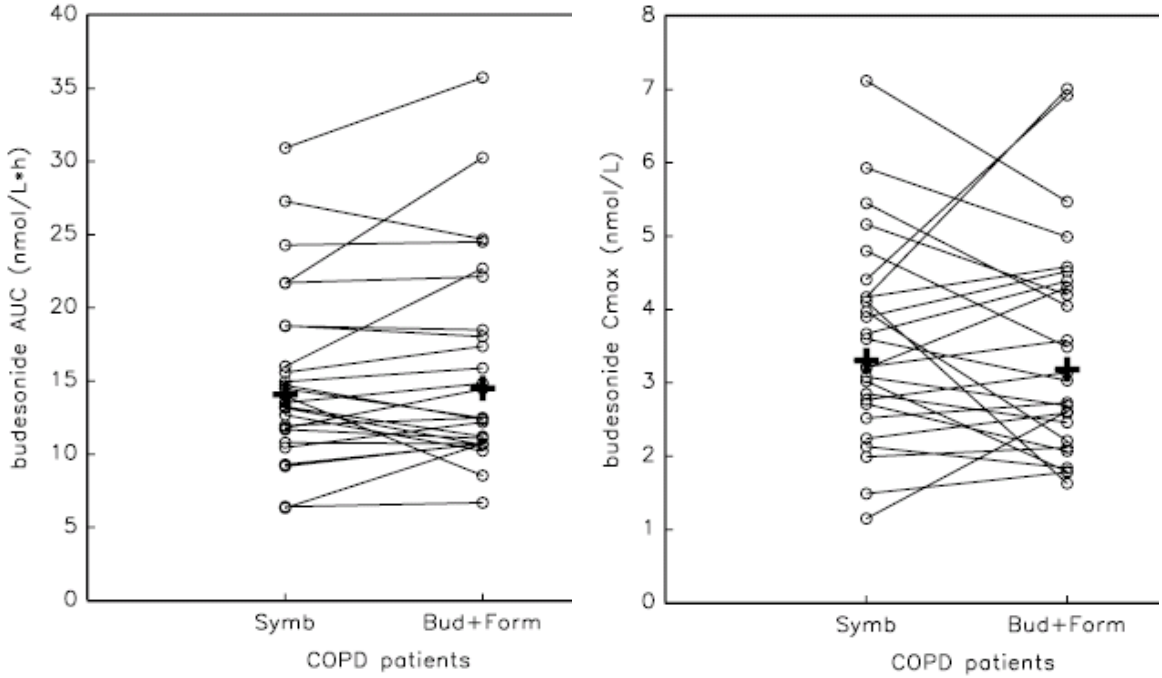


Table 19. Relative bioavailability comparisons of budesonide from Symbicort pMDI vs. individual components coadministered (BUD pMDI + Oxis TBH): Geometric Mean Plasma PK measures and ratios with 90% Confidence Intervals

PK Parameters	Symbicort®** *960/54 mcg – SD study* *320/9 mcg – SS study*	Budesonide + Formoterol *960+54 mcg – SD study* *320+9 mcg – SS study*	Symbicort® vs. Budesonide +Formoterol [Ratio (90% CI)]
Study D5899C00006 (Single-Dose) N = 26 COPD patients			
AUC_{inf} (nmol.hr/L)	14.08	14.49	0.97 (0.91-1.04)
C_{max} (nmol/L)	3.30	3.18	1.04 (0.94-1.15)
T_{max}* (hr)	0.5 (15-240)	0.5 (15-242)	
Study SHINE (Steady-State) N = 238 COPD patients in PK sub-set			
AUC_{0-12h} (nmol.hr/L)	7.24	6.72	1.08 (0.85-1.36)
C_{max} (nmol/L)	1.71	1.48	1.12 (0.90-1.49)
T_{max}* (hr)	0.67 (0.15-4.0)	0.67(0.117-12.117)	

*Median (range); **For SHINE study, n = 53 (Symbicort pMDI arm) n = 56 (Budesonide+Formoterol arm)

On the other hand for formoterol, Figure 8 and Table 20 showed higher exposure (18-22%) from Symbicort compared to two monoproducts coadministered after single dose administration. This has been further confirmed by the comparative multiple-dose PK data from the SHINE study where about 12-16% higher exposure of formoterol was observed with Symbicort compared to two drugs given together.

Figure 8. Individual and mean AUC (left panel) and Cmax (right panel) values for formoterol (total dose: 54 mcg) following single-dose inhalation administration of Symbicort pMDI (12 x 80/4.5 mcg) and Budesonide pMDI (12 x 80 mcg) plus Formoterol TBH (12 x 4.5 mcg)

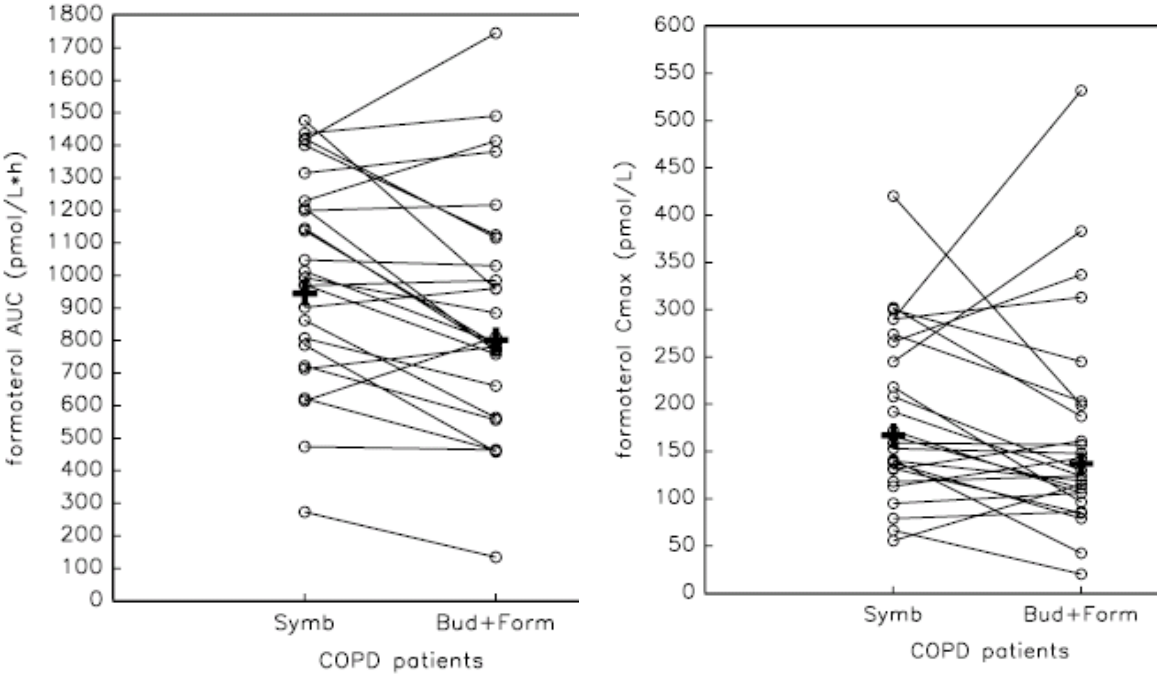


Table 20. Relative bioavailability comparisons of formoterol from SYMBICORT pMDI vs. individual components coadministered (BUD pMDI + Oxis TBH): Geometric Mean Plasma PK measures and ratios with 90% Confidence Intervals

PK Parameters	Symbicort®** *960/54 mcg – SD study* *320/9 mcg – SS study*	Budesonide + Formoterol *960+54 mcg – SD study* *320+9 mcg – SS study*	Symbicort® vs. Budesonide +Formoterol [Ratio (90% CI)]
Study D5899C00006 (Single-Dose) N = 26 COPD patients			
AUC_{inf} (pmol.hr/L)	945	801	1.18 (1.08-1.28)
C_{max} (pmol/L)	167	137	1.22 (1.03-1.44)
T_{max}* (hr)	0.25 (0.25-2)	0.25 (0.25-2)	
Study SHINE (Steady-State) N = 238 COPD patients			
AUC_{0-12h} (pmol.hr/L)	172.50	148.37	1.16 (0.95-1.42)
C_{max} (pmol/L)	30.99	27.63	1.12 (0.92-1.36)
T_{max}* (hr)	1.0 (0.17-12.0)	0.183 (0.12-6.1)	

*Median (range); ** For SHINE study, n = 53 (Symbicort® arm) n = 54 (Budesonide+Formoterol arm)

These results indicate a lack of any appreciable formulation effect for budesonide while demonstrating a small formulation effect for formoterol when delivered through the pMDI device.

2.5 Analytical Section

2.5.1 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Yes. All bioanalytical assays fulfilled the regulatory criterion [refer to the FDA guidance for industry "Bioanalytical Method Validation (Final-May 2001)] of not exceeding 15% (20% for the lowest QC samples) for precision and accuracy during pre-study and in-study validation runs. Study samples were analyzed in runs containing calibrators and quality control samples, as recommended in the FDA guidance. The bioanalytical methods used for the analysis of budesonide and formoterol in plasma were the same in the COPD development program as presented in the asthma NDA (21-929).

Budesonide

The assay of (22RS)-budesonide utilizes solid phase extraction and liquid chromatography atmospheric pressure chemical ionization-tandem mass spectrometry. The calibration range was from 0.01 to 10.0 nM using a sample plasma volume of 1 mL with a satisfactory linear regression analysis (r^2>0.996) for budesonide concentration.

For study D5899C00006, the inaccuracy from the actual budesonide concentration

ranged between -4.0% and 0.2% for the five QC standards (0.01, 0.03, 4, 8, 10 nM) while the inter-assay precision was as high as 13% for QC low (0.01 nM).

Table 21 summarizes the findings of the in-study QC validation runs during sample analysis for study SHINE.

Table 21. Summary statistics of QC results for budesonide in human plasma

	Actual concentration (nM)		
Control sample	**QC low**	**QC medium**	**QC high**
	0.0300	**4.00**	**8.00**
N (number of runs)	53	52	54
Mean concentration	0.0302	4.01	7.92
SD	0.00258	0.156	0.253
Accuracy (%)	101	100	99
Precision (Inter assay) (%)	8.5	3.9	3.2

Formoterol

The assay of formoterol utilizes solid phase extraction followed by reversed-phase liquid chromatography with tandem mass spectrometry. The calibration range was from 5 to 1000 pM using a sample plasma volume of 1 mL with a satisfactory linear regression analysis (r2>0.995) for formoterol concentration.

For study D5899C00006, inter-assay precision and accuracy were determined for each QC standard. The nominal plasma concentrations of formoterol in the QC samples were 10, 375 and 750 pM and the inter-assay CV (precision) were 6.6%, 5.1% and 3.0%, respectively. The mean accuracy from nominal value of the 3 QC samples ranged between 8.4% and -4.6%.

Table 22 summarizes the findings of the in-study QC validation runs during sample analysis for study SHINE.

Table 22. Summary statistics of QC results for formoterol in human plasma (SHINE study)

Nominal Concentration	QC L 10 pM	QC M 375 pM	QC H 750 pM
Mean Observed Conc.	9.82	365	760
%Nominal	98.2	97.3	101
Between Run Precision (%CV)	1.4	3.7	0.0*
Within Run Precision (%CV)	8.0	6.7	8.1
n	55	55	56
Number of Runs	28	28	28

*No significant additional variation was observed as a result of performing the assay in different runs

For both budesonide and formoterol assays, the inter-assay mean precision and accuracy were within ±15% limits for all concentrations in both D5899C00006 and SHINE studies.

3 Labeling Recommendations

Here are the initial labeling comments for sections 5, 7, and 12.2 and 12.3.

1. Section 5 WARNINGS AND PRECAUTIONS
Suggest incorporating the following paragraph as a sub-section under section 5.

Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors
Caution should be exercised when considering the coadministration of SYMBICORT with ketoconazole and other known strong CYP3A4 inhibitors (e.g. ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because increased systemic corticosteroid adverse effects may occur [see drug interactions (7.1), Clinical Pharmacology (12.3)]

2. Section 7 DRUG INTERACTIONS
Suggest incorporating the following paragraph as sub-section 7.1 under section 7.

7.1 Inhibitors of Cytochrome P450 3A4
The main route of metabolism of corticosteroids, including budesonide, a component of SYMBICORT, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a strong inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of inhibitors of CYP3A4 may inhibit the

metabolism of, and increase the systemic exposure to, budesonide. Caution should be exercised when considering the coadministration of SYMBICORT with ketoconazole and other known strong CYP3A4 inhibitors (e.g. ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin)

3. Section 8 USE IN SPECIFIC POPULATIONS
Suggest including the following two sub-sections (8.6 and 8.7) under section 8.

8.6 Hepatic Impairment

Formal pharmacokinetic studies using SYMBICORT have not been conducted in patients with hepatic impairment. However, since both budesonide and formoterol fumarate are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of budesonide and formoterol fumarate in plasma. Therefore, patients with hepatic disease should be closely monitored.

8.7 Renal Impairment

Formal pharmacokinetic studies using SYMBICORT have not been conducted in patients with renal impairment.

4. Section 12.2 Pharmacodynamics
The following is the suggested text for the COPD part of the section related to Symbicort.

Symbicort:

The systemic effects of inhaled corticosteroids are related to the systemic exposure to such drugs. Pharmacokinetic studies have demonstrated that in both adults and children with asthma, the systemic exposure to budesonide is lower with SYMBICORT compared with inhaled budesonide administered at the same delivered dose via a dry powder inhaler. In COPD patients, the systemic exposure to budesonide is comparable between SYMBICORT and inhaled budesonide administered alone at the same delivered dose via a metered dose inhaler [*see Clinical Pharmacology, Pharmacokinetics, SYMBICORT (12.3)]*. Therefore, the systemic effects (HPA axis and growth) of budesonide delivered from SYMBICORT would be expected to be no greater than what is reported for inhaled budesonide when administered at comparable doses [*see Use in Specific Populations, Pediatric Use (8.4)*].

COPD:

Cardiovascular Effects:

In 2 clinical studies, 6 months and 12 months in duration including 3668 COPD patients, no clinically important differences were seen in pulse rate, blood pressure, potassium, and glucose between SYMBICORT, the individual components of SYMBICORT, and placebo. (*see Clinical Studies [14.2]).*

ECGs recorded at multiple clinic visits on treatment in both studies showed no clinically important differences for heart rate, PR interval, QRS duration, heart rate, signs of cardiac ischemia or arrhythmias between SYMBICORT 160/4.5 the monoproducts and placebo, all administered as two inhalations twice daily. Based on ECGs, 6 patients treated with SYMBICORT 160/4.5, 6 patients treated with formoterol 4.5, and 6 patients in the placebo group experienced atrial fibrillation or flutter that was not present at baseline. There were no cases of nonsustained ventricular tachycardia in the SYMBICORT 160/4.5, formoterol 4.5, or placebo groups.

In the 12-month study, 520 patients had evaluable continuous 24-hour ECG (Holter) monitoring prior to the first dose and after approximately 1 and 4 months on treatment. No clinically important differences in ventricular or supraventricular arrhythmias, ventricular or supraventricular ectopic beats, or heart rate were observed among the groups treated with SYMBICORT 160/4.5, formoterol or placebo taken as two inhalations twice daily. Based on ECG (Holter) monitoring, one patient on SYMBICORT 160/4.5, no patients on formoterol 4.5, and three patients in the placebo group experienced atrial fibrillation or flutter that was not present at baseline.

HPA Axis Effects: Twenty-four hour urinary cortisol measurements were collected in a pooled subset (n=616) of patients from two COPD

studies. The data indicated approximately 30% lower mean 24-hour urinary free cortisol values following chronic administration (≥6 months) of SYMBICORT relative to placebo. SYMBICORT appeared to exhibit comparable cortisol suppression to budesonide 160 mcg alone or coadministration of budesonide 160 mcg and formoterol 4.5 mcg. For patients treated with SYMBICORT or placebo for up to 12 months, percentage of patients who shifted from normal to low for this measure were generally comparable.

5. Section 12.3 Pharmacokinetics This section is reorganized under broad sub-sections of Absorption, Metabolism, Distribution, Elimination, Special Population and Drug-Drug Interactions. The following is the suggested text. Note the yellow highlighted text, which would require input from the sponsor.

12.3 Pharmacokinetics

Absorption: *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 contrast, most of the budesonide delivered to the lungs was systemically absorbed. 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.

Following administration of SYMBICORT (160/4.5 mcg, two or four inhalations twice daily) for 5 days in healthy subjects, plasma concentration of budesonide generally increased in proportion to dose. The accumulation index for the group that received two inhalations twice daily was 1.32 for budesonide.

Asthma Patients: In a single-dose study, higher than recommended doses of SYMBICORT (12 inhalations of SYMBICORT 160/4.5 mcg) were administered to patients with moderate asthma. Peak budesonide plasma concentration of

4.5 nmol/L occurred at 20 minutes following dosing. This study demonstrated that the total systemic exposure to budesonide from SYMBICORT was approximately 30% lower than from inhaled budesonide via a dry powder inhaler (DPI) at the same delivered dose. Following administration of SYMBICORT, the half-life of the budesonide component was 4.7 hours.

In a repeat dose study, the highest recommended dose of SYMBICORT (160/4.5 mcg, two inhalations twice daily) was administered to patients with moderate asthma and healthy subjects for 1 week. Peak budesonide plasma concentration of 1.2 nmol/L occurred at 21 minutes in asthma patients. Peak budesonide plasma concentration was about XX% *(Comment: Request sponsor to provide the data as well as data source)* higher in healthy subjects, compared to that in asthma patients. However, the total systemic exposure of budesonide was comparable to that in asthma patients.

Peak steady-state plasma concentrations of budesonide administered by DPI in adults with asthma averaged 0.6 and 1.6 nmol/L at doses of 180 mcg and 360 mcg twice daily, respectively. In asthmatic patients, budesonide showed a linear increase in AUC and C_{max} with increasing dose after both single and repeated dosing of inhaled budesonide.

COPD Patients: In a single-dose study, 12 inhalations of SYMBICORT 80/4.5 mcg (total dose 960/54 mcg) were administered to patients with COPD. Mean budesonide peak plasma concentration of 3.3 nmol/L occurred at 30 minutes following dosing. Budesonide systemic exposure was comparable between SYMBICORT pMDI and coadministration of budesonide via a metered-dose inhaler and formoterol via a dry powder inhaler (budesonide 960 mcg and formoterol 54 mcg). In the same study, an open-label group of moderate asthma patients also received the same higher dose of SYMBICORT. For budesonide, COPD patients exhibited 12% greater AUC and 10% lower C_{max} compared to asthma patients.

In the 6 month pivotal clinical study, steady-state pharmacokinetic data of budesonide was obtained in a subset

of COPD patients with treatment arms of SYMBICORT pMDI 160/4.5 mcg, SYMBICORT pMDI 80/4.5 mcg, budesonide 160 mcg, budesonide 160 mcg and formoterol 4.5 mcg given together, all administered as two inhalations twice daily. Budesonide systemic exposure (AUC and C_{max}) increased proportionally with doses from 80 mcg to 160 mcg and was generally similar between the 3 treatment groups receiving the same dose of budesonide (SYMBICORT pMDI 160/4.5 mcg, budesonide 160 mcg, budesonide 160 mcg and formoterol 4.5 mcg administered together)..

Formoterol:
Inhaled formoterol is rapidly absorbed; peak plasma concentrations are typically reached at the first plasma sampling time, within 5-10 minutes after dosing. As with many drug products for oral inhalation, it is likely that the majority of the inhaled formoterol delivered is swallowed and then absorbed from the gastrointestinal tract.

Healthy Subjects: Following administration of SYMBICORT (160/4.5 mcg, two or four inhalations twice daily) for 5 days in healthy subjects, plasma concentration of formoterol generally increased in proportion to dose. The accumulation index for the group that received two inhalations twice daily was 1.77 for formoterol.

Asthma patients: In a single-dose study, higher than recommended doses of SYMBICORT (12 inhalations of SYMBICORT 160/4.5 mcg) were administered to patients with moderate asthma. Peak plasma concentration for formoterol of 136 pmol occurred at 10 minutes following dosing. Approximately 8% of the delivered dose of formoterol was recovered in the urine as unchanged drug.

In a repeat dose study, the highest recommended dose of SYMBICORT (160/4.5 mcg, two inhalations twice daily) was administered to patients with moderate asthma and healthy subjects for 1 week. Peak formoterol plasma concentration of 28 pmol/L occurred at 10 minutes in asthma patients. Peak formoterol plasma concentration was about XX% *(Comment:*

Request sponsor to provide the data as well as data source) higher in healthy subjects, compared to that in asthma patients. However, the total systemic exposure of formoterol was comparable to that in asthma patients.

COPD patients: Following single-dose administration of 12 inhalations of SYMBICORT 80/4.5, mean peak formoterol plasma concentration of 167 pmol/L was rapidly achieved at 15 minutes after dosing. Formoterol exposure was slightly greater (~16-18%) from SYMBICORT pMDI compared to coadministration of budesonide via a metered-dose inhaler and formoterol via a dry powder inhaler (total dose of budesonide 960 mcg and formoterol 54 mcg). In the same study, an open-label group of moderate asthma patients also received the same higher dose of SYMBICORT. COPD patients exhibited 12-16% greater AUC and C_{max} for formoterol compared to asthma patients.

In the 6 month pivotal clinical study, steady-state pharmacokinetic data of formoterol was obtained in a subset of COPD patients with treatment arms of SYMBICORT pMDI 160/4.5 mcg, SYMBICORT pMDI 80/4.5 mcg, formoterol 4.5 mcg, budesonide 160 mcg and formoterol 4.5 mcg given together, all administered as two inhalations twice daily. The systemic exposure of formoterol as evidenced by AUC, was about 30% and 16% higher from Symbicort pMDI compared to formoterol alone treatment arm and coadministration of individual components of budesonide and formoterol treatment arm, respectively.

Distribution: *Budesonide:* The volume of distribution of budesonide was approximately 3 L/kg. It was 85%-90% bound to plasma proteins. Protein binding was constant over the concentration range (1-100 nmol/L) achieved with, and exceeding, recommended inhaled doses. Budesonide showed little or no binding to corticosteroid binding globulin. Budesonide rapidly equilibrated with red blood cells in a concentration independent manner with a blood/plasma ratio of about 0.8.

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. The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 54-mcg dose.

Metabolism: *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 6β-hydroxybudesonide. The corticosteroid activity of each of these two metabolites was less than 1% of that of the parent compound. No qualitative differences between the *in vitro* and *in vivo* metabolic patterns were detected. Negligible metabolic inactivation was observed in human lung and serum preparations.

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.

Elimination: *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.

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 mcg in a single-dose study in pediatric patients with asthma, 6-11 years of age. Urine was collected for determination of formoterol excretion. Peak budesonide concentrations of 1.4 nmol/L occurred at 20 minutes post-dose. Approximately 3.5% of the delivered formoterol dose was recovered in the urine as unchanged formoterol. This study also demonstrated that the total systemic exposure to budesonide from SYMBICORT was approximately 30% lower than from inhaled budesonide via a dry powder inhaler that was also evaluated at the same delivered dose.

Gender/Race

Specific studies to examine the effects of gender and race on the pharmacokinetics of SYMBICORT have not been conducted. Population PK analysis of the SYMBICORT data indicates that gender does not affect the pharmacokinetics of budesonide and formoterol. No conclusions can be drawn on the effect of race due to the low number of non-Caucasians evaluated for PK.

Renal or Hepatic Insufficiency

There are no data regarding the specific use of SYMBICORT in patients with hepatic or renal 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.

Drug-Drug Interactions

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 P450s

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 non-specific 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.

APPENDIX

3.1 PROPOSED PACKAGE INSERT from the Sponsor

59 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

Partha Roy
12/22/2008 04:13:43 PM
BIOPHARMACEUTICS

Wei Qiu
12/23/2008 08:17:30 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21–929/S012

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	January 23, 2009
To:	Badrul A. Chowdhury, M.D., Director Division of Pulmonary and Allergy Products
Through:	Kristina Arnwine, Pharm.D., Team Leader Denise Toyer, Pharm.D., Deputy Director Division of Medication Error Prevention and Analysis, HFD 420
From:	Lori Cantin, R.Ph., Safety Evaluator Division of Medication Error Prevention and Analysis, HFD-420
Subject:	Labeling Review
Drug Name(s):	Symbicort (Budesonide and Formoterol Fumarate Dihydrate) Inhalation Aerosol 80 mcg/4.5 mcg and 160 mcg/4.5 mcg
ApplicationType/Number:	NDA 21-929
Submission Number:	SE1-012
Applicant:	AstraZeneca
OSE RCM #:	2008-828

CONTENTS

EXECUTIVE SUMMARY

The results of the Labeling Risk Assessment found that the presentation of information in the insert labeling for Symbicort (Budesonide and Formoterol Fumarate Dihydrate) has some inconsistencies and is vulnerable to confusion that may lead to medication error. A detailed discussion can be found in Section 4.1.

The Division of Medication Error Prevention and Analysis (DMEPA) believes the risks we have identified can be addressed and mitigated prior to approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Pulmonary and Allergy Products to evaluate the package insert labeling and medication guide labeling for Symbicort, for the potential to contribute to medication errors.

1.2 REGULATORY HISTORY

Symbicort (Budesonide and Formoterol Fumarate Dihydrate) Inhalation Aerosol was approved on July 21, 2006, for the long-term maintenance treatment of asthma in patients 12 years of age and older. An efficacy supplement (SE1-012) was submitted on April 28, 2008, and provides support for a new indication for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

1.3 PRODUCT INFORMATION

Symbicort (Budesonide and Formoterol Fumarate Dihydrate) Inhalation Aerosol is a combination product containing a corticosteroid and a long-acting beta$_2$-adrenergic agonist. Symbicort is currently indicated for the long-term maintenance treatment of asthma in patients 12 years of age and older. The recommended dose for asthma is 2 inhalations of Symbicort 80/4.5 twice daily or 2 inhalations of Symbicort 160/4.5 twice daily. The proposed usual dose for the COPD indication is 2 inhalations of Symbicort 160/4.5 twice daily. Symbicort is available in two strengths: 80/4.5 (containing 80 mcg of budesonide and 4.5 mcg of formoterol fumarate dihydrate) and 160/4.5 (containing 160 mcg of budesonide and 4.5 mcg of formoterol fumarate dihydrate). Symbicort 80/4.5 and Symbicort 160/4.5 are available in 120 inhalation canister and 60 inhalation canister package sizes.

2 METHODS AND MATERIALS

This section describes the methods and materials used by DMEPA staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessment is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form,

[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because DMEPA staff analyze reported misuse of drugs, our staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted on April 28, 2008, the following labeling for our review:

- Package Insert (no image)
- Medication Guide (no image)

In addition to the labeling submitted by the Applicant, the following materials were also reviewed:

- FDA-proposed labeling dated December 10, 2008.
- Division of Risk Management (DRISK), Patient Labeling and Education Team's Review of the Medication Guide, dated December 30, 2008.

2.2 ADVERSE EVENT REPORTING SYSTEM (AERS)

On December 4, 2008, the Division of Medication Error Prevention and Analysis conducted a search of the FDA Adverse Event Reporting System (AERS) database to determine if any medication errors involving Symbicort have been reported. The following criteria were used: MedDRA High Level Group Term (HLGT) 'Medication Errors' and the Preferred term (PT) 'Pharmaceutical Product Complaint' with the, trade name (Symbicort), and verbatim term 'Symb%'.

The cases were manually reviewed to determine if medication errors occurred. Those cases that did not describe a medication error were excluded from further analysis. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors.

3 RESULTS

3.1 LABELING RISK ASSESSMENT

Review of the package insert labeling identified certain areas of inconsistency that may lead to confusion and medication error.

3.1.1 Insert Labeling

Highlights Section

In the FDA-proposed labeling dated December 10, 2008, the following inconsistencies were noted:

- In the Highlights Section, an asterisk is present following the established name, formoterol fumarate dihydrate and lacks a corresponding statement.
- The established name is presented as 'formoterol' throughout the insert labeling which is not consistent with the established name, formoterol fumarate dihydrate.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

- In the Full Prescribing Information, the statement "(morning and evening, approximately 12 hours apart)" is not used in **Section 2.2 Chronic Obstructive Pulmonary Disease (COPD)**; therefore, it is not consistent with **Section 2.1 Asthma**.

3.1.2 Medication Guide Labeling

A review of the Medication Guide was completed by the Division of Risk Management (DRISK), Patient Labeling and Education Team on December 30, 2008. DMEPA does not have any comments on the Medication Guide in addition to those recommended by DRISK.

3.2 ADVERSE EVENT REPORTING SYSTEM (AERS)

The FDA Adverse Event Reporting System (AERS) search conducted on December 4, 2008, yielded a total of fourteen cases (n=14). Two cases (n=2) involved adverse events in which Symbicort was identified either as a suspect or concomitant medication, and thus were eliminated from further review. Five cases (n=5) were foreign cases reporting either an increased or decreased effect occurring with the use of Symbicort Turbuhaler. The Turbuhaler device is not the same device approved for Symbicort in the United States, thus these reports were eliminated from further review. Four cases (n=4) involved medication errors due to defective devices.

Three cases (n=3) were further evaluated in order to identify factors that contributed to medication error related to the use of Symbicort pMDI. These cases of medication error resulted in either an increased effect or decreased effect due to incorrect use of Symbicort pMDI.

- One case (n=1) reported that the patient was using Symbicort (strength unknown) 4 inhalations twice daily via tracheal. Patient was hospitalized at the time of the occurrence and an adverse event was experienced (chest pain). Physician was aware that the prescribed dose exceeded the recommended dose.
- One case (n=1) reported a decreased effect secondary to use of Symbicort pMDI. Patient followed up with her physician and was informed that she was using the Symbicort pMDI incorrectly. No additional information was provided, therefore, causality could not be determined. No follow up or outcome was reported.
- One case (n=1) reported an increased effect resulting from administration of Symbicort pMDI every 4 hours. The patient experienced an increase in heart rate. No rationale was provided for the increased frequency of administration, thus causality could not be established. The current labeling clearly indicates that Symbicort pMDI should be administered twice daily, thus it is unlikely that incorrect usage in this case is a result of inadequate package insert labeling.

DMEPA does not believe that any of these medication errors cases are likely to have resulted from inadequate insert labeling or medication guide labeling. Thus, these cases will not be further discussed.

4 DISCUSSION

In our analysis of the package insert labeling, we identified problems with inconsistencies and incomplete information. In the beginning of the Highlights Section of the FDA-proposed labeling dated December 10, 2008, an asterisk is presented following the established name, formoterol fumarate dihydrate, however, the corresponding qualifying statement has been deleted. The asterisk is no longer necessary since the amount of formoterol fumarate dihydrate is correctly denoted as 4.5 mcg following the established name.

Additionally, in the Full Prescribing Information, the statement "(morning and evening, approximately 12 hours apart)" was not used in **Section 2.2 Chronic Obstructive Pulmonary Disease (COPD)**. This is not consistent with **Section 2.1 Asthma** and may also have been an oversight.

5 CONCLUSIONS

DMEPA did not identify any vulnerabilities in the insert labeling that could lead to medication errors as a result of the expansion of the indication of use to include maintenance treatment of airflow obstruction in

patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. However, the Labeling Risk Assessment indicates that there are minor inconsistencies in the presentation of information in the package insert labeling. DMEPA believes these inconsistencies can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

6 RECOMMENDATIONS

6.1 COMMENTS TO THE DIVISION

We would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy us on any communication to the applicant with regard to this review. If you have further questions or need clarifications, please contact Sean Bradley, Project Manager, at 301-796-1332.

6.2 COMMENTS TO THE APPLICANT

Based upon our assessment of the labeling, the Division of Medication Error Prevention and Analysis identified the following areas of needed improvement.

Insert Labeling

1. In the Highlights Section of the labeling, delete the asterisk following the established name 'formoterol fumarate dihydrate'.
2. Present the established name consistently throughout the labeling as formoterol fumarate dihydrate.
3. In the Full Prescribing Information, add the statement "(morning and evening, approximately 12 hours apart)" following the statement "two inhalations twice daily' in **Section 2.2 Chronic Obstructive Pulmonary Disease (COPD)** in order to be consistent with **Section 2.1 Asthma**.

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

/s/

Lori Cantin
2/3/2009 06:29:28 PM
DRUG SAFETY OFFICE REVIEWER

Kristina Arnwine
2/3/2009 06:40:26 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
2/4/2009 06:32:48 AM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

To: **Collette Jackson**
Division of Pulmonary and Allergy Products

From: **Iris Masucci, PharmD, BCPS**
for Study Endpoints and Label Development (SEALD) Team, OND

Date: **January 16, 2009**

Re: **Comments on draft labeling for Symbicort (budesonide/formoterol fumarate)**
NDA 21-929/S012

We have reviewed the proposed label for Symbicort (dated 1/9/09) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the Division after a full review of the submitted data.

Please see attached label for recommended changes.

60 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

Iris Masucci
1/22/2009 03:06:36 PM
DDMAC PROFESSIONAL REVIEWER

Laurie Burke
1/22/2009 07:00:38 PM
INTERDISCIPLINARY

INTEROFFICE MEMO

TO: NDA 21-929 SE1-012, Symbicort (Astra-Zeneca)
FROM: Luqi Pei, Ph.D., Senior Pharmacologist
DATE: January 8, 2009

I concur with the recommendation of Dr. Timothy Robison in a pharmacology and toxicology review completed on November 4, 2008. The review recommends the approval of the supplement from the nonclinical perspective and edits of the nonclinical labeling of the product.

Supplement SE1-012 of NDA 21-929 received by the Center on April 29, 2008 contained no nonclinical data. A nonclinical review would normally be unnecessary. Dr. Timothy Robison completed a nonclinical labeling review so that the newly approved labeling would conform to the Agency's to the Draft Guidance for Industry "Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements" (January 2006).

The sponsor proposed a new labeling based on one approved on October 23, 2007. The proposed labeling was generally in compliance with the new labeling format and maintained the content of the approved labeling. Dr. Robison edited the proposed labeling. The edits included creation of additional headings and rearrangement of the text accordingly. The new headings included Sections 8.1, 10, 13.1 and 13.2.

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

/s/

Luqi Pei
1/8/2009 09:14:06 AM
PHARMACOLOGIST

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	December 30, 2008
To:	Badrul Chowdhury, M.D., Director **Division of Pulmonary and Allergy Products (DPAP)**
Through:	Jodi Duckhorn, M.A., Team Leader **Patient Labeling and Education Team** **Division of Risk Management (DRISK)**
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist **Patient Labeling and Education Team** **Division of Risk Management (DRISK)**
Subject:	Review of Patient Labeling (Medication Guide)
Drug Name(s):	• Symbicort (budesonide 80 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalational Aerosol • Symbicort (budesonide 160 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalational Aerosol
Application Type/Number:	NDA 21-929
Submission Number:	012
Applicant/sponsor:	AstraZeneca
OSE RCM #:	2008-828

1 INTRODUCTION

AstraZeneca received original approval of their New Drug Application, NDA 21-929 on July 21, 2006. Symbicort is currently indicated for the long-term maintenance treatment of asthma in patients 12 years of age and older. The most recently approved labeling for Symbicort is dated July 16, 2008 (Supplement 010). On April 28, 2008, AstraZeneca submitted a Supplemental New Drug Application, sNDA 21-929/S-012, proposing a new indication for Symbicort for the (b) (4) maintenance of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). The submission includes draft revised Professional Information in PLR format and also a draft revised Medication Guide for Symbicort. The sponsor submitted revised labeling for Supplement 012 on July 24, 2008 and August 25, 2008 in response to Agency comments and requests.

Since Advair Diskus was required to have a Risk Evaluation and Mitigation Strategy (REMS) related to their indication for COPD and the risk of pneumonia, the review division has determined that it is also appropriate for Symbicort to have a REMS associated with the COPD indication and risk of pneumonia. The sponsor has not yet submitted their REMS.

This DRISK review focuses on the proposed changes to the Medication Guide due to the addition of the new indication and new safety information about pneumonia to the PI, and conversion of the PI to PLR format. The sponsor's proposed REMS will be reviewed by DRISK under separate cover once it is submitted to the Agency.

2 MATERIAL REVIEWED

- SYMBICORT Medication Guide (MG) submitted by the sponsor on August 25, 2008.
- SYMBICORT Professional Information as revised by DPAP on December 10, 2008.

3 DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft MG submitted by the sponsor has a Flesch Kinkaid grade level of 7.7, and a Flesch Reading Ease score of 66.3%. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). The reading scores as submitted by the sponsor are acceptable.

In our review of the MG, we have:

- simplified wording and clarified concepts where possible,
- ensured that the MG is consistent with the PI,
- rearranged information due to conversion of the PI to PLR format,
- removed unnecessary or redundant information
- ensured that the Medication Guide meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and*

Consumer Medication Information for People with Vision Loss. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the MG document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

4 CONCLUSIONS AND RECOMMENDATIONS

1. In the section "What is Symbicort?"

   - Based on the Agency comment to the sponsor that asthma (b) (4) (b) (4) in the PI, in the information below, (b) (4) asthma (b) (4) COPD, since it was the (b) (4) approved indication.
   - A pediatric statement has been added based on the language provided by the RD in draft PI dated December 10, 2008, as follows:

     (b) (4)

     If based on the recommendations from the recent Advisory Committee meeting and further consideration the RD feels that SYMBICORT is not safe and effective in this patient population, section 8.4 of the PI should be modified. The MG should be updated accordingly.

2. The section "Who should not use SYMBICORT?" has been added to reflect the Contraindications section of the PI. The language in the section states:

   Do not use SYMBICORT:
   - to treat sudden severe symptoms of asthma or COPD.
   - if you are allergic to any of the ingredients in SYMBICORT. See the end of the Medication Guide for a list of ingredients in SYMBICORT.

3. In the section "What should I tell my healthcare provider before using SYMBICORT?"
   - We added a bullet for eye problems. Section 5.15 of the PI states that close monitoring is warranted in patients with a change in vision or with a history of increased ocular pressure, glaucoma, or cataracts. If appropriate, also add to ADVAIR Diskus and ADVAIR HFA MG.
   - We modified the allergy bullet to state: "are allergic to any medicines." The section "Who should not take SYMBICORT?" already states that people who are allergic to any of the ingredients in Symbicort should not take it.
   - We modified the breast-feeding bullet to make it consistent with the language under PI section 8.3.
   - We added the important drug interactions under the paragraph which begins with "Tell your healthcare provider about all the medicines you take…" The review division should revise the order of the listed medicines as appropriate. We did not list the antibiotics because there are many erythromycin containing antibiotics. Unless all established and brand names are listed, patients may feel "safe" if they do not see their medicine listed.

4. In the section "How should I use SYMBICORT?"
   - We modified the bullet instructing patients to rinse their mouth after using SYMBICORT as follows:

     Rinse your mouth with water and spit the water out after each dose (two puffs) of SYMBICORT. Do not swallow the water. This will help to lessen the chance of getting fungus infection (thrush) in the mouth and throat.

     We added this language to explain why patients should "rinse and spit out" the water rather than swallowing, to give this information context for helping to prevent thrush. We recommend adding this to ADVAIR Diskus and ADVAIR HFA as well.

   - We added the bullet "Do not spray SYMBICORT in your eyes." The sponsor should provide an instruction for what a patient should do if they accidentally get SYMBICORT in their eyes. Such as "If you accidentally get SYMBICORT in your eyes…" This information should also be added to the PI. The language in the MG must be consistent with the language in the PI.

5. In the section "What are the possible side effects of SYMBICORT?"
   - We added similar language to what is in the approved Advair Diskus MG pertaining to pneumonia in people with COPD.
   - We modified the bullet for eye problems to make it consistent with the language in the Advair HFA MG approved July 31, 2008.
   - We added the most common side effects with Symbicort separated for asthma in adults and children, and COPD.

   For the adverse events in asthma patients:

   (b) (4)

   For the adverse events in COPD patients:

   (b) (4)

   - At the end of the section we added the following language:
     "Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. "

     This verbatim statement is required for all Medication Guides effective January 2008. See 21 CFR 208.20 (b)(7)(iii).

6. In the section "How should I store SYMBICORT?" we added a bullet stating:
   Throw away SYMBICORT when the counter reaches zero ("0") or 3 months after your take SYMBICORT out of its foil pouch.

7. In the section "General Information about Symbicort" we modified the first sentence to state:

   "Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide."

   This is a verbatim statement from 21 CFR 208 (b) (8) (i).

8. We added a section called "What are the ingredients in SYMBICORT?" for consistency with the statement in the section "Who should not take SYMBICORT?" which tells patients that there is a list of ingredients in SYMBICORT at the end of the MG.

9. In the Patient Instructions for Use we have the following comments and recommendations:

   - Add language to figure 1 indicating that this is the "upright position."
   - All figures should be numbered and appropriately referenced in the text. The images associated with the counter are not labeled and referenced.
   - The sponsor should remove all capital letters and used both upper and lower case letters.
   - We modified the priming instructions to make them more patient-friendly.
   - We deleted (b) (4) A bullet has been added to the MG section "How should I store SYMBICORT?" instructing patients to throw away SYMBICORT when the counter reaches zero or 3 months after SYMBICORT is removed from the foil pouch. (b) (4) "How should I store SYMBICORT?"

Please let us know if you have any questions.

38 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

Sharon Mills
12/30/2008 03:21:13 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
12/30/2008 03:30:56 PM
DRUG SAFETY OFFICE REVIEWER

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Pulmonary and Allergy Products

Application Number: NDA 21-929/S-012

Name of Drug: Symbicort® (budesonide/Formoterol) MDI

Applicant: AstraZeneca Pharmaceuticals

Material Reviewed:

Submission Date(s): April 29, 2008

Receipt Date(s): April 29, 2008

Submission Date of Structure Product Labeling (SPL): April 29, 2008

Type of Labeling Reviewed: WORD

Background and Summary

On April 29, 2008, AstraZeneca Pharmaceuticals submitted a supplemental New Drug Application for Symbicort® (budesonide/Formoterol) MDI for the treatment of chronic obstructive pulmonary disease (COPD). Symbicort® was approved for the long term maintenance treatment of asthma in patients 12 years of age and older on July 21, 2006.

The proposed labeling text for Symbicort was provided in SPL. Draft labeling text was provided in Word format (.doc) as a review aid, submitted by AstraZeneca Pharmaceuticals on April 29, 2008.

Review

Primary reviewer: Colette Jackson, Regulatory Health Project Manager
Division of Pulmonary and Allergy Products
OND, ODE II, CDER

The .xml version of the proposed labeling in the new PLR format was reviewed using the Label Review Tool provided by SEALD. The following are comments and recommendations for the proposed labeling that should be conveyed to the applicant in the 74-day letter

Recommendations

Please address the identified deficiency/issue and re-submit the labeling. This updated version of labeling will be used for further labeling discussions.

The following comments pertain to the Hightlights section of the product label.

1. We acknowledge your request to waive the one-half page requirement for the Highlights section. The outcome of your waiver request will be decided during the course of the review.

2. Any reference in Highlights to information appearing in the full prescribing information must be accompanied by the identifying number (in parentheses) corresponding to the location of the information in the Full Prescribing Information (FPI). Under "Dosage and Administration" and "Dosage Forms and Strengths" there are no references the full prescribing information. [See 21 CFR 201.56(d)(3)]

3. Under the Indications and Usage section, major limitations of use must be briefly noted. [See 21 CFR 201.57(a)(6)]

4. Under Recent Major Changes, the corresponding new or modified text under the corresponding sections must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance]

5. The Highlights and Table of Contents do not fit on one page. Insert the Table of Contents on page 2 of the labeling.

6. The same title for the boxed warning that appears in the Highlights and the FPI must also appear at the beginning of the Table of Contents in upper-case letters. Insert the full warning at the beginning of the Table of Contents.

7. The Table of Contents subsection headings must be indented.

8. For pregnancy category C drugs, pregnancy must be listed under the Use in Specific Populations in the Highlights followed by the following statement: "Based on animal data, may cause fetal harm".

Colette Jackson
Regulatory Project Manager

Supervisory Comment/Concurrence:

Sandy Barnes
Chief, Project Management Staff

Drafted: CCJ/ June 23, 2008
Revised/Initialed: Barnes/ June, 2008
Finalized: CCJ/ June, 2008
Filename: NDA 21929 S012 PLR Labeling Review
CSO LABELING REVIEW OF PLR FORMAT

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

/s/

Colette Jackson
7/15/2008 01:48:23 PM
CSO

Sandra Barnes
7/17/2008 06:43:00 PM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-929 Supplement # 012 Efficacy Supplement Type SE- 1

Proprietary Name: Symbicort
Established Name: budesonide/Formoterol
Dosage Form: Metered Dose Inhaler
Strengths: 80/4.5 and 160/4.5

Applicant: AstraZeneca Pharmaceuticals
Agent for Applicant (if applicable):

Date of Application: April 28, 2008
Date of Receipt: April 28, 2008
Date clock started after UN: N/A
Date of Filing Meeting: June 9, 2008
Filing Date: June 27, 2008
Action Goal Date (optional): User Fee Goal Date: February 28, 2009

Indication(s) requested: Chronic Obstructive Pulmonary Disease (COPD)

Type of Original NDA: (b)(1) ☐ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☒ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐N/A Resubmission after refuse to file? ☐N/A
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application.*

Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic ☐ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☐ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES ☒

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐
- Exclusivity requested? YES, 3 Years NO ☐
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES ☒ NO ☐
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐
- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

  If yes, contact PMHT in the OND-IO
- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☒ NO ☐
- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 63,394 (b) (4)
- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) April 19, 2004 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) June 28, 2004 CMC- November 1, 2004 NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES ☒ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☐ YES ☒ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐

If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☒
- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 9, 2008

NDA #: 21-929/S-012

DRUG NAMES: Symbicort® (budesonide/Formoterol) MDI

APPLICANT: AstraZeneca Pharmaceuticals

BACKGROUND: NDA 21-929 was originally approved on July 21, 2006, for the long term maintenance treatment of asthma in patients 12 years of age and older.

ATTENDEES:

Badrul A. Chowdhury, M.D., Ph.D., Division Director, DPADP
Sally Seymour, M.D., Clinical Team Leader, DPADP
Banu Karimi-Shah, M.D., Clinical Reviewer, DPADP
Peter Starke, M.D., Acting Associate Director for Safety
Timothy Robison, Ph.D., Pharmacology/Toxicology Reviewer
Joseph Sun, Ph.D., Pharmacology/Toxicology Team Leader
Ted Guo, Ph.D., Statistical Reviewer
Qian Li, Ph.D., Statistical Team Leader
Partha Roy, Ph.D., Clinical Pharmacology Reviewer
Wei Qiu, Ph.D., Acting Clinical Pharmacology Team Leader
Ramesh Ragavachari, Ph.D., Pharmaceutical Assessment Lead, Post-Marketing, ONDQA
Colette Jackson, Project Manager

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	**Reviewer**
Medical:	Banu Karimi-Shah
Secondary Medical:	Sally Seymour
Statistical:	Ted Guo
Pharmacology:	Timothy Robison
Statistical Pharmacology:	N/A
Chemistry:	Ramesh Ragavachari
Environmental Assessment (if needed):	
Biopharmaceutical:	Partha Roy
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
OPS:	
Regulatory Project Management:	Colette Jackson
Other Consults:	

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☒ NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? ☐ NO ☒
  YES

PHARMACOLOGY/TOX N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? YES ☐ NO ☒
  If yes, was microbiology consulted for validation of sterilization?
  YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☒ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☒ If filed, draft the Pediatric Page at this time.

5. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Colette Jackson
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)
YES ☐ NO ☐

*If "**Yes**," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?
YES ☐ NO ☐

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?
   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No**," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "**No**," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*
Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," to (c), proceed to question 7.*

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No**," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☐ NO ☐

*If "**No**," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

11. Is the application for a duplicate of a listed drug whose only difference is YES ☐ NO ☐

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☐

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES ☐ NO ☐

*If "**Yes**," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*
Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A ☐ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☐

If "**Yes**," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

---

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

/s/

Colette Jackson
7/15/2008 02:20:59 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21–929/S012

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of New Drugs
Division of Pulmonary and Allergy Products (DPAP)

NDA #:	NDA# 21-929, SE01, S-012
Product:	SYMBICORT Inhalation Aerosol **(**Budesonide 160mcg and formoterol fumarate dihydrate 4.5mcg)
SPONSOR:	Astra Zeneca
FROM:	Badrul Chowdhury, MD, PhD, Director, DPAP
DATE:	January 9, 2009

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a REMS for an approved drug if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

Since SYMBICORT was approved July 2006, FDA has become aware of an increased incidence of lower respiratory tract infections in patients with COPD who take SYMBICORT. This information is from controlled clinical trials (one 6-month and one 12-month safety and efficacy trial) submitted with this supplemental new drug application. This information was not available when SYMBICORT was granted marketing authorization. Therefore, we consider this information to be "new safety information" as defined in FDAAA.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits of SYMBICORT outweigh its risks. In reaching this determination we considered the following:

A. SYMBICORT is indicated for maintenance treatment of airflow obstruction in Chronic Obstructive Pulmonary Disease (COPD) COPD patients. The estimated

number of patients in the United States with this condition is approximately 15.3 million. This estimate is based on smoking rates and the spirometric definition for COPD used in the third National Health and Nutrition Examination Survey (NHANES III).[1] We anticipate that COPD patients are likely to be prescribed SYMBICORT.

B. COPD is a chronic progressive lung disease that includes chronic bronchitis, emphysema, or both. The disease is characterized by progressive airflow obstruction. Patients with COPD have progressive shortness of breath, and have frequent exacerbations characterized by increased sputum production and cough, and decline in lung function. COPD is the fourth leading cause of death in the U.S.[2]

C. In clinical studies with SYMBICORT, there was improvement in airflow obstruction and reduction in exacerbations with COPD. Improvement of airflow obstruction was demonstrated in clinical studies lasting 6 months to 12 months in duration.

D. Since COPD is a chronic disease, the expected duration of treatment with SYMBICORT is one year or longer. It is possible that some healthcare providers may maintain some patients with COPD on SYMBICORT for their lifetime.

E. Lower respiratory tract infections are the most serious adverse events associated with the use of SYMBICORT in COPD patients. Respiratory tract infections, particularly in COPD patients, can be serious and can cause substantial morbidity. The precise background incidence of lower respiratory tract infections in COPD patients is not known. Data from a 6 month and 12 month study with SYMBICORT in COPD patients with about 800 patients in the placebo groups showed that 5.1% of patients had lung infections other than pneumonia, which is one estimate of the background rate in COPD patients. In these studies, 7.9% of patients treated with SYMBICORT had lung infections other than pneumonia.

F. SYMBICORT is not a new molecular entity.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that SYMBICORT poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of SYMBICORT. FDA has determined that SYMBICORT is a product that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use SYMBICORT. In addition, patient labeling could help prevent serious adverse events related to the use of the product.

---

[1] Stang P, Lydick E, Silberman C, Kempel A, and Keating ET. The Prevalence of COPD. Using Smoking Rates to Estimate Disease Frequency in the General Population. Chest 2000; 117:354S-359S.

[2] Hoyert DL, Arias E, Smith BL, Murphy SL, Kochanek KD. Deaths: Final data for 1999. National Vital Statistics Report 2001; 49: 1-113.

The elements of the REMS will be the Medication Guide and a timetable for submission of assessment of the REMS.

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

/s/

Badrul Chowdhury
2/27/2009 12:11:54 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21–929/S012

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-929 SUPPL # 012 HFD # 570

Trade Name Symbicort Inhalation Aerosol

Generic Name budesonide/formoterol fumarate dihydrate

Applicant Name AstraZeneca Pharmaceuticals

Approval Date, If Known February 28, 2009

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☒ NO ☐

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	20-929	Pulmicort Respules
NDA#	21-949	Pulmicort Flexhaler
NDA#	20-831	Foradil

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

D5899C001 AND D5899C002

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

D5899C0001 and D5899C0002

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 63394	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 63394	YES ☒	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Colette Jackson
Title: Regulatory Health Project Manager
Date: January 22, 2009

Name of Office/Division Director signing form: Badrul A. Chowdhury, M.D., Ph.D.
Title: Division Director, Divison of Pulmonary and Allergy Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Badrul Chowdhury

2/27/2009 12:14:21 PM

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 21-929 | Supplement Number: 012 | NDA Supplement Type (e.g. SE5): SE1

Division Name: Pulmonary and Allergy | PDUFA Goal Date: February 28, 2009 | Stamp Date: 4/29/2008

Proprietary Name: Symbicort

Established/Generic Name: budesonide/formoterol

Dosage Form: MDI

Applicant/Sponsor: AstraZeneca Pharmaceuticals

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) Asthma in patients 12 years of age and older
(2) _____
(3) _____
(4) _____

Q1: Is this application in response to a PREA PMC? Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMC #:_____

Does the division agree that this is a complete response to the PMC?

☐ Yes. **Skip to signature block.**

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s); ☒ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Chronic Obstructive Pulmonary Disease (COPD)

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☒ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for the remaining pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification**)

☒ Necessary studies would be impossible or highly impracticable because:

- ☒ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

☐ Evidence strongly suggests that product would be ineffective or unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible[#]	Not meaningful therapeutic benefit[*]	Ineffective or unsafe[†]	Formulation failed[Δ]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be ineffective or unsafe in this/these pediatric population(s) (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and F and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Sections D and F and complete the PeRC Pediatric Assessment form); and/or (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Sections E and F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for remaining pediatric subpopulations). Complete Section F on Extrapolation.

Check pediatric subpopulation for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**	
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Yes	No
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.

If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through the partial waivers and deferrals, proceed to Section F. For those pediatric subpopulations for which studies have been completed, proceed to Sections D and F and complete the PeRC Pediatric Assessment form. For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F.

Section D: Completed Studies (for some or all pediatric subpopulations). Complete Section F on Extrapolation.

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F. If there are no further pediatric subpopulations to cover based on the partial waivers, deferrals and completed studies, go to Section F.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations): (Complete section F)

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If studies are not needed because efficacy is being extrapolated from other adult and/or pediatric studies, proceed to Section F. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the target pediatric subpopulation needing studies. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

(Revised: 4/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

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

/s/

Colette Jackson
2/27/2009 12:45:40 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: February 18, 2009

To: Matt Arnold	**From:** Colette Jackson
Company: AstraZeneca	Division of Pulmonary and Allergy Products
Fax number: 302-886-3381	**Fax number:** 301-796-9718
Phone number: 302-886-3303	**Phone number:** 301-796-1230

Subject: NDA 21-929/S-012 FDA Labeling comments

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

NDA 21-929/S-012
Symbicort® Inhalation Aerosol (budesonide/formoterol)

Please refer to your April 28, 2008, supplemental new drug application (sNDA) for Symbicort® Inhalation Aerosol (budesonide/formoterol). The FDA-proposed revisions to your draft labeling for the SYMBICORT Medication Guide have been made using the clean copy of the word version submitted on February 6, 2009. In the revised labeling, FDA insertions are underlined and deletions are strike-out. Be advised that these labeling changes are not the Agency's final recommendations and that additional labeling changes may be forthcoming as the label continues to be reviewed. Please submit revised draft labeling incorporating the changes by close of business February 19, 2009. We have the following comments:

1. The following comments pertain to the Package Insert

   a. In the Highlights Section you state that revisions were made to Adverse Reactions to match the Advair label and that upon inspection of the Advair Package Insert, the events listed are greater than or equal (b) (4) 3%. Note that the Adverse Reactions in the Highlights Section of the Advair label are for events greater than or equal to 3%. Revise the Highlights Section to maintain the adverse reactions as stated in our marked-up label sent to you in our January 30, 2009, communication.

   b. Your proposed revised wording for the onset of action language in the COPD trials with a median time to onset of bronchodilation of 5 minutes. We do not accept your proposal to revise the onset of action language for the following reasons:

      (1) It is not acceptable to use a subset of responders to calculate the median onset time. Your method for calculating the onset of action time included only the patients who responded within 60 minutes post-dose and ignored those who responded after 60 minutes, and those who did not respond.

      (2) You pooled the data from the two studies to calculate the onset of action. We do not accept pooled data to determine the onset of action. The onset of action time should be consistently confirmed in at least two studies. When there is inconsistency in the results among studies, we use the conservative (i.e. the longer) time.

      Therefore, revise the onset of action language as stated in our February 2, 2009, communication.

   c. Your proposa (b) (4) (b nefazodone from the strong CPY 3A4 inhibitor list is not acceptable. Although Serzone (the brand name for nefazodne) was discontinued, many generic products are still on the U.S. market.

d. In section 12.2 "Pharmcodynamics", underline or use a different font for the subheadings "Cardiovascular effects", and "HPA axis effects" throughout that section for clarity.

e. In section 12.3 "Pharmacokinetics" provide the reference for the 27% (b) (4) budesonide Cmax in healthy vs. asthmatics as noted in the package insert.

f. In section 12.3 Pharmacokinetics section, provide the reference for the 42% (b) (4) formoterol Cmax in healthy subjects vs. asthmatics subjects as noted in the package insert.

g. In section 12.3 Pharmacokinetics under Drug –Drug Interactions please insert the word "Ketoconazole" as shown in the package insert.

h. The Safety section 6.2 has been revised to remove the subheading (b) (4) This section is misleading, since the safety experience is from the 2 COPD trials (SUN and SHINE) described in the previous paragraphs. Please insert the missing data in the areas marked "xxx". Table 2 shows the adverse reactions from both studies combined and the Agency considers (b) (4) studies in the COPD population to be trials of several years in duration (e.g. see ADVAIR DISKUS package insert)

i. The Clinical trials section has been edited to clarify the entry criteria vs. the actual characteristics of the patients on study entry. In addition a statement about the lack of efficacy of SYMBICORT 80/4.5 has been added to justify why this dose is not recommended for COPD.

j. Throughout the package insert, there are formatting errors that need to be fixed such as the extra spaces on the Highlights page, and in Tables 2 and 3 where because of the table format the word SYMBICORT is misplaced. Correct the formatting errors throughout the Package Insert.

2. The following comments pertain to the Medication Guide

a. Under "What are the possible side effects with Symbicort?" we added language under "Pneumonia and other lower respiratory tract infections" to put the increased incidence of pneumonia in context with the use of inhaled corticosteroids in COPD patients (See Class language in Package Insert section 5.5 "Warnings and Precautions".

b. Revise the listing of events under the heading "The most common side effects with Symbicort include" to reflect the adverse reactions in the highlights of the package insert (see comment # 1).

If you have any questions, contact Colette Jackson, Regulatory Health Project Manager, at 301-796-1230.

Drafted: CCJ/ February 18, 2009
Initialed:
Barnes/ February 18, 2009
Gilbert-McClain/ February 18, 2009
Chowdhury/ February 18, 2009

Finalized: CCJ/ February 18, 2009

Filename: 21929 s012 February 2009 Labeling Fax no 3.doc

70 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

Colette Jackson
2/18/2009 03:50:15 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: February 3, 2009

To: Matt Arnold	**From:** Colette Jackson
Company: AstraZeneca	Division of Pulmonary and Allergy Products
Fax number: 302-886-3381	**Fax number:** 301-796-9718
Phone number: 302-886-3303	**Phone number:** 301-796-1230

Subject: NDA 21-929/S-012 FDA Labeling comments

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

NDA 21-929/S-012
Symbicort® Inhalation Aerosol (budesonide/formoterol)

Please refer to your April 28, 2008, supplemental new drug application (sNDA) for Symbicort® Inhalation Aerosol (budesonide/formoterol). The FDA-proposed revisions to your SYMBICORT Medication Guide have been made using the clean copy of the word version submitted on January 22, 2009. In the revised labeling, FDA insertions are underlined and deletions are strike-out. Be advised that these labeling changes are not the Agency's final recommendations and that additional labeling changes may be forthcoming as the Medication Guide continues to be reviewed. Please submit revised draft labeling incorporating the changes by COB February 6, 2009. We have the following comments regarding the proposed Onset of Action language in your correspondence dated January 22, 2009:

We have revised your proposed onset of action language

(b) (4)

TO:

Serial FEV_1 measures over 12 hours were obtained in a subset of patients in Study 1 (n = 99) and Study 2 (n =121). The median time to onset of bronchodilation, defined as an FEV_1 increase of 15% or greater increase from baseline, occurred at 15 minutes. Maximum improvement (calculated as the average change from baseline at each time point) in FEV_1 occurred at approximately 2 hours post-dose.

The reasons for the changes are as follows:

1. Although serial FEV_1 over the 12 hour period were (b) (4) respectively, only 99 and 121 patients in the subset were from SYMBICORT 160/4.5 group.

2. When all patients are considered including patients who had responded to the 15% improvement from baseline and those who had not, the onset of action time is 15 minutes because the median onset time in Study SHINE was 15 minutes.

3. We deleted the last phrase (b) (4) because in Study SHINE, the percent change from baseline was above 15% at time points out to 10 hours but not at the (b) (4) post-dose time point.

Include the FDA-revised onset of action language with the revised package insert by Friday February 6th, 2009. If you have any questions, contact Colette Jackson, Regulatory Health Project Manager, at 301-796-1230.

Drafted: CCJ/ February 3, 2009
Initialed:
Barnes/ February 3, 2009
Gilbert-McClain/ February 3, 2009

Finalized: CCJ/ February 3, 2009

Filename: 21929 s012 February 2009 Labeling Fax no 2.doc

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

Colette Jackson
2/3/2009 04:52:18 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 30, 2009

To: Connie Hickman	**From:** Colette Jackson
Company: AstraZeneca	Division of Pulmonary and Allergy Products
Fax number: 302-886-3381	**Fax number:** 301-796-9718
Phone number: 302-886-7865	**Phone number:** 301-796-1230

Subject: NDA 21-929/S-012 FDA Labeling comments

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

NDA 21-929/S-012
Symbicort® Inhalation Aerosol (budesonide/formoterol)

Please refer to your April 28, 2008, supplemental new drug application (sNDA) for Symbicort® Inhalation Aerosol (budesonide/formoterol). The FDA-proposed revisions to your SYMBICORT Medication Guide have been made using the clean copy of the word version submitted on January 9, 2009. In the revised labeling, FDA insertions are underlined and deletions are strike-out. Be advised that these labeling changes are not the Agency's final recommendations and that additional labeling changes will be forthcoming as the label continues to be reviewed. Comments to explain the FDA edits are provided throughout the package insert as appropriate. We have the following general comments. Please submit revised draft labeling incorporating the changes by COB February 6, 2009.

1. The following comments pertain to the HIGHLIGHTS SECTION

   a. The Boxed warning in the highlights was revised to reflect the Advair boxed warning.

   b. The hypersensitivity contraindication from the Full Prescribing Information (FPI) was added.

   c. Table of contents headings were revised (7.1) and added (8.7 and 13.2) to match the Full Prescribing Information.

2. The following comments pertain to the FULL PRESCRIBING INFORMATION

   a. Vertical lines must be added in the left margin next to the text in the FPI that corresponds to the recent Major Changes from Highlights.

   b. Reduce right margin to ½ inch if feasible.

   c. For Section 5 Warnings and Precautions:

      [redacted] (b) (4)

      (2) 5.5 - Maintain [redacted] (b) (4) "pneumonia and other lower respiratory tract infections." The Division maintains that this heading is appropriate for this section. Note that in addition to bronchitis, viral lower respiratory tract infections are also described. Furthermore, in the MedDRA SOC "bronchitis" is classified under "lower respiratory tract infections NEC."

   d. For Section 6 Adverse Reaction:

      We have revised the format of section 6 to be consistent with Advair Diskus. Our previous comments to you regarding PERFOROMIST label notwithstanding, the Division adopted the format for the Advair Diskus label based on the following reasons: In the spirit of the physician labeling rule,

the first section of the adverse reactions section of the label (section 6) should be contain the most serious or significant adverse reactions. Since long acting beta agonists carry a boxed warning, the Division maintains that description of this event is sufficient for this section of the label; with description of other beta-agonist events described in other sections of the label were appropriate. Since corticosteroids do not carry a boxed warning, the Division has prioritized the corticosteroid warnings and chosen the most clinically significant for this section. Please note that the Division intends to maintain this format for all corticosteroid and LABA combo products for consistency.

e. We acknowledge that the regulations allow 8 point font as the smallest font for labeling text. Please use a large font if possible as the fonts for table 1 and 2 are hard to read.

f. For Section 14.2 Clinical Trials (Chronic obstructive Pulmonary Disease):

The Onset of action language for this section of the label is under review. FDA proposed edits will be forthcoming in a subsequent fax.

Drafted: CCJ/ January 29, 2009
Initialed:
Barnes/ January 30, 2009
Gilbert-McClain/ January 30, 2009

Finalized: CCJ/ January 30, 2009

Filename: 21929 s012 Jan 2009 Labeling Fax no 2.doc

61 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

Colette Jackson
1/30/2009 05:27:42 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 16, 2009

To: Connie Hickman	**From:** Colette Jackson
Company: AstraZeneca	Division of Pulmonary and Allergy Products
Fax number: 302-886-3381	**Fax number:** 301-796-9718
Phone number: 302-886-7865	**Phone number:** 301-796-1230

Subject: NDA 21-929/S-012 FDA Labeling comments

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

NDA 21-929/S-012
Symbicort® Inhalation Aerosol (budesonide/formoterol)

Please refer to your April 28, 2008, supplemental new drug application (sNDA) for Symbicort® Inhalation Aerosol (budesonide/formoterol). The FDA-proposed revisions to your SYMBICORT Medication Guide have been made using the clean copy of the word version submitted on April 28, 2008, and taking into account our preliminary draft labeling changes to the PI sent to you on December 10, 2008. In the revised Medication Guide, FDA insertions are underlined and deletions are strike-out. Be advised that these changes are not the Agency's final recommendations. Additional changes to the Medication Guide will be forthcoming as the application continues to be reviewed. Additionally, we are sending section 13.2 of the PI which was inadvertently omitted from the PI in the December 10, 2008, fax. This section will be included in the next FDA-revised Package Insert that we will be sending you. You do not need to re-submit a revised Package Insert at this time. We have the following comments.

1. In 2008, the American society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines For Prescription Labeling and Consumer Medication Information for People with Vision Loss.* They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the Medication Guide (MG) document using the font APHont which was developed by the American Printing House for the Blind specifically for low vision readers.

2. Several reformatted changes to the MG were made based on our comment that asthma (b) (4) in the PI since it was the (b) (4) approved indication.

3. The section "**Who should not use SYMBICORT?**" has been added to reflect the Contraindications section of the PI.

4. In the section "**What should I tell my healthcare provider before using SYMBICORT?**" We did the following:

    - We added a bullet for eye problems. Section 5.15 of the PI states that close monitoring is warranted in patients with a change in vision or with a history of increased ocular pressure, glaucoma, or cataracts.

    - We modified the allergy bullet to state: "are allergic to any medicines." The section "**Who should not take SYMBICORT?**" already states that people who are allergic to any of the ingredients in Symbicort should not take it.

    - We modified the breast-feeding bullet to make it consistent with the language under PI section 8.3.

5. In the section "**How should I use SYMBICORT?**" We did the following:

    - We modified the bullet instructing patients to rinse their mouth after using SYMBICORT to add language to explain why patients should "rinse and spit out" the water rather than swallowing, to give this information context for helping to prevent thrush.

    - We added the bullet "Do not spray SYMBICORT in your eyes." Provide an instruction for what a patient should do if they accidentally get SYMBICORT in their eyes. Such as "If you accidentally get SYMBICORT in your eyes…"

6. In the section "**What are the possible side effects of SYMBICORT**?" We did the following:

    - We added similar language to what is in the approved Advair Diskus MG pertaining to pneumonia in people with COPD.

    - We modified the bullet for eye problems to make it consistent with the language in the Advair HFA MG approved July 31, 2008.

    - We modified the bullet for eye problems to make it consistent with the language in the Advair HFA MG approved July 31, 2008.

    - We added the most common side effects with SYMBICORT separated for asthma in adults and children, and COPD.

    - At the end of the section we added 'Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088." This verbatim statement is required for all Medication Guides effective January 2008. See 21CFR 208.20(b)(7)(iii)

7. In the section "**How should I store SYMBICORT**?" we added a bullet stating:

    "Throw away SYMBICORT when the counter reaches zero ("0") or 3 months after you take SYMBICORT out of its foil pouch."

8. In the section "**General Information about SYMBICORT**" we modified the first sentence to state: "Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide." This is a verbatim statement from 21 CFR 208 9b) (8) (i)

9. We added a section called "**What are the ingredients in SYMBICORT**?" for consistency with the statement in the section "Who should not take SYMBICORT?" which tells patients that there is a list of ingredients in SYMBICORT at the end of the MG.

10. The following comments pertain to the Patient Instructions for Use section

    - Add language to figure 1 indicating that this is the "upright position."
    - Number all figures and reference them appropriately in the text. We note that the images associated with the counter are not labeled and referenced.
    - Remove all capital letters and used both upper and lower case letters.
    - We modified the priming instructions to make them more patient-friendly.
    - We deleted (b) (4) bullet has been added to the MG section "How should I store SYMBICORT?" instructing patients to throw away SYMBICORT when the counter reaches zero or 3 months after SYMBICORT is removed from the foil pouch. The instruction about (b) (4) has been deleted. Storage instructions are already in the MG section "How should I store SYMBICORT?"

11. In the section "**How should I store SYMBICORT**?" we added a bullet stating:

    "Throw away SYMBICORT when the counter reaches zero ("0") or 3 months after you take SYMBICORT out of its foil pouch.

12. In the section "**General Information about SYMBICORT**" we modified the first sentence to state: "Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide." This is a verbatim statement from 21 CFR 208 9b) (8) (i)

13. We added a section called "**What are the ingredients in SYMBICORT**?" for consistency with the statement in the section "Who should not take SYMBICORT?" which tells patients that there is a list of ingredients in SYMBICORT at the end of the MG.

14. We have the following request for clarification about the adverse events listed in the PI as it relates to the Medication Guide

(b) (4)

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

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Drafted: CCJ/ January 15, 2009
Initialed:
Barnes/ January 16, 2009
Robison/ January 16, 2009
Gilbert-McClain/ January 16, 2009

Finalized: CCJ/ January 16, 2009

Filename: 21929 s012 Jan 2009 Labeling Fax.doc

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

/s/

Colette Jackson
1/16/2009 06:04:03 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: December 10, 2008

To: Connie Hickman	**From:** Colette Jackson
Company: AstraZeneca	Division of Pulmonary and Allergy Products
Fax number: 302-886-3381	**Fax number:** 301-796-9718
Phone number: 302-886-7865	**Phone number:** 301-796-1230

Subject: NDA 21-929/S-012 FDA Labeling comments

Total no. of pages including cover: 79

Comments:

Document to be mailed: YES xNO

NDA 21-929/S-012
Symbicort® Inhalation Aerosol (budesonide/formoterol)

Please refer to your April 28, 2008, supplemental new drug application (sNDA) for Symbicort® Inhalation Aerosol (budesonide/formoterol). We have the following labeling comments. The FDA-proposed revisions to your draft labeling for SYMBICORT have been made using the clean copy of the word version of the label submitted on April 28, 2008. In the revised labeling, FDA insertions are underlined and deletions are strike-out. Be advised that these labeling changes are not the Agency's final recommendations and that certain sections of the Package Insert (in particular Clinical Pharmacology) are still under review. Additional labeling changes will be forthcoming as the label continues to be reviewed. FDA-proposed changes to the Medication Guide and Patient Instructions for Use will be sent to you in a subsequent fax.

1. We note that throughout the package insert you have (b) (4) with chronic obstructive disease (COPD) appearing (b) (4) asthma. Revise the label placing asthma first followed by COPD throughout the label, since asthma was the first disease studied, and COPD is an add-on indication to the already approved SYMBICORT product.

2. Several changes in the label (Warnings and Precautions, Clinical Trials Experience) and general changes related to drug class and indications were made throughout the label to harmonize the Symbicort label with the new Advair Diskus label in PLR format.

The following comments pertain to specific sections of the package insert

Section 1: Indications and Usage
- Revise this section so that Asthma (b) (4) and COPD (b) (4)

Section 2: Dosage and Administration

- This section was revised to follow the format and content of Advair Diskus label
- Information that has been struck out is not appropriate in this section per the new PLR format and has been moved to more appropriate sections.
- Section 2.3 Geriatric Use in COPD and Asthma is not required as there is no recommended dosing adjustment.

Section 3: Dosage Forms and Strengths
Information that has been struck out has been moved to the How Supplied section of the label.

Section 5: Warnings and Precautions
- Section 5.5 "Pneumonia and Other Lung Infections." Although – the SYMBICORT COPD studies did not show a pneumonia signal, the Agency considers pneumonia to

be a class effect of corticosteroids in COPD. The SYMBICORT COPD program showed an increase in "Lung infections other than pneumonia) and data from both SHINE and SUN studies (tables 11.3.2.6.14) have been incorporated into the text.

- Section 5.6 Immunosuppression: The paragraph regarding the open label study on responsiveness to varicella vaccine was relocated here from the Drug-Drug interaction section as it is more appropriate here under "Immunosuppression" where the issue of varicella and VZIG is discussed per class labeling.
- Section 5.9: Drug Interactions with Strong Cytochrome P450 3A4 inhibitors) is under review.
- Section 5.13: Reduction in Bone Mineral Density: The study results from the SUN (12 month) study are described in more detail.
- Section 5.15: Glaucoma and Cataracts: The study results from the SUN (12 month) study are presented in more detail.

Section 6: Adverse Reactions

- Revise this section as per our comment #1 so that (b) (4) is Asthma and (b) (4) COPD
- Revise the adverse reactions for the COPD program into short term (6 month) and long-term, and revise the table to present the adverse reactions for the short term (6 month) study only.

Section 8: Use in Special Populations

Revise section 8.5 to comply with the regulatory language in 21 CFR 201.57 (b) (9) (v)

Section 14: Clinical Studies

- Revise the format so that asthma is (b) (4) and COPD is (b) (4)
- For the COPD section, please fill in the appropriate data where "XX" is denoted.
- The (b) (4) because a definition of COPD exacerbation based solely on a change in therapy is inadequate to assess this endpoint. Furthermore, the results were not replicated, as the result was not statistically significant in the 6 month study.
- The (b) (4)
- The table of other secondary endpoints (b) (4) a general statement regarding their supportiveness added.
- Additional changes to the Clinical trial section – specifically the inclusion of figure 3 and 4 and the acute bronchodilation response language in the COPD studies are under review.

Section 16: How Supplied/Storage and Handling

- Information from Dosage Forms and Strengths section of the label has been moved to this section.

Section 17: Patient Counseling Information

- This section was revised to be consistent with Advair Diskus.

If you have any questions, please contact Colette Jackson, Regulatory Health Project Manager, at 301-796-1230.

Enclosure: FDA Proposed Labeling.

75 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

Colette Jackson
12/10/2008 05:48:26 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 26, 2008

To: Connie Hickman	**From:** Colette Jackson
Company: AstraZeneca	Division of Pulmonary and Allergy Products
Fax number: 302-886-2822	**Fax number:** 301-796-9718
Phone number: 302-886-7865	**Phone number:** 301-796-1230

Subject: NDA 21-929/S-012

Total no. of pages including cover: 3

Comments:

Document to be mailed: **YES** **xNO**

NDA 21-929/S-012
Symbicort

We are reviewing your supplemental NDA dated April 28, 2008, and we have the following requests in order to facilitate our review.

1. Table 12.2.6.5.3 in the file *d5899c00002-12-2-06-indiv-efficacy-and-pk-resp-data.pdf* has 24-hr urine cortisol data that may not be correct. These data do not match the data presented in Table 12.2.10.2.1 included in the file *d5899c00002-12-2-10-listing-of-other-safety-data.pdf*, Also, provide the location of the .xpt file for the data listed in Table 12.2.6.5.3.

2. If the above data presented in Table 12.2.6.5.3 is not correct, most likely the plots in Figures 11.2.10.1.11-11.2.10.1.12 may also be incorrect. Re-plot with the correct data.

3. Provide plots of pooled PK/PD (24-hr urine free cortisol and cortisol/creatinine ratio) data for all treatments in order to address the exposure-response relationship, if any.

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

Drafted: November 26, 2008

Initialed: Barnes/ November 26, 2008
Roy/ November 26, 2008
Qiu/ November 26, 2008

Finalized: CCJ/ November 26, 2008

Filename: 21929 s012 nov2008 clin pharm fax

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

/s/

Colette Jackson
11/26/2008 02:18:00 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-929/S-012 **INFORMATION REQUEST LETTER**

AstraZeneca LP
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Attention: Mark DeSiato
Executive Director, Regulatory Affairs

Dear Mr. DeSiato:

Please refer to your April 28, 2008 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symbicort (budesonide/formoterol) Inhalation Aerosol.

We also refer to your submissions dated August 7, and 20, 2008.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental NDA.

The following information request pertains to the "Adverse Events of Interest: Lung Infections" section of the SUN Clinical Study Report (p. 207). It is stated that "*there were 78 subjects with at least 1 event and slightly fewer events on all active treatments compared to placebo…..A total of 49 subjects had pneumonia SAEs during randomized treatment and 12 of these SAEs led to a DAE*." In the paragraph following Table 67 on p. 207, it is stated that "*there were 8 SAEs in the bronchitis category…*" Clarify these numbers as they do not seem to be consistent in subsequent sections where SAEs and DAEs are described. For example, in Table 78 of the SUN CSR (p. 236), there are only 30 pneumonia SAEs reported (as opposed to the 49 stated above) and only 5 bronchitis SAEs (as opposed to 8 stated above). Further, in Table 79 (p. 238), only 8 pneumonia DAEs are listed (as opposed to the 12 listed above). Provide an explanation as to the discrepancy in the numbers and fill in the tables provided below, so that all the data may be readily compared. Provide the same information for the SHINE study as well. If this presentation of data is already present in the NDA submission, provide its location.

Number and % of subjects with pneumonia or other lung infection adverse events by MedDRA preferred term, during randomized treatment (Safety Analysis Set)

	Symb 160	Symb 80	Formoterol	Placebo	Total
Pneumonia (all MedDRA PTs)	N (%)	N (%)	N (%)	N (%)	N (%)

Other Lung Infections (all MedDRA PTs)	N (%)	N (%)	N (%)	N (%)	N (%)

Summary of SAEs by MedDRA Preferred Term, during randomized treatment (Safety Analysis Set)

	Symb 160	Symb 80	Formoterol	Placebo	Total
Pneumonia (all MedDRA PTs)	N (%)	N (%)	N (%)	N (%)	N (%)
Other Lung Infections (all MedDRA PTs)	N (%)	N (%)	N (%)	N (%)	N (%)

Summary of DAEs by MedDRA Preferred Term, during randomized treatment (Safety Analysis Set)

	Symb 160	Symb 80	Formoterol	Placebo	Total
Pneumonia (all MedDRA PTs)	N (%)	N (%)	N (%)	N (%)	N (%)
Other Lung Infections (all MedDRA PTs)	N (%)	N (%)	N (%)	N (%)	N (%)

Please respond to our comments by COB December 5, 2008. If you have any questions, call Colette Jackson, Regulatory Health Project Manager, at 301-796-1230.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Chief, Project Management Staff
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Sandra Barnes

11/25/2008 12:56:00 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-929\S-012 **INFORMATION REQUEST LETTER**

AstraZeneca LP
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Attention: Mark DeSiato
Executive Director, Regulatory Affairs

Dear Mr. DeSiato:

Please refer to your April 28, 2008 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symbicort (budesonide/formoterol) Inhalation Aerosol.

We also refer to your submissions dated August 7, and 20, 2008.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The following information request pertains to Table 11.3.2.6.14 in the SHINE clinical study report. Provide a clarification as to how you arrived at the total number of infections in each treatment group, as well as the totals for other lung infections and pneumonia. For example:

   a. In the budesonide/formoterol free combination group, there are 18 "other lung infections" and 3 pneumonias, yet the total is listed as 20.
   b. In the budesonide 160 BID group, there are 17 "other lung infections" and 5 pneumonias, yet the total is listed as 21.
   c. In the formoterol 4.5 group, there are 13 "other lung infections" listed, however 8 bronchitis + 3 acute bronchitis + 2 LRTI bacterial + 1 lung infection should add to 14.
   d. In the placebo group, there are 10 "other lung infections" and 4 pneumonias, yet the total is listed as 13.

   In addition, provide the data tabulated so that multiple events for the same subject are counted individually in each category.

2. Provide the same clarification and analysis with regard to Table 11.3.2.6.14 in the SUN clinical study report. Also provide the data tabulated so that multiple events for the same subject are counted individually in each category.

3. Tabulate the respiratory infection adverse events under the Respiratory, Mediastinal, and Thoracic Disorders System Organ Class (SOC), rather than under the Infections and Infestations SOC. Further, provide these adverse events groups by High Level Term (HLT) and High Level Group Term (HLGT). If this presentation of data is already present in the NDA submission, provide its location.

Please respond to our comments by COB November 28, 2008. If you have any questions, call Colette Jackson, Regulatory Health Project Manager, at 301-796-1230.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Chief of Project Management
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Sandra Barnes

11/18/2008 11:50:51 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-929/S-012 **PRIOR APPROVAL SUPPLEMENT**

AstraZeneca LP
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Attention: Mark DeSiato
Executive Director, Regulatory Affairs

Dear Mr. DeSiato:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: SYMBICORT® (budesonide/formoterol) Inhalation Aerosol

NDA Number: 21-929

Supplement number: 012

Date of supplement: April 28, 2008

Date of receipt: April 28, 2008

This supplemental application proposes an indication for chronic obstructive pulmonary disease (COPD).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 27, 2008, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 28, 2009.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Products
5901-B Ammendale Road

Beltsville, MD 20705-1266

If you have any question, call Colette Jackson, Regulatory Health Project Manager, at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Colette Jackson
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Colette Jackson

5/22/2008 12:07:10 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Division of Drug, Marketing, Advertising and Communication (DDMAC)
WO Bldg 22 Rm. 1400

FROM:
Colette Jackson
Project Manager
Division of Pulmonary and Allergy Products at 6-1230

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
May 22, 2008		21-929	S-012	April 28, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
SYMBICORT® (budesonide/formoterol) MDI	Standard	Glucocorticosteroid and beta-2 agonist	December 29, 2008

NAME OF FIRM: AstraZeneca Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE—NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Labeling Review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

This is a request for an evaluation and review of the labeling for SYMBICORT®.
This submission is electronic only and is located in the EDR in the submission dated April 28, 2008.

PDUFA DATE: February 28, 2009
CC:
Archival NDA 21-929
HFD-570/Division File
HFD-570/Jackson

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Colette Jackson
5/22/2008 04:58:35 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE

FROM: Colette Jackson
Project Manager
Division of Pulmonary and Allergy Drug Products, HFD-570

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
May 22, 2008		21-929	S-012	April 28, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
SYMBICORT® (budesonide/formoterol) MDI	Standard	Glucocorticosteroid and beta-2 agonist	December 29, 2008

NAME OF FIRM: AstraZeneca Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This is a consult for a labeling review of the prescribing information, medication guide, and a review of the risk management plan for Symbicort.
The prescribing information, medication guide, and risk management plan are electronic and located in the EDR under the submission dated April 28, 2008

PDUFA DATE: February 28, 2009

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) √ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Colette Jackson
5/22/2008 05:00:28 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-929/S-012

AstraZeneca LP
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Attention: Mark DeSiato
Executive Director, Regulatory Affairs

Dear Mr. DeSiato:

Please refer to your April 28, 2008, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SYMBICORT® (budesonide/formoterol) Inhalation Aerosol.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on June 28, 2008, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential filing review issues.

1. (b) (4)

2. (b) (4)

[redacted] (b) (4)

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. After a preliminary review of your submission, including SAS data, we have found that you did not include all randomized patients in your serial PFT data sets. In the protocol and study report, you indicate that the assessment of onset-of-effect was based on a subset of patients. To allow us to do an independent and objective evaluation, clarify the rationale of using only a subset of patients, how the subset was identified, whether all the serial PFT data have been submitted, and whether the analysis of the onset-of-effect has included all patients with serial PFTs.

2. The following comments pertain to the Highlights section of the product label.

    a. We acknowledge your request to waive the one-half page requirement for the Highlights section. The outcome of your waiver request will be decided during the course of the review.

    b. Any reference in Highlights to information appearing in the full prescribing information must be accompanied by the identifying number (in parentheses) corresponding to the location of the information in the Full Prescribing Information (FPI). Under "Dosage and Administration" and "Dosage Forms and Strengths" there are no references the full prescribing information. [See 21 CFR 201.56(d)(3)]

    c. Under the Indications and Usage section, major limitations of use must be briefly noted. [See 21 CFR 201.57(a)(6)]

    d. Under Recent Major Changes, the corresponding new or modified text under the corresponding sections must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance]

    e. The Highlights and Table of Contents do not fit on one page. Insert the Table of Contents on page 2 of the labeling.

    f. The same title for the boxed warning that appears in the Highlights and the FPI must also appear at the beginning of the Table of Contents in upper-case letters. Insert the full warning information at the beginning of the Table of Contents.

    g. The Table of Contents subsection headings must be indented.

h. For pregnancy category C drugs, pregnancy must be listed under the Use in Specific Populations in the Highlights followed by the following statement: "Based on animal data, may cause fetal harm".

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Colette Jackson, Regulatory Project Manager, at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Badrul Chowdhury
7/1/2008 11:13:02 AM