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Study No: FFR10005				
Title: A double blind, randomised, placebo-controlled, single and multiple intranasal dose study to investigate the safety, tolerability and pharmacokinetics of GW685698 in Japanese healthy male subject.				
Rationale: GW685698 (Fluticasone Furoate) is a novel corticosteroid with potent glucocorticoid activity. It has a similar profile to FP in the in vitro and in vivo models investigated to date, including activation of the glucocorticoid response element, inhibition of pro-inflammatory transcription factors such as NFκB and inhibition of antigen induced lung eosinophilia in sensitised rats. Lipophilic glucocorticoids exhibit a high tissue binding and retention. There is a very close relationship between the relative receptor affinity of a glucocorticoid and the amount of the compound bound to tissue. GW685698 has lipophilicity structure and is expected high tissue binding and long retention. A longer lung retention time for GW685698 compared to FP is suggested in inhaled dose study in healthy volunteer and GW685698 is expected longer retention time in epithelium compared to FP. These data may give great support for once daily dosing. GW685698 has already been developed clinically for allergic rhinitis in EU/US. GW685698 was administered intranasally to healthy adult males at single doses from 50µg to 800µg and at once daily 7-day repeat doses of 200 and 800 µg. No safety issues including nasal mucosal irritability were reported. At all dose levels, the systemic exposure was very low and the plasma concentrations of GW685698 were below the LLQ (<10 pg/mL) in most of the samples. In order to develop GW685698 for allergic rhinitis in Japan, this study was carried out to evaluate the safety and pharmacokinetics of GW685698 in healthy Japanese male subjects.				
Phase: I				
Study Period: 9 July 2003 - 9 October 2003				
Study Design: A single center, double-blind, ascending dose with randomised placebo single and multiple intranasal dose study				
Centres: This study was conducted at one center in Japan				
Indication: Allergic rhinitis				
Treatment: After screening, a total of 12 subjects attended the unit for 2 nights 3 days in Periods 1–3 for single dosing and then for 9 nights 10 days in Period 4 for repeat dosing. Six (6) days after the final dose in Period 4, the subjects returned to the unit for post-study examinations (for 2 nights 3 days). GW685698 0.05%, 0.1% or placebo nasal sprays were used. According to the following table, GW685698 100, 200, 400µg or placebo was administered into each nostril once at fasting in Periods 1–3, and GW685698 400µg was administered once daily for 7 days (at fasting on Day 7 only) in Period 4. Each treatment was separated by at least 7 days. The subjects were fasted from midnight prior to each treatment day in Periods 1–3 and Day 7 in Period 4 (with the exception of water or barley tea) until 4 hours post dose.				
Group (Number of subjects)	Single administration			Repeat administration (once daily in the morning for 7 days)
	Period 1	Period 2	Period 3	Period 4
A (n=4)	Placebo	200µg	400µg	400µg
B (n=4)	100µg	Placebo	400µg	400µg
C (n=4)	100µg	200µg	Placebo	Placebo
Objectives: To investigate the safety and tolerability of GW685698 following single and repeat intranasal doses in healthy Japanese male subjects. To investigate the pharmacokinetics of GW685698 following single and repeat intranasal doses in healthy Japanese male subjects. To investigate the systemic pharmacodynamic effects of single and repeat intranasal doses of GW685698 in healthy Japanese male subjects.				
Statistical Methods:				
Safety:				

Safety data obtained up until follow-up or additional examinations were used for safety analyses. Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Terminology. All adverse events that occurred after treatment initiation were listed by treatment group with time of onset, resolution, outcome, severity, frequency and causality. Laboratory data (haematology, biochemistry and urinalysis) were listed using summary statistics (mean, sd, minimum, median, maximum). Laboratory values outside the reference range were listed. Bodyweight, vital signs, ECG, nasal examination, nasal symptoms and other safety data were listed and summarised.

Pharmacokinetics:

Non-compartmental pharmacokinetics parameters (C_{max} , T_{max} and AUC_{0-t}) were calculated from plasma concentrations of GW685698 after single and multiple doses. Due to the limited number of subjects with measurable plasma concentrations, statistical analyses of dose proportionality, accumulation or steady state were not performed.

Pharmacodynamics:

Concentrations of serum cortisol were summarised by treatment group. Serum cortisol weighted mean 0-24 hours data were calculated and summarised by descriptive statistics. The analysis ratios were calculated comparing each active treatment group with placebo.

Study Population: healthy Japanese male volunteers

Number of Subjects:	Total
Planned N	12
Dosed N	12
Completed n (%)	11 (92%)
Total Number Subjects Withdrawn N (%)	1 (8%)
Withdrawn due to Adverse Events n (%)	1 (8%)
Withdrawn due to Lack of Efficacy n (%)	not applicable
Withdrawn for Other Reasons n (%)	0
Demographics	Total
N (ITT)	12
Females: Males	0:12
Mean Age in Years (sd)	24.8 (3.11)
Mean Weight in Kg (sd)	62.68 (6.093)
White n (%)	0

Pharmacokinetics (PK):

Plasma concentrations of GW685698 were quantifiable in one subject following the 400 µg single dose. The C_{max} was 12 pg/mL, t_{max} was 2 hr and AUC_{last} was 36.65 pg.hr/mL. The half-life could not be determined due to poor definition of the plasma concentration-time profile. Other subjects were NQ at all time points.

Following 400µg once daily repeat dosing for 7 days, GW685698 concentrations in plasma were quantifiable in 3 subjects. The median (range) value for C_{max} was 11.9 (10.4– 4.6) pg/mL, for t_{max} was 0.75 (0.5–0.75) hr and for AUC_{last} was 13.77 (7.97–22.77) pg.hr/mL. The half-life could not be determined due to poor definition of the plasma concentration-time profiles.

Pharmacodynamics (PD):

Serum cortisol weighted means over 0-24 hours were analysed. No differences were observed between treatments following single dose but a statistically significant decrease was observed following 400 µg repeat dosing compared to placebo. There were no differences in individual cortisol time-concentration profiles between treatments and no dose-dependent decrease was observed. Large inter-subject's variability were observed in serum cortisol data.

Safety results:

Single and repeated intranasal administrations of up to 400µg GW685698 were safe and well tolerated in 12 Japanese healthy male subjects. Of a total of 12 subjects who received study medication, 6 subjects (50 %) experienced 16 adverse events (15 AEs in GW685698 and one AE in placebo). The most common adverse events were increased reticulocyte count (2 AEs; one following 400 µg single dose and one following single dose placebo) and positive fungal tests (2 AEs; one following 100 µg single dose and one following 400 µg repeat dosing). Both adverse events were mild in intensity and resolved without any treatment. These were judged as related to the investigational products. One subject discontinued the study due to adverse events (convulsion, loss of consciousness, pallor facial and rigidity of limbs) immediately before Period 2 dosing. These adverse events were moderate in intensity, resolved without any treatment and were not considered to be related to the investigational products. Epileptic symptoms had not reported as a medical history in this subject. One subject reported 5 adverse events (otitis media serous, acute sinusitis, pain pharynx, pharynx redness of and ear pain) during Periods 3 and 4. These events were mild in intensity and were not considered to be related to the investigational products. Concomitant drugs were used for the adverse events (otitis media serous and acute sinusitis) after post-study examination. Other adverse events were mild in intensity and were

not considered as drug-related. No other treatments related changes were observed in bodyweight, vital signs, 12-lead ECG, laboratory examination, nasal examinations or HPA axis test.

Adverse Events:						
	Single administration				Repeat administration	
	Placebo (n=11)	100 µg (n=8)	200 µg (n=7)	400 µg (n=8)	Placebo (n=3)	400 µg (n=8)
No. subjects with AEs n (%)	1 (9.09)	1 (12.50)	0	2 (25.00)	0	3 (37.50)
Ear and labyrinth disorders	0	0	0	0	0	1 (12.50)
Ear pain	0	0	0	0	0	1 (12.50)
Infections and infestations	0	0	0	1 (12.50)	0	1 (12.50)
Acute sinusitis	0	0	0	1 (12.50)	0	0
Otitis media serous	0	0	0	0	0	1 (12.50)
Nervous system disorders	0	2 (25.0)	0	0	0	3 (37.50)
Convulsion	0	1 (12.50)	0	0	0	0
Dizziness on standing up	0	0	0	0	0	1 (12.50)
Headache dull	0	0	0	0	0	1 (12.50)
Loss of consciousness	0	1 (12.50)	0	0	0	0
Swaying feeling	0	0	0	0	0	1 (12.50)
Musculoskeletal and connective tissue disorders	0	1 (12.50)	0	0	0	0
Rigidity of limbs	0	1 (12.50)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (12.50)	0	1 (12.50)
Pain pharynx	0	0	0	1 (12.50)	0	0
Pharynx redness of	0	0	0	0	0	1 (12.50)
Vascular disorders	0	1 (12.50)	0	0	0	0
Pallor facial	0	1 (12.50)	0	0	0	0
Investigations	1 (9.09)	1 (12.50)	0	1 (12.50)	0	1 (12.50)
Reticulocyte count increased	1 (9.09)	0	0	1 (12.50)	0	0
Fungal test positive	0	1 (12.50)	0	0	0	1 (12.50)
Serious Adverse Events, n (%):						
No serious adverse events were observed in this study.						

Publications: None