Synopsis

Identifier: RM2008/00212/00 **Study Number:** KG2110375

Title: A Once-Daily Dose-Ranging Study of GSK189075 Versus Placebo In The Treatment of Type 2 Diabetes Mellitus in Treatment-Naïve Subjects.

Investigator(s): This was a multi-center study.

Study center(s): This study was conducted at 130 centers, of which 86 randomized subjects, in 14 countries (9 European, 3 International countries, Canada, and the United States).

Publication(s): None

Study Period: 17 August, 2007 – 5 June 2008

Phase of Development: IIB

Objectives: The primary objective of this study was to determine the dose response and efficacy of a range of once daily doses of GSK189075 (remogliflozin etabonate) versus placebo on the change from baseline in HbA1c.

Secondary Objectives

- To evaluate, alongside once daily dosing, the efficacy of one twice daily (BID) dose of GSK189075, and 30 mg pioglitazone (PIO, once daily) versus placebo, on the change from baseline in HbA1c.
- To evaluate the safety and tolerability of a range of once daily doses of GSK189075 versus placebo alongside one BID dose of GSK189075 and 30 mg PIO.
- To evaluate the effect of a range of once daily doses of GSK189075 versus placebo, alongside one BID dose of GSK189075 and 30 mg PIO, on additional glycemic/PD parameters (i.e., FPG, fructosamine, 24-hour urine glucose excretion, 24-hour urine creatinine, and lipid profiles).
- To evaluate the effect of a range of once daily doses of GSK189075 versus placebo, alongside one BID dose of GSK189075 and 30 mg PIO on body weight.

Methodology: This was a dose-ranging study that evaluated the efficacy, safety, and tolerability of four once daily doses (100 mg, 250 mg, 500 mg, and 1000 mg) and one BID dose (250 mg) of GSK189075, and a once daily dose of PIO, 30 mg, compared with placebo, administered as monotherapy over 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 252 subjects randomized (35 to 37 per group), 250 received at least one dose of double-blind study medication and were included in the Safety Population. Overall, 211 of 250 subjects (84%) in the Safety population completed the study.

Demographics: As shown in the table on the following page, there was a similar proportion of female and male subjects (51% and 49% of the ITT population, respectively); however, the proportion of female subjects across groups ranged from 37% to 68%. The majority of subjects were White/Caucasian (66%) and not Hispanic/Latino (63%), with a mean age of 53 years (85% <65 years of age). Mean body weight was 86 kg and mean BMI was 31 kg/m^2. Mean baseline HbA1c ranged from 7.8% to 8.2% across groups.

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 after Protocol Amendment 2 (dated 04 September, 2007). Amendment 2 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), and broadened body mass index (BMI) exclusion criterion from ≤25 or ≥40 kg/m^2 to ≤22 or ≥43 kg/m^2. 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 (100 mg, 250 mg, 500 mg, or 1000 mg once daily, or 250 mg BID), a PIO (30 mg once daily) treatment group, or placebo for 12 weeks. Randomization was stratified by region (Europe, International, and North America)

		GSK189075 (Once daily)				GSK189075 (BID)	PIO (once daily)	
Subject Disposition	Placebo	100 mg	250 mg	500 mg	1000 mg	250 mg	30 mg	Total
Entered Screening Period								822
Randomized	36	37	35	36	36	37	35	252
Safety Population	36	37	34	36	36	36	35	250
Completed	30 (83)	30 (81)	27 (79)	32 (89)	31 (86)	31 (86)	30 (86)	211 (84)
Prematurely Withdrawn[a]	6 (17)	7 (19)	7 (21)	4 (11)	5 (14)	5 (14)	5 (14)	39 (16)
Reason for premature withdrawal								
Adverse event	0	1 (3)	3 (9)	0	1 (3)	1 (3)	1 (3)	7 (3)
Lost to Follow-up	1 (3)	1 (3)	3 (9)	1 (3)[b]	0	0	0	6 (2)
Protocol violation	0	0	0	0	1 (3)	2 (6)	0	3 (1)
Subject decided to withdraw from study	5 (14)	3 (8)	1 (3)	3 (8)	3 (8)	2 (6)	3 (9)	20 (8)
Lack of efficacy	0	0	0	0	0	0	1 (3)	1 (<1)
Liver function test abnormality	0	1 (3)	0	0	0	0	0	1 (<1)
Other	0	1 (3)	0	0	0	0	0	1 (<1)

a. Percentage of withdrawals based on Safety Population

b. [redacted]

Demographic Characteristic		GSK189075 (once daily)				GSK189075 (BID)	PIO(once daily)	
ITT Population	Placebo N=33	100 mg N=37	250 mg N=33	500 mg N=34	1000 mg N=35	250 mg N=35	30 mg N=34	Total N=241
Age, years: Mean (SD)	52.1 (9.64)	53.5 (9.35)	54.3 (9.71)	53.2 (10.88)	54.3 (10.27)	50.2 (10.29)	52.8 (10.18)	52.9 (10.02)
Sex, n (%):Female	19 (58)	19 (51)	14 (42)	23 (68)	13 (37)	20 (57)	15 (44)	123 (51)
Male	14 (42)	18 (49)	19 (58)	11 (32)	22 (63)	15 (43)	19 (56)	118 (49)
Race, n (%)								
White	24 (73)	20 (54)	23 (70)	23 (68)	24 (69)	23 (66)	23 (68)	160 (66)
Other	9 (27)	17 (46)	10 (30)	11 (32)	11 (31)	12 (34)	11 (32	81 (34)

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;
- Change from baseline to Week 12 in fructosamine (corrected);
- Proportion of subjects at Week 12 with: HbA1c ≤6.5%, HbA1c <7.0%; FPG <7 mmo/L (126 mg/dL), FPG <7.8 mmol/L (140 mg/dL); FPG <5.5 mmol/L (100 mg/dL); and a decrease from baseline of HbA1c ≥0.7%; a decrease from baseline of 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); and
- Change from baseline in 24-hour urine creatinine clearance, 24-hour urine glucose excretion, and 24 hour urine glucose excretion corrected for filtered load.

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 infections (vaginal infections [females] and balanitis [males]), and renal and urinary events.

Pharmacodynamics: 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 two subject self-administered instruments: the Thirst Visual Analog Scale (VAS) and the Overactive Bladder Questionnaire-Short Form (OAB-q SF)

Statistical methods: The primary comparison of interest was to identify the once daily 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.

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, and those for GSK189075 250 mg BID were used to evaluate once daily versus twice daily dosing in the same study.

Comparison of the change in FPG and fructosamine 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) 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 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, 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 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 OAB-q SF and VAS assessments

Summary:

Efficacy:

- GSK189075 administered once daily and 250 mg BID demonstrated improvements in glycemic control. At Week 12:
  - There was significant evidence of a trend in dose response for change from baseline in HbA1c above the lowest dose of 100 mg once daily ($p \leq 0.047$);
  - There were statistically significant decreases in HbA1c compared with placebo of 0.56%, 0.66%, and 0.59% on 250 mg and 1000 mg once daily, and on 250 mg BID, respectively. There were non-significant decreases in HbA1c of 0.34% on 100 mg and 500 mg once daily, and of 0.19% on PIO;
  - There were no statistically significant differences from placebo (21%) in the proportion of subjects who achieved HbA1c <7% (29% to 38% on once daily GSK189075, 43% on 250mg BID, and 32% on PIO);
  - A statistically significantly higher proportion of subjects achieved a decrease from baseline in HbA1c of ≥0.7% on 250 mg once daily (56%), 1000 mg once daily (51%), and 250 mg BID (60%) compared with placebo (27%) ; non-significant on PIO (38%);
  - There were statistically significant decreases in FPG at Week 12 compared with placebo of 0.85 to 1.06 mmol/L on once daily dosing (non-significant at 500 mg; 0.64 mmol/L) and of 1.13 mmol/L on 250 mg BID; non-significant on PIO 0.51 mmol/L;
  - A statistically significantly higher proportion of subjects achieved a target of FPG <7.8 mmol/L at Week 12 on 250 mg (58%) and 1000 mg once daily (60%), and on 250 mg BID (63%) compared with placebo (39%); non-significant on PIO (44%);
  - A statistically significantly higher proportion of subjects achieved a decrease from baseline in FPG of ≥1.7 mmol/L on 250 mg (39%) and 1000 mg once daily (40%), and on 250 mg BID (54%) compared with placebo (15%); and 50% on PIO; and
  - Fructosamine (corrected) showed statistically significant decreases of 24.1 to 36.5 μmol/L on once daily dosing; 29.5 μmol/L on 250 mg BID compared with placebo; and non-significant 13.8 μmol/L decrease on PIO.
- There were generally non-dose ordered changes from baseline in lipid parameters with GSK189075, which at Week 12, relative to placebo were:
  - TG: decreases of 1.7% to 14.8% on once daily dosing and 9.0% decrease on 250 mg BID;

- TC: generally no changes (-3.3% to 1.8%) on once daily dosing and an increase of 4.1% on 250 mg BID;
- HDL-c: increases of 1.7% to 7.4% on once daily dosing and an increase of 4.4% on 250 mg BID;
- LDL-c: changes of -8.9% to +3.7% on once daily dosing and an increase of 9.5% on 250 mg BID; and
- Little or no change in LDL-c/HDL-c and TC/HDL-c ratio with GSK189075 once daily or BID dosing.

- There was a statistically significant decrease in body weight versus placebo at Week 12 in all GSK189075 once daily doses above 100 mg of 1.44 to 1.51 kg. There was a non-significant decrease of 1.09 kg on 250 mg BID and an increase of 1.03 kg on PIO.
- The magnitude of effect of PIO on the various glycemic parameters was lower than historical data and current prescribing information.

Safety:

- Overall GSK189075 was well tolerated based on the short-term AE profile:
  - On-Therapy incidence of AEs was 31% to 59% across the GSK189075 once daily groups and 56% on 250 mg BID group, generally higher than on placebo (22%) and PIO (34%) groups.
  - Two serious AEs were reported on GSK189075: cholelithiasis in one subject on 100 mg once daily, and scapula fracture in one subject on 250 mg BID. Neither event was assessed as related to study drug.
  - Low incidence of withdrawals due to AEs (0% to 9%) across GSK189075 once daily groups; 3% each on 250 mg BID and PIO, and no cases on placebo.
  - Low incidence of commonly reported On-Therapy AEs (*a priori* defined as ≥5% in any treatment group, see table on following page). Of these, the following AEs were reported in ≥3 (8% or 9%) subjects in any treatment group; headache (6% to 11%), UTI (3% to 11%), dizziness (0 to 12%) and nasopharyngitis (0 to 8%) across GSK189075 once daily groups; constipation (8%) on 250 mg BID; nasopharyngitis (9%) on PIO; and no events were reported in ≥3 subjects on placebo.
- The incidence of AEs of special interest:
  - Renal and urinary (On-Therapy): 0 to 6% across GSK189075 once daily groups; 3% on 250 mg BID, 6% on PIO, and none on placebo.
  - UTI (On- and Post-Therapy): 3% to 14% across once daily groups, 6% each on 250 mg BID and PIO, and 3% on placebo.
  - Genital infections (On- and Post-Therapy): 3% to 11% (dose-ordered) across once daily groups, 11% on 250 mg BID, and none on PIO or placebo.

  - Diarrhea-like gastrointestinal events (On-Therapy): 0 to 6% across once daily groups, 3% on 250 mg BID, and none on PIO or placebo.

- Changes from baseline were observed in some renal parameters on GSK189075:
  - No consistent increase in urine volume across once daily groups (range -0.1 to 0.4 L/24 hours); and an increase of 0.2 L/24 hours on 250 mg BID;
  - A non dose-ordered increase in serum urea (BUN) evident by Week 2 which remained (with some fluctuation) to Week 12 in the GSK189075 treatment groups (range 0.01 to 0.92 mmol/L once daily, and 0.79 mmol/L 250 mg BID);
  - There was a transient increase in serum creatinine in the 1000 mg once daily group compared with placebo by Week 2. No consistent changes in eGFR were seen; however, there was a trend for reductions in 24-hour creatinine clearance on once daily dosing (median: 0 to 20 mL/min) and decrease on 250 mg BID (median: 14 mL/min);
  - Albumin tended to increase in the 500 mg and 1000 mg once daily groups (up to 1 g/L), and on 250 mg BID group (up to 0.8 g/L);
- Changes from baseline were observed in some serum electrolytes on GSK189075:
  - Non-dose ordered decreases in uric acid across once daily groups (up to 51.2 μmol/L) and on 250 mg BID (up to 34.1 μmol/L);
  - Increase in serum magnesium at once daily doses of 500 mg and 1000 mg (up to 0.056 mmol/L); and 250 mg BID (up to 0.058 mmol/L);
  - Increase in serum phosphorus in the 250 mg BID group (up to 0.087 mmol/L), with no consistent response in the once daily groups; and
  - No significant changes in serum bicarbonate, sodium, potassium, calcium or chloride in all GSK189075 treatment groups.
- Hematocrit (Hct) and hemoglobin (Hgb) showed increases at 500 mg and 1000 mg once daily (of up to 0.018; and 3.8 g/L, respectively) and 250 mg BID (of up to 0.025 and 5.8 g/L, respectively). There were no clinically significant increases in Hct or Hgb at 100 mg and 250 mg once daily.
- There were no clinically significant changes in liver function tests.
- There were no significant changes in vital signs (heart rate, blood pressure, or ECG recordings).
- The overall incidence of hypoglycemia was low; 1 subject each on GSK189075 100 mg and 1000 mg once daily, two subjects on 500 mg once daily, 1 subject on 250 mg BID, and no subjects on PIO or placebo.
- The safety profile of PIO was generally consistent with historical data and current prescribing information.

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

		GSK189075 (Once daily)				GSK189075 (BID)	PIO (once daily)	GSK189075 Subtotal (N=179)
	Placebo N=36	100 mg N=37	250 mg N=34	500 mg N=36	1000 mg N=36	250 mg N=36	30 mg N=35	
Subjects with any event	8 (22)	15 (41)	20 (59)	11 (31)	21 (58)	20 (56)	12 (34)	87 (49)
Headache	0	4 (11)	2 (6)	2 (6)	3 (8)	0	1 (3)	11 (6)
Urinary tract infection	0	2 (5)	1 (3)	1 (3)	4 (11)	2 (6)	2 (6)	10 (6)
Dizziness	0	1 (3)	4 (12)	0	2 (6)	0	0	7 (4)
Influenza	0	2 (5)	2 (6)	2 (6)	0	0	1 (3)	6 (3)
Nasopharyngitis	0	3 (8)	0	0	0	1 (3)	3 (9)	4 (2)
Constipation	0	0	1 (3)	1 (3)	0	3 (8)	0	5 (3)
Vaginal infection	0	1 (3)	0	1 (3)	2 (6)	1 (3)	0	5 (3)
Abdominal pain upper	2 (6)	0	0	0	1 (3)	0	1 (3)	1 (<1)
Diarrhea	0	0	1 (3)	0	2 (6)	1 (3)	0	4 (2)
Upper respiratory tract infection	1 (3)	0	1 (3)	0	2 (6)	0	0	3 (2)
Cough	0	0	0	0	2 (6)	0	0	2 (1)
Rash	0	0	0	0	0	0	2 (6)	0
Tendonitis	0	0	0	0	2 (6)	0	0	2 (1)

Pharmacodynamics: Increased urine glucose excretion from baseline was seen at all GSK189075 once daily dosing groups (range 19 to 70 g/24 hours) and broadly dose-ordered. An increase of 58 g/24 hours was seen in the GSK189075 250 mg BID group. Slight decreases were seen in the placebo and PIO group.

Health Outcomes: There was no consistent evidence of statistically significant differences in change from baseline at Week 12 in the GSK189075 groups either once daily or at 250 mg BID (or for PIO) compared with placebo for the:

- Thirst VAS assessments.
- Over Active Bladder questionnaire, either on symptom severity scale, or the HRQL (health related) scale.

Conclusions:

- GSK189075 administered at doses of 250 mg and 1000 mg once daily and at 250 mg BID demonstrated improvements in glycemic control as reflected by clinically significant decreases in HbA1c and fasting plasma glucose. There was also a significant reduction in body weight above 100 mg once daily, and a non-significant reduction on 250 mg BID.
    - Increases in HDL-c but not generally LDL-c were noted on once daily doses of GSK189075, with no significant change in the LDL-c/HDL-c ratio.
    - Increases in HDL-c and LDL-c were noted on GSK189075 250 mg BID, but there was no significant change in the LDL-c/HDL-c ratio
- No significant safety or tolerability issues were identified with GSK189075 administered once daily.
    - Two serious adverse events were reported (cholelithiasis and scapular fracture), and there were very few adverse events leading to withdrawal. There were also 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 500 mg once daily, 1000 mg once daily, and 250 mg BID, 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 some of the GSK189075 groups.
    - BUN showed a non-dose ordered increase from baseline on GSK189075, although there were no consistent changes in serum creatinine or eGFR. There was increased urine volume, not dose-ordered, associated with increased glucose excretion with some GSK189075 groups.

Date of Report: Decemeber 2008