

Study No.: 100614
Title: SUCCESS study: SUccessful Control and Clinical Effectiveness of Salmeterol/fluticasone propionate combination in asthma Study, a randomised controlled study to investigate the clinical effectiveness and health outcomes of salmeterol/fluticasone propionate combination in patients with moderate and severe persistent asthma in Korea
Rationale: Researchers have traditionally measured the efficacy of a treatment in terms of the change from baseline seen in single variables (e.g., FEV1 or PEFr, symptom ratings or rescue beta2-agonist use). This may provide an incomplete assessment of disease control in individual patients and may not be sufficient to alter prescribing habits of some doctors. By contrast, clinical effectiveness data generated locally within a country in a real life setting may be more convincing to physicians. The goal of this study is to demonstrate the clinical effectiveness of Salmeterol/fluticasone propionate combination inhalation therapy (SFC) in a real life setting in Korea. It should also demonstrate the reduction of health care burden to the asthmatic patients and the healthcare system compared to current standard of care in real world setting. This study will compare SFC [a combination therapy with ICS and long-acting B2-agonists (LABA)] with current care treatment ie treatment that is physician-determined standard of care.
Phase: IV
Study Period: 14 Jan 2004 ~ 16 Sep 2005
Study Design: This is an open-labelled, prospective, randomised, parallel group clinical study, applying a follow up design of two arms (SFC versus current care), to evaluate the clinical and health outcomes of asthma treatment.
Centres: This study was conducted in 7 University Hospitals and 14 General Practitioners, which randomized 424 subjects in Korea.
Indication: Asthma
Treatment: Subjects received one of the following treatments for the duration of the 52-week treatment period according to the randomisation schedule: SFC 50/250mcg or 50/500 mcg 1 inhalation, twice daily Or Continued their current care therapy. The dose of fluticasone in the SFC arm was set as per recommendation of the GINA guidelines. Inhaled salbutamol was provided to all patients for use on an as-required basis for symptomatic relief.
Objectives: The primary study objective is to demonstrate the clinical effectiveness of SFC therapy compared to the current care in management of moderate to severe persistent asthma patients in Korea.
Primary Outcome/Efficacy Variable: The primary endpoint : mean morning peak expiratory flow (PEFR) (L/min) LOCF at 52 weeks as collected on diary record cards over the last 2 weeks preceding the 52 weeks visit.
Secondary Outcome/Efficacy Variable(s): Asthma exacerbations, mean morning PEFr, percentage of symptom-free days/nights, mean daytime and night-time symptom scores, percentage of rescue-free days/nights, mean daytime and night-time rescue medication use over weeks 12 and at 24, 36 and 52 and number of withdrawals due to lack of efficacy in each arm. Impact of treatment on quality of life (mini-AQLQ) and the proportion of patients achieving well controlled were also measured using the TM Asthma Control Test (ACT).
Statistical Methods: Efficacy analyses The mean morning PEFr at 52 weeks as collected on diary record cards over the last 2 weeks preceding the 52 weeks visit was subjected to the Analysis of Covariance (ANCOVA) including treatment as a fixed factor. According to the study protocol, age, gender, the mean morning PEFr at baseline and type of site (GPs vs Hospital specialists) were considered as covariates. All statistical comparisons were made using two-sided tests at the $\alpha = 0.05$ significance level,
Study Population: This study was conducted on moderate and severe asthmatic patients. Male or female subjects aged ≥ 18 years with a documented clinical history of reversible airways obstruction (history taking is acceptable) for at least 12 months. For entry to the randomised treatment period, subjects had to have a documented historical reversibility of at least 12 % and 200mL in FEV ₁ or 15 % in PEFr after an inhaled β_2 -agonist up to 12 months before or at Visit 2 or an average morning PEFr over the last 4 evaluable days (an evaluable day is defined as a day with complete data) of the run-in period which is between 50% to 80% of the subjects maximum achievable PEFr measured after inhalation of a short acting β_2 -agonist (200-400mcg of salbutamol or albuterol). A subject has following condition was excluded; previous use of ICS /LABA combination inhaler 12 weeks prior to

study participation, hypersensitivity to inhaled steroids or β_2 -agonists, changes to their regular asthma medication within 2 weeks of study participation, a lower respiratory tract infection within 4 weeks of study participation, a smoking history ≥ 10 pack years, have FEV₁ or PEFr less than 50% predictive value.

	SFC arm	Current care arm
Number of Subjects:		
Planned, N	226	113
Randomised, N	284	140
Completed, n (%)	241 (85)	122(87)
Total Number Subjects Withdrawn, N (%)	43 (15)	18(13)
Withdrawn due to Adverse Events n (%)	2(<1)	0
Withdrawn due to Lack of Efficacy n (%)	0	0
Withdrawn for other reasons n (%)	41(15)	18(13)
Demographics		
	SFC arm	Current care arm
N (ITT)	284	140
Females: Males	170: 114	75: 65
Mean Age, years (SD)	47.28 (14.10)	46.42 (13.74)
Race, n (%)	Asian, 284 (100)	Asian, 140 (100)
Mean Weight(kg) (SD)	62.24(10.36)	64.78(10.90)
Mean Height(cm) (SD)	161.39 (8.47)	162.33 (8.79)
Primary Efficacy Results:		
	SFC arm	Current care arm
Morning PEFr(L/min) at 52 weeks		
Number of subjects	271	133
Adjusted mean at 52 weeks (SE)	422.71 (3.05)	395.77 (4.35)
Adjusted mean difference SFC-current care (SE) [95% CI]	26.95 (5.28) [16.56, 37.34]	
p-value	<0.0001	
Secondary Outcome Variable(s):		
	SFC arm	Current care arm
Asthma exacerbation		
Number of subjects	284	139
Asthma exacerbation rate, [95% confidence interval]	0.41[0.34,0.49]	0.72 [0.59,0.88]
Odds ratio SFC to current care [95% confidence interval]	0.57 [0.44, 0.74]	
p-value	<0.0001	
Asthma exacerbation rate requiring oral steroids, Mean(SD)	0.35 (0.29,0.43)	0.63 (0.51,0.78)
Odds ratio SFC to current care [95% confidence interval]	0.56 [0.42, 0.74]	
p-value	<0.0001	
	SFC arm	Current care arm
Percentage of the symptom-free days at 52 weeks		
Number of subjects	239	122
Mean percentage of symptom-free days, (SD)	81.94 (25.54)	73.59 (31.97)
Odds ratio SFC to current care [95% confidence interval]	3.00[1.75, 5.13]	
p-value	<0.0001	
	SFC arm	Current care arm
Percentage of the symptom-free nights at 52 weeks		
Number of subjects	239	122
Mean percentage of symptom-free nights, (52 weeks-Baseline)(SD)	89.74(23.02)	82.43(31.01)
Odds ratio to current care [95% confidence interval]	2.38 [1.33, 4.25]	
p-value	0.0034	
	SFC arm	Current care arm
Mean day-time symptom scores at 52 weeks		
Number of subjects	239	122
Mean day-time symptom score (SD)	0.19 (0.51)	0.39 (0.75)
p-value	0.0068	
	SFC arm	Current care arm
Mean night time symptom scores at 52 weeks		
Number of subjects	239	122
Mean day-time symptom score (SD)	0.12 (0.28)	0.22 (0.44)
p-value	0.0118	

Percentage of Rescue-Free Days at 52 weeks	SFC arm	Current care arm
Number of subjects	239	122
Mean percentage of Rescue-Free Days,(SD)	83.49 (25.62)	78.98 (29.01)
Odds ratio SFC to current care [95% confidence interval]	1.56 [0.90, 2.71]	
Percentage of Rescue-Free Nights at 52 weeks	SFC arm	Current care arm
Number of subjects	239	122
Mean percentage of Rescue-Free Nights, (SD)	92.06 (21.29)	86.79 (25.85)
Odds ratio SFC to current care [95% Confidence interval]	1.87 [1.02,.3.43]	
Mean Daytime Rescue Medication Use at 52 weeks	SFC arm	Current care arm
Number of subjects	239	122
Mean daytime Rescue Medication Use (SD)	0.16 (0.42)	0.27 (0.64)
p-value	0.0366	
Mean Night-time Rescue Medication Use at 52 weeks	SFC arm	Current care arm
Number of subjects	239	122
Mean night-time Rescue Medication Use (SD)	0.10 (0.29)	0.17 (0.38)
p-value	0.0053	
Withdrawals due to Lack of Efficacy (N)	0	0
Overall mean changes in the miniAQLQ		
Number of subjects	240	120
Change in mini-AQLQ (52 weeks-Baseline) (mean, SD)	0.66(0.92)	0.31(0.73)
p-value	0.0007	
Asthma Control Test (ACT) at 52 weeks		
Number of subjects	237	121
Number (%) of patients achieving ACT score \geq 20 (well controlled)	191(80.59%)	81(66.94%)
Odds ratio SFC to current care [95% confidence interval]	2.08 [1.26,3.44]	
p-value	0.0041	
Safety Results: An on therapy AE and SAE was defined as an AE from the start date of study medication to the end date of study completion.		
	SFC arm N=284	Current care arm N=140
Most Frequent Adverse Events – On-Therapy : n (%)	220(77.46)	112(80.00)
Nasopharyngitis	107(37.68)	51(36.43)
Upper respiratory tract infection NOS	63(22.18)	24(17.14)
Headache NOS	30(10.56)	18(12.86)
Rhinitis NOS	12(4.23)	4(2.86)
Gastritis NOS	14(4.93)	4(2.86)
Tonsillitis acute NOS	12(4.23)	2(1.43)
Dyspepsia	11(3.09)	6(4.29)
Oral candidiasis	9(3.17)	1(0.91)
Rhinitis allergic NOS	8(2.82)	7(5.00)
Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]		
	SFC arm N=284	Current care arm N=140
Subjects with non-fatal SAEs, n (%)	6(2.11),[0]	9(6.43),[0]
Upper respiratory tract infection NOS	2(0.70),[0]	0(0.00),[0]
Bronchiectasis NOS	0(0.00),[0]	1(0.71),[0]
Otitis media suppurative chronic NOS	1(0.35),[0]	0(0.00),[0]
Sinusitis chronic NOS	0(0.00),[0]	1(0.71),[0]
Foot fracture	0(0.00),[0]	1(0.71),[0]
Lumbar vertebral fracture	0(0.00),[0]	1(0.71),[0]
Rib fracture	1(0.35),[0]	0(0.00),[0]
Asthma aggravated	0(0.00),[0]	2(1.43),[0]

Pharyngitis	1(0.35),[0]	0(0.00),[0]
Angina pectoris	0(0.00),[0]	1(0.71),[0]
Appendicitis	0(0.00),[0]	1(0.71),[0]
Diverticulitis intestinal	1(0.35),[0]	0(0.00),[0]
Sudden hearing loss NOS	0(0.00),[0]	1(0.71),[0]
Subjects with fatal SAEs, n (%)	1 (0.35) [0]	0 (%) [0]
Septic shock	1(0.35),[0]	0(0.00),[0]
Cerebral infarction fatal	1(0.35),[0]	0(0.00),[0]

Conclusion:

This study showed that salmeterol/FP combination therapy inhalation therapy is clinically more effective than other forms of treatment currently administered by Korean doctors for the management of patients with moderate to severe persistent asthma. Salmeterol/FP combination therapy was statistically significantly superior to current care arm for the mean morning PEFr at 52 weeks (primary endpoint). Asthma exacerbation rate and severe exacerbation rate requiring oral steroids were significantly lower in the salmeterol/FP combination therapy versus current care arm. Salmeterol/FP combination therapy was significantly better than current care in symptom free days/nights, symptom scores and rescue-free nights at 52 weeks. There was no withdrawal due to lack of efficacy in both groups.

After one year of treatment, patients receiving Salmeterol/FP combination inhalation achieved a significantly better asthma-related QoL than patients treated with current care. This study also showed that proportionally more patients can achieve asthma control (ACT) on Salmeterol/FP combination therapy compared with current care treatment.

In the salmeterol/FP therapy arm, 220(77.46%) subjects reported at least one non-serious adverse events with the most frequently reported being nasopharyngitis and upper respiratory tract infection. In the current care arm 112 (80.00%) subjects reported at least one non-serious adverse events with the most frequently reported being nasopharyngitis and upper respiratory tract infection.

In the salmeterol/FP therapy arm 6 subjects reported non-fatal serious adverse events with the most frequently reported being upper respiratory tract infection. In the current care arm 9 subjects reported non-fatal serious adverse events with the most frequently reported being asthma aggravated. There was one subject randomised to the salmeterol/FP therapy arm who experienced fatal serious adverse events during the study period however this case was considered by the Investigator not to be related to salmeterol/FP therapy. In general, for this study population, salmeterol/FP combination therapy was shown to be well tolerated.

Publications: No Publications

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