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<b>Study No.:</b> 104325
<b>Title:</b> A randomised, open label comparative study to determine the proportion of asthma patients on Seretide Diskus 50/250 mcg b.i.d. achieving Total Control when given medication and compliance enhancement training compared to those receiving medication only.
<b>Rationale:</b> Some subjects do not reach asthma control over a sustained period of time - even when dosing is presumably optimal and the correct type of medication has been prescribed. This study was conducted to investigate whether subjects' adherence to treatment (compliance) can be improved by few and simple means such as teaching the subject about the mechanisms of the asthma disease, risk factors, what to avoid and expectations to treatment.
<b>Phase:</b> IV
<b>Study Period:</b> 26 JUL 2005- 29 May 2007
<b>Study Design:</b> Randomised, open-label, parallel-group, comparative study in adult subjects with stable asthma treated as outpatients and failing to achieve the Total Control criterion. The study comprised a 4-week screening period and two 12-week treatment periods. The subjects were provided with an asthma monitor (AM2) for data collection.
<b>Centres:</b> 23 centres in Switzerland and 6 centres in Denmark
<b>Indication:</b> Asthma (persistent)
<b>Treatment:</b> Screening period: subjects continued their current asthma medication; treatment period 1: all subjects were treated with salmeterol/fluticasone propionate 50/250 µg b.i.d. without any other intervention; treatment period 2: after randomisation subjects either received salmeterol/fluticasone propionate 50/250 µg + 3 training sessions of compliance enhancement training (intervention group) or salmeterol/fluticasone propionate 50/250 µg (control group).
<b>Objectives:</b> To determine the proportion of asthma subjects achieving Total Control of their asthma in 7 weeks out of the last 8 consecutive weeks of treatment period 2 when given salmeterol/fluticasone propionate 50/250 µg b.i.d. with compliance enhancement training compared to those given medication alone.
<b>Primary Outcome/Efficacy Variable:</b> Proportion of subjects who achieved Total Control in 7 out of the last 8 consecutive weeks in treatment period 2 with salmeterol/fluticasone propionate 50/250 µg b.i.d. fixed dosing and compliance enhancement training compared with salmeterol/fluticasone propionate 50/250 µg b.i.d. fixed dosing without compliance enhancement training.
<b>Secondary Outcome/Efficacy Variable(s):</b> <ul style="list-style-type: none"> <li>- Proportion of subjects who achieved Total Control with salmeterol/fluticasone propionate 50/250 µg b.i.d. fixed dosing in treatment period 1</li> <li>- Time to first individual week with Total Control in treatment period 2</li> <li>- Morning peak expiratory flow (PEF)</li> <li>- Forced expiratory volume in one second (FEV1)</li> <li>- Asthma symptom score</li> <li>- Rescue medication usage</li> <li>- Number of nights with awakening due to asthma</li> <li>- Asthma severity</li> <li>- Adverse Events</li> <li>- Quality of life (AQLQ)</li> </ul>
<b>Statistical Methods:</b> The ITT population for treatment period 1 (ITT-1) comprised all subjects who received at least a single dose of trial medication in treatment period 1. This population was the primary population for analysis of efficacy and health outcome measures for treatment period 1. The ITT population for treatment period 2 (ITT-2) comprised all subjects randomised to treatment in period 2 who had received at least a single dose of trial medication in treatment period 2. This population was the primary population for analysis of efficacy and health outcome measures of the randomised treatment period 2. Therefore, this was the primary population for the analysis of the primary endpoint of the study. The safety population comprised all subjects receiving at least a single dose of study medication. During each phase of the study, the subject was assessed against Total Control criteria. For each of the definitions of asthma control, a subject was assessed on a weekly basis. An individual week was evaluable, if data were available on all criteria on at least 5 of the 7 days. Each week was classified as controlled, uncontrolled or unevaluable. A subject was considered a treatment success, if he/she achieved 7 totally controlled weeks out of the last documented 8 treatment weeks. Total Control was defined according to the GOAL study (Bateman ED et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. Am J Respir Crit Care Med 2004;

170(8):836-844).

The primary variable was assessed using a 2-sided Fisher's exact test and presented with the associated 95% confidence limits. The two categories "well controlled=total control" vs. "uncontrolled" were used for this analysis exclusively. Therefore, the category "uncontrolled" counted all subjects with either "uncontrolled" or "not evaluable" outcome.

The same endpoint was further investigated using a logistic proportional odds model for ordinal response. The model included the covariates baseline FEV1 and age and the factors sex, (pooled) centre, and treatment group. Treatment estimates (including appropriate 95%-confidence intervals) from this model were presented.

In addition, it was analysed whether there was a difference dependent on asthma severity at Baseline. Based on diary data prior to the baseline visit, the subject's asthma severity classification was determined according to the GINA guideline. The differences between the treatments in terms of asthma control were analysed (2-sided Fisher's exact test and logistic proportional odds model) in a stratified way separately for each of the severity categories mild, moderate and severe persistent asthma.

All secondary efficacy analyses were analysed descriptively with the appropriate statistical methods.

**Study Population:** Male or female subjects  $\geq 18$  years of age diagnosed with persistent asthma and treated as outpatients (for asthma). To be eligible to be included in treatment period 2, subjects had to have failed to achieve the criteria for Total Control during treatment period 1. Subjects were not to be included into the study in case of known or suspected chronic obstructive pulmonary disease, pregnancy or lactation or smoking history  $> 10$  pack-years. Exclusion criterion for entry into treatment period 1 was the achievement of more than one week of Total Control prior to the baseline visit.

	Intervention Group	Control Group
Number of Subjects:		
Planned for treatment period 2, N	125	125
Randomised, N	140	134
Completed, n (%)	128 (91.4)	126 (94.0)
Total Number Subjects Withdrawn, N (%)	12 (8.6)	8 (6.0)
Withdrawn due to Adverse Events n (%)	3 (2.1)	0 (0.0)
Withdrawn due to Lack of Efficacy n (%)	Not assessed	Not assessed
Withdrawn for other reasons n (%)	9 (6.4)	8 (6.0)
<b>Demographics</b>		
N (ITT-1)	140	134
Females: Males	73:67	64:70
Mean Age, years $\pm$ SD	40.5 $\pm$ 13.9	38.7 $\pm$ 14.6
White/caucasian european heritage, n (%)	135 (96.4)	127 (94.8)
Mean body weight, kg $\pm$ SD	76.8 $\pm$ 14.7	76.5 $\pm$ 16.9
<b>Primary Efficacy Results (ITT-2):</b>		
<b>Total asthma control in treatment period 2</b>	<b>Intervention Group (N=137)</b>	<b>Control Group (N=131)</b>
Uncontrolled asthma n (%)	125 (91.2)	121 (92.4)
Total asthma control n (%)	12 (8.8)	10 (7.6)
Odds ratio [95% CI]	1.2 [0.4-3.1]	
p-value (Fisher's exact test)	0.8	
<b>Logistic proportional odds model</b>		
Control versus intervention: estimate [95% CI]	-0.1 [-0.5; 0.4]	
<b>Total asthma control in treatment period 2 by baseline severity</b>		
Baseline asthma severity <i>intermittent</i> (n)	10	15
Uncontrolled asthma n (%)	9 (90.0)	15 (100.0)
Total asthma control n (%)	1 (10.0)	0
Odds ratio [95% CI]	$\infty$ [0.1- $\infty$ ]	
p-value (Fisher's exact test)	0.4	
Baseline asthma severity <i>mild persistent</i> (n)	67	72
Uncontrolled asthma n (%)	60 (89.6)	64 (88.9)
Total asthma control n (%)	7 (10.5)	8 (11.1)
Odds ratio [95% CI]	0.9 [0.3-3.2]	
p-value (Fisher's exact test)	1.0	

Baseline asthma severity <i>moderate persistent</i> (n)	53	41
Uncontrolled asthma n (%)	49 (92.5)	39 (95.1)
Total asthma control n (%)	4 (7.6)	2 (4.9)
Odds ratio [95% CI]	1.6 [0.2-18.4]	
p-value (Fisher's exact test)	0.7	
Baseline asthma severity <i>severe persistent</i> (n)	7	3
Uncontrolled asthma n (%)	7 (100.0)	3 (100.0)
Total asthma control n (%)	0	0
Odds ratio [95% CI]	not done	
p-value (Fisher's exact test)	not done	
<b>Secondary Outcome Variable(s):</b>		
<b>Total asthma control (in treatment period 1)</b>	ITT-1 (N=361) incl. non-randomised subjects	
n (%)	35 (9.7)	
<b>Time to first individual week with total control in treatment period 2 (ITT-2)</b>	<b>Intervention Group</b>	<b>Control Group</b>
Median time, weeks	9	13
<b>Morning PEF</b> (% of predicted normal value, mean $\pm$ SD, ITT-2)		
Screening visit	95.3 $\pm$ 22.0	96.0 $\pm$ 20.1
Baseline visit	96.2 $\pm$ 23.4	95.0 $\pm$ 20.9
Randomisation visit	103.5 $\pm$ 22.7	102.3 $\pm$ 21.6
End-of-study visit	104.3 $\pm$ 23.5	102.5 $\pm$ 21.4
<b>FEV1</b> (% of predicted normal value, mean $\pm$ SD, ITT-2)		
Screening visit	87.8 $\pm$ 19.2	87.4 $\pm$ 15.9
Baseline visit	87.3 $\pm$ 17.9	86.3 $\pm$ 16.3
Randomisation visit	91.3 $\pm$ 18.0	91.1 $\pm$ 15.9
End-of-study visit	91.3 $\pm$ 17.6	90.9 $\pm$ 16.6
<b>Weekly asthma symptom score</b> , range 0-5 (mean $\pm$ SD, ITT-2)		
Last week of baseline period	1.3 $\pm$ 1.0	1.3 $\pm$ 1.0
Last week of treatment period 1	0.8 $\pm$ 1.1	0.7 $\pm$ 1.0
Last week of treatment period 2	0.7 $\pm$ 1.1	0.6 $\pm$ 0.9
<b>Use of rescue medication</b> (% of days with salbutamol use), mean $\pm$ SD, ITT-2)		
Screening period	59.7 $\pm$ 34.6	55.7 $\pm$ 35.3
Treatment period 1	30.2 $\pm$ 32.8	25.1 $\pm$ 31.8
Treatment period 2	20.3 $\pm$ 29.2	19.4 $\pm$ 30.9
<b>Awakening due to asthma</b> (% of nights of assessed period, mean $\pm$ SD, ITT-2)		
Screening period (last 4 weeks before baseline assessed)	4.8 $\pm$ 16.8	2.8 $\pm$ 10.3
Treatment period 1 (last 8 weeks of treatment period 1 assessed)	2.8 $\pm$ 11.9	1.2 $\pm$ 8.8
Treatment period 2 (last 8 weeks of treatment period 2 assessed)	2.4 $\pm$ 11.8	0.3 $\pm$ 1.2
<b>Asthma severity</b> (scale 1-4, mean $\pm$ SD, ITT-2)		
Screening visit	2.4 $\pm$ 0.7	2.2 $\pm$ 0.7
Baseline visit	2.4 $\pm$ 0.7	2.4 $\pm$ 0.6
Randomisation visit	2.1 $\pm$ 0.7	2.1 $\pm$ 0.8
End-of-study visit	1.9 $\pm$ 0.8	1.9 $\pm$ 0.8
<b>Quality of life, AQLQ</b> , range 1-7 (safety population excluding non-randomised subjects)		
AQLQ overall (mean $\pm$ SD):	<b>Intervention Group (N=140)</b>	<b>Control Group (N=134)</b>
Baseline visit	5.6 $\pm$ 0.8	5.6 $\pm$ 0.8
Randomisation visit	5.9 $\pm$ 0.9	5.9 $\pm$ 0.8
End-of-study / withdrawal visit	6.1 $\pm$ 0.9	6.0 $\pm$ 0.9

AQLQ domain: Activity limitation, range 1-7 (mean ± SD):			
Baseline visit	4.7 ± 0.9	4.8 ± 0.9	
Randomisation visit	4.9 ± 1.1	5.0 ± 0.9	
End-of-study / withdrawal visit	5.2 ± 0.9	5.1 ± 0.9	
AQLQ domain: Symptoms, range 1-7 (mean ± SD):			
Baseline visit	5.4 ± 0.9	5.3 ± 1.0	
Randomisation visit	5.9 ± 0.9	5.9 ± 0.9	
End-of-study / withdrawal visit	6.1 ± 0.9	6.0 ± 1.0	
AQLQ domain: Emotional functions, range 1-7 (mean ± SD):			
Baseline visit	5.7 ± 1.1	5.8 ± 1.0	
Randomisation visit	6.1 ± 1.1	6.1 ± 0.9	
End-of-study / withdrawal visit	6.3 ± 0.9	6.2 ± 1.0	
AQLQ domain: Environmental stimuli, range 1-7 (mean ± SD):			
Baseline visit	5.3 ± 1.1	5.5 ± 1.1	
Randomisation visit	5.6 ± 1.1	5.7 ± 1.1	
End-of-study / withdrawal visit	5.9 ± 1.0	5.8 ± 1.2	
Safety Results: Analysis of AEs was differentiated by timing of occurrence, i.e., the 4-week screening period, the 12-week treatment period 1 and the 12-week randomised treatment period 2. In the following, treatment emergent AEs are presented.			
	<b>Intervention Group (N=140)</b>	<b>Control Group (N=134)</b>	<b>Not randomised (N=87)</b>
<b>Most Frequent Non-Serious Adverse Events – On-Therapy (treatment period 1)</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
Subjects with any non-serious AE(s)	52 (37.1)	55 (41.0)	34 (39.1)
Nasopharyngitis	23 (16.4)	21 (15.7)	5 (5.8)
Influenza	4 (2.9)	8 (6.0)	1 (1.2)
Asthma	2 (1.4)	5 (3.7)	4 (4.6)
Pneumonia	2 (1.4)	1 (0.8)	4 (4.6)
Dysphonia	4 (2.9)	0	3 (3.5)
Headache	1 (0.7)	2 (1.5)	1 (1.2)
Depression	2 (1.4)	2 (1.5)	0
Gastrooesophageal reflux disease	0	1 (0.8)	2 (2.3)
Contusion	0	2 (1.5)	1 (1.2)
Rhinitis	0	2 (1.5)	0
Vaginal infection	0	1 (0.8)	1 (1.2)
Pharyngolaryngeal pain	1 (0.7)	1 (0.8)	0
Abdominal pain upper	2 (1.4)	0	0
Hypersensitivity	1 (0.7)	0	1 (1.2)
Seasonal allergy	2 (1.4)	0	0
Sputum abnormal	2 (1.4)	0	0
Muscle spasms	1 (0.7)	1 (0.8)	0
Rash	0	1 (0.8)	1 (1.2)
Palpitations	0	0	2 (2.3)
Idiosyncratic drug reaction	0	0	2 (2.3)
<b>Most Frequent Non-Serious Adverse Events – On-Therapy (treatment period 2)</b>	<b>Intervention Group (N=137)</b>	<b>Control Group (N=131)</b>	
Subjects with any non-serious AE(s)	75 (54.7)	43 (32.8)	
Nasopharyngitis	33 (24.1)	17 (13.0)	
Asthma	5 (3.7)	5 (3.8)	
Influenza	3 (2.2)	5 (3.8)	
Dysphonia	6 (4.4)	1 (0.8)	
Sinusitis	5 (3.7)	0	

Pharyngolaryngeal pain	4 (2.9)	1 (0.8)
Seasonal allergy	3 (2.2)	2 (1.5)
Oral candidiasis	1 (0.7)	2 (1.5)
Pneumonia	3 (2.2)	0
Respiratory tract infection	3 (2.2)	0
Viral infection	2 (1.5)	1 (0.8)
<b>Serious Adverse Events - On-Therapy</b>		
<b>n (%) [n considered by the investigator to be related to study medication]</b>		
	<b>Intervention Group (N=140)</b>	<b>Control Group (N=134)</b>
		<b>Not randomised (N=87)</b>
Subjects with non-fatal SAEs, n (%) [related] (treatment period 1)	1 (0.7) [0]	1 (0.8) [0]
Pneumonia	0	0
Cystitis	0	0
Peptic ulcer	1 (0.7) [0]	0
Cholecystitis	0	0
Cholelithiasis	0	0
Breast cancer	0	1 (0.8) [0]
Subjects with fatal SAEs, n (%) [related]	0	0
	<b>Intervention Group (N=137)</b>	<b>Control Group (N=131)</b>
Subjects with non-fatal SAEs, n (%) [related] (treatment period 2)	2 (1.5) [0]	2 (1.5) [0]
Concussion	1 (0.7) [0]	0
Syncope	0	1 (0.8) [0]
Depression	1 (0.7) [0]	0
Urinary retention	0	1 (0.8) [0]
Subjects with fatal SAEs, n (%) [related]	0	0

**Conclusion:**

In this study, giving compliance enhancement training in addition to salmeterol/fluticasone propionate 50/250 µg b.i.d. did not result in a higher proportion of asthma subjects achieving Total Control compared to subjects receiving medication only. Exploratory analyses of lung function, asthma symptom score and the number of days with use of rescue medication showed improvements under study medication but did not point to differences between the treatment groups. In summary, there were no safety signals detected in this study.

**Publications: None as of date of report.**