Drug Substance(s)	FORMOTEROL (OXIS)	**SYNOPSIS**	
Study Code	D5127L00001		
Date	22 January 2016		

Oxis 9 mcg Turbuhaler 28/60 Clinical Experience Investigation

Study dates:
First subject enrolled: January 2013
Last subject completed: July 2015

Objectives
The purpose of the investigation was to confirm ADR development, etc, under the post-marketing actual use of Oxis 9 mcg Turbuhaler.

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

Target subject population and sample size
Patients treated with Oxis for the first time due to 'relief of various symptoms associated with airway obstructive disorders of chronic obstructive pulmonary disease (Chronic bronchitis, Pulmonary emphysema), which is the indication of this drug.

Target number of patients: 300

Investigational product
Oxis 9 mcg Turbuhaler

Duration of treatment
12 weeks

Variables
Adverse event, blood pressure, pulse, blood sugar, serum potassium, forced vital capacity [FVC], forced expiratory volume [FEV_1], peak flow rate

Subject population
In this investigation, the registration number of patients was 398, and the number of patients whose CRF was collected (the number of patients who completed the investigation) was 396. Regarding the 396 patients whose CRF was collected, 27 patients in total were excluded: 2 for contract violation, 24 for no revisit and 1 for not safety evaluated; the remaining 369 patients were safety evaluable.

Table S1 Subject population

Charcteristic	Statistic	Number of safety evaluable patients (n=369)
Gender	Male	286 (77.5)
	Female	83 (22.5)
Age	Mean ± SD	71.6 ± 11.0
	15≦<65	81 (22.0)
	65≦	288 (78.0)
BMI (kg/m^2)*	Mean ± SD	22.20 ± 3.83
COPD staging classification	I	94 (25.5)
	II	138 (37.4)
	III	68 (18.4)
	IV	12 (3.3)
	Unknown	57 (15.4)
Duration of illness**	Mean ± SD	65.2 ± 60.3
Smoking history	Yes	47 (12.7)
	No	143 (38.8)
	Past	161 (43.6)
	Unknown	18 (4.9)
Smoking amount (pack-year)***	Mean ± SD	45.31 ± 25.84
Previous therapeutic drug for COPD	Yes	210 (56.9)
	No	153 (41.5)
Past medical history	Yes	299 (81.0)
	No	67 (18.2)
Concomitant disease	Yes	90 (24.4)
	No	276 (74.8)

*: n=321, **: n=144, ***: n=284

Summary of safety results

Thirteen ADR events were reported in 11 of 369 safety evaluable patients (3.0%). The cumulative incidence rate of ADR (hereinafter referred to as ADR frequency) was similar to that in the clinical studies before the approval (3.1%: 14/446 patients). The ADRs were: Decreased appetite (2 patients), Nausea (2 patients); Pharyngitis, Hyperkalaemia, Dysgeusia, Angina unstable, Arrtythmia, Palpitations, Laryngeal discomfort, Malaise, and Thirst (1 patient for each event). Serious ADRs were Decreased appetite and Angina unstable which were respectively reported in one patient.

Eighteen SAE events were reported in 9 of 369 safety evaluable patients (2.4%). The SAEs were Pneumonia (2 events), Decreased appetite (2), Squamous cell carcinoma of lung (1), Cerebral infarction (1), Dysgeusia (1), Angina unstable (1), Cyanosis (1), Myocardial infarction (1), Hypoxia (1), Pneumonia aspiration (1), Respiratory failure (1), Dyspepsia (1), Gastrointestinal perforation (1), Rhabdomyolysis (1), Acute kidney injury (1), and Face injury (1). For all events except one event of Decreased appetite and the event of Angina unstable, causal relationship between the event and Oxis was excluded.

The key investigation items of development of ADRs possibly related to pharmacological class effect of beta2 stimulant and development of serious cardiovascular AEs were reviewed. ADRs possibly related to pharmacological class effect of beta2 stimulant were reported in 2 of 369 safety evaluable patients (0.3%): non-serious Arrhythmia and non-serious Palpitations (1 patient for each event). Regarding serious cardiovascular AEs, Angina unstable and

Myocardial infarction were respectively reported in one patient out of 369 safety evaluable patient (0.3%).

Development of COPD exacerbation was reviewed. In this investigation, "COPD exacerbation" was defined as "the case in which aggravated COPD required systemic steroid and hospitalization or one of them". COPD exacerbation was reported in one patient out of 369 safety evaluable patients (0.3%).