The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: SAM49071
Title: A multi-centre, randomised, double blind, stratified, parallel group study to evaluate whether a treatment strategy based on aiming for 'Total control' results in better airway hyper-responsiveness than a treatment strategy based on maintaining the treatment level at which 'Well-controlled' asthma was achieved
Rationale: To investigate if a treatment strategy aiming for Total Control (TC) resulted in reduced airway hyper-responsiveness compared with a treatment based on maintaining the treatment level at which Well Controlled (WC) asthma was achieved.
Phase: IV
Study Period: 28Nov2005 – 06Jul2007
Study Design: Multi-centre, randomised, double blind, stratified, parallel group.
Centres: Subjects randomised in 33 centres in 10 countries: Belgium (2), Estonia (1), Finland (2), France (3), Germany (4), Italy (6), Latvia (2), Netherlands (7), Spain (3), Sweden (3)
Indication: Asthma
Treatment: During the run-in period, all subjects received salmeterol/fluticasone propionate (SFC) 50/250 μg twice daily via the DISKUS™ inhaler. During the treatment period, study medication was administered via the DISKUS inhaler (one inhalation twice daily) as either: SFC 50/250 μg (Maintain WC) SFC 50/500 μg (Aim TC)
Objectives: The primary objective was to evaluate whether there was a reduction in airway hyper-responsiveness (AHR) (assessed by post-saline PC_{20} methacholine[1]) attained as a result of using a treatment strategy of aiming for Total Control compared to treatment based on maintaining the treatment level at which Well Controlled asthma was achieved. [1]Provocative concentration of methacholine causing forced expiratory volume in one second (FEV_1) to fall by 20% from post-saline baseline; referred to as PC_{20} methacholine in remainder of summary
Primary Outcome/Efficacy Variable: Mean change in PC_{20} methacholine following 24 weeks of treatment
Secondary Outcome/Efficacy Variable(s): Number of subjects with Well Controlled asthma or Totally Controlled asthma, and the weekly percentage of subjects with a Well Controlled and Totally Controlled asthma week.
Statistical Methods: The sample size is based on the number of subjects required to detect a single doubling dose difference in PC20 methacholine, with 90% power and a 5% alpha level, using a one sample, two-sided Wilcoxon test, which assumes that the actual distribution of data is normal. Assuming a standard deviation of 2.3 for the log2 PC20 data (based on information from previous challenge studies) the required sample size per group was 60 subjects or 120 subjects in total. (Note that the sample size was not based on the difference between the treatment arms due to current lack of this type of data for SFC 50/500. This was an exploratory study. Subjects needed to be 'Well-controlled' and NOT 'Totally-controlled' at the randomisation visit. Assuming 50% of subjects would achieve a well-controlled status, a further 120 subjects were required, giving a total of 240 subjects. Furthermore, assuming a drop out rate of 25%, this brings the total number of subjects that were required to be enrolled to 320 subjects. The primary population for efficacy and safety analyses was the Intent-to-Treat population, consisting of all randomised subjects who received at least one dose of investigational product. For the primary efficacy endpoint, mean change from baseline in PC_{20} methacholine at Week 24, individual subject means were compared between treatment groups using an analysis of covariance (ANCOVA) model, allowing for the effects due to treatment, baseline (randomisation) PC_{20} methacholine, pre-study medication (ICS dose), age, sex and country amalgamation The analysis was conducted using a two-sided test at the 0.05 significance level. The confidence intervals calculated in the study analyses were symmetric and of size 95%.
Study Population: Male or female subjects ≥ 18 years with a 6 month history of asthma, a PC_{20} methacholine <8 mg/ml and FEV_1 % predicted ≥ 70%. Subjects were required to have received FP 100 μg bd to 250 μg bd or equivalent with or without a LABA for at least 4 weeks before the start of the run-in period. Subjects who had either been hospitalized for their asthma, had an upper or lower respiratory tract infection, or received oral, parenteral or depot corticosteroids within 4 weeks of study entry were not eligible for participation

	Maintain WC SFC 50/250μg bd	Aim TC SFC 50/500μg bd

Number of Subjects:		
Planned, N	60	60
Randomised, N	88	90
Completed, n (%)	85 (97)	86 (96)
Total Number Subjects Withdrawn, N (%)	3 (3)	4 (4)
Withdrawn due to Adverse Events n (%)	1 (1)	0
Withdrawn due to Lack of Efficacy n (%)	0	0
Withdrawn for other reasons n (%)	2 (2)	4 (4)
Demographics	Maintain WC SFC 50/250µg bd N=88	Aim TC SFC 50/500µg bd N=90
Females: Males	54:34	42:48
Mean Age, years (SD)	44.4 (13.56)	42.1 (14.62)
White, n (%)	86 (98)	90 (100)
Primary Efficacy Results:		
PC_{20} methacholine	Maintain WC SFC 50/250µg bd N=88	Aim TC SFC 50/500µg bd N=90
Geometric mean baseline (cv)	1.62 (483.53)	1.83 (619.14)
Adjusted geometric mean (cv), Week 24	2.80 (15.55)	2.80 (15.45)
Aim TC/Maintain WC Ratio 95% CI p-value	1.002 (0.2660) 0.696, 1.442 0.992	
Secondary Outcome Variable:		
Number of subjects with Well Controlled (WC) asthma over Weeks 17-24, n (%) Maintained WC Lost WC Unevaluable	 72 (84) 10 (12) 4 (5)	 64 (74) 16 (19) 6 (7)
Odds of Aim TC to Maintain WC 95% CI	0.58 0.23, 1.43	
Number of subjects with Totally Controlled (TC) asthma over Weeks 17-24, n (%) Achieved TC Not achieved TC Unevaluable	 24 (28) 58 (67) 4 (5)	 22 (26) 58 (67) 6 (7)
Odds of Aim TC to Maintain WC 95% CI	0.75 0.35, 1.61	

Weekly number of subjects with at least a 'Well-Controlled' week n(%)		
Week 1	77/88 (88%)	75/86 (87%)
Week 2	77/87 (89%)	79/87 (91%)
Week 3	74/86 (86%)	77/86 (90%)
Week 4	77/86 (90%)	79/88 (90%)
Week 5	76/85 (89%)	73/88 (83%)
Week 6	74/85 (87%)	75/88 (85%)
Week 7	72/86 (84%)	71/86 (83%)
Week 8	81/86 (94%)	80/86 (93%)
Week 9	78/86 (91%)	78/85 (92%)
Week 10	79/86 (92%)	73/85 (86%)
Week 11	74/86 (86%)	72/85 (85%)
Week 12	75/85 (88%)	73/84 (87%)
Week 13	75/86 (87%)	77/87 (89%)
Week 14	75/86 (87%)	77/87 (89%)
Week 15	71/86 (83%)	77/86 (90%)
Week 16	69/86 (80%)	76/86 (88%)
Week 17	73/86 (85%)	72/85 (85%)
Week 18	78/86 (91%)	76/85 (89%)
Week 19	74/86 (86%)	73/85 (86%)
Week 20	73/84 (87%)	70/82 (85%)
Week 21	74/84 (88%)	72/82 (88%)
Week 22	74/84 (88%)	68/82 (83%)
Week 23	72/84 (86%)	68/82 (83%)
Week 24	49/79 (62%)	55/77 (71%
Weekly number of subjects with a 'Totally-Controlled' week n(%)		
Week 1	24/88 (27%)	23/86 (27%)
Week 2	29/87 (33%)	29/87 (33%)
Week 3	29/86 (34%)	28/86 (33%)
Week 4	25/86 (29%)	30/88 (34%)
Week 5	21/85 (25%)	25/88 (28%)
Week 6	25/85 (29%)	30/88 (34%)
Week 7	32/86 (37%)	34/86 (40%)
Week 8	37/86 (43%)	38/86 (44%)
Week 9	31/86 (36%)	35/85 (41%)
Week 10	33/86 (38%)	31/85 (36%)
Week 11	36/86 (42%)	40/85 (47%)
Week 12	32/85 (38%)	35/84 (42%)
Week 13	30/86 (35%)	37/87 (43%)
Week 14	32/86 (37%)	36/87 (41%)
Week 15	39/86 (45%)	39/86 (45%)
Week 16	37/86 (43%)	36/86 (42%)
Week 17	37/86 (43%)	36/85 (42%)
Week 18	39/86 (45%)	32/85 (38%)
Week 19	37/86 (43%)	39/85 (46%)
Week 20	36/84 (43%)	32/82 (39%)
Week 21	39/84 (46%)	36/82 (44%)
Week 22	35/84 (42%)	35/82 (43%)
Week 23	35/84 (42%)	32/82 (39%)
Week 24	25/79 (32%)	27/77 (35%)
Safety Results: An on- therapy adverse event (AE) was defined as an untoward medical occurrence in a subject where onset date was on or after the first day of treatment and before or on the last day of treatment.		

	Maintain WC SFC 50/250µg bd N=88	Aim TC SFC 50/500µg bd N=90
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)
Subjects with any AEs	39 (44)	36 (40)
Nasopharyngitis	14 (16)	12 (13)
Headache	7 (8)	5 (6)
Pharyngolaryngeal pain	4 (5)	5 (6)
Rhinitis	3 (3)	6 (7)
Back pain	4 (5)	4 (4)
Influenza	3 (3)	5 (6)
Nausea	3 (3)	4 (4)
Cough	1 (1)	5 (6)
Pyrexia	2 (2)	3 (3)
Sinusitis	3 (3)	1 (1)
Dysphonia	1 (1)	3 (3)
Diarrhoea	1 (1)	3 (3)
Bronchitis	0	3 (3)
Fatigue	0	3 (3)

Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]	Maintain WC SFC 50/250µg bd N=88	Aim TC SFC 50/500µg bd N=90
	n (%) [related]	n (%) [related]
Subjects with non-fatal SAEs, n (%)	1 (1) [0]	0
Spinal fracture	1 (1) [0]	0
Headache	1 (1) [0]	0
Haematuria	1 (1) [0]	0
Subjects with fatal SAEs, n (%)	0	0

Conclusion: Both treatments resulted in an increase from baseline in PC_{20} methacholine, but the increased steroid dose (Aim TC strategy, SFC 50/500µg bd) failed to show superiority in the reduction of airway hyper-responsiveness over the maintenance dose (Maintain WC strategy, SFC 50/250µg bd). A large proportion of subjects in both treatment groups maintained their Well Controlled asthma status during the study but there was no difference between treatment groups in the proportion of subjects who maintained Well Controlled asthma or in those who achieved Totally Controlled asthma. A total of 39 (44%) subjects in the Maintain WC group and 36 (40%) subjects in the Aim TC group reported non-serious adverse events, the most common event being nasopharyngitis in both groups. One subject in the Maintain WC group reported serious adverse events (SAEs) of spinal fracture, headache and haematuria, all related to a fall and none assessed as related to treatment. No SAEs were reported in the Aim TC group and there were no fatal SAEs during the study.

Publications: No publication

Date updated: 18-Mar-2008