AstraZeneca

Drug product:	<<>>	**SYNOPSIS**	
Drug substance(s):	Budesonide (S-1320)		
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A randomised, open, parallel-group, 24-week treatment, multicentre, Phase III study to investigate the efficacy and safety of 0.5-1.0 mg daily dose of budesonide inhalation suspension in Japanese children with bronchial asthma aged 6 months-4 years

Co-ordinating investigator

Study centre(s)

This study was conducted at 11 Japanese medical institutions.

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First subject enrolled	7 July 2003	Therapeutic confirmatory study (Phase III)
Last subject completed	26 August 2004	

Objectives

Primary objective:

The primary objective of this study was to investigate the efficacy and safety of budesonide inhalation suspension at a daily dose of 0.5–1.0 mg administered for 12 weeks as once daily or twice daily by inhalation via nebuliser to Japanese young children with bronchial asthma, by

evaluation of the frequency of asthma attacks, frequency and severity of adverse events, and effects on clinical laboratory values.

Secondary objectives:

The secondary objectives of this study were as follows;

- To investigate the efficacy of budesonide inhalation suspension at a daily dose of 0.5–1.0 mg administered for 24 weeks as once daily or twice daily to Japanese young children with bronchial asthma, by assessment of the following variables:
  - Frequency of asthma attacks
  - Treatment score
  - Frequency of cough
  - Disturbance of daily activity
  - Disturbance of nighttime sleep
- To investigate the safety of the treatment with budesonide inhalation suspension administered by inhalation for 12 and 24 weeks in Japanese young children with bronchial asthma, by evaluation of the frequency and severity of adverse events, laboratory measurements, plasma cortisol, physical examination and height.
- To investigate the efficacy and safety of budesonide inhalation suspension at an increased daily dose of 1.0 mg in patients considered to have had insufficient treatment response at a daily dose of 0.5 mg.

Study design

This was a randomised, open, parallel-group, multicentre study to investigate the efficacy and safety of 0.5-1.0 mg daily dose of budesonide inhalation suspension in Japanese children with bronchial asthma aged 6 months-4 years.

Target subject population and sample size

Japanese children with bronchial asthma who required treatment with inhaled steroids aged from 6 months to 4 years.

A total of 60 randomised (30 patients each in the group of 0.25 mg twice daily and in the group of 0.5 mg once daily).

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

Budesonide inhalation suspension was administrated by inhalation with a nebuliser (Pari LC Plus™) at a dose of 0.25–0.5 mg twice daily (morning and evening) or 0.5–1.0 mg once daily

(morning). Treatment was commenced with 0.25 mg twice daily or 0.5 mg once daily. If the investigator(s) judges that sufficient treatment response was not achieved at Week 6, the dose may be increased to 0.5 mg twice daily for subjects who started the treatment at 0.25 mg twice daily, and to 1.0 mg once daily for subjects who started the treatment at 0.5 mg once daily.

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

Lot numbers were: 0.25 mg ampoule, 219537; 0.5 mg ampoule, 219502.

Duration of treatment:

After a run-in period on current treatment for 2 to 4 weeks, patients were to receive treatment with budesonide inhalation suspension for 24 weeks.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: change in the frequency of asthma attacks per week at Week 12 from baseline
- Secondary variables:
  - Change in the frequency of asthma attacks per week from baseline at Weeks 2, 4, 6, 8, 10, 14, 16, 18, 20, 22 and 24.
  - Change in the frequency of cough, treatment score, frequency of disturbance of daily activity, and frequency of disturbance of nighttime sleep per week from baseline at Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24.

Safety

- Frequency and severity of adverse events
- Laboratory measurements (haematology, biochemistry and urinalysis)
- Physical examination
- Height
- Plasma cortisol

Statistical methods

The primary analysis population for the efficacy was the Full Analysis Set (FAS) population. The safety analysis population was all subjects who received at least one dose of the study treatment with any safety data collected.

For the frequency of asthma attacks per week, primary outcome variable, the mean change at Week 12 from the baseline and its 2-sided 95% confidence interval was estimated altogether in all subjects of the analysis set.

All efficacy and safety variables were summarised descriptively.

An interim data lock and interim analysis were performed using data up to Week 12.

Subject population

In total, 74 patients with bronchial asthma were screened and 61 of them were randomised to the study treatment. Patient population and disposition are summarised in Table S1. Thirty three and 28 patients were randomised to 0.25 mg bid and 0.5 mg qd, respectively. Four patients were discontinued: 1 patient in the 0.25 mg bid, who was discontinued by Week 24, and 3 patients in the 0.5 mg qd , who were discontinued by Week 12. The number of patients who completed the study by Week 12 was 33 for 0.25 mg bid and 25 for 0.5 mg qd and by Week 24 was 32 for 0.25 mg bid and 25 for 0.5 mg qd. All patients were Japanese. The mean age of the patients was 29.6 months. Males accounted for 66% and females for 34%. The demographic characteristics were similar between the treatment groups.

Table S1 Subject population and disposition

Demographic or baseline characteristic		Treatment group 0.25 mg bid		0.5 mg qd		Total	
Population							
N randomised (N planned)		33	(30)	28	(30)	61	(60)
Demographic characteristics							
Sex	Male	19	(57.6)	21	(75.0)	40	(65.6)
(n and % of subjects)	Female	14	(42.4)	7	(25.0)	21	(34.4)
Age (months)	Mean [SD]	30.1	[15.3]	29.0	[16.7]	29.6	[15.8]
	Range	8 to 59		7 to 58		7 to 59	
Ethnic (n and % of subjects)	Japanese	33	(100)	28	(100)	61	(100)
Height (cm)	Mean [SD]	87.03	[11.22]	86.79	[12.67]	86.92	[11.81]
	Range	65.2 to 107.1		66.8 to 110.6		65.2 to 110.6	
Weight (kg)	Mean [SD]	12.79	[4.14]	12.46	[3.27]	12.64	[3.74]
	Range	7.8 to 31.6		7.0 to 19.5		7.0 to 31.6	
Baseline characteristics							
Family allergic disease	Yes	27	(81.8)	25	(89.3)	52	(85.2)
(n and % of subjects)	No	6	(18.2)	3	(10.7)	9	(14.8)
Duration of asthma	<6 months	11	(33.3)	6	(21.4)	17	(27.9)
(n and % of subjects)	6 months≤ < 12 months	4	(12.1)	10	(35.7)	14	(23.0)
	12 months≤	18	(54.5)	12	(42.9)	30	(49.2)
Disposition							
N of subjects who	Completed (12 weeks)	33		25		58	
	Completed (24 weeks)	32		25		57	
	Discontinued	1		3		4	
N analysed for safety[a]		33		28		61	
N analysed for efficacy (FAS)		32		28		60	
N analysed for efficacy <PPS (0-12W)>		25		23		48	
N analysed for efficacy <PPS (0-24W)>		24		18		42	

[a] Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing
FAS=Full Analysis Set; N=Number; PPS=Per Protocol Set

Efficacy and pharmacokinetic results

The primary outcome variable for this study was the change in the frequency of asthma attacks per week at Week 12 from baseline. The mean [SD] baseline frequency of asthma attacks per week was 9.92 [4.83]. The mean change of the frequency of asthma attacks per week at Week 12 (FAS with LOCF) from baseline was -6.99 (95%CI: -8.46 to -5.52). There was a statistically significant improvement from baseline in the frequency of asthma attacks per week at Week 12 (FAS with LOCF) (t-test: $p<0.001$). A reduction in the frequency of asthma attacks per week maintained up to Week 24. A reduction in treatment scores and the frequency of coughs per week was seen at Week 12 compared to baseline and maintained up to Week 24. The improvement of daily activities and nighttime sleep obtained during the first 12 weeks treatment were maintained up to 24 weeks.

Table S2 95% confidence interval and p value of t-test for mean change from baseline of asthma attack frequency at Week 12

		Baseline		Week 12		Change		95%CI		
Population	**N**	**Mean**	**[SD]**	**Mean**	**[SD]**	**Mean**	**[SD]**	**Lower**	**Upper**	**p value**
FAS (LOCF)	60	9.92	[4.83]	2.93	[4.57]	-6.99	[5.69]	-8.46	-5.52	<0.001
PPS (0-12W)	45[1)]	9.43	[4.27]	2.37	[3.60]	-7.06	[5.15]	-8.61	-5.51	<0.001
PPS (0-12W) with restrictions*	43[1)]	9.24	[4.27]	2.05	[3.19]	-7.19	[4.99]	-8.73	-5.65	<0.001
PPS (0-24W)	39[1)]	8.82	[3.85]	2.23	[3.46]	-6.59	[4.75]	-8.13	-5.05	<0.001
PPS (0-24W) with restrictions*	37[1)]	8.57	[3.79]	1.85	[2.91]	-6.71	[4.53]	-8.23	-5.20	<0.001

1) The number of patients with both baseline and week 12 data available.
* Excluding data when systemic steroids were used as rescue medication (see Section 5.7.4.2).

Table S 3 The mean change from baseline of asthma attack frequency at Week 24

	Baseline			Week 24			Change		
Population	**N[1)]**	**Mean**	**[SD]**	**N[2)]**	**Mean**	**[SD]**	**N[2)]**	**Mean**	**[SD]**
FAS	60	9.92	[4.83]	54	2.91	[5.08]	54	-6.99	[5.61]
PPS (0-24W)	42	8.80	[3.86]	37	1.97	[3.30]	37	-6.80	[4.46]
PPS (0-24W) with restrictions*	42	8.80	[3.86]	33	1.35	[2.38]	33	-7.13	[4.09]

1) The number of patients with baseline data available.
2) The number of patients with both baseline and week 24 data available.
* Excluding data when systemic steroids were used as rescue medication (see Section 5.7.4.2).

Safety results

Budesonide inhalation suspension was administered for 24 weeks in Japanese children with bronchial asthma aged 6 months - 4 years up to 1.0 mg daily dose. During run-in period, the most common adverse events (with an incidence of at least 5%) by system organ class were infections and infestations (29.5% [18 patients]), respiratory, thoracic and mediastinal disorders (9.8% [6 patients]), gastrointestinal disorders (9.8% [6 patients]) and skin and subcutaneous tissue disorders (9.8% [6 patients]). During the 12-week treatment period, the most common adverse events (with an incidence of at least 30%) by system organ class were infections and infestations (93.4% [57 patients]), respiratory, thoracic and mediastinal disorders (34.4% [21 patients]) and gastrointestinal disorders (31.1% [19 patients]). During the 24-week treatment period, the most common adverse events (with an incidence of at least 30%) by system organ class were infections and infestations (95.1% [58 patients]), gastrointestinal disorders (50.8% [31 patients]), skin and subcutaneous tissue disorders (45.9% [28 patients]), and respiratory, thoracic and mediastinal disorders (41.0% [25 patients]). A general adverse event profile during treatment period was similar to what could be expected for the studied patient population. The adverse events during the 12-week treatment period

with an incidence of at least 5% of the overall population were upper respiratory tract infection (41.0% [25 patients]), pharyngitis (27.9% [17 patients]), asthma (23.0% [14 patients]), gastroenteritis (18.0% [11patients]), bronchitis acute (16.4% [10 patients]), diarrhoea (14.8% [9 patients]), nasopharyngitis (13.1% [8 patients]), eczema (9.8% [6 patients]), pyrexia (9.8% [6 patients]), otitis media (8.2% [5 patients]), otitis media acute (8.2% [5 patients]), conjunctivitis (8.2% [5 patients]), bronchitis (6.6% [4 patients]), impetigo (6.6% [4 patients]) and laryngitis (6.6% [4 patients]).

The adverse events during the 24-week treatment period with an incidence of at least 5% of the overall population were upper respiratory tract infection (52.5% [32 patients]), pharyngitis (36.1% [22 patients]), gastroenteritis (31.1% [19 patients]), asthma (29.5% [18 patients]), bronchitis acute (24.6% [15 patients]), nasopharyngitis (24.6% [15 patients]), diarrhoea (21.3% [13 patients]), bronchitis (18.0% [11 patients]), conjunctivitis (16.4% [10 patients]), dermatitis atopic (13.1% [8 patients]), eczema (11.5% [7 patients]), pneumonia (11.5% [7 patients]), varicella (11.5% [7 patients]), pyrexia (9.8% [6 patients]), otitis media (9.8% [6 patients]), influenza (9.8% [6 patients]), otitis media acute (8.2% [5 patients]), gastroenteritis rotavirus (8.2% [5 patients]), vomiting (8.2% [5 patients]), urticaria (8.2% [5 patients]), impetigo (6.6% [4 patients]), laryngitis (6.6% [4 patients]), acute sinusitis (6.6% [4 patients]), conspitation (6.6% [4 patients]), enterocolitis (6.6% [4 patients]), stomatitis (6.6% [4 patients]), dry skin (6.6% [4 patients]), epistaxis (6.6% [4 patients]), and arthropod bite (6.6% [4 patients]).

Four adverse events were judged to be drug related by the investigator(s) up to Week 12. These adverse events were reported by 3 patients (4.9%): cheilitis (1 patient, 0.25 mg bid), oral candidiasis and stomatitis (1 patient, 0.5 mg qd) and oral candidiasis (1 patient, 0.25 mg bid). However, none of the events were considered as severe nor did they fulfil serious criteria. Two of the adverse events (in the same patient) that were judged as drug-related (0.5 mg qd, oral candidasis and stomatitis) caused the patient to discontinue the study. None of the adverse events reported between Week 12 and Week 24 were judged to be drug related by the investigator(s). Also no patient was discontinued from study treatment due to adverse events between Week 12 and Week 24.

The pattern of AEs was similar between the final dose groups (0.5 mg/day and 1.0 mg/day) except for asthma related SAEs, which was higher in the 1.0 mg/day group. This is expected since patients were selected for the higher dose group based on more severe asthma.

There were a total of 24 serious adverse events in 15 patients during treatment period up to Week 12 and 6 serious adverse events in 5 patients during run-in period. There were a total of 41 SAEs in 24 patients reported during 24-week treatment period: 24 SAEs in 17 patients in 0.25 mg bid and 17 SAEs in 7 patients in 0.5 mg qd. The most frequently reported serious adverse event during run-in, 12-week treatment period and 24-week treatment period was asthma. None of the treatment-emergent serious adverse events were judged by the investigators to be related to the investigational product. No new type of SAE was observed between Week 12 and Week 24. When comparing SAEs in the 2 final dose groups, there were 14 patients (29.2%) with SAEs in 0.5 mg/day and 10 patients (76.9%) with SAEs in 1.0 mg/day up to 24 weeks. It should be noted that patients were not randomised to either of the

doses, but stratified based on disease severity at Week 6. It means that patients with more severe asthma were included in the 1.0 mg/day dose group. This is reflected by higher frequency of asthma related SAEs in this dose group. There were no deaths reported during the study.

Mean plasma cortisol decreased from baseline to week 12, however there was no further decrease between Week 12 and Week 24. All patients except for 4 patients at Week 12 and except for 3 patients at Week 24 had plasma cortisol within the reference range (≥4 μg/dL). All 4 patients with low plasma cortisol at Week 12 had values within the reference range at Week 24. Mean cortisol at Week 24 were at comparable levels in the groups of patients with final dose 0.5 mg/day and 1.0 mg/day. No clinical signs of cortisol deficiency were seen. No notable changes were found in other laboratory parameters. Mean height increased by about 2.6 cm during 12-week treatment period and about 4.2 cm during 24-week treatment period. The mean height increases after 24 weeks of treatment were at comparable levels in the groups of patients with final doses of 1.0 mg/day (5.1 cm) and 0.5 mg/day (3.9 cm).

The adverse event profile during 24-week treatment was similar to that in the 12-week treatment.

There were no new or unexpected observations. The treatment did not raise any safety concerns.

Table S4 Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events during treatment period (safety analysis set) (Week 0 to 12)

Category of adverse event	N (%) of subjects who had an adverse event in each category[a]									
	All		Randomised group				Final dosage			
			0.25 mg bid		0.5 mg qd		0.5 mg / day		1.0 mg / day	
	(n=61)		(n=33)		(n=28)		(n=48)		(n=13)	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Any adverse events	61	(100.0)	33	(100.0)	28	(100.0)	48	(100.0)	13	(100.0)
Serious adverse events leading to death	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Serious adverse events not leading to death	15	(24.6)	11	(33.3)	4	(14.3)	7	(14.6)	8	(61.5)
Discontinuations of study treatment due to adverse events	1	(1.6)	0	(0.0)	1	(3.6)	1	(2.1)	0	(0.0)
Other significant adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Total number of adverse events									
Adverse events	273		158		115		206		67	
Serious adverse events	24		13		11		10		14	
Other significant adverse events	0		0		0		0		0	

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

Table S 5 Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events during treatment period (safety analysis set) (Week 0 to 24)

Category of adverse event	N (%) of subjects who had an adverse event in each category[a]									
	All		Randomised group				Final dosage			
			0.25 mg bid		0.5 mg qd		0.5 mg / day		1.0 mg / day	
	(n=61)		(n=33)		(n=28)		(n=48)		(n=13)	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Any adverse events	61	(100.0)	33	(100.0)	28	(100.0)	48	(100.0)	13	(100.0)
Serious adverse events leading to death	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Serious adverse events not leading to death	24	(39.3)	17	(51.5)	7	(25.0)	14	(29.2)	10	(76.9)
Discontinuations of study treatment due to adverse events	1	(1.6)	0	(0.0)	1	(3.6)	1	(2.1)	0	(0.0)
Other significant adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Total number of adverse events									
Adverse events	502		307		195		376		126	
Serious adverse events	41		24		17		20		21	
Other significant adverse events	0		0		0		0		0	

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

Table S6 Number (%) of subjects with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set) (Week 0 to 12)

		Treatment emergent AE											
		AE during run-in period		All		Randomised group				Final dosage			
						0.25 mg bid		0.5 mg qd		0.5 mg / day		1.0 mg / day	
		(n=61)		(n=61)		(n=33)		(n=28)		(n=48)		(n=13)	
System organ class	Preferred term	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
All Systems	Any AE	28	(45.9)	61	(100.0)	33	(100.0)	28	(100.0)	48	(100.0)	13	(100.0)
INFECTIONS AND INFESTATIONS	Any AE	18	(29.5)	57	(93.4)	32	(97.0)	25	(89.3)	45	(93.8)	12	(92.3)
	UPPER RESPIRATORY TRACT INFECTION	10	(16.4)	25	(41.0)	12	(36.4)	13	(46.4)	19	(39.6)	6	(46.2)
	PHARYNGITIS	2	(3.3)	17	(27.9)	10	(30.3)	7	(25.0)	13	(27.1)	4	(30.8)
	GASTROENTERITIS	2	(3.3)	11	(18.0)	8	(24.2)	3	(10.7)	10	(20.8)	1	(7.7)
	BRONCHITIS ACUTE	1	(1.6)	10	(16.4)	5	(15.2)	5	(17.9)	5	(10.4)	5	(38.5)
	NASOPHARYNGITIS	0	(0.0)	8	(13.1)	4	(12.1)	4	(14.3)	6	(12.5)	2	(15.4)
	OTITIS MEDIA	0	(0.0)	5	(8.2)	3	(9.1)	2	(7.1)	3	(6.3)	2	(15.4)
	OTITIS MEDIA ACUTE	1	(1.6)	5	(8.2)	4	(12.1)	1	(3.6)	4	(8.3)	1	(7.7)
	BRONCHITIS	1	(1.6)	4	(6.6)	2	(6.1)	2	(7.1)	4	(8.3)	0	(0.0)
	IMPETIGO	0	(0.0)	4	(6.6)	2	(6.1)	2	(7.1)	4	(8.3)	0	(0.0)
	LARYNGITIS	0	(0.0)	4	(6.6)	3	(9.1)	1	(3.6)	4	(8.3)	0	(0.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Any AE	6	(9.8)	21	(34.4)	13	(39.4)	8	(28.6)	13	(27.1)	8	(61.5)
	ASTHMA	4	(6.6)	14	(23.0)	9	(27.3)	5	(17.9)	7	(14.6)	7	(53.8)
GASTROINTESTINAL DISORDERS	Any AE	6	(9.8)	19	(31.1)	11	(33.3)	8	(28.6)	13	(27.1)	6	(46.2)
	DIARRHOEA	5	(8.2)	9	(14.8)	6	(18.2)	3	(10.7)	5	(10.4)	4	(30.8)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Any AE	6	(9.8)	18	(29.5)	9	(27.3)	9	(32.1)	13	(27.1)	5	(38.5)
	ECZEMA	0	(0.0)	6	(9.8)	2	(6.1)	4	(14.3)	5	(10.4)	1	(7.7)
EYE DISORDERS	Any AE	0	(0.0)	7	(11.5)	4	(12.1)	3	(10.7)	6	(12.5)	1	(7.7)
	CONJUNCTIVITIS	0	(0.0)	5	(8.2)	3	(9.1)	2	(7.1)	4	(8.3)	1	(7.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Any AE	1	(1.6)	6	(9.8)	4	(12.1)	2	(7.1)	6	(12.5)	0	(0.0)
	PYREXIA	1	(1.6)	6	(9.8)	4	(12.1)	2	(7.1)	6	(12.5)	0	(0.0)

[a] Events with a total frequency of ≥5% across all treatment groups are included in this table.
MedDRA dictionary (version 7.0)

Table S 7 Number (%) of subjects with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set) (Week 0 to 24)

		Treatment emergent AE											
		AE during run-in period		All		Randomised group				Final dosage			
						0.25 mg bid		0.5 mg qd		0.5 mg / day		1.0 mg / day	
		(n=61)		(n=61)		(n=33)		(n=28)		(n=48)		(n=13)	
System organ class	Preferred term	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
All Systems	Any AE	28	(45.9)	61	(100.0)	33	(100.0)	28	(100.0)	48	(100.0)	13	(100.0)
INFECTIONS AND INFESTATIONS	Any AE	18	(29.5)	58	(95.1)	33	(100.0)	25	(89.3)	45	(93.8)	13	(100.0)
	UPPER RESPIRATORY TRACT INFECTION	10	(16.4)	32	(52.5)	18	(54.5)	14	(50.0)	24	(50.0)	8	(61.5)
	PHARYNGITIS	2	(3.3)	22	(36.1)	15	(45.5)	7	(25.0)	16	(33.3)	6	(46.2)
	GASTROENTERITIS	2	(3.3)	19	(31.1)	13	(39.4)	6	(21.4)	16	(33.3)	3	(23.1)
	BRONCHITIS ACUTE	1	(1.6)	15	(24.6)	9	(27.3)	6	(21.4)	9	(18.8)	6	(46.2)
	NASOPHARYNGITIS	0	(0.0)	15	(24.6)	8	(24.2)	7	(25.0)	11	(22.9)	4	(30.8)
	BRONCHITIS	1	(1.6)	11	(18.0)	6	(18.2)	5	(17.9)	9	(18.8)	2	(15.4)
	PNEUMONIA	1	(1.6)	7	(11.5)	3	(9.1)	4	(14.3)	5	(10.4)	2	(15.4)
	VARICELLA	0	(0.0)	7	(11.5)	6	(18.2)	1	(3.6)	4	(8.3)	3	(23.1)
	INFLUENZA	0	(0.0)	6	(9.8)	4	(12.1)	2	(7.1)	5	(10.4)	1	(7.7)
	OTITIS MEDIA	0	(0.0)	6	(9.8)	4	(12.1)	2	(7.1)	4	(8.3)	2	(15.4)
	GASTROENTERITIS ROTAVIRUS	0	(0.0)	5	(8.2)	2	(6.1)	3	(10.7)	3	(6.3)	2	(15.4)
	OTITIS MEDIA ACUTE	1	(1.6)	5	(8.2)	4	(12.1)	1	(3.6)	4	(8.3)	1	(7.7)
	ACUTE SINUSITIS	0	(0.0)	4	(6.6)	3	(9.1)	1	(3.6)	4	(8.3)	0	(0.0)
	IMPETIGO	0	(0.0)	4	(6.6)	2	(6.1)	2	(7.1)	4	(8.3)	0	(0.0)
	LARYNGITIS	0	(0.0)	4	(6.6)	3	(9.1)	1	(3.6)	4	(8.3)	0	(0.0)
GASTROINTESTINAL DISORDERS	Any AE	6	(9.8)	31	(50.8)	18	(54.5)	13	(46.4)	23	(47.9)	8	(61.5)
	DIARRHOEA	5	(8.2)	13	(21.3)	9	(27.3)	4	(14.3)	8	(16.7)	5	(38.5)
	VOMITING	2	(3.3)	5	(8.2)	2	(6.1)	3	(10.7)	3	(6.3)	2	(15.4)
	CONSTIPATION	0	(0.0)	4	(6.6)	3	(9.1)	1	(3.6)	3	(6.3)	1	(7.7)
	ENTEROCOLITIS	0	(0.0)	4	(6.6)	0	(0.0)	4	(14.3)	4	(8.3)	0	(0.0)
	STOMATITIS	0	(0.0)	4	(6.6)	1	(3.0)	3	(10.7)	3	(6.3)	1	(7.7)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Any AE	6	(9.8)	28	(45.9)	15	(45.5)	13	(46.4)	20	(41.7)	8	(61.5)
	DERMATITIS ATOPIC	0	(0.0)	8	(13.1)	3	(9.1)	5	(17.9)	5	(10.4)	3	(23.1)
	ECZEMA	0	(0.0)	7	(11.5)	3	(9.1)	4	(14.3)	6	(12.5)	1	(7.7)
	URTICARIA	1	(1.6)	5	(8.2)	4	(12.1)	1	(3.6)	4	(8.3)	1	(7.7)
	DRY SKIN	1	(1.6)	4	(6.6)	4	(12.1)	0	(0.0)	3	(6.3)	1	(7.7)

Table S 7 **Number (%) of subjects with the most commonly reporteda adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set) (Week 0 to 24) (Continued)**

		Treatment emergent AE									
		AE during run-in period		All		Randomised group				Final dosage	
						0.25 mg bid		0.5 mg qd		0.5 mg / day	1.0 mg / day
		(n=61)		(n=61)		(n=33)		(n=28)		(n=48)	(n=13)
System organ class	**Preferred term**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Any AE	6	(9.8)	25	(41.0)	16	(48.5)	9	(32.1)	15	(31.3)	10	(76.9)
	ASTHMA	4	(6.6)	18	(29.5)	11	(33.3)	7	(25.0)	9	(18.8)	9	(69.2)
	EPISTAXIS	0	(0.0)	4	(6.6)	3	(9.1)	1	(3.6)	4	(8.3)	0	(0.0)
EYE DISORDERS	Any AE	0	(0.0)	12	(19.7)	8	(24.2)	4	(14.3)	10	(20.8)	2	(15.4)
	CONJUNCTIVITIS	0	(0.0)	10	(16.4)	7	(21.2)	3	(10.7)	8	(16.7)	2	(15.4)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	Any AE	1	(1.6)	11	(18.0)	4	(12.1)	7	(25.0)	9	(18.8)	2	(15.4)
	ARTHROPOD BITE	1	(1.6)	4	(6.6)	2	(6.1)	2	(7.1)	3	(6.3)	1	(7.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Any AE	1	(1.6)	6	(9.8)	4	(12.1)	2	(7.1)	6	(12.5)	0	(0.0)
	PYREXIA	1	(1.6)	6	(9.8)	4	(12.1)	2	(7.1)	6	(12.5)	0	(0.0)

[a] Events with a total frequency of ≥5% across all treatment groups are included in this table.
MedDRA dictionary (version 7.0)

Date of the report

27 January 2005