Drug Substance(s) (Symbicort)	Budesonide/Formoterol	**SYNOPSIS**	
Study Code	D589LL00001		
Date	15 July 2016		

Symbicort Turbuhaler 30 doses/60 doses, Clinical Experience Investigation of Symbicort Turbuhaler as Maintenance Therapy and Reliever Therapy

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

Objectives
The purpose of the investigation is to confirm the safety of Symbicort Turbuhaler in patients receiving the drug as maintenance therapy and reliever therapy (hereinafter referred to as 'SMART therapy') under the post-marketing actual use.

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

Target subject population and sample size
Patients receiving Symbicort SMART for the first time due to 'bronchial asthma (in case concomitant use of inhalation steroid or long-acting inhaled beta2 stimulant is required)', which is the indication of Symbicort, and possibly requiring as-needed inhalations during the observation period.

Patients with higher possibility of taking as-needed inhalations frequently (total of the dose for maintenance therapy and as-needed inhalations is 9 and more inhalations/day), described as below, should be prioritized for enrolment.

-Patients experienced acute aggravation of asthma under treatment with maintenance drug.
-Patients experienced episode(s) of hospitalization/emergency visit due to aggravated asthma under treatment with maintenance drug.
-Patients with higher frequency of using SABA (short-acting beta2 stimulant) under treatment with maintenance drug prior to the start of Symbicort SMART.

Target number of patients: 2000

Investigational product
Symbicort Turbuhaler 30/60 doses

Duration of treatment
12 weeks after Symbicort SMART was started

Variables
Adverse event, severe acute exacerbation of asthma

Subject population

In this investigation, the registration number of patients was 2409, and the number of patients whose CRF was collected (the number of patients who completed the investigation) was 2383. Regarding the 2383 patients, 244 patients were excluded from safety analysis (1 patient of "inclusion criteria violation", 2 patients of "non-compliance with this drug", 1 patient of "history of receiving SMART therapy", 235 patients of "no revisit", and 5 patients of "not safety evaluated") , and the remaining 2139 patients were eligible for safety analysis.

Table S1 Subject population

Characteristic	Statistic	Number of safety analysis patients (n=2139)
Gender	Male	727 (34.0)
	Female	1412 (66.0)
Age	Mean ± SD	51.8 ± 17.2
	<15	6 (0.3)
	15≦<25	105 (4.9)
	25≦<35	254 (11.9)
	35≦<45	471 (22.0)
	45≦<55	352 (16.5)
	55≦<65	358 (16.7)
	65≦<75	373 (17.4)
	75≦	220 (10.3)
Severity prior to the start of SMART therapy	Intermittent	439 (20.5)
	Mild persistent	690 (32.3)
	Moderate persistent	809 (37.8)
	Severe persistent	149 (7.0)
	Very severe persistent	18 (0.8)
	Unknown	34 (1.6)
Administration of SABA during one week prior to the start of SMART therapy	No	1502 (70.2)
	Yes	460 (21.5)
	Unknown	177 (8.3)
Hospitalisation/emergency visit due to aggravated asthma during one year prior to the start of SMART therapy	No	1580 (73.9)
	Yes	460 (21.5)
	Unknown	99 (4.6)
Duration of illness (month)	Mean ± SD	104.3 ± 129.6
Height (cm)	Mean ± SD	159.4 ± 9.0
Weight (kg)	Mean ± SD	60.0 ± 13.2
BMI (kg/m^2)	Mean ± SD	23.47 ± 4.27
Smoking history	No	1361(63.6)
	Yes	289(13.5)
	Past	362(16.9)
	Unknown	127(5.9)

Table S1 Subject population

Characteristic	Statistic	Number of safety analysis patients (n=2139)
Atopic diathesis	No	1061 (49.6)
	Yes	786 (36.7)
	Unknown	292 (13.7)
Previous therapeutic drug for asthma	No	617 (28.8)
	Yes	1468 (68.6)
	Unknown	54 (2.5)
Inhalation of Symbicort prior to the start of Symbicort SMART therapy	No	1272 (59.5)
	Yes	867 (40.5)
Past medical history	No	1872 (87.5)
	Yes	248 (11.6)
	Unknown	19 (0.9)
Concomitant disease	No	783 (36.6)
	Yes	1337 (62.5)
	Unknown	19 (0.9)

Summary of safety results

1) Sixty-four events of adverse drug reactions (ADRs) were confirmed in 53 of 2139 safety analysis patients (2.5%). ADRs reported for more than 3 patients were Dysphonia (10 patients, 0.5%), Palpitations (8 patients, 0.4%), Tremor (6 patients, 0.3%), Oropharyngeal pain and Muscle spasms (3 patients for each event, 0.1%). In this investigation, ADRs possibly related to the pharmacological action of beta2 stimulant or steroid were mainly reported. Serious ADRs were Atrial fibrillation, Ventricular extrasystoles, Asthma and Chest discomfort (1 patient for each event, 0.0%). Unexpected ADRs were: Chest discomfort (2 patients, 0.1%); Diabetes mellitus, Hyperkalaemia, Dysarthria (reported AE term: difficulty in articulation), Hypoaesthesia, Mental impairment (reported AE term: thinking reduced), Asthma, Stomatitis, Vomiting, Feeling abnormal, Oedema, Activated partial thromboplastin time prolonged, and Blood cortisol decreased (1 patient for each event, 0.0%). All of the events except asthma and chest discomfort were non-serious ADRs.
2) As the result of reviewing ADR frequency by patient background factor and by treatment factor, significant difference of ADR frequency ($P < 0.05$) was observed for Age (Fisher's exact probability test: not calculated, Cochran-Armitage test: p=0.0285) and with/without previous use of Symbicort prior to the start of SMART therapy ($p<0.0001$).
3) ADR frequency was reviewed by maximum total daily dose to investigate the safety in taking as-needed inhalations frequently (in the case that total of the doses of maintenance therapy and reliever therapy is 9 and more inhalations/day). As a result, ADR frequency was 2.3% (38/1670 patients) for "</= 8DF" and 1.4% (2/144 patients) for ">/= 9 DF", indicating no significant difference (p=0.7659).
4) The key investigation items were examined: i) ADRs possibly related to the pharmacological action of beta2 stimulant, ii) ADRs possibly related to the pharmacological action of steroid.
   i) Twenty-four events of ADRs possibly related to the pharmacological action of beta2 stimulant were reported in 22 of 2139 safety analysis patients (1.0%). The ADRs were Palpitations (8 patients, 0.4%), Tremor (6 patients, 0.3%), Muscle spasm (3 patients, 0.1%), Atrial fibrillation and Tachycardia (2 patients for each event, 0.1%), Diabetes mellitus and Ventricular extrasystoles (1 patient for each event, 0.0%). All of the ADR events except

Atrial fibrillation and Ventricular extrasystoles were non-serious, most of which outcomes were recovery or improvement.

ii) Eighteen events of ADRs possibly related to the pharmacological action of steroid were reported in 17 of 2139 safety analysis patients (0.8%). The ADRs were Dysphonia (10 patients, 0.5%), Bronchitis and Oral candidiasis (2 patients for each event, 0.1%), Nasopharyngitis, Pneumonia, Upper respiratory tract inflammation and Blood cortisol decreased (1 patient for each event, 0.0%). All of these ADR events were non-serious, which outcomes were recovery for 8 events, improvement for 5 events, not recovered for 2 events, and unknown for 3 events.

5) Review of development of severe acute exacerbation of asthma

i) Thirty-three events of severe acute exacerbation of asthma were confirmed in 29 of 2139 safety analysis patients (1.4%).

ii) Patient background factors possibly affect development of severe acute exacerbation of asthma was reviewed. As a result, significant difference in the severe acute exacerbation frequency ($p<0.05$) was recognized for severity prior to the start of SMART therapy (Fisher's exact probability test: $p=0.0001$, Cochran-Armitage test: $p<0.0001$), with/without using SABA during one week prior to the start of SMART therapy ($p<0.0001$), with/without hospitalisation/emergency visit due to aggravated asthma during one year prior to the start of SMART therapy ($p=0.0024$), with/without previous therapeutic drug for asthma ($p=0.0012$), treatment with Symbicort prior to the start of SMART therapy ($p=0.0217$), and with/without concomitant disease ($p=0.0317$).

iii) As the result of reviewing factors related to SMART therapy, significant difference was recognised for with/without as-needed inhalations ($p<0.0001$), maximum daily dose of as-needed inhalations (Fisher's exact probability test: $p=0.0362$, Cochran-Armitage test: $p=0.3485$), maximum daily dose of Symbicort Turbuhaler (Fisher's exact probability test: not calculated, Cochran-Armitage test: $p=0.0003$) and with/without concomitant drug ($p=0.0182$).