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: MOT111809

Title : A Multicenter, Double-Blind, Randomized Placebo-Controlled Phase II Study to Evaluate the Pharmacodynamics, Safety, Tolerability, and Pharmacokinetics of Single Doses of the Oral Motilin Receptor Agonist GSK962040, in Type I Diabetic Male and Female Patients with Gastroparesis

Rationale: The purpose of this study was to assess the pharmacodynamic (PD) effects (gastric emptying), safety, tolerability, and pharmacokinetics (PK) of single doses of GSK962040 in Type I diabetic (T1DM) subjects with gastroparesis.

Phase: II

Study Period: 26 June 2009 – 19 November 2010

Study Design: Randomized, double-blind, placebo-controlled, incomplete block, three period crossover

Centres: Conducted at 2 sites in Sweden and Belgium.

Indication: Diabetic gastroparesis

Treatment: Subjects were assigned to one of the following nine sequences, in a ratio of 1:1:1:1:1:1:1:1:1, P/A/B, P/B/C, P/C/A, A/P/C, B/P/A, C/P/B, A/C/P, B/A/P, C/B/P, in accordance with the randomization schedule generated prior to the start of the study.

Treatment Assignments

Regimen Code	Regimen
A	GSK962040 25 mg
B	GSK962040 50 mg
C	GSK962040 125 mg
P	Placebo

Objectives: The primary objectives were:

- To investigate the PD effect of single doses of GSK962040 on gastric emptying of an isotope-labeled test meal, as measured by the 13C-octanoic acid breath test in Type I Diabetic Mellitus (T1DM) subjects with gastroparesis
- To investigate safety and tolerability of single doses of GSK962040 in T1DM subjects with gastroparesis
- To investigate PK of single doses of GSK962040 in T1DM subjects with gastroparesis

Statistical Methods:

Pharmacodynamic Analyses:

Gastric emptying parameters (t1/2b, tlag and GEC) were statistically analyzed by a mixed model fitting period and treatment as fixed effects, and subject as a random effect. The point estimate and corresponding 95% confidence interval for the difference "GSK962040 - placebo" were constructed for each dose level, using the residual error from the model.

Safety Analyses: These data are summarized descriptively.

Study Population: Eligible subjects were males and females (of non-childbearing potential) between 18 and 70 years of age with controlled T1DM (HbA1C <10%) with onset <30 years of age and documented by history of a diagnosis of moderate to severe gastroparesis (>30% gastric retention of a meal at 2 hours as determined by scintigraphy; or half time of gastric emptying (t1/2b) >109 min as determined by 13C-octanoic acid breath test). This diagnosis must have been accompanied by a minimum 3 month history of relevant symptoms for gastroparesis (e.g., chronic postprandial fullness, postprandial nausea, vomiting).

Number of Subjects	**Total**
Number of subjects planned, N:	18
Number of subjects entered, N:	10
Number of subjects included in All subjects (safety) population, n (%):	10
Number of subjects included in PK population, n (%):	9
Number of subjects completed as planned, n (%):	9
Number of subjects withdrawn (any reason), n (%):	1
Number of subjects withdrawn for SAE, n (%):	1 [a]
Number of subjects withdrawn for AE, n (%):	1 [b]
Demographics	
Age in Years, Mean (range)	45.4 (29 – 64)
Sex, n (%)	
Male:	1 (10%)
Female:	9 (90%)
BMI, Mean (range)	24.999 (19.83 – 31.80)
Height, Mean (range)	165.8 (156 – 180)
Weight, Mean (range)	68.44 (54.0 – 82.0)
Ethnicity, n (%)	
Hispanic or Latino:	0
Not Hispanic or Latino:	10 (100%)
Race, n (%)	
White – White/Caucasian/European Heritage	10 (100%)

[a] One subject was withdrawn after receiving placebo in the first period due to an SAE of QT prolongation and abnormal blood glucose .

[b] The one subject withdrawn for an AE was the same subject as the one withdrawn due to an SAE.

Pharmacodynamics (PD):

Summary of Statistical Analysis of Gastric Emptying Parameters: GSK962040 vs Placebo Comparison

Parameter	**Comparison**	**Test (Active Treatment)**	**Ref (Placebo)**	**Point Estimate (Difference)**	**95% CI**
t½b (mins)	25 mg - Placebo	107.65	147.10	-39.44	(-101.59 , 22.70)
	50 mg – Placebo	108.59	147.10	-38.51	(-100.65 , 23.63)
	125 mg – Placebo	52.11	147.10	**-94.99**	**(-155.84 , -34.15)**
Tlag (mins)	25 mg - Placebo	51.94	98.93	-46.98	(-95.25 , 1.29)
	50 mg – Placebo	68.75	98.93	-30.17	(-78.44 , 18.10)
	125 mg – Placebo	23.74	98.93	**-75.18**	**(-122.48 , -27.89)**
GEC	25 mg - Placebo	2.92	2.59	0.33	(-0.15 , 0.81)
	50 mg – Placebo	2.99	2.59	0.40	(-0.08 , 0.88)
	125 mg – Placebo	3.60	2.59	**1.00**	**(0.54 , 1.47)**

Bolded values: statistically significant difference from placebo (5% level)

Safety results:
AEs and SAEs were collected from the start of Investigational Product and until the follow-up contact.

Summary of Adverse Events in ≥2 Subjects

Adverse Events	Placebo N=10	GSK962040			
		25 mg N=6	50 mg N=6	125 mg N=6	Total N=9
	n (%)	n (%)	n (%)	n (%)	n (%)
Any AE	7 (70%)	3 (50%)	5 (83%)	3 (50%)	8 (89%)
AEs reported in ≥2 subjects					
Headache	1 (10%)	1 (17%)	3 (50%)	1 (17%)	3 (33%)
Flatulence	2 (20%)	1 (17%)	1 (17%)	1 (17%)	2 (22%)
Vomiting	1 (10%)	0	1 (17%)	1 (17%)	2 (22%)
Constipation	0	1 (17%)	0	1 (17%)	2 (22%)
Blood glucose decreased	1 (10%)	0	1 (17%)	1 (17%)	2 (22%)

Source: Table 11.02

Pharmacokinetics (PK): Summary of Selected Plasma GSK962040 Pharmacokinetic Parameters

GSK962040 PK Parameter	N	GSK962040 25 mg	GSK962040 50 mg	GSK962040 125 mg
AUC(0-∞) (ng.h/mL)	6			
Geom. Mean		4103.1	6193.8	16774.2
CVb%		(46.8)	(61.9)	(59.6)
AUC(0-24) (ng.h/mL)	6			
Geom. Mean		2691.3	4280.5	11175.1
CVb%		(49.6)	(56.4)	(56.0)
Cmax (ng/mL)	6			
Geom. Mean		288.3	488.0	1124.9
CVb%		(65.2)	(64.7)	(58.7)
tmax (h)	6			
Median		1.2	1.0	1.5
Range		(0.5 – 3.0)	(0.5 – 3.0)	(0.5 – 3.0)
tlag (h)	6			
Median		0	0	0
Range		(0 – 0.3)	(0 – 0.5)	(0 – 0)
t½ (h)	6			
Geom. Mean		14.5	12.0	14.5
CVb%		(58.5)	(62.9)	(25.0)
CL/F (L/h)	6			
Geom. Mean		6.1	8.1	7.5
CVb%		(46.7)	(61.9)	(59.5)
V/F (L)	6			
Geom. Mean		127.2	139.8	156.0
CVb%		(61.4)	(78.2)	(53.2)

Serious Adverse Events: One subject, on placebo, experienced a serious adverse event of moderate abnormal blood glucose and QT prolongation which was not considered drug-related. The subject did receive a single dose of placebo while in the hospital; however, she was withdrawn from the study without having received any doses of GSK962040.