Pharmacokinetics and Pharmacodynamics of the SGLT2 Inhibitor
Remogliflozin Etabonate in Subjects with Mild and Moderate Renal Impairment

Robin O’Connor-Semmes, Susan Walker, Anita Kapur, Elizabeth K Hussey, June Ye, Laurene Wang-Smith, Wenli Tao, Robert L. Dobbins, Bentley Cheatham and William O. Wilkison


BHV Pharma, 6601 Six Forks Rd., Suite 140. Raleigh, NC 27615 (S.W., B.C. and W.O.W.)
Running title:
PK and PD of remogliflozin in patients with mild and moderate renal impairment

Corresponding author:
William O. Wilkison, PhD
6601 Six Forks Rd.
Suite 140
Raleigh, NC, 27615
Phone: 919-480-1518
FAX: 919-480-1519
Email: bill@bhvpharma.com

Document statistics
Number of text pages: 10
Number of tables: 5
Number of figures: 5
Number of references: 24
Number of words in Abstract: 179
Number of words in Introduction: 711
Number of words in Discussion: 681

Non-standard abbreviations:
RE remogliflozin etabonate
SGLT sodium/glucose cotransporter
PK pharmacokinetics
PD pharmacodynamics
T2DM type 2 diabetes mellitus
CKD chronic kidney disease
Abstract

Remogliflozin etabonate (RE), the prodrug of remogliflozin, is an inhibitor of the sodium glucose-dependent renal transporter 2 (SGLT2), enabling urinary glucose excretion to reduce hyperglycemia for the treatment of type 2 diabetes. Renal function declines more rapidly in patients with type 2 diabetes, making it difficult or unsafe to continue on some anti-diabetic therapeutics. In an initial effort to understand the potential utility of RE in patients with renal impairment, the pharmacodynamics and pharmacokinetics of RE were evaluated in a single oral dose (250 mg) in patients with renal impairment as compared to control subjects. As shown by pharmacodynamic measurements of urinary glucose excretion, there was no clinically significant reduction in the ability of remogliflozin to inhibit SGLT2. In addition, there were no significant changes in AUC (0-inf) or t_{1/2} of remogliflozin, suggesting renal impairment does not alter the pharmacokinetics of remogliflozin. In contrast to other SGLT2 inhibitors which accumulate in patients with renal impairment, adjustment in the dosage of RE in subjects with mild or moderate renal impairment is not indicated based on the observations in this study.
Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is rapidly increasing worldwide. Diabetes is the leading cause of chronic kidney disease (CKD) in the United States, with 22% of the U.S. population suffering from this disease. Moreover, diabetes accounts for 43.5% of prevalent kidney failure, increasing to 61% with patients over the age of 65 (Bailey et al., 2014).

The kidney plays a major role in the clearance of drugs, in general, and of glucose lowering agents used for T2DM, in particular (Sun et al., 2006). Therefore, the management of glycemia in patients with diabetes and CKD is quite challenging and the questions of which hypoglycemic agents to use in T2DM subjects with CKD and their dosing parameters are of major practical importance.

Besides the mode of action of glucose-lowering agents, renal function should also be taken into account by the physician. Indeed, renal impairment may deeply impact the pharmacokinetics of these agents and thereby influence choices, dosing, and monitoring of these drugs according to the reduction of glomerular filtration rate (GFR) (Cavanaugh, 2007; Haneda and Morikawa, 2009; Snyder and Berns, 2004). The situation is even more complex in the elderly population, where renal impairment and polymedication are more common (Ferrannini et al., 2013). Sodium/glucose cotransporters (SGLT) are expressed in the absorptive epithelia of the gastrointestinal tract (SGLT1) and renal tubules (SGLT1 and SGLT2). SGLT2 is primarily expressed on the luminal side of the S1 segment of the renal proximal tubule and is responsible for approximately 90% of renal glucose reabsorption; whereas renal SGLT1 is located in the distal S3 segment, and is responsible for the remaining 10% of renal glucose reabsorption (Chao and Henry, 2010; DeFronzo et al., 2012; Kanai et al., 1994; Tonelli et al., 2006). Thus, SGLT2 is the primary pathway for renal glucose reabsorption. Once reabsorbed across renal epithelium, glucose is transported to the blood by facilitated diffusion through the GLUT2 transporter. The uptake of glucose in the proximal tubules is highly efficient, resulting in complete reabsorption of glucose in subjects with plasma glucose concentrations below 180 mg/dL. Inhibitors of SGLT2 have acute
and chronic effects on plasma glucose concentration, providing therapeutic benefits to patients with T2DM (Wright et al., 2011). A number of SGLT2 inhibitors such as dapagliflozin, canagliflozin and ipragliflozin, have altered pharmacokinetic and/or pharmacodynamic properties when administered to subjects with mild or moderate renal impairment (FDA, 2011; FDA, 2013; Isaji, 2007; Macha et al., 2014; Yale et al., 2013). Remogliflozin etabonate (RE) is a SGLT2 inhibitor that causes a concentration-dependent increase in urine glucose excretion (Hussey et al., 2013; Kapur et al., 2013). RE reduces postprandial glucose excursions, HbA1c and fasting plasma glucose without inducing hypoglycemia in subjects with T2DM (Dobbins et al., 2012; Sykes et al., 2015a; Sykes et al., 2015b). RE is an O-linked glycoside, where as other SGLT2 inhibitors are C-linked glycosides. RE is the ester prodrug of remogliflozin, a selective and nanomolar potent inhibitor of SGLT2. In a PK/PD study with healthy volunteers and type 2 diabetics, RE was generally well-tolerated; there were no serious adverse events.

RE is rapidly absorbed and converted to the active entity remogliflozin (time to maximum plasma concentration [Cmax;Tmax] approximately 1 h) by esterases present in the gastrointestinal tract (O'Connor-Semmes et al., 2013). Generally exposure to remogliflozin is proportional to the administered dose. Remogliflozin is extensively metabolized to several metabolites (Fujimori et al., 2008), and is rapidly eliminated (mean plasma T1/2 = 120 min) independent of dose administered (Kapur et al., 2013). Multiple CYP, glucuronidases, and non-CYP enzymes (e.g., glucosidases) are involved in the majority of remogliflozin clearance (Sigafoos et al., 2012). Two active metabolites, GSK279782 and GSK333081 are biotransformed from remogliflozin via CYP3A4. Three other inactive metabolites, GSK355993, GSK1997711, and GSK1997714, made up the majority of the glucuronidated species with GSK1997711 being the most abundant. Products of remogliflozin metabolism are eliminated primarily via renal excretion with 92.8% of the dose recovered in the urine. Because of these considerations, this study was designed to evaluate safety, PK and PD of RE in subjects with mild and moderate renal impairment. We observed that the pharmacokinetics of remogliflozin and its metabolites are not significantly altered
in subjects with either mild or moderate renal impairment, suggesting that dose-alteration for renal impaired type 2 diabetics may not be necessary.
Material and Methods

This clinical study was conducted in accordance with Good Clinical Practices, subject privacy requirements, and the guiding principles of the Declaration of Helsinki. Written informed consent was obtained from each subject prior to any study specific procedure. The ClinicalTrials.gov identifier is NCT00501462.

Study Design. This phase 1, open-label, single-dose, parallel-group study was designed to characterize the pharmacokinetics of a single 250 mg oral dose of remogliflozin etabonate [GSK189075 (remogliflozin etabonate; RE), GSK189074 (remogliflozin)]. Previous studies have demonstrated that 250 mg QD is a sufficient dose to significantly inhibit SGLT2 and provide therapeutic benefit in subjects with T2DM (Sykes et al., 2015a; Sykes et al., 2015b). Subjects with normal renal function were recruited to match subjects with chronic renal impairment for gender, age (±5 years), and BMI (±15%). Subjects with normal renal function (CLcr > 80 mL/min) were considered as a match for either subjects with mild renal impairment (CLcr between 50 and 80 mL/min) or moderate renal impairment (CLcr between 30 and 49 mL/min). Subjects with T2DM were included if they met all of the inclusion/exclusion criteria. Subjects were allowed necessary medications for management of their medical conditions (for example anti-hypertensives and anti-diabetic medications [except metformin]), provided they met the definition of a stable regimen and were medically able to withhold their medications starting at a minimum of eight hours before study drug administration. Medications were withheld throughout the PK sampling period.

Patients with renal impairment were required to be clinically stable as assessed by the investigators. Stable renal function was defined as ≤25% difference in estimated creatinine clearance (CLcr) during the 30 days prior to study drug administration. Renal function was based on Cockcroft-Gault equation using serum creatinine values obtained on two occasions separated by at least two weeks within the screening period. Each serum creatinine collection for estimation of CLcr was drawn within the 30-day period prior to study drug administration.
**Treatment Procedures.** Subjects arrived at the clinic a day before (Day -1) drug administration and urine samples were collected. On Day 1 subjects received a single oral dose of 250 mg of remogliflozin. Fifteen minutes later, subjects were given a breakfast meal. This was followed by lunch, 6 hours later, and dinner, 12 hours after drug administration.

All meals were standardized with respect to nutrient and caloric content. Blood samples were collected for pharmacokinetic analysis of drug and metabolite concentrations (Kapur et al., 2013) starting immediately prior to study drug administration and following dosing at scheduled times over 24 hours.

Urine was collected for analysis of volume, glucose, creatinine, and electrolyte (Na, Cl, K, Mg, and Ca) concentrations and osmolality over intervals beginning 24 hours before and for 24 hours following dosing. Serum glucose and creatinine were collected for calculation of the percent of glucose filtered. Urine collected after dosing was stored for analysis of remogliflozin and GSK279782.

Among the 12 subjects with normal renal function, 8 were used as the matched normal for mild renal impairment, and 7 were used as the matched normal for moderate renal impairment. Thus, 3 subjects (Subject Nos. 53002, 53046, and 53087) with normal renal function were included in both normal matched groups. The CLcr values determined on Day -1 and Day 1 based on actual measurements of 0- to 24-hr urinary creatinine excretion for subjects with renal impairment and their matched normal subjects are summarized in Table 1 and demographics summarized in Table 2.

**Statistical Methods.** Descriptive statistics, including arithmetic mean and associated 95% confidence interval (CI), standard deviation, minimum, median, maximum, coefficient of variation (%CV), were provided for all plasma and urine pharmacokinetic (PK) and pharmacodynamic parameters. For most plasma PK parameter analytes, the geometric mean and the associated 95% CI were calculated by renal function group. For t\textsubscript{max}, only median, minimum and maximum values were provided by renal function group.
For summaries of log-transformed variables, the between-subject %CV was calculated as:

\[ \%CV_{b} = 100 \times \sqrt{e^{\text{SD}^2} - 1}, \]

with the SD of the log-transformed data. For summaries of untransformed variables, the between-subject %CV was calculated as:

\[ \%CV_{b} = 100 \times \frac{\text{SD}}{\text{Mean}}, \]

with the SD and Mean of the untransformed data.

The effect of renal impairment on PK of RE and its metabolites in urine and plasma was evaluated by descriptively comparing PK parameters of subjects with mild or moderate renal impairment to their matched control subjects with normal renal function.

Following loge-transformation, plasma \( C_{\text{max}} \) and AUC (0-\( \infty \)) were analyzed separately by ANOVA, fitting a single term for renal function group. Point estimates and associated 90% confidence intervals (CI) for the differences in least squares means were constructed using the residual variance. Point and confidence limits estimates for the differences in least squares means were then exponentially back transformed to construct the point estimate and 90% CI for the ratios of the geometric least squares means for mild:matched normal and moderate:matched normal, respectively.

Model and distributional assumptions underlying each analysis were assessed by visual inspection of residual plots. In addition, exploratory sensitivity mixed model analyses were performed to evaluate the relationship of GSK189074 \( C_{\text{max}} \) and AUC (0-24) as a function of the measured Day 1 CL\( \text{cr} \) while controlling for age, sex and race. The PK parameters were log transformed prior to analysis. Model and distributional assumptions underlying each analysis were assessed by visual inspection of residual plots.

Results

**Safety and Adverse Events.** Nine subjects reported a total of eighteen adverse events (AEs), regardless of causality. All were mild except for one headache unrelated to the study drug. Four AEs were drug-related and symptoms consisted of dizziness, dysgeusia, presyncope, and nausea. The only AE that was reported by more than one subject in any specific group was mild erythema,
unrelated to the study drug. No action was taken due to any drug-related AEs and all AEs were resolved by the end of the study. With respect to specific markers of renal toxicity, there were no changes in urinary microalbumin or electrolyte composition or concentration in response to remogliflozin etabonate dosing (not shown). Additionally, 12 week studies dosing remogliflozin etabonate up to 1000 mg twice daily did not indicate any changes in renal capacity or function (Sykes et al., 2015a; Sykes et al., 2015b).

**Plasma Pharmacokinetics.** Plasma concentration-time data for the prodrug and its metabolites were available from 12 subjects with mild renal impairment and 7 subjects with moderate renal impairment, and 12 subjects with normal renal function. A few of the normal match subjects were used in both comparisons. In general, RE (prodrug) concentrations were measurable from 0.25 hours post dose and up to 3 to 4 hours post dose in all subjects. Plasma concentrations of the remogliflozin (active entity) appeared rapidly and were measurable starting at 0.25 hours post dose in almost all subjects, lasting up to at least 12 to 16 hours in all subjects (Figure 1).

Based on the geometric mean values for remogliflozin, there was an approximate 10% increase in AUC and $t_{1/2}$ of remogliflozin, and slight-to-no increase in $C_{\text{max}}$ of remogliflozin in subjects with renal impairment (Table 3). There was essentially no difference in the unbound fraction of remogliflozin in plasma among the 4 renal function groups. Remogliflozin was present in plasma at 60-80 fold higher concentrations than the parent prodrug, and there was no change in the AUC ratio, $m/p$ between groups. These data indicated no alterations in the metabolic formation or elimination of remogliflozin in renal impairment. In all groups, the $\text{CLr}$ of remogliflozin was a relatively small fraction of the estimated total $\text{CL/F}$.

Plasma concentrations of GSK279782 and GSK333081 (major metabolites of RE) also appeared rapidly in plasma. These metabolites were measurable as early as 0.25 hours post dose in the majority of subjects and at 0.5 hours post dose in all subjects. GSK279782 continued to be measurable up to 16 hours post dose in subjects with normal renal function or mild renal impairment, but up to 24 hours post dose in several subjects with moderate renal impairment.
GSK333081 continued to be measurable up to 12 hours post dose in subjects with normal renal function, up to 12 to 16 hours in subjects with mild renal impairment, and up to 16 hours in subjects with moderate renal impairment.

The statistical results of the observed geometric mean ratios of the various renal function groups PK parameters are presented in Table 4. Sensitivity analyses explored the impact of measured Day 1 CLcr on remogliflozin (GSK189074) C$_{\text{max}}$ and AUC$_{0-\infty}$. Scatter plots of AUC$_{0-\infty}$ C$_{\text{max}}$ show little association of CLcr on exposure (Figures 2 and 3).

**Urine Pharmacokinetics.** The cumulative amount of intact remogliflozin and GSK279782 excreted over the 0 to 24 hour post dose urine collection interval, Ae (0 to 24), and percent of RE dose recovered in urine as remogliflozin or GSK279782 over the 24 hour collection interval, and the renal clearance (CLr) of each metabolite for each renal function group are summarized in Table 5. The percent dose recovered as remogliflozin or GSK279782 in urine was reduced in subjects with renal impairment. Similarly, renal clearance values, total and unbound, for each analyte were also largely reduced in subjects with renal impairment, and the extent of reduction was greater in subjects with moderate renal impairment.

**Pharmacodynamic/pharmacokinetic Results.** Figure 4 shows the Day -1(pre-dose) 0-6 hour % filtered glucose (%FG) as a function of Day -1 0-6 hour measured urine creatinine clearance and the Day 1 0-6 hour UGE as % filtered glucose (%FG) as a function of Day 1 0-6 hour measured urine creatinine clearance. Consistent with inhibition of SGLT2 by RE, the amount of glucose excreted in the urine was significantly increased on Day 1, compared to Day -1 (mild-12.4-fold increase; mild match- 36.3-fold increase; moderate-4.7-fold increase; moderate match- 30.4-fold increase). This was clearly demonstrated across all subjects and levels of renal impairment. With the addition of a regression line with a near zero slope for Day 1, no trends suggesting differences in UGE as % filtered glucose were evident across the levels of renal impairment on Day 1 (Figure 4).

The amount of urine glucose excreted during the first 6 hours after dosing demonstrated a trend of increasing amounts in subjects with higher creatinine clearance levels. Variability levels
appeared higher at the lower end of the urine creatinine clearance (Figure 5).

Although the slope of the regression line (amt=37.78mmol+ 0.521mmol*min/mL*clcr) is statistically significant (p-value<0.001), the slope shows a modest increase. For instance, an increase from moderately impaired (<50 mL/min) to normal (>80 mL/min) in urine creatinine clearance would suggest an increase of approximately 16 mmoles over 6 hours. Clearly, more renal filtration provides better efficacy for SGLT2 inhibitors in general.
Discussion

Following oral administration, RE is rapidly and extensively converted to remogliflozin, which then undergoes considerable metabolism and rapid clearance. As reported in prior studies, only 7.9% of the dose recovered in urine was remogliflozin (Fujimori et al., 2008). A $^{14}\text{C}$-prodrug mass-balance study showed that metabolites accounted for more than 76% dose recovery. Overall, 93% of the radiolabelled dose is recovered in urine (of which approximately 90% has been identified as remogliflozin or metabolites). Based on these previous studies, it was anticipated that remogliflozin would not accumulate in renal impaired subjects, nor would a loss of SGLT2 inhibitory activity be observed. Consistent with this hypothesis, the pharmacokinetics of remogliflozin etabonate and its metabolites following a single oral dose of 250 mg RE in subjects with mild or moderate renal impairment showed only minimal ($\leq 10\%$) increases in AUCs and/or $t_{1/2}$ of remogliflozin. Moreover, pharmacodynamic measurements of urine glucose excretion indicated no alteration of the ability of remogliflozin to inhibit SGLT2 in these subjects.

The PK results of this study indicate that no dose adjustment of RE in subjects with mild or moderate renal impairment would be necessary. The importance of this finding is that at least three SGLT2 inhibitors–canagliflozin, dapagliflozin, and empagliflozin–have presented with significant plasma accumulation in mild and moderately renal impaired subjects (FDA, 2011; FDA, 2013; Macha 2014). Interestingly, while the plasma concentrations of these compounds were elevated, there was a corresponding decrease in urinary glucose excretion. Whether this is directly coupled to the decreased filtration rate in these renal compromised subjects or an effect of the accumulation of compound/metabolites is unclear. Remogliflozin is a competitive inhibitor of SGLT2 with respect to glucose (Fujimori et al., 2008), which likely ameliorates any potential drug-drug interaction possibilities for patients taking concurrent medications. In fact, few compounds appear to interfere with the ability of remogliflozin to inhibit SGLT2 or its metabolism (Sigafoos et al., 2012).

With respect to pharmacodynamic parameters, the amount of glucose excreted in the urine was significantly increased following dosing with RE in all groups, as anticipated. Urine glucose
excretion was higher in the respective matched groups compared to the mild and moderate impairment groups on Day 1. Subjects with diabetes mellitus were not excluded from this study and several subjects with high serum glucose concentrations, particularly in the moderate impairment group, contributed to the variability observed in urine glucose excretion on both the baseline and treatment days. The percent of filtered glucose excreted was consistent across the renal function groups following dosing with RE, despite a lower filtration rate in the impaired groups. This observation suggests that, while less glucose may be delivered to the site of action (SGLT2 in the kidney), glucose reabsorption is inhibited to the same degree in subjects with renal impairment when RE is administered. The effect of RE in severe renal impairment will need to be examined, but the mechanism of action for glucose lowering suggests limited efficacy in these subjects. This is in contrast to canagliflozin which shows significant decreases in UGE as % filtered glucose in renal impaired subjects (Yale et al., 2013).

With regard to the metabolites of remogliflozin, the mean plasma AUCs were increased by about 30-50% and 30-70% for GSK279782 and GSK333081, respectively, with similar increases in unbound AUCs, in subjects with mild to moderate renal impairment. The greater increases in AUCs for these two metabolites, as compared to remogliflozin, are consistent with the greater involvement of renal excretion of these polar metabolites as the elimination pathway. However, both of these metabolites represent a small percentage of the total remogliflozin amount (<5% combined). Therefore, the small increases in AUC for GSK279782 and GSK333081 are likely of little consequence in renal impairment.

In summary, mild and moderate renal impairment does not result in clinically meaningful effects on the plasma exposure or plasma half-lives of RE and remogliflozin, consistent with the known extensive metabolism as the primary elimination pathway for these compounds. The amount of glucose excreted in the urine was modestly higher as creatinine clearance increased. However, the percent of filtered glucose excreted was unchanged across the different levels of renal impairment. Based on the results of this study, no dose-adjustment of RE is recommended in
subjects with mild or moderate renal impairment.
Acknowledgments

The study protocol and informed consent were approved by Crescent City Institutional Review Board New Orleans, Louisiana, USA, and Independent Investigational Review Board, Inc., Plantation, Florida, USA, and Human Subjects Research Committee, Minneapolis, Minnesota, USA. Carter DC, Covance CRU Austin TX; Marbury TC, Orlando Clinical Research; Smith WB, New Orleans Center for Clinical Research, Knoxville; Swan SK, DeVita Clinical Research MN.

Authorship contributions

Participated in research design: O’Connor-Semmes, Kapur, Hussey, Dobbins

Conducted experiments: O’Connor-Semmes, Kapur, Hussey, Dobbins

Performed data analysis: O’Connor-Semmes, Walker, Kapur, Hussey, Ye, Wang-Smith, Tao, Dobbins, Cheatham, Wilkison,

Wrote or contributed to writing of the manuscript: Wilkison, Walker, Cheatham, O’Connor-Semmes, Walker, Dobbins
References


Footnote

This work was supported by GlaxoSmithKline.
Figure Legends

Figures 1a and 1b. Plots of Mean GSK 189074 Plasma Concentrations vs. Time Linear and Semi-Log Scales.

Figure 2. Scatter Plot of Plasma Remogliflozin (AUC (0-Inf) (Hr*Ng/L) vs. Urine Creatinine Clearance (Clcr mL/hr) Day 1, 0-6 Hours.

Figure 3. Plot of Remogliflozin (GSK189074) C_{max} vs Day 1 CLcr (mL/min).

Figure 4. Scatter Plots of % Filtered Urine Glucose, 0-6hr (mmol/L) vs. Measured Urine Creatinine Clearance (mL/min) 0-6 hours, Day -1 and Day 1

Figure 5. Scatter Plot of Urine Glucose Excreted Amount Day 1, 0-6hr (mmol) vs. Urine Creatinine Clearance (mL/min) Day 1, 0-6 hours.
Table 1. Summary of 0-24/hr Creatinine Clearance Values by Renal Function Group

<table>
<thead>
<tr>
<th>Renal Function Group</th>
<th>Screening CLcr by Cockcroft-Gault (mL/min)</th>
<th>Measured CLcr on Day -1 (mL/min)</th>
<th>Measured CLcr on Day 1 (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Renal Impairment (N = 12)</td>
<td>64.77 (52.9 – 73.4)</td>
<td>75.5 (44.3 – 115)</td>
<td>73.5 (47.8 – 111)</td>
</tr>
<tr>
<td>Normal Match, Mild Impairment (N = 8)</td>
<td>101.34 (80.9 – 136.4)</td>
<td>118 (92.5 – 161)</td>
<td>93.0 (84.1 – 156)</td>
</tr>
<tr>
<td>Moderate Renal Impairment (N = 7)</td>
<td>39.31 (31.7–48.7)</td>
<td>45.1 (35.9 – 69.0)</td>
<td>42.4 (33.5 – 56.4)</td>
</tr>
<tr>
<td>Normal Match, Mod. Impairment (N = 7)</td>
<td>99.94 (84.0 – 146.9)</td>
<td>96.7 (92.5 – 123)</td>
<td>91.1 (83.2 – 123)</td>
</tr>
</tbody>
</table>

1Values are median (range).
Normal (>80 mL/min)
Mild renal impairment-CKD 2 (50-80 mL/min)
Moderate renal impairment-CKD 3 (30-49 mL/min)
Table 2. Comparison of Demographics between Renal Impaired and Normal Subjects

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Mild Renal Impairment</th>
<th>Normal Match for Mild*</th>
<th>Moderate Renal Impairment</th>
<th>Normal Match for Moderate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in Years, Mean</td>
<td>64.4 (45, 75)</td>
<td>62.3 (50, 72)</td>
<td>55.1 (29, 72)</td>
<td>54.0 (27, 71)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female:</td>
<td>5 (41.7%)</td>
<td>2 (25.0%)</td>
<td>4 (57.1%)</td>
<td>4 (57.1%)</td>
</tr>
<tr>
<td>Male:</td>
<td>7 (58.3%)</td>
<td>6 (75.0%)</td>
<td>3 (42.9%)</td>
<td>3 (42.9%)</td>
</tr>
<tr>
<td>BMI, kg/m², Mean (Range)</td>
<td>27.111 (23.12, 35.75)</td>
<td>29.055 (24.54, 34.03)</td>
<td>24.859 (19.65, 31.19)</td>
<td>24.907 (19.74, 30.51)</td>
</tr>
<tr>
<td>Weight, kg, Mean (Range)</td>
<td>79.46 (66.4, 106.3)</td>
<td>88.95 (72.9, 115.2)</td>
<td>69.97 (54.4, 89.5)</td>
<td>68.91 (52.7, 79.3)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino:</td>
<td>1 (8.3%)</td>
<td>1 (12.5%)</td>
<td>0</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td>Not Hispanic or Latino:</td>
<td>11 (91.7%)</td>
<td>7 (87.5%)</td>
<td>7 (100.0%)</td>
<td>6 (85.7%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American/African</td>
<td>3 (25.0%)</td>
<td>0</td>
<td>1 (14.3%)</td>
<td>0</td>
</tr>
<tr>
<td>American Indian or</td>
<td>0</td>
<td>1 (12.5%)</td>
<td>0</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td>White – White/Caucasian/</td>
<td>9 (75.0%)</td>
<td>7 (87.5%)</td>
<td>7 (100.0%)</td>
<td>6 (85.7%)</td>
</tr>
</tbody>
</table>

* Includes 3 subjects who were considered matches for both mild and moderate impaired
### Table 3. Remogliflozin (GSK189074) Plasma PK Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mild Renal Impairment (N=12)</th>
<th>Normal Match for Mild Impairment (N=8)</th>
<th>Moderate Renal Impairment (N=7)</th>
<th>Normal Match for Moderate Impairment (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(0-∞) hr.ng/mL</td>
<td>2137 (51)</td>
<td>1973 (38)</td>
<td>2588 (26)</td>
<td>2262 (38)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; ng/mL</td>
<td>1089 (76)</td>
<td>807 (86)</td>
<td>1000 (31)</td>
<td>1072 (64)</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; hr</td>
<td>0.75 (0.50-1.0)</td>
<td>0.75 (0.50-2.0)</td>
<td>1.0 (0.80-1.5)</td>
<td>0.75 (0.50-1.0)</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; hr</td>
<td>1.69 (16)</td>
<td>1.55 (7.0)</td>
<td>1.73 (11)</td>
<td>1.48 (9.8)</td>
</tr>
</tbody>
</table>

*Values are geometric mean (%CV) for each parameter, except for t<sub>max</sub> which are median (range).*
<table>
<thead>
<tr>
<th>Analyte</th>
<th>PK Parameter</th>
<th>Mild Renal Impairment / Matched Normal</th>
<th>Moderate Renal Impairment / Matched Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>REMOGLIFLOZIN ETABONATE</td>
<td>AUC(0-t)</td>
<td>1.20 (0.749, 1.92)</td>
<td>1.18 (0.677, 2.04)</td>
</tr>
<tr>
<td></td>
<td>C_{max}</td>
<td>1.56 (0.841, 2.90)</td>
<td>0.753 (0.365, 1.55)</td>
</tr>
<tr>
<td></td>
<td>t_{1/2}</td>
<td>1.11 (0.678, 1.83)</td>
<td>1.76 (0.990, 3.12)</td>
</tr>
<tr>
<td>REMOGLIFLOZIN</td>
<td>AUC(0-∞)</td>
<td>1.08 (0.798, 1.47)</td>
<td>1.14 (0.800, 1.64)</td>
</tr>
<tr>
<td></td>
<td>C_{max}</td>
<td>1.35 (0.836, 2.18)</td>
<td>0.933 (0.533, 1.63)</td>
</tr>
<tr>
<td></td>
<td>t_{1/2}</td>
<td>1.09 (0.998, 1.20)</td>
<td>1.17 (1.05, 1.31)</td>
</tr>
<tr>
<td></td>
<td>AUC ratio, m/lp</td>
<td>0.903 (0.622, 1.31)</td>
<td>0.974 (0.630, 1.51)</td>
</tr>
<tr>
<td></td>
<td>%Dose Recovered</td>
<td>0.687 (0.501, 0.941)</td>
<td>0.408 (0.264, 0.586)</td>
</tr>
<tr>
<td></td>
<td>CLR</td>
<td>0.633 (0.473, 0.847)</td>
<td>0.357 (0.255, 0.499)</td>
</tr>
<tr>
<td></td>
<td>AUC(0-∞), u</td>
<td>1.08 (0.790, 1.47)</td>
<td>1.12 (0.781, 1.62)</td>
</tr>
<tr>
<td></td>
<td>CLR, u</td>
<td>0.630 (0.470, 0.845)</td>
<td>0.350 (0.250, 0.491)</td>
</tr>
<tr>
<td>GSK279782</td>
<td>AUC(0-∞)</td>
<td>1.51 (0.930, 2.45)</td>
<td>1.34 (0.763, 2.37)</td>
</tr>
<tr>
<td></td>
<td>C_{max}</td>
<td>1.69 (0.959, 2.99)</td>
<td>1.02 (0.524, 1.99)</td>
</tr>
<tr>
<td></td>
<td>t_{1/2}</td>
<td>1.09 (0.955, 1.25)</td>
<td>1.15 (0.960, 1.34)</td>
</tr>
<tr>
<td></td>
<td>AUC ratio, m/lp</td>
<td>1.39 (0.834, 2.32)</td>
<td>1.18 (0.645, 2.14)</td>
</tr>
<tr>
<td></td>
<td>%Dose Recovered</td>
<td>0.734 (0.424, 1.27)</td>
<td>0.337 (0.179, 0.634)</td>
</tr>
<tr>
<td></td>
<td>CLR</td>
<td>0.528 (0.357, 0.781)</td>
<td>0.252 (0.160, 0.395)</td>
</tr>
<tr>
<td></td>
<td>AUC(0-∞), u</td>
<td>1.55 (0.962, 2.50)</td>
<td>1.35 (0.771, 2.36)</td>
</tr>
<tr>
<td></td>
<td>CLR, u</td>
<td>0.541 (0.370, 0.792)</td>
<td>0.253 (0.163, 0.391)</td>
</tr>
<tr>
<td>GSK333081</td>
<td>AUC(0-∞)</td>
<td>1.29 (0.872, 1.92)</td>
<td>1.68 (1.06, 2.67)</td>
</tr>
<tr>
<td></td>
<td>C_{max}</td>
<td>1.32 (0.812, 2.16)</td>
<td>1.21 (0.681, 2.14)</td>
</tr>
<tr>
<td></td>
<td>t_{1/2}</td>
<td>1.20 (1.01, 1.43)</td>
<td>1.28 (1.04, 1.57)</td>
</tr>
</tbody>
</table>

*Values are point estimate (90% confidence interval) of the geometric least-square mean ratio PK parameter, renal impairment versus matched normal.
Table 5. Summary of Urine Excretion and Renal Clearance Data of Remogliflozin and GSK279782*

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Mild Renal Impairment (N=12)</th>
<th>Normal Match for Mild Impairment (N=8)</th>
<th>Moderate Renal Impairment (N=7)</th>
<th>Normal Match for Moderate Impairment (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ae(0-24) (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remogliflozin</td>
<td>9.89 (45)</td>
<td>14.4 (24)</td>
<td>6.45 (66)</td>
<td>15.8 (20)</td>
</tr>
<tr>
<td>GSK279782</td>
<td>2.20 (99)</td>
<td>2.99 (63)</td>
<td>1.55 (91)</td>
<td>4.61 (48)</td>
</tr>
<tr>
<td></td>
<td>Percent Dose Recovered (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remogliflozin</td>
<td>4.85 (45)</td>
<td>7.06 (24)</td>
<td>3.16 (66)</td>
<td>7.75 (20)</td>
</tr>
<tr>
<td>GSK279782</td>
<td>1.19 (99)</td>
<td>1.62 (63)</td>
<td>0.84 (91)</td>
<td>2.49 (48)</td>
</tr>
<tr>
<td></td>
<td>CLr (mL/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remogliflozin</td>
<td>76.9 (49)</td>
<td>122 (28)</td>
<td>41.5 (43)</td>
<td>116 (21)</td>
</tr>
<tr>
<td>GSK279782</td>
<td>56.3 (72)</td>
<td>107 (28)</td>
<td>26.0 (68)</td>
<td>103 (16)</td>
</tr>
<tr>
<td></td>
<td>CLr.u (mL/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remogliflozin</td>
<td>25.0 (46)</td>
<td>38.7 (32)</td>
<td>13.2 (43)</td>
<td>37.6 (27)</td>
</tr>
<tr>
<td>GSK279782</td>
<td>24.0 (69)</td>
<td>44.3 (24)</td>
<td>10.6 (69)</td>
<td>41.8 (16)</td>
</tr>
</tbody>
</table>

*Values are geometric mean (%CV) for each parameter.
Figure 1. Plots of Mean GSK189074 Plasma Concentrations vs Time Profiles

A. Linear Plot

B. Semi-log Plot

△ Mild (N=12)   △ Mild Match (N=8)   ● Moderate (N=7)   ○ Moderate Match (N=7)
AUC(0-inf) = 3085 - 8.527*CLcr

RSquare 0.09381
RSquare Adj 0.06458
Figure 3. Plot of Remogliflozin (GSK189074) C\text{max} vs Day 1 CLcr

\[ C_{\text{max}} = 1344 - 1.764^{*}\text{CLcr} \]

RSquare = 0.005437
RSquare Adj = -0.02665
Figure 4: Scatter Plot of 0-6hr % Filtered Urine Glucose(%FG) vs. 0-6hr Measured Urine Creatinine Clearance

Regression Day -1 %FG = 7.809 - 0.06011*CLcr
RSquare 0.08950
RSquare Adj 0.05811

Regression Day 1 %FG = 47.67 - 0.01491*CLcr
RSquare 0.001427
RSquare Adj -0.03186
Figure 5. Scatter Plot of Day 1 Urine Glucose Amount Excreted vs. Day 1 Urine Creatinine Clearance

0-6hr UGE = 37.783 + 0.52058*CLcr

RSquare 0.3160
RSquare Adj 0.2933
p-value <0.001