Drug Substance(s) Study Code Date	Budesonide (Pulmicort) D525AL00001 6 June 2016	**SYNOPSIS**	

Pulmicort 100 mcg Turbuhaler 112 doses, Pulmicort 200 mcg Turbuhaler 56 doses, Pulmicort 200 mcg Turbuhaler 112 doses, Specific Clinical Experience Investigation

Study dates:
First subject enrolled: September 2010
Last subject completed: September 2015

Objectives
The purpose of the investigation was to confirm mainly safety (ADR development, effects on growth rate, effects on adrenal function, and frequency of infection etc) under the post-marketing actual long-term use of Pulmicort 100/200 mcg Turbuhaler in children of age >/=5 years and < 15 years. In this investigation, efficacy (the data of Japanese Paediatric Asthma Control Program (hereinafter referred to as JPAC), QOL questionnaire for pediatric patients with bronchial asthma and their parents or caregivers, the brief revised edition 2008 (Gifu) (hereinafter parental questionnaire), and peak expiratory flow (PEF) values was investigated under the post-marketing actual use of Pulmicort 100/200 mcg Turbuhaler.

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

Target subject population and sample size
Patients of age >/=5 years and < 15 years, treated with Pulmicort Turbuhaler for the first time due to asthma, which is the indication of this drug.

Target number of patients: 300

Investigational product
Pulmicort 100 mcg Turbuhaler 112 doses, Pulmicort 200 mcg Turbuhaler 56/112 doses

Duration of treatment
Three years

Variables
Adverse event, height, weight, PEF values, JPAC, parental questionnaire

Subject population
In this investigation, the registration number of patients was 301, and the number of patients whose CRF was collected (the number of patients who completed the investigation) was 299. Regarding the 299 patients whose CRF was collected, 22 patients in total were excluded from safety analysis: 1 for contract violation, 20 for no revisit, and 1 for not safety evaluated; the remaining 277 patients were eligible for safety analysis.
Regarding the 277 safety evaluable patients, 71 patients were excluded from efficacy analysis as they had not been evaluated for efficacy (due to lack of data both at the start and at least

any one point during treatment with the drug for the investigation items concerning clinical course or peak flow rate); the remaining 206 were eligible for efficacy analysis.

Table S1 Subject population

Charcteristic	Statistic	Number of safety evaluable patients (n=277)
Gender	Male	171 (61.7)
	Female	106 (38.3)
Age	Mean ± SD	8.5 ± 2.4
	5≦<10	188 (67.9)
	10≦<15	89 (32.1)
Duration of illness (month)	Mean ± SD	57.2 ± 31.8
Height (cm)	Mean ± SD	129.8 ± 14.8
Weight (kg)	Mean ± SD	29.7 ± 10.5
Staging classification	Intermittent	57 (20.6)
	Mild persistent	111 (40.1)
	Moderate persistent	99 (35.7)
	Severe persistent	8 (2.9)
	Very severe persistent	0
	Unknown	2 (0.7)
allergic diathesis	No	64 (23.1)
	Yes	188 (67.9)
	Unknown	25 (9.0)
Previous therapeutic drug for asthma	No	60 (21.7)
	Yes	201 (72.6)
	Unknown	16 (5.8)
Past medical history	No	218 (78.7)
	Yes	51 (18.4)
	Unknown	8 (2.9)
Concomitant disease	No	119 (43.0)
	Yes	150 (54.2)
	Unknown	8 (2.9)

Summary of safety results

1) Ten events of adverse drug reactions (ADRs) were reported in 5 of 277 safety evaluable patients (1.8%). The reported ADRs were Acute sinusitis (1 event), Acute tonsillitis (1), Bronchitis (1), Gastroenteritis (1), Oral candidiasis (1), Pertussis (1), Enteritis infectious (1), Streptococcal infection (1), Lymphadenitis (1), and Asthma (1), all of which were non-serious. As to unexpected ADRs, seven events were reported in 3 patients: Acute sinusitis (1 event), Gastroenteritis (1), Pertussis (1), Enteritis infectious (1), Streptococcal infection (1), Lymphadenitis (1), and Asthma (1). There was no increase of ADR frequency in this investigation compared to that at the approval (3.3%, 4/123 patients).

2) Regarding serious AEs, three events were reported in 2 of 277 patients (0.7%). The serious AEs were Bronchitis (1 event), Gastroenteritis (1), and Asthma (1), in all of which causality with Pulmicort Turbuhaler was excluded. Among them, unexpected serious AEs were Gastroenteritis (1) and Asthma (1).

3) Analysis of factors possibly affecting the safety was not performed because ADRs were reported only in five patients.

4) The key investigation items were examined: i) effects on growth rate, ii) effects on adrenal cortical function, and iii) frequency of infection.

i) Effects on growth rate

Variations from the start of the drug concerning height and weight were confirmed at each evaluation point (Month 6, Year 1, Year 1.5, Year 2, Year 2.5 and Year 3 after the start). In both male and female patient groups (each group of >/=5 years and <10 years; >/=10 years and <15 years), steady increase of variations from the start of the drug was confirmed at each evaluation point except at Year 2.5 and Year 3, when there were not enough number of patients to evaluate. In addition, most measured values were equal to or more than Mean-2SD by age, which was based on the data of School Health Statistical Survey in Japanese children (2009) conducted by Ministry of Education, Culture, Sports, Science and Technology, indicating no obvious tendency of growth suppression by Pulmicort Turbuhaler.

ii) Effects on adrenal cortical function

Regarding the 277 safety evaluable patients, there was no ADR related to adrenal cortical function suppression.

iii) Frequency of infection

Infections were observed in 63 of 277 safety evaluable patients (22.7%). The main infectious events were Bronchitis in 30 patients (10.8%), Upper respiratory tract inflammation in 23 patients (8.3%), Influenza in 14 patients (5.1%), Gastroenteritis in 14 patients (5.1%), and Pharyngitis in 10 patients (3.6%), indicating the majority of respiratory infections.

Among them, AE (ADR) events in which the causality with Pulmicort Turbuhaler could not be excluded were Bronchitis (1 event), Gastroenteritis (1), Streptococcal infection (1), Acute sinusitis (1), Acute tonsillitis (1), Oral candidiasis (1), Pertussis (1), and Enteritis infectious (1), and all of them were non-serious. In addition, serious AEs were Bronchitis (1 event) and Gastroenteritis (1), for both of which the reporting physician excluded causality with Pulmicort Turbuhaler.

Summary of efficacy results

In this investigation, to grasp asthma-control level under actual use of Pulmicort Turbuhaler, the data of JPAC, parental questionnaire, and PEF values were collected before and after Pulmicort Turbuhaler treatment. The above data were to be collected at the start of Pulmicort Turbuhaler, and Month 6, Year 1, Year 1.5, Year 2, Year 2.5, and Year 3 after the start of the drug, and at completion of the investigation.

1) JPAC score

The mean variation of JPAC score from the start of the drug was 2.8 +/- 3.3 at Month 6, 2.9 +/- 3.4 at Year 1, 3.0 +/- 3.7 at Year 1.5, 3.5 +/- 3.7 at Year 2, 3.2 +/- 3.8 at Year 2.5, 3.0 +/- 3.6 at Year 3, and 3.3 +/- 3.7 at completion of the investigation, indicating significant increase of JPAC score from that at the start of the drug ($p < 0.0001$).

Variations of JPAC score at Year 2 and at completion of the investigation were reviewed by patient background factor and by treatment factor to analyse factors affecting the efficacy. As the result, the variation of JPAC score at Year 2 showed significant

difference by with/without atopic predisposition ($p = 0.0058$) and by daily dose ($p = 0.0395$). However, even in the patient group with smaller variation, the variation of JPAC score increased significantly at Year 2 from that at the start of the drug ($p < 0.05$). Therefore, there should be no problem.

2) Parental questionnaire

In this investigation, score by factor included in the parental questionnaire (emotional stress, factor of asthmatic attack, instability of asthmatic symptom, acceptance of asthma, load of stress) (hereinafter referred to as score by factor) was calculated, and the variation of score by factor from the baseline was reviewed at Month 6, Year 1, Year 1.5, Year 2, Year 2.5, Year 3, and at completion. As the result, the mean score improved compared to the baseline score for each factor.

3) PEF on awakening

The mean variation of PEF value from the start of the drug was 26.6 +/- 31.4 L/min at Month 6, 44.9 +/- 45.3 L/min at Year 1, 47.1 +/- 47.5 L/min at Year 1.5, 65.8 +/- 49.7 L/min at Year 2, 85.9 +/- 36.0 L/min at Year 2.5, 98.8 +/- 38.3 L/min at Year 3, and 58.1 +/- 65.6 L/min at completion of the investigation, indicating significant increase of PEF value from the start of the drug at all evaluation points ($p < 0.0001$).

The mean variation of %PEF value at 54 weeks from the start of the drug was 9.54 +/- 19.87% in the long-term Phase III study. The mean variation of %PEF value at 1 year from the start of the drug was 7.63 +/- 16.85% in this investigation, indicating significant increase of %PEF value from the start of the drug ($p=0.0046$).