## Synopsis

**Identifier:** RM2006/00553/00 **Study Number:** KG2104940

**Title:** A double-blind, randomized, placebo-controlled, repeat dose study to compare the safety, tolerability, pharmacokinetics and pharmacodynamics of GSK189075 with GW869682 in subjects with type 2 diabetes mellitus

**Investigators:** (i) [redacted] (ii) [redacted] (iii) [redacted]

**Study Centers:** (i) [redacted] Germany; (ii) [redacted] Germany; (iii) [redacted] USA.

**Publication(s):** None at the time of this report.

**Study Period:** 18 January 2006 - 06 June 2006

**Phase of Development:** II

**Objectives:**

***Primary Objective***

- To evaluate the safety and tolerability of repeated oral administration at 3 dose levels of GSK189075 in subjects with type 2 diabetes mellitus (T2DM).

***Secondary Objectives***

- To compare the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) parameters of GW869682 with GSK189075 in a single, placebo-controlled 2-week repeated oral dose trial.
- To assess the PK profile of GSK189075 and its active entity, GSK189074 as well as metabolites (GSK279782, and GSK333081) in subjects with T2DM.
- To determine the effects of repeated dosing of GSK189075 on pharmacodynamic endpoints including fluid/electrolyte balance, urinary glucose excretion and circulating glucose concentrations in subjects with T2DM.
- To ascertain dose-response and exposure-response relationships of GSK189075, GSK189074 and metabolites with PD endpoints.
- To determine if there were changes in fatty acid composition in the non-polar lipid classes (provided that there were changes in plasma glucose and urine glucose which indicated that it was appropriate to explore this objective).

**Methodology:**

This is a double-blind, randomized, placebo-controlled, repeat-dose study comparing GSK189075 and GW869682 in subjects with T2DM. Individuals were assigned into

three cohorts and randomized to GSK189075, GW869682, or placebo. Separate placebos were provided to match each active compound; thus the study was blinded with respect to each compound, but not between compounds. Each cohort was completed before the next cohort began. The planned GSK189075 doses were 100mg every 12 hours (q12h) (i.e. twice daily [BID]) before breakfast and dinner, 1000mg every 24 hours (q24h) (i.e. once daily [QD]) before breakfast, and 1000mg q12h (i.e. BID) before breakfast and dinner for 12 days. The GW869682 dose was 1000mg given three times daily (TID) before each meal (at 0, 6 and 12 hours) for 12 days.

Safety data were reviewed at the end of dosing for Cohort 1 (GSK189075 100mg BID, GW869682 TID, or placebo), prior to dose escalation for Cohort 2; PK data were not reviewed after Cohort 1 due to prior knowledge of the PK parameters at this dose. Safety data and plasma concentration data were reviewed at the end of dosing for Cohort 2 (GSK189075 1000mg QD, GW869682 TID, or placebo) prior to dose escalation for Cohort 3 (GSK189075 1000mg BID, GW869682 TID, or placebo). PK parameters were evaluated under fed conditions with the first dose on Day 1 and at steady-state on Day 11 of dosing. The PD endpoints included urine glucose excretion (Days -2, 1, and 11) and plasma glucose, insulin and C-peptide profiles measured over 24 hours (Days -2, 1 and 11) and for 6 hours following a 50g oral glucose tolerance test (OGTT) (Days -1 and 12).

Subjects who were eligible to participate and who chose to enroll in the study were removed from their previous oral antidiabetic therapy for a minimum of 2 weeks prior to administration of study drug. After the washout period, subjects were admitted to the clinical research unit 3 nights prior to receiving the first dose of study drug to establish baseline parameters. Subjects remained in the unit until approximately 12 hours after the administration of the last dose of study medication in the dosing period. Following 12 days of dosing, subjects were discharged on Day 13 from the unit provided there were no safety or tolerability concerns. A follow-up safety visit was conducted during the interval from 7 to 14 days after the final dose of study drug was administered. The subjects were involved in the study for approximately 8-10 weeks (from screening to follow-up).

PK assessments were performed on Day 1 following the first dose of each study drug and at steady-state on Day 11 following the morning dose of each study drug. Blood samples for assessing plasma PK of GSK189075 and its metabolites, or plasma PK of GW869682 and its metabolite, were collected on Days 1 and 11 at pre-dose and at the following post-dose times (in hours): 0.25 (immediately before breakfast), 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6 (immediately before the mid-day dose as applicable, 15 minutes before lunch), 8 and 12 (immediately before the evening dose as applicable, and 15 minutes before dinner). Urine samples for determining urinary recovery of the metabolites of GSK189075 were collected at pre-dose and over the post-dose intervals of 0-3, 3-6, 6-9, 9-12, and 12-24 hours. Plasma concentrations of GSK189075 and its three metabolites (GSK189074, GSK279782 and GSK333081), or concentrations of GW869682 and its metabolite GW869683, were measured by two validated liquid chromatography tandem mass spectrometric detection (LC/MS/MS) methods, respectively. Urine concentrations of GSK189074, GSK279782 and GSK333081 were measured with another validated LC/MS/MS method.

**Number of Subjects:**

| | Placebo | 075 100mg BID | 075 1000mg QD | 075 1000mg BID | 682 1000mg TID |
|---|---|---|---|---|---|
| Planned, N | 9 | 9 | 9 | 9 | 9 |
| Randomized, N | 9 | 9 | 9 | 9 | 10 |
| Withdrawn prior to dosing, n (%) | 1 (11) | 0 | 0 | 0 | 1 (10) |
| Positive drug screen | 1 (11) | 0 | 0 | 0 | 0 |
| Triglyceride too high | 0 | 0 | 0 | 0 | 1 (10) |
| Received Study Drug[1], N | 8 | 9 | 9 | 9 | 9 |
| Completed, n (%) | 8 (100) | 9 (100) | 9 (100) | 9 (100) | 9 (100) |
| Withdrawn (any reason), n (%) | 0 | 0 | 0 | 0 | 0 |

075 = GSK189075; 682 = GW869682

1. These subjects comprise the Safety Population.

**Diagnosis and Main Criteria for Inclusion:**

- Subjects with documented T2DM:
  - whose glycated hemoglobin (HbA1c) levels were between 7.0 to 9.0%, inclusive, on monotherapy with at least 850mg per day of metformin. These subjects had to be both willing and medically able to discontinue their diabetic medications from at least 2 weeks prior to the first dose of study medication until the last assessment of the last dosing period of this study, OR
  - whose HbA1c levels were between 7.5 to 9.0%, inclusive, and who were drug naïve or controlled by diet.
- Adult men and women of non-childbearing potential (post-menopausal or surgically sterile) between 30-70 years of age, inclusive. No attempt was made to balance the number of men and women enrolled in the study.
- Body weight ≥50kg for men and ≥45kg for women and body mass index (BMI) within the range 20-35kg/$m^2$, inclusive.
- A negative pre-study urine drug screen to screen for a minimum of the following drugs: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines.
- Negative test results for hepatitis C antibodies or hepatitis B surface antigen or human immunodeficiency virus (HIV) at screening.
- No significant concomitant health problems other than T2DM and otherwise healthy as judged by a responsible physician. No clinically significant abnormality identified on the medical or laboratory evaluation, including 12-lead electrocardiogram (ECG).
- Subjects taking stable regimens of aspirin, angiotensin converting enzyme (ACE) inhibitors, beta-blockers, calcium channel blockers and 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) were allowed if their dose

regimen(s) remained constant throughout the study period. Concurrent usage of prescribed medications other than the medications listed above could be allowed to continue only with sponsor's consent. Stable regimens were those that had not required dosage adjustments within 30 days prior to screening and which remained the same throughout the end of the trial. Concomitant medications were withheld on PK sampling days.

- Additionally, subjects were excluded for significant renal disease as manifested by one of the following:
  - Creatinine clearance < 60mL/min (estimated from serum creatinine (SCr) and demographic data using the MDRD calculation):
  - Urine protein/creatinine (mg/mg) ratio >2.5; or urine albumin concentration ≥ 300μg/mg of creatinine.
  - Known loss of a kidney, either by surgical ablation, injury, or disease.

**Treatment Administration:**

The planned GSK189075 doses were 100mg BID before breakfast and dinner, 1000mg QD before breakfast, and 1000mg BID before breakfast and dinner for 12 days. The GW869682 dose was 1000mg TID before each meal (at 0, 6 and 12 hours) for 12 days. For each cohort, the planned dosing followed the scheme provided in following table:

| *Number of Subjects* | *Dose*[1] | *Number of Tablets per Dose* | *Dosing Frequency* | *Batch Numbers* |
|---|---|---|---|---|
| *Cohort 1 (subjects* [redacted] | | | | |
| *9* | *GSK189075 100mg* | *1 x 100mg* | *BID* | *041030730* |
| *2* | *GSK189075 placebo* | *1* | *BID* | *051094434* |
| *3* | *GW869682 1000mg* | *4 x 250mg* | *TID* | *051095681* |
| *1* | *GW869682 placebo* | *4* | *TID* | *041023061* |
| *Cohort 2 (subjects* [redacted] | | | | |
| *9* | *GSK189075 1000mg* | *4 x 250mg* | *QD* | *051088955; 051104115* |
| *2* | *GSK189075 placebo* | *4* | *QD* | *051089734* |
| *3* | *GW869682 1000mg* | *4 x 250mg* | *TID* | *051095681* |
| *1* | *GW869682 placebo* | *4* | *TID* | *041023061* |
| *Cohort 3 (subjects* [redacted] | | | | |
| *9* | *GSK189075 1000mg* | *4 x 250mg* | *BID* | *051088955; 051104115* |
| *2* | *GSK189075 placebo* | *4* | *BID* | *051089734* |
| *3* | *GW869682 1000mg* | *4 x 250mg* | *TID* | *051095681* |
| *1* | *GW869682 placebo* | *4* | *TID* | *041023061* |

1. Blinding was within each compound and not between compounds.

**Criteria for Evaluation:**

***Primary Endpoint***

- Safety and tolerability: adverse events (AEs) and clinically relevant changes in vital signs (blood pressure and heart rate), electrocardiogram (ECG) parameters, clinical laboratory data (serum electrolytes, fluid balance, and creatinine clearance).

***Secondary Endpoints***

- The plasma PK parameters determined for each analyte (GSK189075, GSK189074, GSK279782, GSK333081, GW869682 and GW869683) on Day 1 and Day 11 included the area under the plasma concentration vs. time curve (AUC) from time zero to the last time point with measurable analyte concentration, AUC(0-t); AUC extrapolated to infinity, AUC(0-∞); AUC over a dosing interval, AUC(0-τ); AUC over a daily (or 24-hour) interval, AUC(0-24); maximum observed plasma concentration (Cmax); time to maximum observed plasma concentration (tmax); and terminal half life (t½). Apparent total body clearance (CL/F) was estimated for GSK189075 and GSK189074. In addition, the metabolite to parent AUC ratios (AUC ratio,m/p) were calculated for GSK189074, GSK279782, GSK333081 and GW869683 on Day 11 using AUC(0-τ) when estimable, or otherwise AUC(0-t) values.
- Urinary excretion data on Day 1 and Day 11 were analyzed for the three metabolites of GSK189075 to determine the amount of metabolites excreted during each urine collection interval, Ae; the cumulative amount excreted over a dosing interval, Ae(0-τ); and the percent of GSK189075 dose recovered in urine as each metabolite, and as all three metabolites. In addition, renal clearance (CLr) was estimated for each of the three metabolites of GSK189075.
- Plasma glucose concentration profiling: fasting plasma glucose, post-OGTT glucose [AUC glucose (0-6h) and weighted mean], total daily glucose [AUC glucose (0-24h) and weighted mean].
- Plasma insulin concentration profiling: fasting plasma insulin, post-OGTT insulin [AUC insulin (0-6h) and weighted mean], total daily insulin [AUC insulin (0-24h) and weighted mean].
- Plasma C-peptide concentration profiling: fasting plasma C-peptide, post-OGTT C-peptide [AUC C-peptide (0-6h) and weighted mean], total daily C-peptide [AUC C-peptide (0-24h) and weighted mean].
- Urine volume, urinary glucose concentration for calculation of urine glucose excretion and % excretion of the filtered glucose load, urinary creatinine concentration.
- Weight, BMI, waist and hip circumference, waist to hip ratio.
- Exploratory endpoints, such as changes in fatty acid composition in the non-polar lipid classes, were to be analyzed provided there were significant pharmacodynamic effects on urine glucose and plasma glucose.

**Statistical Methods:**

***Safety Analyses***

*Ad hoc*, retrospectively-defined comparisons of placebo with each active dose of GSK189075 and GW869682 were assessed in terms of change from baseline for pre-dose blood pressure (systolic and diastolic) during Day 7 to Day 12. The pre-dose blood pressure assessments on Day -2 were used for baseline. This analysis used analysis of covariance (ANCOVA) with the baseline-adjusted parameter as the dependent variable, allowing for effects due to treatment and baseline. The difference in least squares treatment means (LSmeans) and its associated standard error were used to provide the estimated treatment difference and its associated 95% confidence interval (CI).

***Pharmacokinetic Analyses***

Plasma concentration vs. time data of each analyte were analyzed by noncompartmental PK methods using WinNonlin® Version 4.1 to determine PK parameters. The urinary excretion or recovery data for the metabolites of GSK189075 were calculated by Microsoft Excel and WinNonlin 4.1.

Descriptive statistics (including geometric mean and associated 95% confidence interval [CI]) of PK parameters of each analyte on Days 1 and 11 were calculated for each dosing regimen. The accumulation of each analyte from Day 1 to Day 11 following each dosing regimen was assessed by comparing Cmax and AUC(0-$\tau$) between Day 11 and Day 1, using analysis of variance (ANOVA) on $\log_e$-transformed parameter values, with day as a fixed effect and subject as a random effect. The effect of time invariance was assessed by comparing AUC(0-$\tau$) of Day 11 to AUC(0-$\infty$) of Day 1 using ANOVA on $\log_e$-transformed parameter values, with day as a fixed effect and subject as a random effect. Accumulation and time invariance were assessed by parameter ratio between Days (Day 11 vs. Day 1) by exponentiating the difference in the geometric least-squares means (Day 11 - Day 1) and associated 90% CI for each dosing regimen. In addition, t½ and CLr values were compared between Days 1 and 11 for each analyte, as applicable, using ANOVA on $\log_e$-transformed parameter values, as that described for accumulation assessment.

***Pharmacodynamic Analyses***

Comparisons of placebo with each active dose of GW869682 and GSK189075, and of GW869682 dose with each active dose of GSK189075, were assessed in terms of change from baseline for the following PD parameters:

- Fasting plasma glucose (FPG) concentrations on Day 1, Day 11 and Day 12. For FPG, Day -2 was used as the baseline for change from baseline to Day 1 and Day 11, and Day -1 was used as the baseline for change from baseline to Day 12.
- Plasma glucose, insulin and C-peptide AUC(0-6) and AUC(0-24) on Day 1 and Day 11. Day -2 was used as the baseline for these 24-hour plasma PD profiles.
- Post-OGTT plasma glucose, insulin and C-peptide AUC(0-6) weighted mean on Day 12. Day -1 was used as the baseline for these post-OGTT plasma PD profiles.

Analysis of covariance (ANCOVA) was used with the baseline-adjusted parameter as the dependent variable, allowing for effects due to treatment and baseline. No imputation method was used in this analysis.

PROC MIXED from Statistical Analysis Software (SAS®) was used to produce the ANCOVA. Least squares means (LSmeans) from the ANCOVA model were used to estimate the within treatment mean change from baseline. The difference in LSmeans and its associated standard error were used to provide the estimated treatment difference and associated 95% CI.

**Summary:**

**Demographics:**

**Summary of Demographic Characteristics: Safety Population**

| | Placebo | 075 100mg BID | 075 1000mg QD | 075 1000mg BID | 682 1000mg TID |
|---|---|---|---|---|---|
| | N=8 | N=9 | N=9 | N=9 | N=9 |
| Age (years): Adults (protocol range 30-70 years) | | | | | |
| Median | 49.5 | 54.0 | 62.0 | 53.0 | 57.0 |
| Range | 44-61 | 45-69 | 45-66 | 46-65 | 39-69 |
| Sex, n (%) | | | | | |
| Female | 2 (25) | 2 (22) | 2 (22) | 2 (22) | 1 (11) |
| Male | 6 (75) | 7 (78) | 7 (78) | 7 (78) | 8 (89) |
| Ethnicity n (%) | | | | | |
| Hispanic or Latino | 0 | 0 | 0 | 0 | 0 |
| Not Hispanic or Latino | 8 (100) | 9 (100) | 9 (100) | 9 (100) | 9 (100) |
| Race | | | | | |
| African American/African Heritage | 1 (13) | 0 | 0 | 0 | 1 (11) |
| Asian – East Asian Heritage | 0 | 0 | 0 | 1 (11) | 0 |
| White – White/Caucasian/European Heritage | 7 (88) | 9 (100) | 9 (100) | 8 (89) | 8 (89) |

075 = GSK189075; 682 = GW869682

**Safety:**

**Number (%) of Subjects with Adverse Events During the Placebo Run-in Period: Safety Population**

| | Placebo | 075 100mg BID | 075 1000mg QD | 075 1000mg BID | 682 1000mg TID |
|---|---|---|---|---|---|
| | N=8 | N=9 | N=9 | N=9 | N=9 |
| | n (%) | n (%) | n (%) | n (%) | n (%) |
| Any AE | 1 (13) | 0 | 2 (22) | 4 (44) | 4 (44) |
| Any AE Related to Investigational Product | 0 | 0 | 1 (11) | 4 (44) | 0 |
| AEs Reported by ≥2 Subjects in Any Group | | | | | |
| Headache | 1 (13) | 0 | 2 (22) | 2 (22) | 1 (11) |
| Flatulence | 0 | 0 | 0 | 2 (22) | 1 (11) |

n (%) = number (percent) of subjects reporting adverse event
075 = GSK189075; 682 = GW869682

**Number (%) of Subjects with Adverse Events During the Treatment Period: Safety Population**

| | Placebo | 075 100mg BID | 075 1000mg QD | 075 1000mg BID | 682 1000mg TID |
|---|---|---|---|---|---|
| | N=8 | N=9 | N=9 | N=9 | N=9 |
| | n (%) | n (%) | n (%) | n (%) | n (%) |
| Any AE | 3 (38) | 4 (44) | 2 (22) | 4 (44) | 7 (78) |
| Any AE Related to Investigational Product | 2 (25) | 2 (22) | 0 | 3 (33) | 5 (56) |
| AEs Reported by ≥2 Subjects in Any Group | | | | | |
| Flatulence | 0 | 1 (11) | 1 (11) | 0 | 5 (56) |
| Headache | 2 (25) | 0 | 0 | 1 (11) | 1 (11) |
| Polyuria | 1 (13) | 0 | 0 | 0 | 3 (33) |

n (%) = number (percent) of subjects reporting adverse event
075 = GSK189075; 682 = GW869682

No subject died, experienced a serious adverse event (SAE), or withdrew due to an AE. No subject became pregnant.

Overall evaluation of clinical laboratory tests, heart rate and ECG data in subjects receiving GSK189075, GW869682 or placebo revealed no obvious patterns or trends to indicate clinically significant drug-related effects.

Transient increases from pre-treatment levels in serum creatinine and blood urea nitrogen (BUN) were observed in GSK189075 groups and in the GW869682 group. These transient increases were not considered to be of clinical significance; no subject had a serum creatinine or BUN value that met pre-defined criteria for clinical concern.

Trends for reductions in systolic and diastolic blood pressure from baseline, compared to placebo, were noted in GSK189075 and GW869682 groups; these changes were not dose dependent. The relevance of these data is unclear, given the small number of subjects studied and the observed differences in mean baseline values for systolic and diastolic blood pressure between the GSK189075 treatment groups and placebo. No event of symptomatic hypotension was reported in this study.

**Pharmacokinetics:**

*GSK189075 Regimens*

A total of 9 subjects each received and completed one of the three dosing regimens of GSK189075 for 12 days. Plasma concentrations of the parent drug, GSK189075, in subjects receiving the 100mg BID regimen were low and only measurable in a limited number of samples, thus not all PK parameters of GSK189075 at this dose level can be assessed. PK parameter estimates of the active moiety, GSK189074, and the prodrug GSK189075 on Day 1 and Day 11 following each dosing regimen are summarized as follows.

| GSK189075 | Day 1 (First Dose) | | | Day 11 (Steady-State) | | |
|---|---|---|---|---|---|---|
| PK Parameter | 100mg BID | 1000mg QD | 1000mg BID | 100mg BID | 1000mg QD | 1000mg BID |
| AUC(0-τ) | n = 2 | n = 8 | n = 9 | n = 5 | n = 9 | n = 9 |
| (h.ng/mL) | 22.9 (18) | 134 (47) | 141 (37) | 14.7 (39) | 179 (38) | 167 (43) |
| AUC(0-24) | n = 2 | n = 8 | n = 9 | n = 5 | n = 9 | n = 9 |
| (h.ng/mL) | 45.9 (18) | 134 (47) | 282 (37) | 29.4 (39) | 179 (38) | 334 (43) |
| t½ | n = 2 | n = 8 | n = 9 | n = 5 | n = 9 | n = 9 |
| (h) | 0.709 (169) | 0.507 (50) | 0.631 (43) | 0.404 (54) | 0.636 (80) | 0.496 (66) |
| Cmax | n = 9 | n =9 | n =9 | n = 9 | n = 9 | n = 9 |
| (ng/mL) | 16.9 (98) | 219 (59) | 226 (61) | 16.3 (67) | 247 (52) | 255 (89) |
| tmax | n = 9 | n =9 | n =9 | n = 9 | n = 9 | n = 9 |
| (h) | 0.32 (0.25-1.00) | 0.50 (0.25-0.75) | 0.50 (0.25-0.75) | 0.50 (0.25-0.77) | 0.50 (0.25-0.75) | 0.50 (0.25-0.75) |

Values are geometric mean (%CVb) for each parameter, except for tmax which are median (range).
nc = not calculated

| GSK189074 | Day 1 (First Dose) | | | Day 11 (Steady State) | | |
|---|---|---|---|---|---|---|
| PK Parameter | 100mg BID (n = 9) | 1000mg QD (n = 9) | 1000mg BID (n = 9) | 100mg BID (n = 9) | 1000mg QD (n = 9) | 1000mg BID (n = 9) |
| AUC(0-τ) | 699 | 7888 | 9270 | 783 | 8745 | 8936 |
| (h.ng/mL) | (45) | (27) | (32) | (34) | (29) | (32) |
| AUC(0-24) | 1398 | 7889 | 18540 | 1566 | 8745 | 17871 |
| (h.ng/mL) | (45) | (27) | (32) | (34) | (29) | (32) |
| t½ | 1.42 | 1.43 | 1.47 | 1.39 | 1.45 | 1.52 |
| (hr) | (11) | (6.9) | (7.0) | (7.3) | (6.1) | (4.8) |
| Cmax | 363 | 4830 | 6436 | 427 | 6088 | 5754 |
| (ng/mL) | (36) | (32) | (57) | (32) | (32) | (63) |
| tmax | 0.55 | 0.73 | 0.75 | 0.75 | 0.75 | 0.75 |
| (h) | (0.25-3.00) | (0.50-0.83) | (0.50-1.00) | (0.50-0.78) | (0.50-0.92) | (0.50-1.50) |
| AUC Ratio,m/p | nc | nc | nc | 96.2 | 60.0 | 65.6 |
| | | | | (52) | (27) | (47) |

Values are geometric mean (%CVb) for each parameter, except for tmax which are median (range).
nc = not calculated

Following single- or repeat-dose administration of GSK189075, it was rapidly absorbed and converted to its active moiety, GSK189074, followed by the formation of GSK279782 and GSK333081. All metabolites of GSK189075 rapidly appeared in the plasma, with median tmax occurring shortly, within 15 to 30 minutes, after that of the parent prodrug. Pharmacokinetics of GSK189075 and its metabolites were similar following single- and repeat-dose administration, with no apparent changes in the absorption or elimination characteristics across the three dosing regimens. Plasma concentrations of GSK189074 were at least 60 times the concentrations of GSK189075, consistent with the prodrug concept. GSK279782 and GSK333081 were present in plasma at about 20% and 8% of the concentrations of the parent compound, GSK189074.

There was relatively large intersubject variability in Cmax and AUC values of GSK189074 and its metabolites, generally ranging from 30 to 60% across dosing regimens.

Results of statistical analysis to determine accumulation ratios and time invariance for the active moiety GSK189074 following multiple-dose administration of each GSK189075 dosing regimen are summarized as follows:

| GSK189074 | Accumulation Ratio (Day 11/Day 1) | | | Time Invariance (Day 11/Day 1) | | |
|---|---|---|---|---|---|---|
| PK Parameter | 100mg BID | 1000mg QD | 1000mg BID | 100mg BID | 1000mg QD | 1000mg BID |
| AUC(0-τ) | 1.12 (1.01, 1.25) | 1.11 (0.99, 1.25) | 0.96 (0.87, 1.07) | na | na | na |
| Cmax | 1.18 (0.92, 1.50) | 1.26 (1.08, 1.46) | 0.89 (0.76, 1.06) | na | na | na |
| AUC[1] | na | na | na | 1.12 (1.00, 1.24) | 1.11 (0.99, 1.25) | 0.96 (0.87, 1.07) |
| t½ | na | na | na | 0.99 (0.94, 1.04) | 1.01 (0.99-1.04) | 1.04 (1.00, 1.08) |
| CLr | na | na | na | 1.04 (0.93, 1.16) | 0.92 (0.84, 1.00) | 1.26 (1.02, 1.56) |

Values are point estimate (90% CI) of the parameter ratio.
na = not applicable.
1. AUC ratio for time invariance is AUC(0-τ) on Day 11 divided by AUC(0-∞) on Day 1.

The Cmax and AUC(0-τ) values of GSK189074, and other analytes derived from GSK189075 on Day 11 were either not significantly different from those on Day 1 or just about 10-20% higher than those on Day 1 across the three dosing regimens. This indicates no accumulation or only mild accumulation of plasma exposure to GSK189075 and its metabolites following repeated oral doses on a QD or BID regimens, consistent with the short t½ estimates for the four analytes. There was no difference in plasma half-lives of any of the four analytes between Day 1 and Day 11 across the three dosing regimens. Similarly, there was generally no significant difference in renal clearance of any of the three metabolites of GSK189075 between Day 1 and Day 11 across dosing regimens. Mean plasma profiles of each analyte were almost superimposable on Day 1 and Day 11.

The total amount of GSK189075 metabolites excreted over a dosing interval, Ae(0-τ), and the percent of GSK189075 dose recovered in urine over a dosing interval as each

metabolite, and as all three metabolites, and CLr of each metabolite are summarized as follows:

| | Day 1 (First Dose) | | | Day 11 (Steady State) | | |
|---|---|---|---|---|---|---|
| Analyte | 100mg BID (n = 9) | 1000mg QD (n = 9) | 1000mg BID (n = 9) | 100mg BID (n = 9) | 1000mg QD (n = 9) | 1000mg BID (n = 9) |
| Ae(0-τ) (mg) | | | | | | |
| GSK189074 | 7.51 (35) | 85.2 (6) | 86.5 (59) | 8.71 (37) | 87.5 (16) | 96.8 (39) |
| GSK279782 | 1.15 (56) | 18.7 (58) | 14.1 (57) | 1.60 (58) | 18.7 (54) | 14.5 (39) |
| GSK333081 | 0.858 (40) | 10.2 (23) | 10.0 (65) | 1.04 (37) | 11.8 (29) | 12.3 (47) |
| Total | 9.52 (36) | 114 (13) | 111 (58) | 11.4 (39) | 118 (16) | 124 (38) |
| Percent Dose Recovered over a Dosing Interval (%) | | | | | | |
| GSK189074 | 9.21 (35) | 10.5 (6) | 10.6 (59) | 10.7 (37) | 10.7 (16) | 11.9 (39) |
| GSK279782 | 1.55 (56) | 2.53 (58) | 1.91 (57) | 2.16 (58) | 2.53 (54) | 1.96 (39) |
| GSK333081 | 1.16 (40) | 1.38 (23) | 1.36 (65) | 1.41 (37) | 1.60 (29) | 1.66 (47) |
| Total | 11.9 (36) | 14.4 (14) | 13.9 (58) | 14.3 (39) | 14.9 (16) | 15.5 (38) |
| CLr (mL/min) | | | | | | |
| GSK189074 | 177 (29) | 187 (31) | 147 (48) | 187 (39) | 173 (31) | 174 (33) |
| GSK279782 | 138 (24) | 166 (29) | 142 (42) | 155 (40) | 166 (35) | 166 (32) |
| GSK333081 | 370 (56) | 325 (30) | 262 (43) | 326 (45) | 316 (34) | 302 (30) |

Values are arithmetic mean (%CV).

Approximately 14-15% of the oral GSK189075 dose was recovered in urine as the three metabolites, and only about 11% of the dose was recovered as the active moiety, GSK189074. Renal clearance values for each analyte were similar between Day 1 and Day 11 and between dosing regimens.

*GW869682 Regimen*

A total of 9 subjects received and completed the dosing regimen of 1000mg GW869682 TID for 12 days. PK parameter estimates of the active moiety, GW869683, and the prodrug GW869682 on Day 1 and Day 11 are summarized as follows:

| | Day 1 (First Dose) | | Day 11 (Steady State) | |
|---|---|---|---|---|
| | GW869682 | GW869683 | GW869682 | GW869683 |
| AUC(0-τ) (h.ng/mL) | n = 9 | n = 9 | n = 8 | n = 8 |
| | 62.9 (52) | 2576 (26) | 65.9 (57) | 2728 (31) |
| AUC(0-24)(h.ng/mL) | n = 9 | n = 9 | n = 8 | n = 8 |
| | 189 (52) | 7729 (26) | 198 (57) | 8183 (31) |
| t½ (h) | n = 9 | n = 9 | n = 8 | n = 8 |
| | 0.510 (44) | 1.80 (17) | 0.574 (23) | 1.87 (13) |
| Cmax (ng/mL) | n = 9 | n = 9 | n = 9 | n = 9 |
| | 97.0 (25) | 2024 (31) | 82.5 (148) | 1872 (103) |
| tmax (h) | n = 9 | n = 9 | n = 9 | n = 9 |
| | 0.50 (0.50-0.78) | 0.50 (0.50-1.02) | 0.50 (0.50-2.00) | 0.77 (0.50-4.00) |
| AUC Ratio, m/p | na | nc | na | n = 8 |
| | | | | 49.3 (38) |

Values are geometric mean (%CVb) for each parameter, except for tmax which are median (range).
na = not applicable, nc = not calculated.

Results of statistical analysis of accumulation and time invariance for GW869682 and its active moiety GW869683 following administration of 1000mg GW869682 TID are summarized as follows:

| | Accumulation Ratio (Day 11/Day 1) | | Time Invariance (Day 11/Day 1) | |
|---|---|---|---|---|
| | GW869682 | GW869683 | GW869682 | GW869683 |
| AUC(0-τ) | 1.02 (0.89, 1.18) | 1.05 (0.98, 1.12) | na | na |
| Cmax | 0.85 (0.45, 1.62) | 0.92 (0.55, 1.56) | na | na |
| AUC[1] | na | na | 1.02 (0.88, 1.17) | 0.94 (0.86, 1.03) |
| t½ | na | na | 1.11 (0.81, 1.51) | 1.04 (0.91, 1.20) |

Values are point estimate (90% CI) of the parameter ratio.
na= not applicable.
1. AUC ratio for time invariance is AUC(0-τ) on Day 11 divided by AUC(0-∞) on Day 1.

Similar findings in the pharmacokinetic characteristics of the prodrug GW869682 and its active moiety GW869683 as those for GSK189075 and GSK189074 were obtained, i.e., relatively short plasma half-lives for both compounds, much greater plasma exposure to the active moiety than to the prodrug, relative large intersubject variability in plasma exposure, linear kinetics in the disposition of each compound, and no accumulation of plasma exposure to either compound following repeated TID dosing of GW869682.

**Pharmacodynamics:**

Summaries of the analysis of plasma glucose parameters are shown in the following tables:

Results from Analysis of Change from Baseline in Fasting Plasma Glucose Concentration (mmol/L) on Day11 and Day 12

| | Placebo | GSK189075 100mg BID | GSK189075 1000mg QD | GSK189075 1000mg BID | GW869682 1000mg TID |
|---|---|---|---|---|---|
| | N=8 | N=9 | N=9 | N=9 | N=9 |
| Day -2 | | | | | |
| Mean (SD) | 9.1 (1.63) | 9.5 (0.95) | 9.6 (1.68) | 9.3 (1.23) | 9.0 (1.43) |
| Day -1 | | | | | |
| Mean (SD) | 8.9 (2.05) | 9.6 (1.12) | 10.1 (1.95) | 9.0 (1.47) | 9.3 (1.87) |
| Day 11 | | | | | |
| Mean (SD) | 8.4 (2.12) | 7.7 (1.10) | 8.2 (1.54) | 6.5 (0.96) | 7.2 (1.55) |
| Mean Change (SD)[1] | -0.8 (1.36) | -1.8 (1.41) | -1.4 (1.23) | -2.8 (0.88) | -1.9 (2.16) |
| Difference from Placebo on Day 11[2] | | | | | |
| Mean | - | -0.87 | -0.39 | -1.99 | -1.16 |
| 95% CI | - | (-2.17, 0.44) | (-1.70, 0.92) | (-3.29, -0.68) | (-2.46, 0.15) |
| p-value | - | 0.1856 | 0.5502 | 0.0037 | 0.0801 |
| Difference from GW869682 on Day 11[2] | | | | | |
| Mean | - | 0.29 | 0.77 | -0.83 | - |
| 95% CI | - | (-0.98, 1.56) | (-0.51, 2.04) | (-2.10, 0.43) | - |
| p-value | - | 0.6493 | 0.2305 | 0.1917 | - |
| Day 12 | | | | | |
| Mean (SD) | 8.4 (1.85) | 7.3 (0.86) | 8.4 (1.07) | 6.2 (1.09) | 7.5 (1.58) |
| Mean Change (SD)[3] | -0.7 (1.38) | -2.2 (1.19) | -1.2 (0.93) | -3.1 (1.06) | -1.5 (1.83) |
| Difference from Placebo on Day 12[2] | | | | | |
| Mean | - | -1.29 | -0.26 | -2.29 | -0.85 |
| 95% CI | - | (-2.41, -0.17) | (-1.38, 0.86) | (-3.41, -1.18) | (-1.96, 0.27) |
| p-value | - | 0.0247 | 0.6379 | 0.0002 | 0.1317 |
| Difference from GW869682 on Day 12[2] | | | | | |
| Mean | - | -0.44 | 0.59 | -1.44 | - |
| 95% CI | - | (-1.53, 0.65) | (-0.51, 1.68) | (-2.53, -0.36) | - |
| p-value | - | 0.4149 | 0.2839 | 0.0105 | - |

1. Change from baseline (i.e. change from Day -2).
2. Based on ANCOVA.
3. Change from baseline (i.e. change from Day -1).

Results from Analysis of Change from Baseline in Plasma Glucose Parameters on Day 11

| | Placebo | GSK189075 100mg BID | GSK189075 1000mg QD | GSK189075 1000mg BID | GW869682 1000mg TID |
|---|---|---|---|---|---|
| | N=8 | N=9 | N=9 | N=9 | N=9 |
| AUC(0-6) weighted mean (mmol/L) | | | | | |
| Day -2 (Baseline) | | | | | |
| Mean (SD) | 10.9 (1.79) | 11.0 (1.50) | 11.6 (2.08) | 10.5 (1.98) | 10.8 (2.06) |
| Day 11 | | | | | |
| Mean (SD) | 9.5 (1.60) | 8.1 (1.25) | 8.6 (1.33) | 7.2 (1.19) | 8.2 (1.63) |
| Mean Change (SD)[1] | -1.3 (1.18) | -2.8 (1.57) | -3.0 (1.28) | -3.3 (1.55) | -2.5 (1.84) |
| Difference from Placebo on Day 11[2] | | | | | |
| Mean | - | -1.42 | -1.23 | -2.14 | -1.23 |
| 95% CI | - | (-2.53, -0.32) | (-2.35, -0.12) | (-3.24, -1.03) | (-2.33, -0.12) |
| p-value | - | 0.0128 | 0.0309 | 0.0004 | 0.0306 |
| Difference from GW869682 on Day 11[2] | | | | | |
| Mean | - | -0.20 | -0.01 | -0.91 | - |
| 95% CI | - | (-1.27, 0.87) | (-1.09, 1.08) | (-1.98, 0.16) | - |
| p-value | - | 0.7079 | 0.9888 | 0.0934 | - |
| AUC(0-24) weighted mean (mmol/L) | | | | | |
| Day -2 | | | | | |
| Mean (SD) | 9.8 (1.49) | 10.4 (1.51) | 11.1 (1.63) | 9.8 (1.69) | 10.0 (2.20) |
| Day 11 | | | | | |
| Mean (SD) | 8.7 (1.45) | 7.8 (1.20) | 8.6 (1.00) | 6.9 (1.03) | 7.8 (1.67) |
| Mean Change (SD)[1] | -1.1 (0.95) | -2.6 (1.40) | -2.5 (0.82) | -2.8 (1.17) | -2.2 (1.67) |
| Difference from Placebo on Day 11[2] | | | | | |
| Mean | - | -1.22 | -0.76 | -1.74 | -1.01 |
| 95% CI | - | (-2.15, -0.29) | (-1.72, 0.20) | (-2.67, -0.81) | (-1.94, -0.08) |
| p-value | - | 0.0119 | 0.1155 | 0.0005 | 0.0342 |
| Difference from GW869682 on Day 11[2] | | | | | |
| Mean | - | -0.21 | 0.25 | -0.73 | - |
| 95% CI | - | (-1.11, 0.69) | (-0.67, 1.17) | (-1.63, 0.17) | - |
| p-value | - | 0.6403 | 0.5888 | 0.1101 | - |

1. Change from baseline (i.e. change from Day -2).
2. Based on ANCOVA.

Results from Analysis of Change from Baseline in Plasma Glucose Parameter Following OGTT on Day 12

| | Placebo | GSK189075 100mg BID | GSK189075 1000mg QD | GSK189075 1000mg BID | GW869682 1000mg TID |
|---|---|---|---|---|---|
| | N=8 | N=9 | N=9 | N=9 | N=9 |
| AUC(0-6) weighted mean (mmol/L) | | | | | |
| Day -1 (Baseline) | | | | | |
| Mean (SD) | 12.0 (2.03) | 13.4 (2.28) | 13.2 (2.68) | 11.0 (2.84) | 12.9 (3.26) |
| Day 12 | | | | | |
| Mean (SD) | 10.7 (2.09) | 9.1 (1.19) | 9.0 (0.91) | 8.0 (2.28) | 8.9 (1.60) |
| Mean Change (SD)[1] | -1.31 (1.37) | -4.3 (2.24) | -4.2 (2.07) | -3.0 (3.85) | -3.9 (2.48) |
| Difference from Placebo on Day 12[2] | | | | | |
| Mean | - | -1.91 | -1.95 | -2.45 | -1.94 |
| 95% CI | - | (-3.49, -0.33) | (-3.52, -0.38) | (-4.02, -0.89) | (-3.50, -0.38) |
| p-value | - | 0.0190 | 0.0165 | 0.0030 | 0.0164 |
| Difference from GW869682 on Day 12[2] | | | | | |
| Mean | - | 0.03 | -0.01 | -0.51 | - |
| 95% CI | - | (-1.48, 1.54) | (-1.52, 1.50) | (-2.06, 1.04) | - |
| p-value | - | 0.9678 | 0.9920 | 0.5066 | - |

1. Change from baseline (i.e. change from Day -1).
2. Based on ANCOVA.

- There was a statistically significant decrease from baseline in pre-dose fasting plasma glucose concentration, compared to placebo, for the GSK189075 1000mg BID group on Day 11 and Day 12, and for the GSK189075 100mg BID group on Day 12.
- There was a statistically significant decrease from baseline in pre-dose fasting plasma glucose concentration, compared to the GW869682 1000mg TID regimen, for the GSK189075 1000mg BID group on Day 12.
- There was a statistically significant decrease from baseline in AUC(0-6) weighted mean plasma glucose on Day 11 for all active treatment groups, compared to placebo. There was evidence of a dose response, with the GSK189075 1000mg BID regimen having the greatest effect.
- There was a statistically significant decrease from baseline in AUC(0-24) weighted mean plasma glucose on Day 11 for all active treatment groups, except for the GSK189075 1000mg QD regimen, compared to placebo. There was evidence of a dose response, with the GSK189075 1000mg BID regimen having the greatest effect.
- There was a statistically significant decrease from baseline in AUC(0-6) weighted mean plasma glucose following the OGTT on Day 12 for all active treatment groups, compared to placebo. There was evidence of a dose response, with the GSK189075 1000mg BID regimen having the greatest effect.
- No statistically significant differences were observed, compared to placebo, for change from baseline in derived plasma insulin parameters on Day 11 or on Day 12 (following the OGTT) for any of the active treatment groups.

- No statistically significant differences were observed, compared to placebo, for change from baseline in derived plasma C-peptide parameters on Day 11 for any of the active treatment groups.
- There was a statistically significant decrease from baseline in AUC(0-6) weighted mean plasma C-peptide on Day 12 following the OGTT for all active treatment groups except for the GSK189075 1000mg BID group.

A summary of change of percent of filtered glucose excreted in urine from baseline is shown in the following table:

Change from Baseline in %Filtered Glucose Excreted in Urine for the 0-24 hour Period on Day 1 and Day 11: Data from Subjects with %Filtered Glucose Excreted ≤100

| | Placebo | GSK189075 100mg BID | GSK189075 1000mg QD | GSK189075 1000mg BID | GW869682 1000mg TID |
|---|---|---|---|---|---|
| | N=8 | N=9 | N=9 | N=9 | N=9 |
| Day -2 | | | | | |
| N | 8 | 5 | 4 | 7 | 6 |
| Mean (SD) | 5.5 (6.40) | 2.0 (2.91) | 3.7 (3.48) | 1.2 (0.90) | 1.9 (2.78) |
| Day 1 | | | | | |
| N | 8 | 7 | 4 | 7 | 6 |
| Mean (SD) | 2.9 (2.35) | 45.9 (13.51) | 47.5 (9.06) | 57.6 (10.85) | 44.3 (19.96) |
| Mean Change (SD)[1] | -2.7 (4.37) | 42.6 (16.25)[2] | 43.8 (9.45) | 56.5 (11.16) | 42.4 (19.45) |
| Day 11 | | | | | |
| N | 7 | 7 | 4 | 7 | 6 |
| Mean (SD) | 2.0 (2.00) | 40.2 (15.46) | 47.4 (11.02) | 48.9 (9.48) | 35.8 (11.22) |
| Mean Change (SD)[1] | -4.1 (5.10) | 36.8 (17.43)[2] | 43.8 (10.08) | 47.7 (8.71) | 34.0 (9.88) |

1. Change from baseline (percent of filtered glucose excreted over the 0-24h interval on Day -2 was used as the baseline for change over the corresponding time interval on Days 1 and 11).
2. n = 5.

Note that the number of subjects (n) with observations was reduced as (i) subjects with %filtered glucose excreted >100 are excluded from this summary and, (ii) observations were missing for some subjects.

Over the 0-24 hour collection period on Day 1 and Day 11, an increase from baseline in the amount of filtered glucose excreted in urine was observed for all active treatment groups, relative to placebo. It is difficult to see a dose response relationship due to variability in the data.

No consistent patterns or trends were observed for the amount of creatinine present in the urine for the 0-24 hour period on Day 1, Day 11 or Day 12 (following the OGTT) across regimens, when compared to pre-treatment (Day -1 or Day -2).

Small decreases from baseline in body weight, BMI, and hip circumference were observed on Day 13 for all groups, including the placebo group; there was no evidence of a dose response for the active treatment groups. No consistent patterns or trends were observed for waist circumference or waist to hip ratio.

**Pharmacokinetics/Pharmacodynamics**

With the drug exposures achieved in this study, increasing GSK189074 AUC(0-24) does not further increase urine glucose excretion over a 24-hour interval, or further reduce plasma glucose AUC(0-24) levels.

**Conclusions:**

*Safety/Tolerability*

- Repeat oral doses of GSK189075 100mg BID, 1000mg QD and 1000mg BID for 12 days were similarly well-tolerated in subjects with T2DM, in terms of the proportion of subjects reporting AEs (44%, 22% and 44%, respectively), compared to the placebo group (38%).
- A higher proportion of subjects reported AEs for the GW869682 1000mg TID group (78%) compared to the placebo group (38%). Flatulence and polyuria were the most common AEs for the GW869682 1000mg TID group.
- No subject died, experienced a serious adverse event, or withdrew due to an AE.
- Overall evaluation of clinical laboratory tests, heart rate and ECG data in subjects receiving GSK189075, GW869682 or placebo revealed no obvious patterns or trends to indicate clinically significant drug-related effects.
- Trends for reductions in systolic and diastolic blood pressure from baseline, compared to placebo, were noted in GSK189075 and GW869682 groups; these changes were not dose dependent.

*Pharmacokinetics*

- The disposition of GSK189075 and its active moiety, GSK189074, and two metabolites, GSK279782 and GSK333081, follows linear kinetics after single- or repeat-dose administration of GSK189075 over the dose range studied.
- There was no accumulation or only 10-20% accumulation of plasma exposure to GSK189075, GSK189074 and its metabolites following repeated doses across the three dosing regimens. Steady-state plasma profiles of GSK189075 and its active moiety and metabolites can be reasonably predicted based on Day 1 (single-dose) PK data.
- The tmax and t½ values for GSK189075, GSK189074 and its metabolites and the renal clearance estimates for GSK189074 and its metabolites were not significantly different following single- or repeat-dose administration and were similar among the three dosing regimens of GSK189075, i.e., 100mg BID, 1000mg QD and 1000mg BID.
- Plasma concentrations of the active moiety GSK189074 were at least 60 times the concentrations of the parent prodrug; and plasma concentrations (AUCs) of GSK279782 and GSK333081 were approximately 20% and 8% of the concentrations (AUC) of GSK189074, respectively.

- There was approximate dose proportionality in plasma exposure to GSK189075, GSK189074 and its metabolites between the three dosing regimens.
- Approximately 14-15% of an oral GSK189075 dose was recovered in urine as the active moiety GSK189074 (~11% of dose), and its metabolites, GSK279782 (~2% of dose) and GSK333081 (~1.5% of dose). These urinary recovery data were similar following single- or repeat-dose administration across the three dosing regimens.
- The disposition of GW869682 and its active moiety, GW869683, follows linear kinetics after single- or repeat-dose administration of GSK189075. There was no accumulation of plasma exposure to GW869682 or GW869683 and no change in t½ estimates of both analytes following repeated oral doses of 1000mg GW869682 TID.
- Plasma concentrations (AUC) of the active moiety GW869683 were about 50 times the concentrations (AUC) of the parent prodrug GW869682.

*Pharmacodynamics*

- All three GSK189075 regimens and the GW869682 regimen caused statistically significant decreases in post-prandial plasma glucose concentrations on Day 11 and post-OGTT glucose concentrations on Day 12, compared to placebo. The magnitude of the reduction in plasma glucose concentrations was greatest for the GSK189075 1000mg BID regimen.
- The GSK189075 1000mg BID regimen and the GSK189075 100mg BID regimen caused a statistically significant reduction in fasting plasma glucose on Day 11 and/or Day 12, compared to placebo.
- Both GSK189075 and GW869682 caused an increase in urine glucose concentrations on Day 1 and Day 11 relative to baseline and placebo.

*Pharmacokinetics/Pharmacodynamics*

- With the drug exposures achieved in this study, increasing GSK189074 AUC(0-24) does not further increase urine glucose excretion over a 24-hour interval, or further reduce plasma glucose AUC(0-24) levels.

**Date of Report:**

July 2007