AstraZeneca

Clinical Study Report

Drug substance:	Budesonide
Document No.:	SD-004-CR-0768
Edition No.:	Version 1
Study code:	SD-004-0768
Date:	15 May 2007

Investigation of safety and efficacy of budesonide inhalation suspension in the long-term use in Japanese children with bronchial asthma (open long-term extension study following study SD-004-0765)

Study dates:	First patient enrolled: 6 January 2004 Last patient completed: 22 November 2006
Phase of development:	Therapeutic confirmatory (Phase III)
Co-ordinating investigator:	Not applicable in this study.

This study has been performed in compliance with Good Clinical Practice.

Drug product:	Pulmicort® Respules®	**SYNOPSIS**	
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Co-ordinating investigator

Not applicable in this study.

Study centre(s)

This study has been conducted at 10 centres in Japan.

Publications

Nishima S, Morikawa A, Nishimuta T. Proper use of budesonide inhalation suspension in treatment for paediatric bronchial asthma. Journal for the Japanese Society of Paediatric Allergy and Clinical Immunology 2006; 20 (3): 218-30. (Japanese Publication)

Study dates		**Phase of development**
First patient enrolled	6 January 2004	Therapeutic confirmatory (Phase III)
Last patient completed	22 November 2006	

Objectives

Primary objective:
To assess the safety profile of long-term use of budesonide inhalation suspension in Japanese young children with bronchial asthma, by evaluation of frequency and intensity of adverse events, plasma cortisol, physical examination, height, weight and clinical laboratory values.

Secondary objectives:
To assess the efficacy of budesonide inhalation suspension administered once daily or twice daily to Japanese young children with bronchial asthma by overall evaluation on asthma control by investigator.

Study design

This is an open multi-centre study.

Target subject population and sample size

Young children with bronchial asthma who completed the study SD-004-0765 prior to this study, who were expected to gain clinical benefit from continued administration of budesonide inhalation suspension as judged by the investigator(s), and whose legal representative agreed on his or her participation in this study. Fifty-four (54) patients entered this study.

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

Budesonide inhalation suspension was administrated by inhalation with a nebuliser (Pari LC Plus™) twice daily (morning and evening) or once daily (morning or evening) at the discretion of the investigator(s). The dose could be adjusted as appropriate within the range of 0.25-1.0 mg/day according to the symptoms (only once daily for 0.25 mg/day).

Budesonide inhalation suspension was supplied in a 2-mL ampoule at a concentration of 0.125 mg/mL or 0.25 mg/mL.

Duration of treatment

Patients received treatment with budesonide inhalation suspension from their enrolment until market launch of the drug or until the patient became 5 years old, whichever came first. If no other effective therapy was available for the patient's bronchial asthma, as judged by the investigator(s), the treatment with the investigational product could be continued in the patient after the patient reached the age of 5 years until a switch to other treatment became available.

Criteria for evaluation (main variables)

Safety

- Primary outcome variables:
  - Frequency and intensity of adverse events
  - Laboratory measurements (haematology, clinical chemistry and urinalysis)
  - Physical examination
  - Height and weight
  - Plasma cortisol

Efficacy and pharmacokinetics

- Secondary outcome variables:
  - Overall evaluation on asthma control by investigator

Statistical methods

The statistical analysis for efficacy and safety assessment was based on all patients enrolled into this study whose post-dose data were available (all patients treated, APT).

Overall evaluation on asthma control by investigator at every visit was descriptively summarised. All the safety data was also descriptively summarised.

Subject population

Subject population and disposition are presented in Table S1.

A total of 54 patients entered this extension study. Twenty-five patients completed the final evaluation visit of the study; the final evaluation visit was defined as the 2nd regular visit after the launch date of Pulmicort® Inhalation Suspension (Pulmicort® Respules®) in Japan, 15 September 2006. The most common reason for discontinuation before the final visit was consent withdrawal. All the 54 patients were included in the analysis set for safety and efficacy assessment (APT).

Table S1 Subject population and disposition

Demographic or baseline characteristic			
Population			
Number of patients who entered this study		54	
Demographic characteristics			
Sex (n and % of subjects)	Male	34	(63.0)
	Female	20	(37.0)
Age at entry to this study (months)	Mean ± SD	36.3 ± 16.4	
	Range	13 to 65	
Ethnic (n and % of subjects)	Japanese	54	(100.0)
Height at entry to this study (cm)	Mean ± SD	91.47 ± 10.99	
	Range	72.8 to 113.4	
Weight at entry to this study (kg)	Mean ± SD	14.04 ± 4.03	
	Range	8.7 to 34.5	
Disposition			
N of subjects who	completed the final visit of the study	25	
Number of patients for evaluation (All Patients Treated; APT[a])		54	

[a] Number of subjects who were enrolled in this study and had at least 1 data after dosing
Data derived from Tables 11.1.1, 11.1.3 and 11.1.4, Section 11.1.

Efficacy and pharmacokinetic results

Table S2 presents a summary of overall evaluation on asthma control, assessed by investigator, every 24 weeks and last observation (LOCF). Overall, budesonide inhalation suspension provided good asthma control throughout the treatment period. The percentage of the patients with "very good", "good" or "poor" assessment at LOCF in the APT population was 59.3%, 33.3% and 7.4%, respectively.

Table S2 Overall evaluation on asthma control assessed by investigator[Note] (All Patients Treated)

		Overall evaluation on asthma control		
Week	**N**	**Very good**	**Good**	**Poor**
Week 24	53	22 (41.5%)	22 (41.5%)	9 (17.0%)
Week 48	50	29 (58.0%)	17 (34.0%)	4 (8.0%)
Week 72	38	18 (47.4%)	15 (39.5%)	5 (13.2%)
Week 96	29	12 (41.4%)	17 (58.6%)	0 (0.0%)
Week 120	23	11 (47.8%)	11 (47.8%)	1 (4.3%)
Last observation (LOCF)	54	32 (59.3%)	18 (33.3%)	4 (7.4%)

Note: Patients for whom assessment result was not available for some reason were not included in the calculation at each timepoint.

Data derived from Table 11.2.1, Section 11.2.

Safety results

Table S3 presents overall frequency of adverse events during the whole treatment period.

No deaths were reported in this study. A total of 68 other serious adverse events were reported in 24 patients (44.4%). All of the 54 patients in the safety assessment had at least 1 adverse event. There were no discontinuations due to adverse events, and no other significant adverse events were identified.

Table S3 Number of patients who had at least 1 adverse event in any category during whole treatment period in this study and total numbers of adverse events[a] (All Patients Treated)

Category of adverse event	Number of patients who had an adverse event in each category[b]
Number of patients included in the safety assessment	54
Any adverse events	54 (100%)
Serious adverse events	
Adverse events leading to death	0 (0.0%)
Other serious adverse events	24 (44.4%)
Discontinuations of study treatment due to adverse events	0 (0.0%)
Other significant adverse events	0 (0.0%)
Drug-related adverse events	5 (9.3%)
	Total number of adverse events
Adverse events	1242
Other serious adverse events	68
Other significant adverse events	0

a This summary table does not include adverse events that were still present at the entry to SD-004-0768 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.

Data derived from Table 11.3.2.1, Section 11.3.2.

Table S4 presents a summary of commonly reported adverse events during the treatment period (frequency 10% or higher), by Preferred Term (MedDRA 7.0).

No new or unexpected safety concern was identified in the pattern of adverse events reported in this study, as compared to that in the preceding study SD-004-0765. Most commonly reported adverse events were upper respiratory infection, symptoms related to common cold such as pharyngitis and nasopharyngitis, and gastroenteritis.

Table S4 Number of patients with the most commonly reported (cut-off 10%) adverse events during whole treatment period of this study, by Preferred Term[a] (All Patients Treated)

Preferred term	N	%
Upper respiratory tract infection	45	(83.3%)
Pharyngitis	27	(50.0%)
Gastroenteritis	26	(48.1%)
Nasopharyngitis	25	(46.3%)
Conjunctivitis	24	(44.4%)
Bronchitis	23	(42.6%)
Influenza	23	(42.6%)
Impetigo	17	(31.5%)
Otitis media	17	(31.5%)
Asthma	17	(31.5%)
Eczema	16	(29.6%)
Arthropod bite	16	(29.6%)
Dermatitis atopic	14	(25.9%)
Urticaria	14	(25.9%)
Rhinitis allergic	14	(25.9%)
Conjunctivitis allergic	13	(24.1%)
Varicella	12	(22.2%)
Bronchitis acute	10	(18.5%)
Rhinitis	10	(18.5%)
Sinusitis	10	(18.5%)
Heat rash	10	(18.5%)
Diarrhoea	10	(18.5%)
Pyrexia	10	(18.5%)
Constipation	8	(14.8%)
Stomatitis	8	(14.8%)
Gastroenteritis viral	7	(13.0%)
Otitis media acute	7	(13.0%)
Pneumonia	7	(13.0%)
Dermatitis contact	7	(13.0%)
Dry skin	7	(13.0%)
Mumps	6	(11.1%)
Tonsillitis	6	(11.1%)
Enteritis	6	(11.1%)

a This summary table does not include adverse events that were still present at the entry to SD-004-0768 study.

Data derived from Table 11.3.2.2, Section 11.3.

No concerns were raised in the clinical laboratory test results. The mean morning plasma cortisol values in this study SD-004-0768 were lower than the baseline for study SD-004-0765 throughout the treatment period; however, no continuous decrease in the mean plasma cortisol value was seen. No signs or symptoms suggesting adrenal insufficiency were seen. No adverse effects on patient growth were observed during the treatment period up to 168 weeks, including the 24-week treatment period in study SD-004-0765.

Date of the report

15 May 2007

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