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Study No: HZA112018
Title : Phase I study of GW685698X — A randomized, double blind, placebo controlled, parallel-group, repeat dose study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of inhaled dose from a novel dry powder device in healthy Japanese male subjects —
Rationale: GW685698X (fluticasone furoate) is novel corticosteroid discovered by GlaxoSmithKline. Chemical structure of GW685698X is similar to fluticasone propionate (FP) that has been launched in Japan as inhaled corticosteroid (Flutide® DISKUS) and intranasal solution (Flunase® Nasal Solution) and is displaced ester moiety of FP by furoate. GW685698X has already used as a treatment of allergic rhinitis, which has been approved in overseas and submitted for approval in Japan. An inhaled steroid of GW685698X is being developed for the treatment of bronchial asthma as part of a combination with LABA and a standalone product. This study was conducted to provide the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) data after administration of GW685698X as single and once daily inhaled dosing for 7 days in healthy Japanese male subjects.
Phase: I
Study Period: 24 September 2008 - 19 December 2008
Study Design: This study was a single centre, randomized, double blind, placebo controlled, dose ascending, parallel-group dose design of single and once daily repeat inhaled doses of GW685698X or placebo (via a novel dry powder inhaler).
Centres: A single centre in Japan
Indication: None
Treatment: Forty eight healthy subjects received single and repeat inhaled doses of GW685698X (200, 400 or 800µg) or placebo. Forty eight healthy subjects split into 3 cohorts of 16 subjects, twelve of whom were randomised to receive active drug. Each subject was received the first dose on Day 1 and followed by once a daily dosing for 7 days from Day 5 to Day11.
Objectives: The primary objective was to evaluate the safety and tolerability of GW685698X following repeat inhaled doses at 200, 400 and 800µg in healthy Japanese male subjects. The secondary objectives were: to investigate the pharmacokinetics of GW685698X following single and repeat inhaled doses at 200, 400 and 800µg in healthy Japanese male subjects; and to investigate the effects on serum cortisol of GW685698X following single and repeat doses at 200, 400 and 800µg in healthy Japanese male subjects.
Statistical Methods:
Safety:
<ul style="list-style-type: none"> • Adverse events: AEs recorded in CRFs by the investigator/subinvestigator were coded with the ICH Medical Dictionary for Regulatory Activities (MedDRA ver 11.0) and were classified according to system organ class (SOC) and preferred term (PT). Listings and summary tables by subject, by treatment, and by severity were prepared for all AEs that occurred in the study. • Clinical laboratory evaluations: A listing by subject was prepared for clinical laboratory data. Data exceeding the reference values were listed separately. • Adrenocortical function test: For serum cortisol concentration and the result of judgement on rapid ACTH test, listings by treatment were prepared. For urine 17-OHCS concentration, listing by treatment was prepared. Ratio of pre dose to post dose and summary statistic were calculated by treatment. • Oropharyngeal fungi test: Listing by treatment was prepared for this test result. • Other safety measures: For body weight, blood pressure, heart rate, body temperature, and 12-lead ECG parameter, summary statistics were calculated and listings were prepared. A separate listing of normal/abnormal result of 12-lead ECG was prepared.
Pharmacokinetics:
<ul style="list-style-type: none"> • Plasma concentration: For plasma concentrations of GW685698X, summary statistics were calculated by treatment and assessment point, and figures showing mean and median plasma concentration-time profiles were prepared. Listing and figures showing plasma concentration-time profiles for individual subjects were also prepared. • Calculation of pharmacokinetic parameters: From the plasma concentration-time data in individual subjects, the selected pharmacokinetic parameters were determined using non-compartmental pharmacokinetic analysis.

- Dose proportionality: Dose proportionality was graphically presented for C_{max} and AUC.
- Steady state: Steady state was graphically presented for trough levels of GW685698X.
- Assessment of accumulation: To assess possible accumulation after repeat inhaled doses, $AUC_{0-\infty}$, AUC_{0-t} , and C_{max} on Day 1 and Day 11 were used to calculate the accumulation ratios, R_o , $R[C_{max}]$ and R_s .

Pharmacodynamics:

- Serial time point measurements: For serum concentrations of cortisol, summary statistics were calculated by treatment and assessment point, and figures showing mean and median plasma concentration-time profiles were prepared. Listing and figures showing plasma concentration-time profiles for individual subjects were also prepared.
- Pharmacodynamic parameters: From the serum cortisol concentration-time data, AUC_{0-24} was determined by linear trapezoidal rule on Day -1, Day 1 and Day 11 and weighted mean was derived by calculating 0 to 24 hours.

Study Population: Japanese healthy male subjects aged between 20 and 64 years of age inclusive with a body weight ≥ 50 kg and body mass index within the range 18.5-25.0kg/m².

Number of Subjects:	200 µg	400 µg	800 µg	Placebo
Planned N	12	12	12	12
Dosed N	12	12	12	12
Completed n (%)	12 (100)	12 (100)	12 (100)	12 (100)
Total Number Subjects Withdrawn N (%)	0 (0)	0 (0)	0 (0)	0 (0)
Demographics	200 µg	400 µg	800 µg	Placebo
N (ITT)	12	12	12	12
Females: Males	0:12	0:12	0:12	0:12
Mean Age in Years (sd)	28.8 (5.91)	28.3(3.14)	23.8 (3.47)	24.4 (4.46)
Mean Height in cm (sd)	171.3 (5.60)	171.4 (5.02)	169.8 (5.54)	171.2 (6.46)
Mean Weight in Kg (sd)	64.43 (7.122)	62.65 (6.510)	60.26 (7.272)	61.96 (4.906)
Mean Body Mass Index (kg/m ²) (sd)	21.92 (1.749)	21.28 (1.591)	20.84 (1.821)	21.18 (1.694)
Asian — Japanese, n (%)	12 (100)	12 (100)	12 (100)	12 (100)

Pharmacokinetics (PK): PK parameters after single and 7-day repeat inhaled dosing of GW685698X are summarized in the table below.

Parameter	Dose	Day	N	Mean (SD)	Geometric Mean	90%CI
C_{max} (pg/mL)	200 µg	1	12	37.69 (9.590)	36.50	30.719, 43.360
		11	12	63.66 (13.753)	62.31	54.284, 71.515
	400 µg	1	12	57.76 (15.121)	55.94	47.237, 66.246
		11	12	124.85 (29.049)	121.99	105.922, 140.490
	800 µg	1	12	106.87 (23.012)	104.55	90.868, 120.301
		11	12	228.29 (55.460)	222.28	190.698, 259.099
AUC _{0-t} (h•pg/mL)	200 µg	1	12	249.78 (107.712)	224.62	161.551, 312.303
		11	12	1128.61 (286.556)	1090.10	908.116, 1308.562
	400 µg	1	12	896.94 (346.908)	834.93	645.845, 1079.363
		11	12	2834.87 (671.186)	2767.66	2397.578, 3194.864
	800 µg	1	12	2331.64 (580.578)	2256.14	1890.215, 2692.907
		11	12	5756.36 (1452.687)	5600.65	4804.706, 6528.450
Parameter	Dose	Day	N	Median	Minimum	Maximum
t_{max} (h)	200 µg	1	12	0.500	0.25	1.00
		11	12	2.000	0.08	3.00
	400 µg	1	12	1.000	0.25	2.00
		11	12	2.000	1.00	2.00
	800 µg	1	12	1.000	0.50	2.00
		11	12	1.500	0.50	3.00

Accumulation ratios of GW685698X: The statistical summary of GW685698X accumulation assessment is presented below.						
Parameter	Dose	N	Ratio of Geometric Mean		95% CI	
R[C _{max}]	200 µg	12	1.707		1.4885, 1.9580	
R[C _{max}]	400 µg	12	2.181		1.9027, 2.4993	
Ro		12	2.616		2.3314, 2.9354	
Rs		8	1.145		0.9858, 1.3290	
R[C _{max}]		12	2.126		1.9383, 2.3319	
Ro	800 µg	12	2.324		2.1254, 2.5403	
Rs		12	1.022		0.9451, 1.1062	
Pharmacodynamics (PD): PD parameters of serum cortisol after single and 7-day repeat inhaled dosing of GW685698X are summarized in the table below.						
Parameter	Day	n	200 µg	400 µg	800 µg	Placebo
AUC ₀₋₂₄ (h.nmol/L)	Day -1	12	5193.1 (1342.65)	4504.9 (792.98)	5298.3 (548.63)	4930.5 (1044.15)
	Day 1	12	4521.0 (1096.26)	4829.1 (808.96)	3502.2 (751.20)	5453.3 (788.09)
	Day 11	12	3204.0 (498.32)	2641.4 (682.77)	236.7 (361.39)	4538.8 (710.13)
Weighted mean (0 – 24 h) (nmol/h)	Day -1	12	216.4 (55.94)	187.7 (33.04)	220.8 (22.86)	205.4 (43.51)
	Day 1	12	188.4 (45.68)	201.2 (33.71)	145.9 (31.30)	227.2 (32.84)
	Day 11	12	133.5 (20.76)	110.1 (28.45)	9.9 (15.06)	189.1 (29.59)
Mean (SD)						
Pharmacokinetics/pharmacodynamics Results : Since dose-dependent decreases were observed in the AUC ₀₋₂₄ of GW685698X and the serum cortisol weighted mean 0-24 hours after administration, an additional analysis was performed using sigmoid E _{max} model. Its results suggested a correlation between the systemic exposure level and the decrease in serum cortisol concentration.						
Safety results:						
Adverse events (AEs) were collected from screening until follow-up. All AEs reported by more than one subject are presented below.						
Adverse Events:			200 µg	400 µg	800 µg	Placebo
N (ITT)			12	12	12	12
No. subjects with AEs n (%)			4 (33)	1 (8)	5 (42)	1 (8)
Infections and infestations						
Hordeolum			1 (8)	0	0	0
Nervous system disorders						
Headache			0	0	1 (8)	0
Gastrointestinal disorders						
Nausea			0	0	1 (8)	0
Vomiting			0	0	1 (8)	0
Dental caries			0	0	0	1 (8)
Musculoskeletal and connective tissue disorders						
Back pain			0	0	1 (8)	0
Clinical Laboratory test						
White blood cell count increased			0	1 (8)	3 (25)	0
Alanine aminotransferase increased			2 (17)	0	0	0
Aspartate aminotransferase increased			1 (8)	0	0	0
Blood potassium increased			1 (8)	0	0	0
Blood urine present			0	0	1 (8)	0
Serious Adverse Events, n (%) : There were no serious adverse events in this study.						