Drug product:	Pulmicort® Turbuhaler®	**SYNOPSIS**	
Drug substance(s):	Budesonide		
Edition No.:	1.0		
Study code:	D5254C00006		
Date:	9 March 2009		

An open-label, multi-center, long term study to investigate the safety and efficacy of budesonide Turbuhaler® treatment for 48 weeks (following 6 weeks Phase III study) in Japanese children with bronchial asthma aged 5 years to 15 years old.

Study centre(s)

This study was conducted at 28 centres in Japan.

Publications

None at the time of writing this report.

Study dates

First patient enrolled 12 December 2006

Last patient completed 6 October 2008

Phase of development

Therapeutic confirmatory (III)

Objectives

Primary objectives

The primary objective of this study was to investigate the safety of budesonide Turbuhaler® with a daily dose of 100 µg to 800 µg for 54 weeks including the prior 6-week Phase III study (Study D5254C00769) in Japanese children with bronchial asthma aged 5 years to 15 years old in need of inhaled glucocorticosteroid treatment by assessment of the following variables:

- Primary variable: adverse events
- Secondary variables: clinical laboratory tests, vital signs, plasma cortisol, height, weight

Secondary objectives

The secondary objectives of this study were:

- To investigate the safety of budesonide Turbuhaler® with a daily dose of 100 µg to 800 µg for 26 weeks including the prior 6-week Phase III study in Japanese children with bronchial asthma aged 5 years to 15 years old in need of inhaled glucocorticosteroid treatment by assessment of the following variables:

  – Adverse events, clinical laboratory tests, vital signs, plasma cortisol, height, weight

- To investigate the efficacy of budesonide Turbuhaler® with a daily dose of 100 µg to 800 µg during 26- and 54-week treatment including the prior 6-week Phase III study in Japanese children with bronchial asthma aged 5 years to 15 years old in need of inhaled glucocorticosteroid treatment by assessment of the following variables:

  – morning PEF (mPEF), morning PEF % of predicted normal (%mPEF), evening PEF (ePEF), evening PEF % of predicted normal (%ePEF), respiratory condition at asthma attacks (daytime and night-time), presence of cough related to asthma (daytime and night-time), use of inhaled short-acting β_2 agonist (daytime, night-time and total), disturbance of daily activity, disturbance of night-time sleep

  – FEV_1, FEV_1 % of predicted normal (%FEV_1), FVC

Study design

This was an open-label, multi-centre, long-term study in Japanese children with bronchial asthma aged 5 to 15 years, and conducted as an extension of the Phase III study D5254C00769.

Target patient population and sample size

Japanese paediatric patients aged 5 to 15 years with mild persistent to severe persistent type 1 asthma according to Japanese Paediatric Guideline for the Treatment and Management of Asthma 2005 in need for inhaled glucocorticosteroid treatment and completed the Phase III study D5254C00769. A total of 241 patients entered this study.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Test products

The following products were used in this study.

- Budesonide Turbuhaler® 100 µg (Pulmicort® 100 Turbuhaler®: dry powder inhaler, budesonide 100 µg per dose; 112 doses per inhaler)

- Budesonide Turbuhaler® 200 µg (Pulmicort® 200 Turbuhaler®: dry powder inhaler, budesonide 200 µg per dose, 112 doses per inhaler)

Patients who had been randomised to the budesonide group in the Phase III study D5254C00769 were assigned to the budesonide group in this study and started study treatment at one of the following four doses depending on asthma symptom during the last 4 weeks.

- 100 μg once daily (100 μg/day) by use of budesonide Turbuhaler® 100 μg (one inhalation once daily)
- 100 μg twice daily (200 μg/day) by use of budesonide Turbuhaler® 100 μg (one inhalation twice daily)
- 200 μg twice daily (400 μg/day) by use of budesonide Turbuhaler® 200 μg (one inhalation twice daily)
- 400 μg twice daily (800 μg/day) by use of budesonide Turbuhaler® 200 μg (two inhalations twice daily)

Patients were to take the investigational product at approximately the same time every morning and evening after PEF measurement. When patients were treated at 100 μg once daily, they could take the investigational product every morning or evening after PEF measurement but had to keep the timing (morning or evening) until a change in dosing regimen.

Conventional therapy

Patients who had been randomised to the fluticasone group in the Phase III study D5254C00769 were assigned to the conventional therapy group. In the conventional therapy group, the investigator(s) decided the medications for the patient according to the Japanese Paediatric Guideline for the Treatment and Management of Asthma 2005.

Duration of treatment

48 weeks (following 6 week treatment in the Phase III study D5254C00769)

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

mPEF, %mPEF, ePEF, %ePEF, respiratory condition at asthma attacks (daytime and night-time), presence of cough related to asthma (daytime and night-time), use of inhaled short-acting β_2-agonist (daytime, night-time and total), disturbance of daily activity, disturbance of night-time sleep, FEV_1, $\%FEV_1$, FVC

Safety

- **Primary outcome variable**

  Adverse events

- **Secondary outcome variable**

Clinical laboratory tests, vital signs, morning plasma cortisol, height, weight

Statistical methods

The safety analysis set was used in the analysis of safety outcome variables. The safety analysis set was defined as all the patients who entered this study with available safety data after the entry. The safety and efficacy outcome variables were summarised using descriptive statistics for each treatment group.

Patient population

A total of 241 patients entered this extension study at 28 centres (budesonide [BUD] group: n=121, conventional therapy [CONV] group: n=120). Nineteen patients discontinued the study during treatment (BUD group: n=12, CONV group: n=7), and 222 patients completed 54-week treatment including the prior 6-week Phase III study D5254C00769 (BUD group: n=109, CONV group: n=113). There were few major protocol deviations (ie, deviation from inclusion/exclusion and discontinuation criteria). All of the 241 patients were included in the analysis set for efficacy and safety. The demographic and baseline characteristics were similar between the treatment groups (Table S1). Treatment compliance in BUD group was more than 80% in most patients.

Table S1 Patient population and disposition

Demographic or baseline characteristics		Treatment group		Total
		BUD	CONV	
Population				
N of patients completing Phase III study D5254C00769		121	122	243
N of patients who entered this study		121	120	241
Demographic or other characteristics				
Sex (n and % of patients)	Male	85 (70.2)	93 (77.5)	178 (73.9)
	Female	36 (29.8)	27 (22.5)	63 (26.1)
Age[a] (years, n and % of patients)	5-9	73 (60.3)	77 (64.2)	150 (62.2)
	10-15	48 (39.7)	43 (35.8)	91 (37.8)
Age[a] (years)	Mean (SD)	8.9 (2.6)	8.6 (2.3)	8.8 (2.4)
	Range	5 to 15	5 to 14	5 to 15
Weight (kg)	Mean (SD)	29.9 (10.4)	31.1 (11.2)	30.5 (10.8)
	Range	15.4 to 65.5	15.7 to 66.3	15.4 to 66.3
Height (cm)	Mean (SD)	131.1 (14.4)	131.3 (14.7)	131.2 (14.5)
	Range	106.4 to 165.1	101.7 to 166.9	101.7 to 166.9
Ethnicity (n and % of patients)	Japanese	121 (100.0)	120 (100.0)	241 (100.0)
Use of ICS at enrolment to study D5254C00769 (n and % of patients) and daily dose of ICS (µg/day)	No	59 (48.8)	68 (56.7)	127 (52.7)
	Yes	62 (51.2)	52 (43.3)	114 (47.3)
	Mean (SD)[b]	131.5 (51.4)	141.3 (54.0)	136.0 (52.6)

Demographic or baseline characteristics	Treatment group		Total
	BUD	CONV	
Baseline characteristics			
Mean (SD) %mPEF[c] (%)	67.47 (12.69)	67.57 (14.27)	67.52 (13.47)
Mean (SD) mPEF[c] (L/min)	177.6 (54.8)	176.8 (55.8)	177.2 (55.2)
Mean (SD) $\%FEV_1$[d] (%)	90.33 (14.64)	89.46 (18.18)	89.90 (16.47)
Mean (SD) FEV_1[d] (L)	1.588 (0.532)	1.573 (0.507)	1.581 (0.519)
Mean (SD) respiratory condition at asthma attacks[c,e] (daytime, point/day)	0.199 (0.297)	0.191 (0.276)	0.195 (0.286)
Mean (SD) respiratory condition at asthma attacks[c,e] (night-time, point/day)	0.163 (0.266)	0.173 (0.267)	0.168 (0.266)
Mean (SD) inhaled SABA use via pMDI[c] (total, puff/day)	0.236 (0.623)	0.264 (0.478)	0.250 (0.555)
Mean (SD) inhaled SABA use via nebuliser[c] (total, puff/day)	0.128 (0.354)	0.114 (0.351)	0.121 (0.352)
Disposition			
N (%) of patients completed 54-week treatment[f]	109	113	222
N (%) of patients withdrawn after entering this study	12	7	19
N analysed for safety[g]	121	120	241
N analysed for efficacy[h]	121	120	241

BUD: budesonide, CONV: conventional therapy (0-6 week: Fluticasone in Phase III study D5254C00769), ICS: inhaled corticosteroids, pMDI: pressured metered dose inhaler, SABA: short-acting β_2 agonist,

[a] Data as of enrolment in Phase III study D5254C00769.
[b] Nominal dose.
[c] Average value over last 14 days in run-in period in Phase III study D5254C00769.
[d] Measurement value at Week 0 in Phase III study D5254C00769.
[e] Respiratory condition was scored according to following scales. None: 0, Mild: 1, Moderate: 2, Severe: 3, Respiratory insufficiency: 4.
[f] Including 6-week treatment period in the Phase III study D5254C00769.
[g] Number of patients who entered this study with available safety data after the entry
[h] Number of patients who entered this study with available efficacy data after the entry

Efficacy results

Improvements from baseline were observed in the lung function variables (%mPEF, mPEF, %ePEF, ePEF, $\%FEV_1$, FEV_1, and FVC) and the variables related to asthma control (respiratory condition at asthma attacks, presence of cough related to asthma, use of inhaled short-acting β_2 agonist via pMDI and via nebuliser, disturbance of daily activity, and disturbance of night-time sleep) during treatment with BUD Turbuhaler® with a daily dose of 100 µg to 800 µg (Table S2). The major part of the improvement in those efficacy variables was seen in the first few weeks after the start of BUD treatment in the preceding Phase III study, and was maintained up to 54 weeks during this long-term study. During this long-term study, the improvement in all efficacy variables except for %mPEF, mPEF, %ePEF, and ePEF was similarly maintained up to 54 weeks in CONV group. Improvements in %mPEF, mPEF, %ePEF, and ePEF were maintained in CONV group, but numerically not as well as in BUD group. In 15 of the 121 patients in BUD group the dose was decreased to 100 µg once daily, and 9 of them continued on 100 µg once daily at Week 54, while the dose was increased due to insufficient asthma control in 6 patients. Total duration of 100 µg/day treatment in the 15 patients was 290 weeks, with individual durations ranging from 1.6 to 36.0 weeks, and a

median of 20.1 weeks. The maximal duration of continuous treatment with 100 µg/day (ie, the longest consecutive period each patient was treated with 100 µg/day without changing the dose) was a median of 19.4 weeks (range: 1.6 to 36.0 weeks). In addition, in 17 of the 121 patients in BUD group the dose was increased to 400 µg twice daily (800 µg/day), and 9 of them continued on 400 µg twice daily at Week 54. In 8 of them the dose was decreased due to improvement in asthma control thereafter.

Table S2 Summary of efficacy variables[a] (Mean ± SD: missing values imputed by linear interpolation and LOCF) (efficacy analysis set)

Variables	Treatment	n	Baseline[b]	Observed values		Change from baseline	
				Week 6[c]	Week 54[d]	Week 6	Week 54
%mPEF	BUD	121	67.47 ± 12.69	74.97 ± 16.93	77.01 ± 19.43	7.50 ± 15.21	9.54 ± 19.87
(%)	CONV	120	67.57 ± 14.27	74.35 ± 17.68	73.41 ± 19.31	6.78 ± 14.09	5.84 ± 17.81
mPEF	BUD	121	177.6 ± 54.8	198.8 ± 66.2	215.9 ± 75.8	21.2 ± 40.0	38.4 ± 55.9
(L/min)	CONV	120	176.8 ± 55.8	194.9 ± 63.9	208.7 ± 78.8	18.1 ± 39.0	31.9 ± 52.5
%ePEF	BUD	121	72.58 ± 12.26	78.77 ± 16.20	78.74 ± 20.36	6.19 ± 15.51	6.16 ± 20.94
(%)	CONV	120	73.68 ± 14.65	78.15 ± 17.40	74.97 ± 19.02	4.47 ± 13.33	1.29 ± 17.30
ePEF	BUD	121	192.2 ± 61.2	209.2 ± 68.2	220.5 ± 78.7	17.0 ± 39.9	28.3 ± 60.6
(L/min)	CONV	120	193.2 ± 60.2	204.9 ± 65.3	213.0 ± 79.9	11.7 ± 36.3	19.8 ± 50.2
$\%FEV_1$	BUD	121	90.33 ± 14.64	91.95 ± 13.88	91.83 ± 15.11	1.62 ± 11.65	1.50 ± 15.59
(%)	CONV	120	89.46 ± 18.18	93.39 ± 14.52	91.77 ± 12.38	3.93 ± 15.36	2.31 ± 16.63
FEV_1	BUD	121	1.588 ± 0.532	1.653 ± 0.554	1.787 ± 0.568	0.065 ± 0.184	0.198 ± 0.257
(L)	CONV	120	1.573 ± 0.507	1.712 ± 0.575	1.857 ± 0.590	0.139 ± 0.331	0.284 ± 0.349
FVC	BUD	121	1.880 ± 0.647	1.923 ± 0.666	2.095 ± 0.667	0.043 ± 0.190	0.216 ± 0.256
(L)	CONV	120	1.869 ± 0.668	1.994 ± 0.703	2.159 ± 0.703	0.124 ± 0.347	0.290 ± 0.387
Scored[e] respiratory condition at asthma attacks (daytime, point/day)	BUD	121	0.199 ± 0.297	0.076 ± 0.193	0.060 ± 0.208	-0.123 ± 0.312	-0.139 ± 0.334
	CONV	119	0.191 ± 0.276	0.065 ± 0.202[g]	0.034 ± 0.144[g]	-0.125 ± 0.277	-0.156 ± 0.302
Scored[e] respiratory condition at asthma attacks (night-time, point/day)	BUD	121	0.163 ± 0.266	0.063 ± 0.163	0.042 ± 0.168	-0.100 ± 0.296	-0.120 ± 0.290
	CONV	119	0.173 ± 0.267	0.066 ± 0.211[g]	0.026 ± 0.128[g]	-0.107 ± 0.276	-0.147 ± 0.300
Coughs[f] related to asthma (daytime, time/day)	BUD	121	0.289 ± 0.317	0.144 ± 0.252	0.094 ± 0.234	-0.145 ± 0.339	-0.195 ± 0.364
	CONV	119	0.291 ± 0.319	0.154 ± 0.292[g]	0.096 ± 0.246[g]	-0.136 ± 0.316	-0.194 ± 0.339
Coughs[f] related to asthma (night-time, time/day)	BUD	121	0.247 ± 0.279	0.110 ± 0.196	0.090 ± 0.239	-0.137 ± 0.307	-0.157 ± 0.315
	CONV	119	0.251 ± 0.296	0.130 ± 0.263[g]	0.071 ± 0.196[g]	-0.120 ± 0.293	-0.180 ± 0.280
Number of inhalations of SABA via pMDI (total, puff/day)	BUD	121	0.236 ± 0.623	0.076 ± 0.296	0.027 ± 0.145	-0.160 ± 0.572	-0.210 ± 0.647
	CONV	119	0.264 ± 0.478	0.042 ± 0.203[g]	0.022 ± 0.143[g]	-0.221 ± 0.450	-0.242 ± 0.485
Number of inhalations of SABA via nebuliser (total, puff/day)	BUD	121	0.128 ± 0.354	0.082 ± 0.333	0.058 ± 0.301	-0.046 ± 0.271	-0.070 ± 0.415
	CONV	119	0.114 ± 0.351	0.036 ± 0.196[g]	0.017 ± 0.101[g]	-0.078 ± 0.332	-0.097 ± 0.368

Variables	Treatment	n	Baseline[b]	Observed values		Change from baseline	
				Week 6[c]	Week 54[d]	Week 6	Week 54
Disturbance[f] of daily activity (time/day)	BUD	121	0.064 ± 0.135	0.023 ± 0.074	0.026 ± 0.136	-0.040 ± 0.130	-0.037 ± 0.141
	CONV	119	0.046 ± 0.111	0.030 ± 0.123[g]	0.029 ± 0.139[g]	-0.017 ± 0.137	-0.017 ± 0.141
Disturbance[f] of night-time sleep (time/day)	BUD	121	0.041 ± 0.111	0.024 ± 0.100	0.012 ± 0.092	-0.016 ± 0.123	-0.029 ± 0.134
	CONV	119	0.045 ± 0.131	0.023 ± 0.095[g]	0.003 ± 0.014[g]	-0.021 ± 0.116	-0.042 ± 0.132

BUD: budesonide, CONV: conventional therapy (0-6 week: Fluticasone in Phase III study D5254C00769), pMDI: pressured metered dose inhaler, SABA: short-acting β_2 agonist

[a] Presentation of treatment week is based on the start date of study treatment in the Phase III study D5254C00769 as Week 0.

[b] Measurement value at Week 0 in Phase III study D5254C00769 for $\%FEV_1$, FEV_1 and FVC, and average value over last 14 days in run-in period in Phase III study D5254C00769 for other variables.

[c] Week 6 value for phase III study D5254C00769. Average value over Weeks 5 and 6 was used for data calculation except for $\%FEV_1$, FEV_1 and FVC.

[d] Only applicable to $\%FEV_1$, FEV_1 and FVC. Average value over Week 53 and 54 was used for data calculation for other variables.

[e] Respiratory condition was scored according to following scales; None: 0, Mild: 1, Moderate: 2, Severe: 3, Respiratory insufficiency: 4.

[f] Presence or absence of cough or disturbance was dichotomised as follows; Present: 1, Absent: 0.

[g] n=120

Safety results

BUD Turbuhaler® with a daily dose of 100 µg to 800 µg was generally safe and well tolerated for up to 54 weeks in Japanese children with bronchial asthma. A total of 751 AEs were reported for 118 of the 121 patients (97.5%) in BUD group, and 704 AEs were reported for 116 of the 120 patients (96.7%) in CONV group. The incidences of AEs were comparable in the treatment groups (Table S3). Most of the AEs were of mild intensity. Five drug-related AEs (dysphonia, epistaxis, pharyngitis, blood cortisol decreased) were reported for 4 of the 121 patients (3.3%) in BUD group. These events were of mild intensity and did not lead to discontinuation of the patients from the study. No deaths were reported during the study. The incidence of SAEs was low in both the treatment groups (BUD group: 12 events in 10 patients, CONV group: 16 events in 11 patients). All of them were confirmed to be recovered. Out of them, 5 SAEs in 5 patients in BUD group and 8 SAEs in 6 patients in CONV group were asthma. The incidence of DAEs was low in BUD group (2 events in 2 patients), and no DAE was reported in CONV group. All of them were asthma. None of the DAEs was judged as possibly drug-related by the investigator. No other significant adverse events were reported during the course of the study. Most common AEs were upper respiratory tract infection, bronchitis, gastroenteritis, pharyngitis, influenza and rhinitis allergic. The most common AEs generally reflected health problems based on the signs and symptoms of underlying disease in an asthma paediatric population. Overall the AE profiles were similar for BUD group and CONV group (Table S4). There was no trend of increase in incidence of AEs in longer treatment period to 54 weeks. A total of 34 AEs were reported for 12 of the 17 patients in BUD group during 800 µg/day treatment, and the pattern for nature and severity of the AEs was similar in patients receiving 800 µg/day compared to that of the whole group of patients. There were no serious adverse events in the patients treated with 800 µg/day.

No clinically important changes were identified in clinical laboratory variables including plasma cortisol levels in either treatment group. There were no important trends of increase or

decrease in these variables during 54-week treatment period and no differences between the two treatment groups. Long-term use of BUD Turbuhaler® did not result in any apparent effect on clinical laboratory variables including plasma cortisol. There were no findings for clinical laboratory values, height, weight, vital signs and plasma cortisol that gave any reason for concern regarding the safety of BUD treatment.

Table S3 Number (%) of patients who had an adverse event in any category, and total numbers of adverse events[a] (safety analysis set)

Category of adverse event	N (%) of patients who had an adverse event in each category[b]	
	BUD (n=121)	CONV (n=120)
Any adverse events	118 (97.5%)	116 (96.7%)
Serious adverse events		
Serious adverse events leading to death	0	0
Serious adverse events not leading to death	10 (8.3%)	11 (9.2%)
Discontinuations of study treatment due to adverse events	2 (1.7%)	0
Other significant adverse events	0	0
Any drug-related adverse events[c]	4 (3.3%)	-
	Total number of adverse events	
Adverse events	751	704
Serious adverse events	12	16
Discontinuations of study treatment due to adverse events	2	0
Other significant adverse events	0	0
Any drug-related adverse events[c]	5	-

BUD: budesonide, CONV: conventional therapy (0-6 week: Fluticasone in Phase III study D5254C00769)

[a] This summary table includes adverse events reported during treatment period in preceding Phase III study D5254C00769 (but not include adverse events reported in patients who did not enter this study).

[b] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[c] The causality was judged by the investigator. There is a reasonable possibility that the event may have been caused by budesonide.

Table S4 Number (%) of patients with the most commonly reported[a] adverse events by preferred term (MedDRA 10.1), sorted by decreasing order of frequency in budesonide group[b] (safety analysis set)

Preferred term	BUD	CONV
N of patients for safety	121	120
No of patients with adverse event	118 (97.5%)	116 (96.7%)
Upper respiratory tract infection	49 (40.5%)	45 (37.5%)
Bronchitis	34 (28.1%)	36 (30.0%)
Gastroenteritis	33 (27.3%)	32 (26.7%)
Pharyngitis	32 (26.4%)	30 (25.0%)

Preferred term	BUD	CONV
Influenza	28 (23.1%)	35 (29.2%)
Rhinitis allergic	25 (20.7%)	21 (17.5%)
Nasopharyngitis	24 (19.8%)	16 (13.3%)
Conjunctivitis allergic	14 (11.6%)	18 (15.0%)
Eczema	14 (11.6%)	12 (10.0%)
Headache	13 (10.7%)	6 (5.0%)
Otitis media	12 (9.9%)	13 (10.8%)
Impetigo	10 (8.3%)	5 (4.2%)
Urticaria	10 (8.3%)	13 (10.8%)
Acute tonsillitis	9 (7.4%)	9 (7.5%)
Contusion	8 (6.6%)	9 (7.5%)
Asthma	7 (5.8%)	6 (5.0%)
Chronic sinusitis	7 (5.8%)	12 (10.0%)
Conjunctivitis	7 (5.8%)	2 (1.7%)
Abdominal pain	6 (5.0%)	4 (3.3%)
Dermatitis atopic	6 (5.0%)	5 (4.2%)

BUD: budesonide, CONV: conventional therapy (0-6 week: Fluticasone in Phase III study D5254C00769)

[a] This table uses a cut-off of ≥5% of patients in total of each treatment group.

[b] This summary table includes adverse events reported during treatment period in preceding Phase III study D5254C00769 (but not include adverse events reported in patients who did not enter this study).