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: MTL114422
Title : A Randomized, Placebo Controlled Dose Escalation Study to Evaluate Safety, Tolerability, and Pharmacokinetics of Single Oral Doses of GSK1322888 in Healthy Caucasian and Japanese Asian Adult Subjects
Rationale: Study MTL114422 was the first administration of GSK1322888 in humans.
Phase: I
Study Period: 29 NOV 2010 to 23 MAR 2011
Study Design: Randomized, placebo-controlled, single-blind, 4-way crossover study, conducted in 2 cohorts.
Centres: Conducted at a single site in Australia
Indication: Delayed gastric emptying
Treatment: Subjects received oral GSK1322888 or placebo capsules, in a 3:1 ratio, in accordance with the randomization schedule. Subjects received placebo and 3 of the 4 active doses.
Objectives: The primary objectives of the study were: • To assess the safety and tolerability of GSK1322888 following single, oral doses in healthy subjects. • To characterize the pharmacokinetics of GSK1322888 following single, oral doses in healthy subjects. One of the secondary objectives was to investigate the pharmacodynamic effect and dose/exposure response relationship for gastric emptying of an isotopically-labeled test meal, as measured by the ^{13}C-octanoic acid breath test following single oral doses of GSK1322888. One exploratory objective was to determine the effect of GSK1322888 on gastric emptying as determined by wireless motility capsule.
Statistical Methods: Safety and pharmacokinetic data were descriptively analyzed. Gastric emptying oral breath test parameters (t1/2b, tlag and GEC) and wireless motility capsule parameters (100% gastric emptying time (GET), total bowel transit time, small bowel transit time and colonic transit time) were statistically analyzed by a mixed model fitting period and treatment as fixed effects, and subject as a random effect. The baseline measurements were fitted as a covariate. The point estimate and corresponding 95% confidence interval for the difference "GSK1322888 - placebo" were constructed for each dose level, using the residual error from the model.
Study Population: Eligible subjects were males and females (of non-childbearing potential) between 18 (20 for Japanese) and 65 years of age, body weight ≥50 kg and BMI within the range 18.5-29.9 kg/m^2, AST, ALT, alkaline phosphatase and bilirubin ≤1.5xULN, and average QTc, QTcB or QTcF <430 msec. For Japanese subjects, Japanese ancestry was defined as being born in Japan, having four ethnic Japanese grandparents, holding a Japanese passport or identity papers and being able to speak Japanese.

Number of Subjects	**Cohort 1**	**Cohort 2**	**Total**
Number of subjects entered, N:	9	8	17
Number of subjects included in All subjects (safety) population, n (%):	9 (100%)	8 (100%)	17 (100%)
Number of subjects included in PK population, n (%):	8 (89%)	8 (100%)	16 (94%)
Number of subjects completed as planned, n (%):	8 (89%)	8 (100%)	16 (94%)
Number of subjects withdrawn (any reason), n (%):	1 (11%)	0	1 (6%)
Number of subjects withdrawn for SAE:	0	0	0
Number of subjects withdrawn for AE, n (%):	1 (11%) [1]	0	1 (6%)
Demographics			
Age in Years, Mean (range)	24.0 (20 - 28)	25.9 (22 – 35)	24.9 (20 – 35)
Sex, n (%)			
Female:	0	0	0
Male:	9 (100%)	8 (100%)	17 (100%)
BMI, Mean (range))	22.78 (19.8 – 26.9)	24.98 (21.8 – 28.8)	23.81 (19.8 – 28.8)
Height (cm), Mean (range)	174.8 (159 – 184)	177.0 (169 – 182)	175.8 (159 – 184)
Weight (kg), Mean (range)	70.08 (50.1 – 83.5)	78.26 (69.8 – 94.5)	73.93 (50.1 – 94.5)
Ethnicity, n (%)			
Caucasian	4 (44%)	4 (50%)	8 (47%)
Japanese	5 (56%)	4 (50%)	9 (53%)
Race, n (%)			
Asian – Japanese Heritage	5 (56%)	4 (50%)	9 (53%)
White	4 (44%)	4 (50%)	8 (47%)
1. One subject on placebo was withdrawn after Period 1 and was replaced			
Pharmacokinetics (PK) Endpoints: There did not appear to be any difference in PK concentrations or parameters between the two ethnicities (Caucasian and Japanese)			

Treatment	N	AUC(0-∞) (ng*hr/mL)	AUC(0-t) (ng*hr/mL)	Cmax (ng/mL)	tmax[1] (hr)	tlag[1] (hr)	t1/2 (hr)	CL/F (L/hr)	Vz/F (L)
1 mg	6	68.7 (26.8)	54.8 (32.5)	2.25 (33.0)	3.50 (2.00, 10.00)	0.50 (0.25, 0.75)	22.3 (16.6)	14.6 (26.8)	469 (33.2)
2 mg	6	149 (29.9)	117 (18.0)	5.20 (24.2)	2.25 (2.00, 3.00)	0.50 (0.25, 0.52)	26.1 (37.2)	13.4 (29.9)	503 (16.9)
5 mg	6	511 (28.6)	404 (21.9)	21.1 (33.9)	2.25 (1.50, 3.00)	0.38 (0.00, 0.75)	27.1 (35.8)	9.79 (28.6)	383 (25.6)
10 mg	10	762 (24.7)	634 (25.1)	31.2 (33.5)	2.25 (1.00, 4.00)	0.00 (0.00, 0.25)	23.2 (20.4)	13.1 (24.7)	439 (30.7)
20 mg	6	1323 (11.1)	1152 (7.65)	73.9 (14.7)	1.50 (1.00, 2.00)	0.25 (0.00, 0.25)	19.7 (17.2)	15.1 (11.1)	429 (8.30)
40 mg	6	2702 (11.9)	2421 (10.8)	162 (15.0)	1.50 (1.00, 2.50)	0.00 (0.00, 0.25)	18.1 (14.0)	14.8 (11.9)	387 (14.7)
80 mg	6	5896 (21.7)	5343 (22.0)	406 (24.9)	1.50 (0.50, 2.00)	0.00 (0.00, 0.00)	17.9 (12.6)	13.6 (21.7)	351 (25.3)

1. PK parameters presented as Geometric Mean (CVb%;), except for tmax and tlag which are presented as Median (min, max).
AUC=area under the concentration-time curve; Cmax=maximum observed concentration; tmax=time to maximum observed concentration; tlag=lag time; t1/2=terminal phase half life; CL/F=apparent clearance following oral dosing; Vz/F=apparent volume of distribution

Pharmacodynamic (PD) Endpoints: Gastric half emptying time (t1/2b), was significantly decreased by approximately 30 to 40 min (approximately 35% decrease) across the dose range 10 mg to 80 mg when compared to placebo. Other gastric emptying oral breath test parameters Tlag and GEC also showed a significant difference to placebo at these dose levels.

There was no apparent difference in gastric emptying oral breath test parameters between the two ethnicities (Caucasian and Japanese).

Parameter	Comparison	Least Squares Mean		Point Estimate	95% Confidence Interval	CVw%
		Test	Ref			
t1/2b (mins)	1 mg vs Placebo	103.026	93.182	9.845	(-17.648, 37.337)	18.50
	2 mg vs Placebo	73.380	93.182	-19.802	(-49.750, 10.147)	18.50
	5 mg vs Placebo	77.716	93.182	-15.466	(-40.256, 9.324)	18.50
	10 mg vs Placebo	64.330	93.182	-28.852	(-47.937, -9.767)	18.50
	20 mg vs Placebo	57.307	93.182	-35.875	(-62.931, -8.819)	18.50
	40 mg vs Placebo	52.320	93.182	-40.861	(-70.232, -11.491)	18.50
	80 mg vs Placebo	61.879	93.182	-31.302	(-56.385, -6.219)	18.50

Wireless motility capsule 100% gastric emptying time was significantly decreased by approximately 72 to 155 min (approximately 50%-75% decrease) across the dose range 10 to 80 mg when compared to placebo. There was no difference between any GSK1322888 dose levels and placebo for the other wireless motility capsule parameters (total bowel, small bowel and colonic transit times).

There was no apparent difference in wireless motility capsule parameters between the two ethnicities (Caucasian and Japanese).

Parameter	Comparison	Least Squares Mean		Point Estimate	95% Confidence Interval	CVw%
		Test	Ref			
100% GET (min)	1 mg vs Placebo	212.4	159.5	52.9	(-18.2, 124.0)	45.18
	2 mg vs Placebo	113.8	159.5	-45.6	(-158.0, 66.7)	45.18
	5 mg vs Placebo	104.6	159.5	-54.9	(-119.4, 9.6)	45.18
	10 mg vs Placebo	56.4	159.5	-103.1	(-153.5, -52.6)	45.18
	20 mg vs Placebo	87.2	159.5	-72.3	(-140.4, -4.1)	45.18
	40 mg vs Placebo	3.8	159.5	-155.7	(-267.6, -43.9)	45.18
	80 mg vs Placebo	47.4	159.5	-112.2	(-176.0, -48.2)	45.18

Safety results: AEs were collected from the start of study treatment until the follow-up contact. There was no dose-response in the types or numbers of reported AEs. Additionally, there was no apparent difference between the Caucasians and Japanese subjects in the types and frequency of reported AEs.

	Number of Subjects								
		GSK1322888							
	PBO N=15	1 mg N=6	2 mg N=6	5 mg N=6	10 mg N=10	20 mg N=6	40 mg N=6	80 mg N=6	Total N=17
Any event-All Subjects	4 (27%)	2 (33%)	0	5 (83%)	5 (50%)	4 (67%)	4 (67%)	1 (17%)	14 (82%)
Any event-Caucasian	1 (14%)	1 (33%)	0	2 (67%)	1 (25%)	2 (67%)	2 (67%)	1 (33%)	6 (75%)
Any event-Japanese	3 (38%)	1 (33%)	0	3 (100%)	4 (67%)	2 (67%)	2 (67%)	0	8 (89%)
Adverse Events									
Rash erythematous [1]	1 (7%)	0	0	3 (50%)	1 (10%)	0	0	0	4 (24%)
Skin irritation [1]	0	1 (17%)	0	0	0	1 (17%)	1 (17%)	0	2 (12%)
Pigmentation disorder	0	0	0	1 (17%)	0	0	0	0	1 (6%)
Rash	1 (7%)	0	0	0	0	0	0	0	1 (6%)
Headache	2 (33%)	1 (17%)	0	0	1 (10%)	1 (17%)	2 (33%)	0	4 (24%)
Dizziness	0	0	0	0	0	1 (17%)	0	0	1 (6%)
Oropharyngeal pain	1 (7%)	0	0	0	1 (10%)	0	1 (17%)	0	3 (18%)
Nasal obstruction	0	0	0	0	0	0	1 (17%)	0	1 (6%)
Abdominal discomfort	0	0	0	0	1 (10%)	0	0	0	1 (6%)
Abdominal pain lower	0	1 (17%)	0	0	0	0	0	0	1 (6%)
Diarrhea	0	0	0	0	0	0	0	0	1 (6%)
Neutropenia	0	0	0	0	0	0	1 (17%)	0	1 (6%)

1. Based on discussions with the investigator at dose escalation meetings, AEs of rash and skin irritation were principally considered to be related to electrocardiogram electrodes and were not considered related to drug.

Drug-Related Adverse Events:	Number of Subjects								
		GSK1322888							
	PBO N=15	1 mg N=6	2 mg N=6	5 mg N=6	10 mg N=10	20 mg N=6	40 mg N=6	80 mg N=6	Total N=17
Any drug-related AE-All Subjects	0	1 (17%)	0	0	2 (20%)	2 (33%)	1 (17%)	0	4 (24%)
Any event-Caucasian	0	1 (33%)	0	0	0	1 (33%)	1 (33%)	0	2 (25%)
Any event-Japanese	0	0	0	0	1 (33%)	1 (33%)	0	0	2 (22%)
Headache	0	1 (17%)	0	0	1 (10%)	1 (17%)	1 (17%)	2 (33%)	3 (18%)
Diarrhea	0	0	0	0	1 (10%)	0	0	0	1 (6%)
Dizziness	0	0	0	0	0	1	0	0	1

						(17%)			(6%)
Serious Adverse Events: There were no serious adverse events reported during this study.									