Synopsis

Identifier: RM2007/00761/00 **Study Number:** KG2105255

Title: A Dose-Ranging Study of GSK189075 versus Placebo in the Treatment of Type 2 Diabetes Mellitus in Treatment-Naïve Subjects.

Investigator(s): This was a multicenter study.

Study center(s): This study was conducted at 121 centers, of which 95 randomized subjects, in 18 countries (9 European and 8 International countries, and the United States).

Publication(s): None

Study Period: 10 January, 2007 – 03 March, 2008

Phase of Development: IIB

Objectives: The primary objective of this study was to determine the dose response and efficacy of a range of twice daily (BID) doses of GSK189075 (remogliflozin etabonate) and 30 mg pioglitazone (PIO; once daily) versus placebo on the reduction of glycosylated hemoglobin (HbA1c).

Secondary objectives were to evaluate:

- the safety and tolerability of a range of BID doses of GSK189075 and 30 mg PIO;
- the effect of a range of BID doses of GSK189075 and 30 mg PIO, compared with placebo, on additional glycemic/pharmacodynamic parameters in a fasted state (plasma glucose, serum insulin, serum fructosamine, serum lipid profiles);
- the effect of a range of BID doses of GSK189075 and 30 mg PIO, compared with placebo, on glycemic/pharmacodynamic profiles during a 75 g oral glucose tolerance test (OGTT; plasma glucose/insulin/c-peptide over a 2-hour period) in a sub-group of subjects; and
- the effect of a range of BID doses of GSK189075 and 30 mg PIO, compared with placebo, on body weight and waist circumference.

Pharmacokinetic objectives were to characterize:

- the population-derived PK parameters of GSK189075, GSK189074, and GSK279782 in all subjects; and
- the exposure and HbA1c response relationship.

Exploratory objectives were to:

- perform a retrospective evaluation of stored plasma and serum samples on exploratory pharmacodynamic (PD) endpoints (possibly including, but not limited to, adiponectin, leptin, glucagon-like peptide [GLP-1]). These stored samples may also be used to evaluate biological responses related to type 2 diabetes mellitus (T2DM) OKor medically related conditions.
- perform a retrospective evaluation of stored whole blood samples using transcriptome analysis or other RNA expression research, stored plasma samples using proteomic analysis, and stored serum samples using metabolomic analysis to examine the molecular profile of blood samples for factors that may influence biological and therefore clinical responses to GSK189075, if deemed appropriate. These stored samples may also be used to evaluate biological responses related to T2DM or medically related conditions.
- assess the effect of GSK189075 and PIO on insulin sensitivity and β-cell function as measured by the Quantitative Insulin Sensitivity Check Index (QUICKI) and the homeostasis model assessment (HOMA; HOMA-%S and HOMA-%B); and
- assess the effect of GSK189075 and PIO on subject recorded outcomes of hunger and satiety, thirst, frequency and bother of micturition and nocturia, and treatment satisfaction.

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled, PIO-controlled, parallel-group, dose-ranging study that evaluated the efficacy, safety and tolerability of five GSK189075 dose regimens BID (50 mg, 100 mg, 250 mg, 500 mg, or 1000 mg) for 12 weeks in treatment-naïve subjects with T2DM. The study comprised three periods: Screening, Treatment, and Follow-up. Total duration of participation in the study for an individual subject was approximately 16 weeks.

Number of subjects: The number of subjects randomized in each treatment group and their study disposition is provided in the table on the following page. Of the 336 subjects randomized (47 to 49 per group), 334 received at least one dose of double-blind study medication and were included in the Safety Population. Overall, 288 of 334 subjects (86%) in the Safety population completed the study.

Demographics: As shown in the table on the following page, the majority of subjects was male (58% of the ITT Population). A majority of the subjects were White/Caucasian (86%) of European heritage (86%), not Hispanic/Latino (76%), with a mean age of 55 years (83% <65 years of age). Mean body weight was 87.3 kg and mean BMI was 31 kg/m^2. Mean baseline HbA1c ranged from 8% to 8.2% across groups.

	Number of Subjects, n (%)							
Subject Disposition		GSK189075 (BID)					PIO (once daily)	
	Placebo	50 mg	100 mg	250 mg	500 mg	1000 mg	30 mg	Total
Entered Screening Period								930
Randomized	48	47	48	49	48	48	48	336
Safety Population	48	47	48	48	48	47	48	334
Completed	33 (69)	42 (89)	43 (90)	38 (79)	44 (92)	42 (89)	46 (96)	288 (86)
Prematurely Withdrawn[a]	15 (31)	5 (11)	5 (10)	10 (21)	4 (8)	5 (11)	2 (4)	46 (14)
Reason for premature withdrawal								
Adverse event	0	2 (4)	0	1 (2)	2 (4)	2 (4)	0	7 (2)
Lost to Follow-up	1 (2)	1 (2)	1 (2)	2 (4)	1 (2)	0	0	6 (2)
Protocol violation	3 (6)	1 (2)	1 (2)	0	1 (2)	1 (2)	1 (2)	8 (2)
Subject withdrew consent	4 (8)	0	1 (2)	5 (10)	0	1 (2)	1 (2)	12 (4)
Lack of efficacy	3 (6)	1 (2)	0	0	0	0	0	4 (1)
Liver function test abnormality[b]	0	0	1 (2)	0	0	0	0	1 (<1)
Serum creatinine increase from baseline	0	0	0	0	0	1 (2)	0	1 (<1)
Other	4 (8)[c]	0	1 (2)	2 (4)[d]	0	0	0	7 (2)

a. Percentage of withdrawals based on Safety Population
b. The LFT was pre-therapy, and the subject was withdrawn due to a viral infection.
c. Reason for withdrawal for 3 subjects inadvertently misclassified, should have been classified as: 1 lack of efficacy, 1 lost to follow-up, and 1 protocol violation.
d. Reason for withdrawal for one subject should have been classified as protocol violation.

Demographic Characteristic		GSK189075 (BID)					PIO (once daily)	
ITT Population	Placebo N=47	50 mg N=46	100 mg N=44	250 mg N=45	500 mg N=48	1000 mg N=47	30 mg N=47	Total N=323
Age, years: Mean (SD)	55.8 (9.75)	54.2 (9.11)	56.0 (8.30)	45.0 (9.57)	54.3 (9.24)	52.4 (9.03)	54.5 (9.55)	54.6 (9.23)
Sex, n (%): Female	18 (38)	22 (48)	15 (34)	16 (36)	20 (43)	20 (43)	24 (51)	135 (42)
Male	29 (62)	24 (52)	29 (66)	29 (64)	27 (57)	27 (57)	23 (49)	198 (58)
Race, n (%)								
White	40 (91)	36 (82)	32 (76)	38 (88)	41 (93)	40 (89)	38 (84)	265 (86)
Other	1 (2)	2 (5)	3 (7)	1 (2)	2 (5)	1 (2)	3 (7)	13 (4)

Diagnosis and main criteria for inclusion: Male or female outpatients between 18 and 70 years of age (inclusive) who had a documented diagnosis of T2DM, were treatment-naïve (i.e., had not taken insulin or any oral or injectable anti-diabetic medication in the past 3 months and had not taken a glucose lowering agent for ≥4 weeks at any time in the past, or subjects who were newly diagnosed and treated with diet and exercise for a minimum of 6 weeks), and had an HbA1c of ≥7.0% and ≤9.5% at Visit 1. The majority of subjects were randomized prior to Protocol Amendment 3 (dated 31 August, 2007). Amendment 3 changes included lowering the HbA1c inclusion criterion from ≥7.5% to ≥7.0% and allowing women of childbearing potential to enter the study provided they used an approved method of birth control (i.e., intrauterine device, condom or occlusive cap [diaphragm or cervical/vault caps] plus spermicidal agent). Subjects with HbA1c <7.5% required a fasting fingerstick glucose ≥7 mmol/L (126 mg/dL) at Week 0 prior to randomization. Subjects with a glomerular filtration rate <60 mL/min at Visit 1 were excluded.

Treatment administration: After a 2-week Screening period , at Visit 3 (Week 0), eligible subjects were randomized equally into one of five GSK189075 treatments groups (50 mg, 100 mg, 250 mg, 500 mg, or 1000 mg BID), a PIO (30 mg once daily) treatment group, or placebo for 12 weeks. The randomization was stratified based on subject's participation (yes/no) in the OGTT assessments. This was for the administrative purpose of creating balance across treatment groups for the OGTT analyses (i.e., it was not a prognostic stratification variable).

Criteria for evaluation: The primary efficacy endpoint was change from baseline (Week 0) in HbA1c (%) at Week 12.

Secondary efficacy endpoints were:

- Change from baseline in HbA1c (%) at Weeks 4 and 8;
- Change from baseline to Week 12 in FPG, fructosamine, and fasting insulin;
- Proportion of subjects at Week 12 with: HbA1c ≤6.5% and <7.0%; FPG <7 mmo/L (126 mg/dL) and <7.8 mmol/L (140 mg/dL); FPG <5.5 mmol/L (100mg/dL); and a decrease from baseline of HbA1c ≥0.7% and FPG ≥1.7 mmol/L (30 mg/dL).
- Change from baseline to Week 12 in lipid parameters (triglycerides [TG], total cholesterol [TC], low-density lipoprotein cholesterol [LDL-c], and high-density lipoprotein cholesterol [HDL-c]);
- Change from baseline to Week 12 in body weight (kg).
- Change from baseline to Week 12 in waist circumference (cm).

Other exploratory efficacy endpoint(s): Percent change from baseline to Week 12 in insulin sensitivity and β-cell function as measured by the HOMA model and QUICKI index.

Safety Parameters: Changes in physical examination, vital signs (blood pressure and heart rate), clinical laboratory tests, adverse events (AEs), hypoglycemic events, and electrocardiograms. Adverse events of special interest included: urinary tract infections, genital fungal infections (vaginal infections [females] and balanitis [males]), and renal and urinary events.

Pharmacodynamics: Change in plasma glucose, insulin, and C-peptide during a 2-hr OGTT. Change from baseline in 24-hour urine creatinine clearance, 24-hour urine glucose excretion, and 24 hour urine glucose excretion corrected for filtered load.

Health Outcomes: The effect of the study treatment on subject reported heath outcomes was assessed using four subject self-administered instruments: the Hunger, Craving and Fullness (HCF) Questionnaire; the Thirst Visual Analog Scale (VAS); the Overactive Bladder Questionnaire-Short Form (OAB-q SF); and the Satisfaction with Oral Anti-Diabetic Agents Questionnaire (SOADAS).

Population pharmacokinetics, and exposure and HbA1c response relationship will be reported separately.

Statistical Methods: The primary comparison of interest was to identify the BID GSK189075 NOSTASOT (no statistical evidence of trend) dose for change from baseline in HbA1c at Week 12 and was supplemented by comparisons between each GSK189075 treatment group and placebo. The population for efficacy analysis was the Intent-to-Treat (ITT) Population (with last observation carried forward [LOCF]), which consisted of all randomized subjects who received at least one dose of study medication, had a baseline assessment and at least one corresponding On-Therapy (scheduled or unscheduled) efficacy assessment. In addition, sensitivity analyses were performed on the ITT without LOCF and Per-protocol (PP) Populations. An investigation into the dose-response curve was also conducted.

Change from baseline in HbA1c at Week 12 was analyzed using Tukey's trend test procedure to identify the highest dose that did not show statistically significant evidence of trend in dose response (i.e., determine the NOSTASOT dose). This step-down procedure protected the overall two-sided significance level which was set at 5%. The procedure was implemented using a sequence of ordinal contrasts within an analysis of covariance (ANCOVA). The ANCOVA model included terms for treatment group and baseline HbA1c. Secondary analyses were not adjusted for multiplicity; therefore caution should be used in the interpretation of p-values for secondary analysis endpoints.

The model-adjusted mean change from baseline in HbA1c at Week 12 was presented for each treatment group. The p-value for the trend test was presented. This was supplemented, for information purposes with estimates of the treatment difference between each GSK189075 dose and placebo, together with 95% confidence intervals (CIs) and two-sided p-values (5% level). The PIO group was tested against placebo using a 2-sided test with a 5% level of significance, but was not compared with GSK189075. Results of the test between PIO and placebo were used for benchmarking purposes.

Comparison of the change in FPG, fructosamine, and fasting insulin from baseline at Week 12 between each active treatment group and placebo was assessed using ANCOVA including terms for treatment and baseline measurement. Point estimates, p-values and corresponding 95% CIs for treatment differences versus placebo were calculated.

Differences between each GSK189075 treatment group and placebo in the proportion of subjects who achieved each of the following at Week 12: HbA1c (≤6.5%, <7%) targets; FPG (<7 mmol/L [126 mg/dL], <7.8 mmol/L [140 mg/dL]) targets; decrease from baseline in HbA1c ≥0.7%; and decrease from baseline in FPG ≥1.7 mmol/L [30 mg/dL]), respectively, were assessed based on a logistic regression model with terms for treatment and baseline measurement. A summary was also provided for the proportion of subjects who achieved the FPG target of <5.5 mmol/L (100 mg/dL).

For all lipid (TGs, TC, LDL-c, HDL-c), HOMA (insulin sensitivity and β-Cell function) and QUICKI assessments, the percentage change from baseline (based on log-transformed data) was summarized at each treatment week where data were collected. Statistical analysis of change from baseline using log-transformed values for HOMA (and for lipids as post-hoc analyses) was performed at Week 12, using ANCOVA with terms for treatment and log-transformed baseline. Point estimates, p-values, and corresponding 95% CIs for treatment ratios to placebo were calculated.

For body weight and waist circumference, the change from baseline was summarized at each treatment week the data were collected. Statistical analysis for body weight was performed at Week 12, using ANCOVA with terms for treatment and baseline measurement. Point estimates, p-values, and corresponding 95% CIs for treatment differences to placebo were calculated.

Analyses of clinical safety were conducted using the Safety Population which consisted of all subjects who received at least one dose of study medication. Adverse events were summarized by the number and percentage of subjects reporting AEs. Laboratory values and vital signs were summarized. Change from baseline in systolic blood pressure (BP) and diastolic BP at Week 12 were analyzed using ANCOVA as for the efficacy endpoints.

For OGTT assessments, the OGTT population with LOCF was used. The difference between each active treatment group and placebo were assessed in terms of change from Baseline (Week 0) at Week 12 in the weighted means based on AUC during a 2-hour OGTT for plasma glucose, insulin and C-peptide following OGTT. An ANCOVA model was used with change from baseline in weighted means as the dependent variable, allowing for the effects due to baseline and treatment. Weighted means derived at Baseline (Week 0) served as baseline values. Point estimates, p-values, and corresponding 95% CIs for treatment differences from placebo were calculated. Values and change from baseline to Week 12 for creatinine clearance and percent of filtered glucose excreted in urine (24-hour sample) was summarized by treatment group.

For Health Outcomes assessment, the Health Outcomes population with LOCF was used. Analysis of covariance (ANCOVA) was used to assess change from baseline at Week 12 for derived endpoints for HCF, OAB-q SF, and VAS assessments, whereas analysis of variance was used to assess Total Score at Week 12 for the SOADAs assessment.

Summary:

Efficacy:

- There were broadly dose-dependent improvements in glycemic control on GSK189075. At week 12 all GSK189075 doses produced a statistically significant trend in dose response for change from baseline in HbA1c ($p<0.001$). Additionally, these improvements were generally clinically and statistically significant ($p<0.05$) for each GSK189075 dose compared to placebo, as follows:
    - HbA1c decrease of 0.73% on 50mg and 0.64% to 1.07% across 100 mg to 1000 mg (and 0.76% on PIO 30 mg);
    - HbA1c rates for achievement of <7% target of 42% to 64%;
    - HbA1c rates for decrease from baseline of ≥0.7% of 63% to 87%;
    - FPG decrease of 0.87 to 2.07 mmol/L;
    - FPG rates for achievement of target <7.0 mmol/L and <7.8 mmol/L of 35% to 48% and 52% to 74%, respectively;
    - FPG rates for decrease from baseline of ≥1.7 mmol/L of 33% to 65%;
    - Fructosamine (corrected) decrease of 39.6 to 56.6 mcmol/L;
- There were minimal non-significant decreases in fasting insulin in GSK189075 groups (and PIO), but the analysis was sensitive to outliers.
- There were broadly dose-dependent statistically significant improvements in HOMA-%B of 20.8% to 46.3% on GSK189075 compared with placebo and significant improvements of 22.9% to 28.2% on HOMA-%S at 100 mg, 500 mg, and 1000 mg GSK189075 doses.
- There were generally non-dose ordered changes in lipid parameters, which at Week 12 compared to baseline on GSK189075 were as follows:
    - TG increase of 8% on 100 mg and decrease of 3.8% to 13.7% at other doses; increase on placebo of 7.5%;
    - TC increase of 5.2% to 7.1%; increase on placebo of 3.7%;
    - HDL-c increase of 3.7% to 12.2%; decrease on placebo of 2.1%;
    - LDL-c increase of 6.0% to 11.5%; increase on placebo of 2.1%; and
    - Little or no change in the LDL-c /HDL-c ratio.
- There were broadly dose-dependent statistically significant decreases in body weight at all GSK189075 doses versus placebo (1.36 to 3.51 kg) at Week 12, whereas weight increased significantly with PIO 30 mg (1.26 kg).

- The effect of PIO on the various glycemic parameters was consistent with historical data and current prescribing information.

Safety:

- Overall GSK189075 was well tolerated based on the short-term AE profile:
  - Similar incidence of On-Therapy AEs across treatment groups; 35% to 47% on GSK189075, 38% on placebo, and 46% on PIO;
  - No serious AEs reported during the study;
  - Low incidence of withdrawals due to AEs (0 to 6% on GSK189075, no cases on placebo or PIO); and
  - Low incidence of the most commonly reported AEs: constipation (0 to 6%) on GSK189075, diarrhea (6%) on placebo, and headache (10%); UTI (8%), and diarrhea (6%) on PIO.
- There was a low incidence of the adverse events of special interest on GSK189075:
  - Renal and urinary: 7% versus 6% on placebo and PIO;
  - UTI: 1% versus none on placebo and 8% on PIO;
  - Genital fungal events: 3% versus none on placebo and PIO; and
  - Diarrhea-like events: 2% versus 6% on placebo and PIO.
- Changes from baseline were observed in some renal parameters on GSK189075:
  - Urine volume increased, ranging from 0.1 to 0.5 L/24 hours;
  - Serum creatinine and eGFR showed no consistent changes. However creatinine clearance decreased by up to 24 ml/min (1000 mg BID) at Week 12;
  - BUN increased by up to 0.8 mmol/L at Week 12;
  - Urinary NAG corrected for creatinine increased by Week 2 (up to 0.887 μmol/L) and progressively declined thereafter; and
  - Albumin and total protein tended to increase by Week 2 and fluctuated thereafter.
- Changes from baseline were observed in some serum electrolytes on GSK189075 with urine electrolytes generally showing a similar trend.
  - By Week 2, serum magnesium and phosphorus increased (up to 0.069 mmol/L, and 0.99mmol/L respectively), and uric acid decreased (up to 51.2 μmol/L).
  - Serum bicarbonate, sodium, potassium, calcium or chloride showed no significant changes.
- Hct and Hgb showed a non-dose ordered increase from baseline on GSK189075 (up to 0.019 and 6.5 g/L, respectively, at Week 12), returning to within baseline levels post-therapy.
- Liver function tests showed no clinically significant changes.

- Vital signs (heart rate, blood pressure or ECG recordings) showed no significant changes.
- The overall incidence of hypoglycemia was low: 2 subjects on GSK189075, 1 on placebo, and none on PIO.
- The safety profile of PIO was consistent with historical data and current prescribing information.

Summary of Most Common (>=5% in Any Group) On-Therapy Adverse Events by Treatment (Safety Population)

	Number of Subjects, n (%)							
		GSK189075 (BID)					Pio (once daily)	GSK189075
	Placebo N=48	50 mg N=47	100 mg N=48	250 mg N=48	500 mg N=48	1000 mg N=47	30 mg N=48	Subtotal N=238
Subjects with any event	18 (38)	18 (38)	17 (35)	19 (40)	18 (38)	22 (47)	22 (46)	94 (39)
Headache	0	1 (2)	2 (4)	1 (2)	2 (4)	1 (2)	5 (10)	7 (3)
Diarrhea	3 (6)	1 (2)	1 (2)	1 (2)	0	2 (4)	3 (6)	5 (2)
Constipation	0	1 (2)	1 (2)	2 (4)	3 (6)	0	0	7 (3)
Urinary tract infection	0	2 (4)	1 (2)	0	0	0	4 (8)	3 (1)

Pharmcokinetics:

- The GSK189075 drug exposure profiles demonstrated appropriate exposure in this study and generally showed increasing concentrations with increasing dose.

Pharmacodynamics:

- Statistically significant decreases in post OGTT AUC (0-2 hour) weighted mean glucose levels from baseline were observed at all GSK189075 doses (non dose-ordered) and PIO at Week 12 compared with placebo.
- There was no consistent evidence of statistically significant difference in change from baseline at Week 12 in the GSK189075 groups (or for PIO) compared with placebo for post OGTT:
    - AUC(0-2 hour) weighted mean for plasma insulin levels.
    - AUC(0-2 hour) weighted mean for plasma C-peptide levels.
- Increased urine glucose excretion from baseline was observed at all GSK189075 doses (range: 61 to 96 g/24 hours) and was broadly dose ordered. Slight decreases were seen in the placebo and PIO groups.

Health Outcomes:

- There was no consistent evidence of statistically significant differences in change from baseline at Week 12 in the GSK189075 groups (or for PIO) compared with placebo for the:
    - Thirst VAS assessments
    - Over Active Bladder questionnaire, either on symptom bother scale, or the HRQL (health related) scale.
    - Hunger, Craving Fullness (HCF) assessments.
- Mean values for the Satisfaction with Oral Anti-Diabetic (SOADAs) questionnaire were higher at all GSK189075 doses (and PIO) compared with placebo. Changes were not dose-ordered and were statistically significant in the 50 mg and 1000 mg GSK189075 groups (and PIO).

Conclusions:

- GSK189075 broadly demonstrated a dose-dependent improvement in glycemic control as demonstrated by clinically and statistically significant decreases in HbA1c, fasting plasma glucose, and post-OGTT glucose. There was also a significant reduction in weight with GSK189075.
    - Increases in HDL-c and LDL-c were noted on GSK189075, but there was no significant change in the LDL-c/HDL-c ratio.
- No significant safety or tolerability issues were identified with GSK189075.
    - No serious adverse events were reported, and there were very few adverse events leading to withdrawal. There were also very few adverse events related to UTI, genital fungal infections, renal and urinary, and diarrhea-like gastrointestinal events.

- Hct and Hgb showed a non-dose ordered increase from baseline on GSK189075, which returned to within baseline levels Post-therapy.
- There were no clinically significant changes in liver function tests or serum electrolytes. Small increases in serum magnesium and phosphate and a decrease in serum uric acid were noted in the GSK189075 groups.
- BUN showed a non-dose ordered increased from baseline on GSK189075, although there were no consistent changes in serum creatinine or eGFR. There was increased urine volume, associated with increased glucose excretion.

Date of Report: September 2008