AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Budesonide Respules® (S-1320)
Study Code	D5259C00001
Edition Number	1.0
Date	8 January 2010

An evaluation of efficacy and safety of corresponding doses of Pulmicort Turbuhaler® and Pulmicort Respules® in Japanese asthmatic adult patients (open, multicenter, phase III study)

Study dates:	First patient enrolled: 19 February 2009 Last patient completed: 22 August 2009
Phase of development:	Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study centre(s)

This study was conducted at 7 centres in Japan. The first patient was enrolled on 19 February 2009 and the last subject completed the study on 22 August 2009.

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was:

- To show similarity of efficacy on Pulmicort Respules 1.0 mg/day or 2.0 mg/day for 6 weeks in the treatment period and the corresponding doses of Pulmicort Turbuhaler 400 µg/day or 800 µg/day for 4 weeks in the observation period in Japanese adult asthmatic patients 16 years and older.

The secondary objectives of this study were:

- To confirm the tolerability and safety on Pulmicort Respules 1.0 mg/day or 2.0 mg/day for 6 weeks in the treatment period and the corresponding doses of Pulmicort Turbuhaler 400 µg/day or 800 µg/day for 4 weeks in the observation period in Japanese adult asthmatic patients 16 years and older.

- To evaluate appropriateness of given 1 mg/day of Pulmicort Respules in a once or twice daily regimen for 6 weeks after Pulmicort Turbuhaler 400 µg /day for 4 weeks in the observation period in Japanese adult asthmatic patients 16 years and older.

Study design

This is an open, multicentre, phase III study in Japanese asthmatic patients with age of 16 years or older.

Target population and sample size

Japanese adult asthmatic patients aged 16 years or older under prescribed treatment with ICS at least 3 months and with stable asthma symptom during the 4 weeks prior to starting observation, and with $FEV_{1.0}$ >60% of predicted normal value pre-bronchodilator.

A total of 100 patients were to be enrolled.

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

- Pulmicort Respules 0.5 mg: Inhalation suspension, budesonide 0.5 mg/ampoule (2 mL) (Batch number: 305189)

- Pulmicort Turbuhaler 200 µg: Dry powder inhaler, budesonide 200 µg/dose, 112 doses/Turbuhaler (Batch number: KH109)

Duration of treatment

This study consisted of the period from informed consent until the start of the investigational product for 1 to 4 week, the observation period for 4 weeks and the treatment period for 6 weeks.

Criteria for evaluation - efficacy (main variables)

- Primary outcome variable:
  - The change in morning peak expiratory flow (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 period)
- Secondary variables:
  The change in the following variables from baseline (mean of the last 14 days of the observation period) to Week 6 (mean of the last 14 days of the treatment period)
  - Evening PEF (ePEF)
  - Asthma symptom score - daytime, night-time and total
  - Use of rescue medication - daytime, night-time and total
  - Night-time awakenings due to asthma symptoms

  The change in the following variables at Week 6 (Visit 5) from baseline (Visit 3)
  - Forced expiratory volume in one second ($FEV_{1.0}$), Forced vital capacity (FVC)

Criteria for evaluation - safety (main variables)

- Adverse events (AEs)
- Laboratory variables (clinical chemistry, haematology and urinalysis)
- Blood pressure and pulse rate

Statistical methods

For mPEF, the primary variable, the mean and 2-sided 95% confidence interval of changes from baseline (mean during the last 2 weeks of the observation period) to end of treatment (mean during the last 2 weeks of treatment period) were estimated based on combined data of dose groups, and the overall similarity of mPEF between Pulmicort Turbuhaler and Pulmicort Respules was investigated visually. To investigate the similarity of Pulmicort Turbuhaler and

Pulmicort Respules at corresponding doses, the mean and 2-sided 95% confidence interval of changes from baseline to the last 2 weeks of treatment were estimated for each dose group. Other efficacy variables were analysed similarly.

Subject population

The disposition and demographic and key baseline characteristics of the patients in this study are summarised in Table S 1. In total, 113 patients were enrolled at 7 centres in Japan. Of those 108 patients were treated with Pulmicort Turbuhaler in the observation period, and 105 patients were treated with Pulmicort Respules in the treatment period. A total of 3 and 6 patients discontinued study treatment in the observation and the treatment periods, respectively. The number of analysed patients was 108 in the safety analysis set and 106 in the FAS. The patient population enrolled into this study was well controlled and considered to be consistent with those defined by the study protocol.

Table S 1 Patient population and disposition (FAS)

		Low dose n=53		**High dose n=53**		**Total n=106**	
Population							
Number of treated (Number of planned)		54	(50)	54	(50)	108	(100)
Demographic characteristics							
Age (year)	Mean (SD)	43.8	(13.5)	43.9	(13.4)	43.9	(13.4)
	Range	(20 to 70)		(24 to 78)		(20 to 78)	
Sex	Male	19	(35.8%)	14	(26.4%)	33	(31.1%)
	Female	34	(64.2%)	39	(73.6%)	73	(68.9%)
Ethnic group	Japanese	53	(100.0%)	53	(100.0%)	106	(100.0%)
Weight (kg)	Mean (SD)	60.0	(11.5)	60.5	(12.4)	60.3	(11.9)
	Range	(40 to 92)		(39 to 88)		(39 to 92)	
Height (cm)	Mean (SD)	162.5	(8.7)	160.5	(8.6)	161.5	(8.7)
	Range	(148 to 183)		(139 to 184)		(139 to 184)	
Duration of asthma (year)	Mean (SD)	13.94	(14.77)	11.63	(12.26)	12.78	(13.56)
	Range	(0.5 to 44.7)		(0.7 to 51.8)		(0.5 to 51.8)	
Nicotine use	Never	40	(75.5%)	44	(83.0%)	84	(79.2%)
	Current	4	(7.5%)	6	(11.3%)	10	(9.4%)
	Former	9	(17.0%)	3	(5.7%)	12	(11.3%)

To be continued.

Table S 1 Patient population and disposition (FAS)

		Low dose n=53	High dose n=53	Total n=106
Baseline characteristics				
Daily dose of ICS before enrolment (µg) [1]	Mean (SD)	400.0 (0.0)	792.5 (54.9)	596.2 (200.9)
	Range	(400 to 400)	(400 to 800)	(400 to 800)
$FEV_{1.0}$ (L)	Mean (SD)	2.692 (0.686)	2.663 (0.763)	2.678 (0.723)
	Range	(1.48 to 4.58)	(1.37 to 4.99)	(1.37 to 4.99)
$FEV_{1.0}$ (% of predicted normal)	Mean (SD)	92.54 (15.79)	95.08 (15.54)	93.81 (15.64)
	Range	(64.1 to 123.3)	(61.7 to 144.0)	(61.7 to 144.0)
Disposition				
Number of patients who completed				
Observation period		53	52	105
Treatment period		53 [2]	46	99
Number of patients who discontinued				
Observation period		1	2	3
Treatment period		0	6	6
Number of analysed patients for safety		54	54	108
Number of analysed patients for FAS		53	53	106

1) Budesonide equivalent
2) Once daily: n=28, Twice daily: n=25

Summary of efficacy results

The mean changes in mPEF at Week 6 (LOCF) from baseline as primary variable are presented in Table S 2. The mean change in mPEF from baseline to Week 6 (LOCF) was estimated to be 3.3 L/min (95% confidence interval: -0.9 to 7.4 L/min) in total patients. Similar patterns of mean change in mPEF from baseline to Week 6 (LOCF) were observed in low and high dose groups.

Table S 2 Mean change in mPEF (L/min) at Week 6 (LOCF) from baseline (FAS)

		Baseline [1]		Week 6 (LOCF) [2]		Change from baseline		
Dose group	**n**	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**(95% CI)**
Low dose	53	403.7	(108.0)	407.7	(106.6)	4.0	(22.2)	(-2.1 to 10.2)
High dose	52	371.4	(114.2)	373.9	(111.4)	2.5	(20.8)	(-3.3 to 8.3)
Total	105	387.7	(111.7)	391.0	(109.8)	3.3	(21.4)	(-0.9 to 7.4)

1) Mean of the last 14 days of the observation period
2) Mean of the last 14 days of the treatment period
CI: confidence interval

The mean changes in mPEF at Week 6 (LOCF) from baseline in once daily and twice daily regimen in low dose group are shown in Table S 3. Similar patterns of mean change in mPEF from baseline to Week 6 (LOCF) were observed in once daily and twice daily regimens in low dose group.

Table S 3 Mean change in mPEF (L/min) at Week 6 (LOCF) from baseline in once daily and twice daily regimen in low dose group (FAS)

		Baseline [1)]		Week 6 (LOCF) [2)]		Change from baseline		
Dose regimen	**n**	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**(95% CI)**
Once daily	28	408.8	(104.9)	412.0	(102.2)	3.2	(24.1)	(-6.1 to 12.6)
Twice daily	25	397.9	(113.3)	402.9	(113.3)	5.0	(20.4)	(-3.4 to 13.4)

1) Mean of the last 14 days of the observation period
2) Mean of the last 14 days of the treatment period
CI: confidence interval

The mean changes in secondary variables related to daily date at Week 6 (LOCF) from baseline are shown in Table S 4. The results from secondary variables supported the findings for the primary variable. Overall, no clinically relevant differences between treatment groups were observed in the secondary variables.

Table S 4 Mean change in secondary variables related to daily date at Week 6 (LOCF) from baseline (FAS)

		Baseline [1)]		Week 6 (LOCF) [2)]		Change from baseline		
Variables	**n**	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**(95% CI)**
ePEF (L/min)								
Low dose	53	411.1	(110.1)	413.8	(108.4)	2.7	(17.4)	(-2.1 to 7.5)
High dose	52	375.7	(111.5)	380.5	(111.3)	4.8	(19.0)	(-0.4 to 10.1)
Total	105	393.6	(111.7)	397.3	(110.6)	3.8	(18.1)	(0.2 to 7.3)
Asthma symptom score (Day time)								
Low dose	53	0.096	(0.213)	0.106	(0.266)	0.011	(0.201)	(-0.045 to 0.066)
High dose	52	0.152	(0.307)	0.177	(0.346)	0.025	(0.197)	(-0.030 to 0.080)
Total	105	0.124	(0.264)	0.141	(0.309)	0.018	(0.198)	(-0.021 to 0.056)
Asthma symptom score (Night-time)								
Low dose	53	0.056	(0.162)	0.063	(0.191)	0.007	(0.147)	(-0.034 to 0.048)
High dose	52	0.088	(0.237)	0.126	(0.384)	0.038	(0.218)	(-0.023 to 0.098)
Total	105	0.072	(0.202)	0.094	(0.303)	0.022	(0.185)	(-0.014 to 0.058)

To be continued.

Table S 4 Mean change in secondary variables related to daily date at Week 6 (LOCF) from baseline (FAS)

		Baseline [1)]		Week 6 (LOCF) [2)]		Change from baseline		
Variables	**n**	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**(95% CI)**
Asthma symptom score (Total)								
Low dose	53	0.152	(0.339)	0.170	(0.434)	0.018	(0.334)	(-0.075 to 0.110)
High dose	52	0.242	(0.515)	0.303	(0.688)	0.062	(0.360)	(-0.039 to 0.162)
Total	105	0.196	(0.436)	0.236	(0.575)	0.039	(0.346)	(-0.028 to 0.106)
Use of rescue medication (Daytime)								
Low dose	53	0.013	(0.080)	0.031	(0.161)	0.018	(0.164)	(-0.028 to 0.063)
High dose	52	0.056	(0.162)	0.073	(0.200)	0.017	(0.158)	(-0.027 to 0.060)
Total	105	0.035	(0.128)	0.052	(0.182)	0.017	(0.160)	(-0.014 to 0.048)
Use of rescue medication (Night-time)								
Low dose	53	0.005	(0.027)	0.016	(0.098)	0.011	(0.079)	(-0.011 to 0.033)
High dose	52	0.012	(0.047)	0.090	(0.338)	0.078	(0.300)	(-0.006 to 0.161)
Total	105	0.009	(0.038)	0.053	(0.249)	0.044	(0.220)	(0.001 to 0.086)
Use of rescue medication (Total)								
Low dose	53	0.019	(0.100)	0.047	(0.259)	0.028	(0.244)	(-0.039 to 0.096)
High dose	52	0.068	(0.177)	0.163	(0.457)	0.094	(0.376)	(-0.010 to 0.199)
Total	105	0.043	(0.145)	0.104	(0.373)	0.061	(0.317)	(-0.000 to 0.122)
Night-time awakenings due to asthma symptoms								
Low dose	53	0.062	(0.222)	0.027	(0.142)	-0.035	(0.192)	(-0.088 to 0.018)
High dose	52	0.023	(0.079)	0.051	(0.170)	0.027	(0.127)	(-0.008 to 0.063)
Total	105	0.043	(0.168)	0.039	(0.157)	-0.004	(0.165)	(-0.036 to 0.028)

1) Mean of the last 14 days of the observation period
2) Mean of the last 14 days of the treatment period
CI: confidence interval

The mean changes in $FEV_{1.0}$ and FVC at Week 6 or withdrawal from baseline are shown in Table S 5. The mean changes in $FEV_{1.0}$ and FVC from baseline to Week 6 (or withdrawal) were estimated to be 0.079 L (95% confidence interval: 0.031 to 0.127 L) and 0.105 L (95% confidence interval: 0.049 to 0.160 L) in total patients, respectively. Similar patterns of mean change in $FEV_{1.0}$ and FVC from baseline to Week 6 (or withdrawal) were observed in low and high dose groups.

Table S 5 Mean change in $FEV_{1.0}$ and FVC at Week 6 or withdrawal from baseline (FAS)

		Baseline [1)]		Week 6/withdrawal		Change from baseline		
Variables	**n**	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**(95% CI)**
$FEV_{1.0}$								
Low dose	53	2.701	(0.697)	2.797	(0.807)	0.096	(0.292)	(0.016 to 0.177)
High dose	49	2.692	(0.756)	2.752	(0.832)	0.060	(0.179)	(0.008 to 0.111)
Total	102	2.697	(0.722)	2.776	(0.815)	0.079	(0.244)	(0.031 to 0.127)
FVC								
Low dose	53	3.335	(0.900)	3.453	(1.023)	0.119	(0.324)	(0.029 to 0.208)
High dose	49	3.407	(0.987)	3.497	(1.078)	0.090	(0.232)	(0.023 to 0.157)
Total	102	3.370	(0.939)	3.475	(1.045)	0.105	(0.283)	(0.049 to 0.160)

1) Visit 3
CI: confidence interval

Summary of safety results

A summary of AEs in each category is presented in Table S 6. Twenty-four (24) AEs were reported for 20 of the 108 patients (18.5%) in the observation period, 50 AEs were reported for 40 of the 105 patients (38.1%) in the treatment period. The majority of AEs was of mild intensity, and no severe AEs were reported. No deaths, serious AEs (SAEs) other than death and other significant AEs (OAEs) were reported in this study. Two discontinuations of study treatment due to AEs (DAEs) (nausea/asthma and asthma) were reported in the treatment period.

Table S 6 Number (%) of patients who had at least 1 AE and total number of events in any category (Safety analysis set)

	Observation period			Treatment period		
	Low dose	High dose	Total	Low dose	High dose	Total
AE category	**n=54**	**n=54**	**n=108**	**n=53**	**n=52**	**n=105**
Number of patients who had an AE in each category [1]						
Any AEs	10 (18.5)	10 (18.5)	20 (18.5)	20 (37.7)	20 (38.5)	40 (38.1)
AEs with mild intensity	7 (13.0)	9 (16.7)	16 (14.8)	18 (34.0)	17 (32.7)	35 (33.3)
AEs with moderate intensity	3 (5.6)	1 (1.9)	4 (3.7)	2 (3.8)	3 (5.8)	5 (4.8)
AEs with severe intensity	0	0	0	0	0	0
AEs with outcome death	0	0	0	0	0	0
SAEs not leading to death	0	0	0	0	0	0
AEs leading to discontinuation of treatment	0	0	0	0	2 (3.8)	2 (1.9)
Other significant AEs	0	0	0	0	0	0
Drug-related AEs [2]	0	2 (3.7)	2 (1.9)	6 (11.3)	9 (17.3)	15 (14.3)
Total number of AEs [3]						
Any AEs	12	12	24	24	26	50
AEs with mild intensity	9	11	20	22	22	44
AEs with moderate intensity	3	1	4	2	4	6
AEs with severe intensity	0	0	0	0	0	0
AEs with outcome death	0	0	0	0	0	0
SAEs not leading to death	0	0	0	0	0	0
AEs leading to discontinuation of treatment	0	0	0	0	3	3
Other significant AEs	0	0	0	0	0	0
Drug-related AEs [2]	0	2	2	7	11	18

1) Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
2) Assessed by the investigator.
3) Multiple events in the same category are counted multiple times in that category. Multiple events belonging to more than one category are counted multiple times in each of those categories.

The most commonly reported AEs (those with an incidence more than 1.0% on preferred term (PT) level in total at the observation period or the treatment period) in the study are shown in Table S 7. The most commonly reported AEs in the study were NASOPHARYNGITIS (5.6% in the observation period and 6.7% in the treatment period). OROPHARYNGEAL DISCOMFORT was 0.0% in the observation period and 4.8% in the treatment period. All events reported as OROPHARYNGEAL DISCOMFORT were of mild intensity, and were reported on the first day in the treatment period.

Table S 7 Number (%) of patients with the most commonly reported AEs by preferred term (Safety analysis set)

	Observation period			Treatment period		
	Low dose	High dose	Total	Low dose	High dose	Total
PT [1), 2), 3), 4)]	n=54	n=54	n=108	n=53	n=52	n=105
NASOPHARYNGITIS	2 (3.7)	4 (7.4)	6 (5.6)	4 (7.5)	3 (5.8)	7 (6.7)
OROPHARYNGEAL DISCOMFORT	0	0	0	2 (3.8)	3 (5.8)	5 (4.8)
ASTHMA	0	0	0	0	2 (3.8)	2 (1.9)
ECZEMA	0	1 (1.9)	1 (0.9)	2 (3.8)	0	2 (1.9)
UPPER RESPIRATORY TRACT INFECTION	0	0	0	1 (1.9)	1 (1.9)	2 (1.9)
UPPER RESPIRATORY TRACT INFLAMMATION	2 (3.7)	0	2 (1.9)	2 (3.8)	0	2 (1.9)
OROPHARYNGEAL PAIN	1 (1.9)	0	1 (0.9)	2 (3.8)	0	2 (1.9)
DYSPHONIA	1 (1.9)	1 (1.9)	2 (1.9)	1 (1.9)	0	1 (1.0)

1) A patient experiencing more than one AE within a PT was counted once within that PT.
2) This table used a cut-off of 1.0% of patients in total at the observation period or the treatment period.
3) Table is sorted by frequency of total at the treatment period.
4) MedDRA 12.0

There were no clinically significant changes in clinical laboratory values and vital sign in this study.

The safety profile for Pulmicort Respules was similar between 1.0 mg/day and 2.0 mg/day, and between once and twice daily regimens regarding incidence and nature of adverse events, clinical laboratory values, and vital signs.