Drug product:	Pulmicort® Turbuhaler®	**SYNOPSIS**	
Drug substance(s):	Budesonide		
Edition No.:	1.0		
Study code:	D5254C00769		
Date:	1 April 2008		

A randomised, open-label, parallel-group, 6-week treatment, multi-centre, Phase III study to investigate the efficacy and safety of 100 µg twice daily and 200 µg twice daily of budesonide Turbuhaler® and 50 µg twice daily and 100 µg twice daily of fluticasone Diskus® in Japanese children with bronchial asthma aged 5 years to 15 years old

Study dates		**Phase of development**
First patient enrolled	16 October 2006	Therapeutic confirmatory (III)
Last patient completed	29 October 2007	

Objectives

Primary objective

The primary objective of this study was to investigate the effect of budesonide Turbuhaler® 100 µg/dose twice daily and 200 µg/dose twice daily for 6 weeks in Japanese children with bronchial asthma aged 5 years to 15 years old in need for inhaled corticosteroid treatment by assessment of the following variables:

Primary variable:

- Change in morning PEF % of predicted normal (%mPEF) from baseline (mean of the last 14 days of the observation period) to Week 6 (mean of the last 14 days of the treatment).

Secondary variables:

- Change in %mPEF from baseline (mean of the last 14 days of the observation period) to Week 2, Week 4, and Week 6 (mean over 14 days prior to Week 2, Week 4, and Week 6, respectively).
- Change in the following variables from baseline (mean of the last 14 days of the observation period) to Week 2, Week 4, Week 6 (mean over 14 days prior to Week 2, Week 4, and Week 6, respectively and mean of the last 14 days of the treatment):
  - morning PEF (mPEF), evening PEF (ePEF), ePEF % 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
- Change in the following variables from baseline (Visit 2) to Visit 3 and Visit 4:
  - FEV_1, FEV_1 % of predicted normal (%FEV_1), FVC

Secondary objectives

The secondary objectives of this study were:

To investigate the safety of budesonide Turbuhaler® 100 µg/dose twice daily and 200 µg/dose twice daily for 6 weeks in Japanese children with bronchial asthma aged 5 years to 15 years old in need for inhaled glucocorticosteroid treatment in terms of the following variables:

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

To compare the efficacy of budesonide Turbuhaler® 100 µg/dose twice daily and 200 µg/dose twice daily for 6 weeks to that of fluticasone Diskus® 50 µg/dose twice daily and 100 µg/dose twice daily for 6 weeks in Japanese children with bronchial asthma aged 5 years to 15 years old in need for inhaled glucocorticosteroid treatment in terms of the following variables:

- Change in the following variables from baseline (mean of the last 14 days of the observation period) to Week 2, Week 4, Week 6 (mean over 14 days prior to Week 2, Week 4, and Week 6, respectively and mean of the last 14 days of the treatment):
  - 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
- Change in the following variables from baseline (Visit 2) to Visit 3 and Visit 4:
  - FEV_1, %FEV_1, FVC

Study design

A randomised, open-label, parallel group, multicentre study

Target patient population and sample size

Japanese paediatric patients aged 5 to 15 years with mild persistent to severe persistent 1 asthma according to Japanese Paediatric Guideline for the Treatment and Management of Asthma 2005 in need for inhaled corticosteroid treatment.

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

Patients took one oral inhalation from the Turbuhaler® twice daily (ie, 100 μg twice daily or 200 μg twice daily) during the treatment period.

Reference products

The following reference products were used in this study:

- Fluticasone Diskus® 50 μg (Flutide® 50 Diskus®: dry powder inhaler; fluticasone propionate 50 μg per dose; 60 doses per inhaler)
- Fluticasone Diskus® 100 μg (Flutide® 100 Diskus®: dry powder inhaler; fluticasone propionate 100 μg per dose; 60 doses per inhaler)

The patient took one oral inhalation from the Diskus® twice daily (ie, 50 μg twice daily or 100 μg twice daily) during the treatment period.

Duration of treatment

6 weeks

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- **Primary outcome variable:**

Change in %mPEF from baseline (mean of the last 14 days of the observation period) to Week 6 (mean of the last 14 days of the treatment).

- **Secondary outcome variables:**

  Change in %mPEF from baseline (mean of the last 14 days of the observation period) to Week 2, Week 4, and Week 6 (mean over 14 days prior to Week 2, Week 4, and Week 6, respectively).

  Change in the following variables from baseline (mean of the last 14 days of the observation period) to Week 2, Week 4, Week 6 (mean over 14 days prior to Week 2, Week 4, and Week 6, respectively and mean of the last 14 days of the treatment):

  – 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

  Change in the following variables from baseline (Visit 2) to Visit 3 and Visit 4:

  – FEV_1, $\%FEV_1$, FVC

Safety

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

Statistical methods

The primary population for efficacy analysis in this study was the Full Analysis Set (FAS). The change in %mPEF from baseline to Week 6 with last observation carried forward (LOCF) in budesonide group was tested using Paired t test with 2-sided significance level 0.05 and the p-value was calculated. Similarly, the p-value for fluticasone group was calculated as a reference. In addition, an explanatory analysis was made based on a model of analysis of variance (ANOVA) to calculate the estimate of difference and its 95% confidence interval with regard to the change in %mPEF from baseline for the following comparisons; budesonide and fluticasone groups, the low dose subgroups of budesonide and fluticasone, and the high dose subgroups of budesonide and fluticasone.

Patient population

In total, 294 patients were enrolled and 249 patients were randomised to either of the two treatment groups (budesonide [BUD] group: n=125, fluticasone [FP] group: n=124) at 28 centres. Of these, 244 patients received the study treatment (BUD group: n=120 [58 at 100 µg twice daily, ie, low dose (LD) level and 62 at 200 µg twice daily, ie, high dose (HD) level], FP group: n=124 [64 at 50 µg twice daily, ie, LD level and 60 at 100 µg twice daily, ie, HD level]). Four patients discontinued study treatment and 240 patients completed the study (BUD group: n=118 [LD level: n=58, HD level: n=60], FP group: n=122 [LD level: n=63, HD level: n=59]). The number of analysed patients was 244 (BUD group: n=120 [LD level: n=58,

HD level: n=62], FP group: n=124 [LD level: n=64, HD level: n=60]) in the FAS and safety analysis set. There were few major protocol deviations (ie, deviation from inclusion/exclusion and discontinuation criteria). The treatment groups overall and within each dose level (LD and HD) were generally well matched with regard to demographic and baseline characteristics (Table S1). The compliance was generally good and uniform between the treatment groups and each dose level of the drugs.

Table S1 Patient population and disposition

Demographic or baseline characteristics		Treatment group		Total
		Budesonide	Fluticasone	
Population				
N of patients received the study treatment		120	124	244
Demographic or other characteristics				
Sex (n and % of patients)	Male	83 (69.2)	95 (76.6)	178 (73.0)
	Female	37 (30.8)	29 (23.4)	66 (27.0)
Age (years, n and % of patients)	5-9	71 (59.2)	78 (62.9)	149 (61.1)
	10-15	49 (40.8)	46 (37.1)	95 (38.9)
Age (years)	Mean (SD)	9.0 (2.6)	8.6 (2.3)	8.8 (2.4)
	Range	5 to 15	5 to 14	5 to 15
Weight (kg)	Mean (SD)	30.0 (10.5)	31.2 (11.2)	30.6 (10.8)
Height (cm)	Mean (SD)	131.4 (14.3)	131.5 (14.8)	131.4 (14.5)
Ethnicity (n and % of patients)	Japanese	120 (100.0)	124 (100.0)	244 (100.0)
Use of ICS at enrolment (n and % of patients)	No	59 (49.2)	68 (54.8)	127 (52.0)
and daily dose of ICS	Yes	61 (50.8)	56 (45.2)	117 (48.0)
	Mean (SD) [a]	130.3 (51.1)	142.0 (53.7)	135.9 (52.5)
Baseline characteristics				
Mean (SD) %mPEF[b] (%)		67.53 (12.57)	67.59 (14.13)	67.56 (13.36)
Mean (SD) mPEF[b] (L/min)		178.2 (54.1)	177.6 (56.4)	177.9 (55.2)
Mean (SD) %FEV_1[c] (%)		90.45 (14.56)	89.45 (18.10)	89.94 (16.43)
Mean (SD) FEV_1[c] (L/min)		1.595 (0.531)	1.581 (0.510)	1.588 (0.520)
Mean (SD) respiratory condition at asthma attacks[b,d] (daytime, point/day)		0.205 (0.298)	0.197 (0.281)	0.201 (0.289)
Mean (SD) respiratory condition at asthma attacks[b,d] (night-time, point/day)		0.163 (0.267)	0.170 (0.264)	0.167 (0.265)
Mean (SD) inhaled SABA use via pMDI[b] (total, puff/day)		0.238 (0.626)	0.261 (0.472)	0.249 (0.552)
Mean (SD) inhaled SABA use via nebuliser[b] (total, puff/day)		0.128 (0.356)	0.114 (0.347)	0.121 (0.351)
Disposition				
N (%) of patients who	Completed	118	122	240
	Discontinued	2	2	4
N analysed for efficacy (FAS)		120	124	244
N analysed for safety[e]		120	124	244

ICS: inhaled corticosteroid, SABA: short-acting β_2 agonist, pMDI: pressured metered dose inhaler, FAS: Full Analysis Set

[a] Nominal dose

[b] Average value over last 14 days in run-in period

[c] Measurement value at Week 0.

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

[e] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing

Efficacy and pharmacokinetic results

Mean change in %mPEF as primary variable at Week 6 (LOCF) from baseline was statistically significant ($p<0.0001$) with mean increase of 8.04% of predicted normal in BUD (LD+HD) group (Table S2). The groups treated with BUD 100 µg twice daily and 200 µg twice daily improved numerically in %mPEF at Week 2, Week 4, and Week 6.

For the secondary lung function variables (mPEF, %ePEF, ePEF, %FEV_1, FEV_1, and FVC), mean changes at Week 6 (LOCF) from baseline were statistically significant with mean increase of 22.2 L/min, 6.49%, 17.2 L/min, 3.64%, 0.070 L, and 0.048 L in BUD (LD+HD) group, respectively. Mean changes in the secondary variables related to asthma control except for use of inhaled short-acting β_2 agonist via nebuliser (daytime and total) and disturbance of night-time sleep at Week 6 (LOCF) from baseline statistically significantly decreased in BUD (LD+HD) group. In addition, BUD 100 µg twice daily and 200 µg twice daily groups improved numerically in the secondary variables for lung function and asthma control (ie, 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 via pMDI and via nebuliser [daytime, night-time and total], disturbance of daily activity, disturbance of night-time sleep) at Week 2, Week 4, and Week 6.

The estimates of difference in change in %mPEF at Week 6 (LOCF) between the treatment groups, between the LD levels, and between the HD levels were 0.95% (95% CI: -2.77 to 4.67), 2.69% (95% CI: -2.58 to 7.95), and -0.79% (95% CI: -6.05 to 4.47), respectively (Table S3). There were no statistically significant differences in improvement of the secondary variables except for FEV_1 and FVC between the BUD group and the FP group.

Table S2 Change in %mPEF at Week 6 (LOCF) from baseline (FAS)

Treatment	Dose	n	Baseline[a]	Week 6[b] (LOCF)	Change from baseline	
			Mean (SD)	Mean (SD)	Mean (SD)	p-value[c]
Budesonide	100 µg bid	58	70.10 (12.41)	77.11 (16.53)	7.01 (14.20)	-
	200 µg bid	62	65.12 (12.32)	74.12 (17.11)	9.01 (15.90)	-
	Total	120	67.53 (12.57)	75.56 (16.83)	8.04 (15.07)	<.0001
Fluticasone	50 µg bid	64	70.71 (13.36)	75.03 (19.05)	4.32 (16.01)	-
	100 µg bid	60	64.27 (14.28)	74.06 (17.01)	9.79 (12.40)	-
	Total	124	67.59 (14.13)	74.56 (18.02)	6.97 (14.58)	<.0001

bid: twice daily, LOCF: Last Observation Carried Forward

[a] Average value over last 14 days in run-in period

[b] Average value over last 14 days in treatment period using LOCF method for missing values

[c] Paired t-test

Table S3 Estimated difference between each doses of budesonide and fluticasone and its 95% confidence interval regarding change from baseline in %mPEF [a] (FAS)

Difference between:	Estimate of difference	95% confidence interval	
		Lower	Upper
Budesonide low dose vs fluticasone low dose	2.69	-2.58	7.95
Budesonide high dose vs fluticasone high dose	-0.79	-6.05	4.47
Budesonide group total vs fluticasone group total	0.95	-2.77	4.67

Note: ANOVA model including treatments, dose and interaction between treatments and doses was used for calculation of estimated values.

[a] Defined as difference from average value over last 14 days in treatment period using LOCF method for missing values to average value over last 14 days in run-in period

Safety results

Both BUD and FP treatments were safe and well tolerated. The incidences of AEs were comparable in the treatment groups (BUD group 50.8% [61/120 patients], FP group 48.4% [60/124 patients]) (Table S4). Upper respiratory tract infection was the most common adverse events in both the treatment groups, and overall the AE profiles were similar for BUD group and FP group (Table S5). Most of the AEs were of mild or moderate intensity. One drug-related AE (BUD HD: dysphonia) was reported for 1 of the 244 patients (0.4%). No deaths were reported in the study. The incidence of SAEs was low in both the treatment groups (BUD group: 6 events in 4 patients, FP group: 6 events in 5 patients) and there was no SAE that was assessed as causally related to the investigational product. The incidence of DAEs was low in the two groups (BUD group: 1 event in 1 patient, FP group: 3 events in 2 patients) and there was no DAE that was judged as possibly drug-related by the investigator. No other significant AEs were identified in this study. 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 either treatment.

Budesonide Turbuhaler® 100 µg twice daily and 200 µg twice daily were generally safe and well tolerated during 6-week treatment in Japanese children with bronchial asthma. The safety profile of budesonide and fluticasone was comparable.

Table S4 Number (%) of patients who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)

Category of adverse event	N (%) of patients who had an adverse event in each category[a]					
	Budesonide			Fluticasone		
	100 µg bid (n=58)	200 µg bid (n=62)	Total (n=120)	50 µg bid (n=64)	100 µg bid (n=60)	Total (n=124)
Any adverse events	33 (56.9)	28 (45.2)	61 (50.8)	30 (46.9)	30 (50.0)	60 (48.4)
Serious adverse events						
Serious adverse events leading to death	0	0	0	0	0	0
Serious adverse events not leading to death	1 (1.7)	3 (4.8)	4 (3.3)	4 (6.3)	1 (1.7)	5 (4.0)
Discontinuations of study treatment due to adverse events	0	1 (1.6)	1 (0.8)	1 (1.6)	1 (1.7)	2 (1.6)

Category of adverse event	N (%) of patients who had an adverse event in each category[a]					
	Budesonide			Fluticasone		
	100 µg bid (n=58)	200 µg bid (n=62)	Total (n=120)	50 µg bid (n=64)	100 µg bid (n=60)	Total (n=124)
Other significant adverse events	0	0	0	0	0	0
	Total number of adverse events					
Adverse events	61	48	109	47	50	97
Serious adverse events	1	5	6	5	1	6
Other significant adverse events	0	0	0	0	0	0

bid: twice daily

[a] 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.

Table S5 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 (safety analysis set)

Preferred term	Budesonide			Fluticasone		
	100 µg bid	200 µg bid	Total	50 µg bid	100 µg bid	Total
N of patients for safety	58	62	120	64	60	124
No of patients with adverse event	33 (56.9%)	28 (45.2%)	61 (50.8%)	30 (46.9%)	30 (50.0%)	60 (48.4%)
Upper respiratory tract infection	10 (17.2%)	2 (3.2%)	12 (10.0%)	5 (7.8%)	7 (11.7%)	12 (9.7%)
Influenza	6 (10.3%)	3 (4.8%)	9 (7.5%)	4 (6.3%)	3 (5.0%)	7 (5.6%)
Gastroenteritis	3 (5.2%)	5 (8.1%)	8 (6.7%)	2 (3.1%)	4 (6.7%)	6 (4.8%)
Nasopharyngitis	4 (6.9%)	2 (3.2%)	6 (5.0%)	3 (4.7%)	1 (1.7%)	4 (3.2%)
Pharyngitis	2 (3.4%)	4 (6.5%)	6 (5.0%)	2 (3.1%)	1 (1.7%)	3 (2.4%)
Bronchitis	2 (3.4%)	2 (3.2%)	4 (3.3%)	4 (6.3%)	2 (3.3%)	6 (4.8%)
Conjunctivitis allergic	2 (3.4%)	1 (1.6%)	3 (2.5%)	0	3 (5.0%)	3 (2.4%)
Dermatitis atopic	3 (5.2%)	0	3 (2.5%)	0	0	0
Headache	1 (1.7%)	2 (3.2%)	3 (2.5%)	0	1 (1.7%)	1 (0.8%)
Rhinitis allergic	1 (1.7%)	2 (3.2%)	3 (2.5%)	1 (1.6%)	1 (1.7%)	2 (1.6%)
Abdominal pain	1 (1.7%)	1 (1.6%)	2 (1.7%)	0	0	0
Acute tonsillitis	0	2 (3.2%)	2 (1.7%)	0	1 (1.7%)	1 (0.8%)
Arthralgia	2 (3.4%)	0	2 (1.7%)	0	0	0
Diarrhoea	2 (3.4%)	0	2 (1.7%)	1 (1.6%)	0	1 (0.8%)
Eczema	1 (1.7%)	1 (1.6%)	2 (1.7%)	0	2 (3.3%)	2 (1.6%)
Pharyngolaryngeal pain	1 (1.7%)	1 (1.6%)	2 (1.7%)	0	0	0
Rhinitis	2 (3.4%)	0	2 (1.7%)	1 (1.6%)	1 (1.7%)	2 (1.6%)
Acute sinusitis	0	1 (1.6%)	1 (0.8%)	2 (3.1%)	0	2 (1.6%)
Asthma	0	1 (1.6%)	1 (0.8%)	2 (3.1%)	1 (1.7%)	3 (2.4%)
Otitis media	0	1 (1.6%)	1 (0.8%)	1 (1.6%)	2 (3.3%)	3 (2.4%)
Urticaria	1 (1.7%)	0	1 (0.8%)	1 (1.6%)	2 (3.3%)	3 (2.4%)
Chronic sinusitis	0	0	0	2 (3.1%)	4 (6.7%)	6 (4.8%)
Heat rash	0	0	0	1 (1.6%)	1 (1.7%)	2 (1.6%)
Pyrexia	0	0	0	2 (3.1%)	0	2 (1.6%)
Contusion	0	0	0	1 (1.6%)	1 (1.7%)	2 (1.6%)

bid: twice daily

[a] This table uses a cut-off of ≥1% of patients in total of each treatment group.