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Study No.: SAS101877		
Title: A randomised, open label, five-way crossover study to assess the systemic exposure of fluticasone propionate (FP) and salmeterol (SALM) from SERETIDE™/ADVAIR™ 250 HFA MDI without spacer, with AeroChamber-Plus spacer, with AeroChamber-Max spacer, with VOLUMATIC™ spacer and SERETIDE™/ADVAIR™ 500 DISKUS™/ACCUHALER™ in adult subjects with mild or intermittent asthma		
Rationale: There is a lack of in vivo data on the effect of spacer devices on the drug delivery and systemic exposure for fluticasone propionate (FP) and salmeterol (SALM) and no data are available for the FP/SALM combination product. The effect of a spacer is difficult to predict from in vitro data as there are a number of variables to be considered. Spacers can overcome the poor co-ordination of the inhalation effort with the actuation of the metered dose inhaler (MDI), thereby improving drug deposition in the lung. Since more time is available for aerosol dispersion prior to inhalation, the emitted fine particle mass dose is increased and larger particles of drug are removed. These larger particles are then no longer available to deposit in the mouth and throat, thereby potentially reducing side-effects and exposure from swallowed drug. Since FP has negligible oral bioavailability, the removal of the larger particles is unlikely to have notable impact. In contrast, SALM does have significant oral absorption, and in this case the use of a spacer might reduce systemic exposure. There are two main types of spacer device, large and small volume. In addition, a new spacer device has been manufactured with anti-electrostatic coating to reduce the tendency of drug particles to be attracted to the device surface. This study is intended to investigate the impact of a range of spacer devices, the AeroChamber Max (with the anti-electrostatic coating), the AeroChamber Plus and the VOLUMATIC™ on the systemic exposure to FP and SALM when delivered as the combination product via MDI. A comparison was also made to the dry powder formulation in the DISKUS™ inhaler.		
Phase: I		
Study Period: 27 May 2004 – 3 August 2004		
Study Design: Single-dose, randomised, open-label, five-way crossover		
Centres: 1 centre in the Netherlands		
Indication: Asthma		
Treatment: Subjects received a single dose of each of the following treatments: two inhalations of Salmeterol/Fluticasone Propionate 250 HFA MDI (MDI) two inhalations of Salmeterol/Fluticasone Propionate 250 HFA MDI with aerochamber-plus spacer (MDI + Plus) two inhalations of Salmeterol/Fluticasone Propionate 250 HFA MDI with aerochamber-max spacer (MDI + Max) two inhalations of Salmeterol/Fluticasone Propionate /250 HFA MDI with volumatic spacer (MDI + Vol) one inhalation of Salmeterol/Fluticasone Propionate 500 DISKUS/ACCUHALER (DISKUS). Subjects were randomised to one of 20 treatment sequences. There was a wash-out period of at least 5 days between study periods.		
	Study Drug	
Property		
Formulation	Salmeterol/Fluticasone Propionate HFA 25/250µg	Salmeterol/Fluticasone Propionate 50/500µg
Dosage Form	Metered Dose Inhaler (MDI), 120 Dose	DISKUS™/ACCUHALER™ Inhaler (DISKUS), 60 Dose
Unit Dose Strength	250µg per actuation	500µg per blister
Manufacturer	GSK	GSK
Route of Administration	Inhaled	Inhaled
Spacer	Physical description	Manufacturer
VOLUMATIC™	Made of clear plastic. 750mL chamber	GSK
AeroChamber-Plus	Made of clear and coloured plastic. 149mL chamber	Trudell
AeroChamber-Max	Made of clear and coloured plastic. 198mL chamber	Trudell
Spacer devices were prepared according to the manufacturers instructions before first use. This involved washing the AeroChamber – Plus and AeroChamber-Max spacers but not the VOLUMATIC.		

Objectives:

To estimate the difference in fluticasone propionate (FP) systemic exposure following a single dose of Salmeterol/Fluticasone Propionate HFA MDI administered via the AeroChamber-Max® spacer compared to a single dose of Salmeterol/Fluticasone Propionate HFA MDI administered via the VOLUMATIC™ spacer in adult asthma subjects

To estimate the difference in FP systemic exposure following a single dose of Salmeterol/Fluticasone Propionate HFA MDI administered via the AeroChamber-Plus® spacer compared to a single dose of Salmeterol/Fluticasone Propionate HFA MDI administered via the VOLUMATIC spacer in adult asthma subjects

To estimate the difference in FP systemic exposure following a single dose of Salmeterol/Fluticasone Propionate HFA MDI administered via the AeroChamber-Max spacer compared to a single dose of Salmeterol/Fluticasone Propionate HFA MDI administered via the AeroChamber-Plus spacer in adult asthma subjects

Statistical Methods:

Statistical methods: 19 subjects were enrolled so that at least 16 evaluable adult male and female subjects completed the study. The sample size calculation for this study was based on the number of subjects needed to achieve an acceptable level of precision when estimating the differences between treatment groups.

Pharmacokinetics: Descriptive statistics were calculated on the plasma concentration levels of FP and SALM. The following treatment comparisons were made for FP and SALM AUC_(0-t) and FP C_{max}:

- MDI + Max versus MDI + Vol
- MDI + Plus versus MDI + Vol
- MDI + Max versus MDI + Plus

The following secondary treatment comparisons were made for FP AUC_(0-t) and FP C_{max}:

- MDI + Max versus MDI
- MDI + Plus versus MDI
- MDI + Vol versus MDI
- MDI + Max versus DISKUS
- MDI + Plus versus DISKUS
- MDI + Vol versus DISKUS
- DISKUS versus MDI

Log_e-transformed AUC_(0-t) and C_{max} were analysed separately and for both FP and salmeterol using a mixed effect model with treatment and period fitted as fixed effects and subject fitted as a random effect. From these analyses, the primary and secondary treatment comparisons were made and presented as ratios.

Treatment ratios were calculated by back-transforming the difference between the adjusted means. Using the pooled estimate of variance, 90% confidence intervals were calculated for the difference and then back-transformed.

There was no adjustment for multiple comparisons.

Safety: All safety data were analysed descriptively.

Study Population: mild or intermittent asthma, male or female non-smokers, between 18 and 65 years of age (inclusive) with a body mass index (BMI) within the range of 19 to 30 kg/m² inclusive.

Number of Subjects:	19	
Planned, N	20	
Randomised, N	19	
Completed, n (%)	19 (100%)	
Total Number Subjects Withdrawn, N (%)	0 (0%)	
Withdrawn due to Adverse Events n (%)	0 (0%)	
Withdrawn due to Lack of Efficacy n (%)	0 (0%)	
Withdrawn for other reasons n (%)	0 (0%)	
Demographics		
N (ITT)	19	
Females: Males	10:9	
Mean Age, years (SD)	32.3 (14.17)	
White, n (%)	17 (89%)	
Pharmacokinetic Results:		
Fluticasone Propionate	AUC (0-t)	Cmax

	Ratio	90% CI	Ratio	90% CI
MDI + Max versus MDI + Vol	2.47	(1.79, 3.42)	2.57	(2.03, 3.27)
MDI + Plus versus MDI + Vol	1.76	(1.27, 2.44)	2.00	(1.57, 2.55)
MDI + Max versus MDI + Plus	1.40	(1.02, 1.94)	1.29	(1.01, 1.64)
MDI + Plus versus MDI	1.40	(1.01, 1.94)	1.27	(1.00, 1.61)
MDI + Max versus MDI	1.97	(1.42, 2.72)	1.63	(1.28, 2.07)
MDI + Vol versus MDI	0.79	(0.57, 1.10)	0.63	(0.50, 0.80)
MDI + Plus versus DISKUS	1.30	(0.94, 1.79)	1.48	(1.17, 1.89)
MDI + Max versus DISKUS	1.82	(1.32, 2.52)	1.91	(1.50, 2.43)
MDI + Vol versus DISKUS	0.74	(0.53, 1.02)	0.74	(0.58, 0.94)
DISKUS versus MDI	1.08	(0.78, 1.49)	0.85	(0.67, 1.08)

Salmeterol	AUC (0-t)		Cmax	
	Ratio	90% CI	Ratio	90% CI
MDI + Max versus MDI + Vol	5.31	(3.38, 8.34)	1.80	(1.38, 2.36)
MDI + Plus versus MDI + Vol	3.58	(2.26, 5.65)	1.26	(0.96, 1.66)
MDI + Max versus MDI + Plus	1.48	(0.96, 2.29)	1.43	(1.10, 1.85)
MDI + Plus versus MDI	1.08	(0.70, 1.67)	1.51	(1.16, 1.95)
MDI + Max versus MDI	1.60	(1.04, 2.45)	2.15	(1.67, 2.77)
MDI + Vol versus MDI	0.30	(0.19, 0.47)	1.19	(0.91, 1.56)
MDI + Plus versus DISKUS	4.35	(2.79, 6.79)	1.39	(1.07, 1.81)
MDI + Max versus DISKUS	6.45	(4.17, 9.99)	1.99	(1.53, 2.58)
MDI + Vol versus DISKUS	1.22	(0.77, 1.93)	1.10	(0.84, 1.45)
DISKUS versus MDI	0.25	(0.16, 0.38)	1.08	(0.83, 1.40)

	MDI +Max N=19	MDI + Plus N=19	MDI + Vol N=19	MDI N=19	DISKUS N=19
Most Frequent Adverse Events	n(%)	n(%)	n(%)	n(%)	n(%)
Subjects with any AE(s), n(%)	6 (32)	2 (11)	4 (21)	5 (26)	7 (37)
Headache	2 (11)	0 (0)	2 (11)	2 (11)	2 (11)
Serious Adverse Events n (%) [n considered by the investigator to be related, probably related or possibly related to study medication]:					
Subjects with any SAE Includes non-fatal and fatal SAEs	0	0	0	0	0

Publications:
No Publication

Date Updated: 17-Aug-2005