Drug Substance(s) (Symbicort)	Budesonide/Formoterol	**SYNOPSIS**	
Study Code	D589DL00001		
Date	27 October 2016		

Symbicort Turbuhaler 30 doses/60 doses, Specific Clinical Experience Investigation for long-term use

Study dates:
First subject enrolled: November 2012
Last subject completed: December 2015

Objectives
The purpose of the investigation is to confirm the safety and efficacy in long-term use of Symbicort Turbuhaler in patients with chronic obstructive pulmonary disease (hereinafter referred to as COPD) under actual drug use in the post-marketing phase.

Study design
The investigation was carried out with central registration method.

Target subject population and sample size
Among patients treated with the drug due to 'relief of various symptoms associated with airway obstructive disorders of COPD (chronic bronchitis, pulmonary emphysema), which is the indication of the drug, those who received the drug for the first time.

Target number of patients: 1000

Investigational product
Symbicort Turbuhaler 30/60 doses

Duration of treatment
1 year

Variables
Adverse event, clinical course (respiratory function test, CCQ (Clinical COPD Questionnaire)), severe acute exacerbation of COPD

Subject population
In this investigation, the registration number of patients was 1183, and after 14 patients whose CRF was not collected were excluded, the number of patients whose CRF was collected was 1169. Regarding the 1169 patients with CRF, 46 patients in total were excluded for not receiving the drug, history of receiving the drug, no revisit, or not safety evaluated. The remaining 1123 patients were safety evaluable. Regarding the 1123 safety evaluable patients, 1 patient receiving the drug for the indication other than those of re-examination and 370 patients without the data of clinical course were excluded from efficacy analysis; the remaining 752 were eligible for efficacy analysis.

Table S1 Subject population

Characteristic	Statistic	Number of safety analysis patients (n=1123)
Gender	Male	938 (83.5)
	Female	185 (16.5)
Age	Mean ± SD	71.2 ± 10.6
	<45	24 (2.1)
	45≦<55	56 (5.0)
	55≦<65	173 (15.4)
	65≦<75	403 (35.9)
	75≦<85	377 (33.6)
	85≦	90 (8.0)
COPD staging classification	I	238 (21.2)
	II	422 (37.6)
	III	271 (24.1)
	IV	105 (9.3)
	Unknown	85 (7.6)
	Not reported	2 (0.2)
Duration of illness (month)	Mean ± SD	68.5 ± 71.1
Height (cm)	Mean ± SD	161.7 ± 8.0
Weight (kg)	Mean ± SD	58.6 ± 11.6
BMI (kg/m^2)	Mean ± SD	22.36 ± 3.76
Smoking history	No	106 (9.4)
	Yes	344 (30.6)
	Past	648 (57.7)
	Unknown	23 (2.0)
	Not reported	2 (0.2)
Hospitalization due to COPD within a year prior to the start of Symbicort	No	987 (87.9)
	Yes	91 (8.1)
	Unknown	44 (3.9)
	Not reported	1 (0.1)
Glucocorticosteroid treatment due to COPD within a year prior to the start of Symbicort	No	966 (86.0)
	Yes	126 (11.2)
	Unknown	30 (2.7)
	Not reported	1 (0.1)
Previous therapeutic drug for asthma	No	468 (41.7)
	Yes	630 (56.1)
	Unknown	24 (2.1)
	Not reported	1 (0.1)
Past medical history	No	884 (78.7)
	Yes	231 (20.6)
	Unknown	7 (0.6)
	Not reported	1 (0.1)
Concomitant disease	No	278 (24.8)
	Yes	837 (74.5)
	Unknown	7 (0.6)

Table S1 Subject population

Characteristic	Statistic	Number of safety analysis patients (n=1123)
	Not reported	1 (0.1)

Summary of safety results

[1] Total 82 events of ADRs were reported in 65 of 1123 safety evaluable patients (5.8%). ADRs reported in 3 or more patients were Dysphonia in 21 patients (1.9%), Oropharyngeal discomfort in 7 patients (0.6%), Palpitations in 5 patients (0.4%), Bronchitis in 4 patients (0.4%), Oral candidiasis in 4 patients (0.4%), Pneumonia in 4 patients (0.4%), and Cough in 3 patients (0.3%).

Among the reported ADR events, serious ADRs were Pneumonia in 4 patients (0.4%), Angina unstable in 1 patient (0.1%), Cardiac failure in 1 patient (0.1%), and Compression fracture in 1 patient (0.1%). The outcomes of all of the events were recovery or improvement. Regarding ADR development by observation period, no increase of ADR frequency was recognised with long-term use of the drug.

Unexpected ADRs were Herpes zoster, Oesophageal candidiasis, Diabetes mellitus, Angina unstable, Cardiac failure, Asthma, Chronic obstructive pulmonary disease, Increased viscosity of bronchial secretion, Upper-airway cough syndrome, Constipation, Dysphagia, Glossodynia, Stomatitis, Buccal mucosal roughening, Genital haemorrhage, Chest pain, Feeling abnormal, and Compression fracture, all of which were reported in one patient each. All of the reported events were non-serious ADR except Angina unstable, Cardiac failure, and Compression fracture.

[2] One hundred and twenty-five events of serious AEs were reported in 84 of 1123 safety evaluable patients (7.5%). Among them, serious AEs reported in 3 or more patients were Pneumonia in 21 patients (1.9%), Chronic obstructive pulmonary disease in 16 patients (1.4%), Lung neoplasm malignant/Small cell lung cancer/Squamous cell carcinoma of lung in 9 patients (0.8%), Cardiac failure in 8 patients (0.7%), and Pneumothorax in 3 patients (0.3%). Causal relationship with the drug was not excluded only for 4 events of Pneumonia, 1 event of Angina unstable, 1 event of Cardiac failure, and 1 event of Compression fracture, but excluded for all remaining events.

[3] As a result of reviewing the patient's background factors influencing ADR development and treatment factors related to Symbicort administration, the factors with which significant difference in ADR frequency ($P< 0.05$) was noted were "with/without previous therapeutic drug for COPD" ($p=0.0136$) and "treatment duration (Fisher's exact test: $p<0.0001$, Cochran-Armitage test: $p<0.0001$)".

[4] The key investigation items of 1) ADRs possibly related to pharmacological effect of beta2 stimulant, 2) ADRs possibly related to pharmacological effect of inhalation steroid, 3) serious cardiovascular AEs, and 4) pneumonia-related AEs were reviewed.

1) Regarding ADRs possibly related to pharmacological effect of beta2 stimulant, 14 events were reported in 13 patients (1.2%): Palpitations (5 events), Atrial fibrillation (2 events), Muscle spasms (2 events), Diabetes mellitus (1 event), Tremor (1 event), Supraventricular extrasystoles (1 event), Tachycardia (1 event), and Blood pressure increased (1 event). All of the events were non-serious.

2) Regarding ADRs possibly related to pharmacological effect of inhalation steroid, 39 events were reported in 37 patients (3.3%): Dysphonia (21 events), Oral candidiasis (5 events), Bronchitis (4 events), Pneumonia (4 events), Nasopharyngitis (1 event), Oesophageal candidiasis (1 event), Diabetes mellitus (1 event), Upper respiratory tract inflammation (1 event), and Compression fracture (1 event). All of the events were non-

serious except 4 events of Pneumonia and 1 event of Compression fracture. The outcomes of the most events were recovery or improvement.
3) Sixteen events of serious cardiovascular AEs were reported in 15 patients (1.3%). The details were Cardiac failure (8 events), Angina unstable (2 events), Cardiac failure congestive (2 events), Cor pulmonale (1 event), Myocardial infarction (1 event), Right ventricular failure (1 event), and Sudden death (1 event). As causal relationship between each event and the drug was excluded by the reporting physician for all events except 1 event of Angina unstable and 1 event of Cardiac failure. Among the patients who developed cardiac failure, 6 of 8 patients originally had complication of heart disease.
4) Seventy-four events of pneumonia-related AEs were reported in 61 patients (5.4%). The details were Pneumonia (29 events), Pneumonia bacterial (2 events), Interstitial lung disease (2 events), Pneumonia aspiration (2 events), Pneumonia klebsiella (1 event) and Pneumonia mycoplasmal (1 event). Among them, serious adverse events were Pneumonia (21 events), Interstitial lung disease (2 events), Pneumonia aspiration (2 events), Pneumonia bacterial (1 event) and Pneumonia mycoplasmal (1 event). Causal relationship with the drug was excluded by the reporting physician for all events except 4 events of Pneumonia.
Additionally, development of COPD aggravated was confirmed since the aggravation potentially affect to the development of pneumonia. As a result, thirty-seven events of COPD aggravated were reported. Among of them, 16 events were reported as serious.

Summary of efficacy results

In this investigation, to grasp clinical course of COPD under actual drug use of Symbicort Turbuhaler, clinical questionnaire about chronic obstructive pulmonary disease [COPD] (hereinafter referred to as CCQ) was used before and after treatment with Symbicort Turbuhaler, as well as respiratory function test (FVC [forced vital capacity], FEV_1 [forced expiratory volume in 1 second]).

1) Regarding mean variation of respiratory function tests (FVC, FEV_1) from the baseline at Week 12, Week 26, 1 year, and the time patients were finally observed, significant improvement was recognised at any point compared to the baseline ($p<0.0001$).

2) The mean variations of scores of symptoms, functional state, and mental state, and total CCQ score improved significantly at any point from the baseline: Week 12, Week 26, 1 year, and the time patients were finally observed. The data were collected in CCQ, a questionnaire developed for determination of health condition of COPD patients ($p<0.0001$).

Summary of COPD exacerbation

COPD exacerbation was confirmed in 45 of 1123 safety evaluable patients (4.0%). The data were reviewed by with/without concurrent asthma. As a result, the frequency of COPD exacerbation was higher in the population without concurrent asthma (4.6%, 39/849 patients) compared to those with concurrent asthma (2.2%, 6/274 patients).

Regarding treatment of the event for the 45 patients, "use of systemic steroid and hospitalisation were required" in 19 patients, "use of systemic steroid was required (without hospitalisation)" in 16 patients, "hospitalisation was required (without use of systemic steroid)" in 9 patients, and "hospitalisation was required while use of systemic steroid was unknown" in one patient.