

Study No.: GLP107865						
Title: Clinical assessment of GSK716155 for Type 2 Diabetes Mellitus - A Phase I/II study to investigate the safety, pharmacokinetics and pharmacodynamics of GSK716155 in Japanese subjects with type 2 diabetes mellitus-						
Rationale: To investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of GSK716155 (a novel analogue of GLP-1) in Japanese subjects with type 2 diabetes mellitus (T2DM)						
Phase: I/II						
Study Period: 01 August 2007 to 07 April 2008						
Study Design: a multicenter, single-blinded, placebo-controlled, randomized, staggered-parallel, escalating dose						
Centres: 3 centers in Japan						
Indication: Type 2 Diabetes Mellitus						
Treatment: Subjects were randomized in 4 cohorts of 10 subjects per cohort (8 received GSK716155 and 2 received placebo) and were assigned to receive placebo or one of four doses of GSK 716155 (15 mg once a week [weekly], 30 mg once a week [weekly], 50 mg once every other week [biweekly], and 100 mg once every four weeks [monthly]). This study was composed of a screening (SCR) period, a four-week treatment period and a five-week follow-up period.						
Objectives: To investigate the safety, tolerability of GSK716155 in Japanese subjects with T2DM, and to evaluate pharmacokinetics and pharmacodynamic effects of GSK716155 in Japanese subjects with T2DM.						
Primary Outcome/Efficacy Variable: Adverse events, clinical laboratory tests, vital signs, 12-lead electrocardiogram, GSK716155 concentrations in plasma, Pharmacodynamic parameters (change from baseline and weighted mean AUC ₀₋₄ in plasma glucose, glucagon, insulin, and C-peptide levels)						
Secondary Outcome/Efficacy Variable(s): Other metabolic parameters (change from baseline in free fatty acids, glycosylated albumin, adiponectin, and glycosylated hemoglobin)						
Statistical Methods: A total of 40 subjects with T2DM were enrolled into the study. Of 40 subjects who entered the study, 32 and 8 were randomized to receive treatment with GSK716155 and placebo, respectively. The subjects were enrolled into 4 cohorts of 10 subjects per cohort (8 received GSK716155 and 2 received placebo). Subjects received placebo from different cohort are combined for safety/efficacy evaluation. All subjects were evaluated for safety, GSK716155 concentrations in plasma and PD parameters. Descriptive statistics were calculated to summarize the data for demography, clinical laboratory evaluations, and other safety measures. Statistical analyses were performed using Version 8.2 of the SAS® system. The plasma GSK716155 concentration data were summarized by mean, standard deviation and median at each time point and pharmacodynamic parameters were summarized by mean, standard deviation, CV%, minimum, median, maximum and 95% confidence interval for the mean.						
Study Population: Japanese subjects with T2DM, 20 to 70 years old, body mass index (BMI) ≤ 35 kg/m ² , Fasting Plasma Glucose (FPG) level ≤240 mg/dL, HbA _{1c} level 6.5 to 10.0%, and creatinine clearance 60 mL/min and more by the Cockcroft-Gault formula at SCR, controlled by diet or taking a single oral antidiabetic (OAD) agent, and with at least a 3 months history of T2DM.						
	Doses of GSK716155				Placebo	Total
	15 mg weekly	30 mg weekly	50 mg biweekly	100 mg monthly		
Number of Subjects:	8	8	8	8	8	40
Planned, N	8	8	8	8	8	40
Randomised, N	8	8	8	8	8	40
Completed, n (%)	7 (87.5)	8 (100)	8 (100)	8 (100)	8 (100)	39 (97.5)
Total Number Subjects	1 (12.5)	0	0	0	0	1 (2.5)

Withdrawn, N (%)						
Withdrawn due to Adverse Events n (%)	0	0	0	0	0	0
Withdrawn due to Lack of Efficacy n (%)	0	0	0	0	0	0
Withdrawn for other reasons n (%)	1 (12.5)	0	0	0	0	1 (2.5)
Demographics						
N	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	40 (100)
Females: Males	0: 8	1: 7	1: 7	0: 8	3: 5	5: 35
Mean Age, years (Min, Max)	54.9 (41, 62)	53.3 (43, 66)	53.0 (28, 67)	53.6 (35, 62)	57.5 (40, 69)	54.5 (28, 69)
Race, n (%): Asian - Japanese Heritage	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	40 (100)
BMI (kg/m ²): Mean (Min, Max)	24.53 (20.5, 31.3)	22.60 (20.5, 27.1)	24.12 (21.1, 29.6)	25.74 (21.2, 34.6)	25.65 (19.8, 30.5)	24.53 (19.8, 34.6)
Primary Outcome Variable(s): Adverse events, clinical laboratory tests, vital signs, 12-lead electrocardiogram: See Safety Results below						
Pharmacokinetic s:	Doses of GSK716155					
	15 mg weekly N=8	30 mg weekly N=8	50 mg biweekly N=8	100 mg monthly N=8		
	Mean (Min, Max)	Mean (Min, Max)	Mean (Min, Max)	Mean (Min, Max)		
Plasma Concentration of GSK716155						
Day 1	Predose	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	6 hr	21 (0, 166)	332 (144, 523)	246 (0, 596)	646 (173, 1253)	
Day 2	24 hr	159 (0, 594)	1009 (248, 2056)	865 (311, 1912)	2243 (904, 4370)	
Day 3	48 hr	311 (129, 728)	1526 (465, 2333)	1619 (604, 2846)	3351 (1545, 5261)	
Day 8	168 hr	534 (352, 744)	1578 (727, 2184)	2113 (918, 3638)	4042 (1798, 6231)	
Day 15	336 hr	766 (480, 1027)	2190 (1612, 3075)	1056 (537, 1685) ^a	1885 (649, 3135)	
Day 17	384 hr	n/a	n/a	3913 (1894, 6470)	n/a	
Day 22	504 hr	850 (536, 1340) ^a	2451 (1362, 3631)	3113 (1776, 4440) ^a	870 (216, 1638)	
Day 24	552 hr	965 (673, 1399) ^a	3817 (2500, 6254)	n/a	n/a	
Day 29	672 hr	770 (432, 1230) ^a	2331 (1573, 3448)	1515 (908, 2344)	341 (0, 611)	
Day 43	1008 hr	199 (65, 486)	399 (0, 748)	421 (228, 751)	63 (0, 157)	
n/a - Not applicable a: n=7						

Pharmacodynamic parameters:	Doses of GSK716155				Placebo N=8
	15 mg weekly N=8	30 mg weekly N=8	50 mg biweekly N=8	100 mg monthly N=8	
Fasting Plasma Glucose (mg/dL)					
Mean Baseline (SD)	145 (26)	166 (38)	148 (43)	172 (50)	164 (35)
Change from baseline: Mean (95% CI)					
Day 29	-22.43 (-33.70, -- 11.15) ^a	-32.63 (-54.73, - 10.52)	-19.13 (-38.41, 0.16)	-13.13 (-42.86, 16.61)	3.88 (-17.07, 24.82)
Placebo adjusted change from baseline: Mean (95% CI) , p-value compared with placebo					
Day 29	-34.5 (-52.60, -- 16.49) ^a p=0.0005	-35.6 (-52.84, - 18.29) p=0.0002	-31.3 (-48.74, -13.83) p=0.0009	-13.2 (-30.51, 4.11) p=0.1304	
Glucose AUC ₀₋₄ Weighted Mean (mg/dL)					
Mean Baseline (SD)	230 (45)	271 (56)	225 (47)	266 (57)	240 (48)
Change from baseline: Mean (95% CI)					
Day 29	-42.24 (-63.32, -21.17) ^a	-67.09 (-90.57, -43.60)	-33.10 (-46.94, -19.26)	-26.87 (-64.53, 10.79)	7.31 (-20.99, 35.61)
Placebo adjusted change from baseline: Mean (95% CI) , p-value compared with placebo					
Day 29	-51.6 (-79.90, -- 23.39) ^a p=0.0007	-64.5 (-92.37, - 36.66) p<0.0001	-45.2 (-72.56, -17.74) p=0.0020	-25.9 (-53.60, 1.77) p=0.0656	
Fasting Insulin (pM)					
Mean Baseline (SD)	154 (160)	107 (78)	272 (410)	100 (59)	213 (308)
Change from baseline: Mean (95% CI)					
Day 29	-43.71 (-136.00, 48.57) ^a	3.00 (-31.55, 37.55)	-93.25 (-252.86, 66.36)	-2.00 (-49.30, 45.30)	-38.63 (-187.07, 109.82)
Insulin AUC ₀₋₄ Weighted Mean (pM)					
Mean Baseline (SD)	259 (118)	168 (87)	351 (429)	206 (112)	291 (220)
Change from baseline: Mean (95% CI)					
Day 29	36.69 (-33.86, 107.23) ^a	18.62 (-11.95, 49.18)	-48.13 (-158.68, 62.41)	0.52 (-47.41, 48.45)	-9.19 (-39.36, 20.99)
Fasting Glucagon (pM)					
Mean Baseline (SD)	48 (19)	28 (15)	37 (45)	85 (55)	52 (36) ^a
Change from baseline: Mean (95% CI)					
Day 29	-0.37 (-16.72, 15.99) ^a	-3.29 (-5.72, -0.86)	-13.72 (-40.77, 13.33)	-13.02 (-32.44, 6.41) ^a	-3.16 (-12.27, 5.95) ^a
Glucagon AUC ₀₋₄ Weighted Mean (pM)					
Mean Baseline (SD)	48 (26)	28 (13)	43 (59)	87 (68)	53 (35) ^a
Change from baseline: Mean (95% CI)					

Day 29	-0.37 (-16.72, 15.99) ^a	-3.29 (-5.72, -0.86)	-13.72 (-40.77, 13.33)	-13.02 (-32.44, 6.41) ^a	-3.16 (-12.27, 5.95) ^a
Fasting C-peptide (pM)					
Mean Baseline (SD)	619 (357)	272 (179)	626 (588)	483 (128)	570 (362)
Change from baseline: Mean (95% CI)					
Day 29	-129.00 (-303.90, 45.90) ^a	44.13 (-45.89, 134.14)	-34.00 (-414.31, 346.31)	-23.63 (-97.30, 50.05)	-59.38 (-282.36, 163.61)
C-peptide AUC ₀₋₄ Weighted Mean (pM)					
Mean Baseline (SD)	1223 (709)	611 (298)	1104 (653)	863 (359)	917 (303)
Change from baseline: Mean (95% CI)					
Day 29	157.66 (-128.18, 443.50) ^b	85.13 (-43.29, 213.54)	-121.62 (-469.91, 226.68) ^a	4.03 (-116.97, 125.03)	3.39 (-163.46, 170.24)
a: n=7 b: n=6					
Secondary Outcome Variable(s):					
	Doses of GSK716155				Placebo N=8
	15 mg weekly N=8	30 mg weekly N=8	50 mg biweekly N=8	100 mg monthly N=8	
Free Fatty Acids (mEq/L)					
Change from baseline: Mean (SD)					
Day 29	-0.13 (0.19) ^a	-0.11 (0.11)	-0.18 (0.15)	0.10 (0.21)	-0.10 (0.07)
Glycosylated albumin (%)					
Change from baseline: Mean (SD)					
Day 29	-2.99 (1.38) ^a	-4.14 (1.45)	-2.78 (2.31)	-2.09 (2.69)	0.44 (1.68)
Adiponectin (mcg/mL)					
Change from baseline: Mean (SD)					
Day 29	-0.04 (0.79) ^a	0.35 (1.58)	-0.00 (0.90)	-1.05 (11.44)	0.54 (1.46)
HbA _{1c} (%)					
Change from baseline: Mean (SD)					
Day 29	-0.66 (0.11) ^a	-0.71 (0.29)	-0.66 (0.34)	-0.66 (0.65)	-0.09 (0.51)
Day 43	-0.80 (0.20) ^a	-0.79 (0.21)	-0.65 (0.38)	-0.61 (0.69)	0.06 (0.63)
Placebo adjusted change from baseline: Mean (95% CI), p-value compared with placebo					
Day 29	-0.58 (-1.02, -- 16.49) ^a p=0.0129	-0.57 (-1.01, -0.13) p=0.0120	-0.63 (-1.07, -0.19) p=0.0061	-0.51 (-0.95, -0.07) p=0.0253	
Day 43	-0.87 (-1.36, -- 0.39) ^a p=0.0009	-0.78 (-1.26, -0.30) p=0.0022	-0.79 (-1.27, -0.31) p=0.0019	-0.59 (-1.07, -0.10) p=0.0184	
a: n=7					

Safety Results:

	Doses of GSK716155				Placebo N=8
	15 mg weekly N=8	30 mg weekly N=8	50 mg biweekly N=8	100 mg monthly N=8	
Most Frequent Adverse Events On-Therapy: n (%)					
Subjects with any AE(s), n(%)	3 (38)	1 (13)	1 (13)	6 (75)	3 (38)
Flatulence	0	0	0	3 (38)	1 (13)
Nausea	1 (13)	0	1 (13)	2 (25)	0
Vomiting	0	0	0	3 (38)	0
Upper respiratory tract infection	2 (25)	0	0	1 (13)	0
Abdominal pain	1 (13)	0	0	1 (13)	0
Serious Adverse Events - On-Therapy: Deaths, non-fatal SAEs or withdrawal due to AEs were not observed.					
Clinical laboratory tests, vital signs, 12-lead electrocardiogram: There was no clinically significant laboratory abnormalities, change in vital signs, and findings in ECG results during the study.					

Conclusion:

AEs occurred 2 and more subjects in any groups of GSK716155-treated population were flatulence, vomiting, nausea in 100 mg monthly group and upper respiratory tract infection in 15 mg weekly group. Deaths, non-fatal SAEs or withdrawal due to AEs were not observed. In addition to the planned PK summaries, a population analysis was performed to characterize PK parameters for GSK716155 in the current study. The median t_{1/2} of GSK716155 was 5.3 days and ranged from 4.6 to 5.9 days across subjects. GSK716155 had a plasma CL/F of 68.7 mL/hr, and V/F of 12.6 L. Fasting Plasma Glucose at Day 29 was significantly improved in 15 mg weekly (-34.5 mg/dL, p=0.0005), 30 mg weekly (-35.6 mg/dL, p=0.0002), and 50 mg biweekly (-31.3 mg/dL, p=0.0009) groups, except 100 mg monthly group (-13.2 mg/dL, p=0.1304), compared to placebo. Reductions in HbA_{1c} at Day 29 and Day 43 were statistically significant in 15 mg weekly (Day 29: -0.58%, p=0.0129, Day 43: -0.87%, p=0.0009), 30 mg weekly (Day 29: -0.57%, p=0.0120, Day 43: -0.78%, p=0.0022), 50 mg biweekly (Day 29: -0.63%, p=0.0061, Day 43: -0.79%, p=0.0019), and 100 mg monthly (Day 29: -0.51%, p=0.0253, Day 43: -0.59%, p=0.0184) groups compared to placebo. Other PD parameters for GSK716155 showed modest reductions of glucagon, free fatty acids levels, and glycosylated albumin that were not in dose dependent fashion. Insulin, C-peptide or adiponectin showed no clinically significant effect/change.

Publications: None