



Research Article

# Bioequivalence Study of Fixed-Dose Combination of Remogliflozin Etabonate 100 mg/Vildagliptin 50 mg with Individual Components in Healthy Indian Male Subjects under Fed Conditions

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## Abstract

**Background and Objective.** Combination of sodium glucose co-transporter-2 (SGLT2) and dipeptidyl peptidase-4 (DPP4) inhibitors has shown promising results in the treatment of type 2 diabetes mellitus. A Fixed Dose Combination (FDC) of remogliflozin and vildagliptin will reduce the pill burden and help improve treatment compliance. This study was conducted to establish the bioequivalence of an oral FDC of remogliflozin etabonate (100mg) and vildagliptin (50mg) with single tablets of Remo<sup>®</sup> (remogliflozin etabonate; 100 mg) and Galvus<sup>®</sup> (vildagliptin; 50 mg)

**Methods.** Pharmacokinetic parameters i.e. maximum concentration ( $C_{max}$ ) and area under concentration–time curve ( $AUC_{0-t}$ , and  $AUC_{0-\infty}$ ) were calculated to determine bioequivalence. Safety was assessed and adverse events were monitored throughout the trial.

**Results.** For both remogliflozin and vildagliptin, 90% confidence interval (CI) of the geometric least-squares mean ratios of  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  values between FDC and reference products fell within the standard regulatory bioequivalence range of 85.0-125.0%. Remogliflozin etabonate and its metabolite, GSK279782, also demonstrated geometric least-squares mean ratio of ~ 100%. No clinical abnormalities or adverse events were reported during the study.

**Conclusion.** The FDC of remogliflozin etabonate and vildagliptin was bioequivalent to the reference products (Remo<sup>®</sup> and Galvus<sup>®</sup>) under fed state without any safety concerns.

**Keywords:** Remogliflozin Etabonate; Vildagliptin; Type 2 Diabetes Mellitus; Fixed Dose Combination; Glycemic Control

**Abbreviations:** T2DM: Type 2 Diabetes Mellitus; SGLT2: Sodium Glucose Co-Transporter-2; DPP-4: Dipeptidyl Peptidase-4 BMI: Body Mass Index; ECG: Electrocardiogram; IMP: Investigational Medical Product; NCA: Non-Compartmental Analysis; CTCAE: Common Terminology Criteria for Adverse Events; ICMR: Indian Council of Medical Research; ICH: International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; CDSCO: Central Drugs Standard Control Organization; CIs: Confidence Intervals

## Introduction

Regulating renal glucose reabsorption has proven to be an effective strategy for improving glycemic control and reducing plasma glucose concentration without severe adverse effects in T2DM patients. The primary biological target in this approach is the high-capacity, low-affinity SGLT2, a transport protein distributed on the luminal surface of cells in the S1 segment of the proximal tubule that is responsible for reabsorption of 80-90% of the glucose filtered through the glomerulus [1]. Inhibition of SGLT2 leads to significantly increased urinary glucose excretion, resulting in decreased plasma glucose concentration. The effectiveness of this mechanism has resulted in the development of a class of SGLT2 inhibitors called gliflozins, including dapagliflozin, empagliflozin, and canagliflozin, which in addition to reducing hyperglycemia [2,3] have also demonstrated cardiovascular benefits in T2DM patients [1,4,5].

Remogliflozin etabonate (GSK189075) is an orally available prodrug of remogliflozin that has fast absorption after oral administration and rapidly converts to remogliflozin (GSK189074), which itself is metabolized to the highly selective SGLT2 inhibitor GSK279782. Vildagliptin is an orally available cyanopyrrolidine-based DPP-4 inhibitor that distributes evenly throughout plasma and red blood cells. After rapid absorption, the cyano moiety hydrolyzes into an inactive metabolite that is primarily excreted in the urine. The present study was conducted to assess the bioequivalence of a single dose of combination oral tablet of remogliflozin etabonate 100 mg with vildagliptin 50 mg FDC to remogliflozin etabonate 100 mg tablet and vildagliptin 50 mg tablet, in healthy, adult, male subjects under fed conditions with evaluation of safety and tolerability of this combination product.

## Methods

The study was conducted from December 2019 to January 2020 at Panexcell Clinical Lab Private Ltd., Rabale, Navi Mumbai, India.

## Subjects

The study included male subjects aged from 18 to 45 years

with a BMI ranging from 18.5 to 29.9 kg/m<sup>2</sup> (both inclusive), body weight not less than 50.0 kg, and normal health as determined by personal medical history and laboratory evaluations (hematology, biochemistry, and serological tests). Standard exclusion criteria concerning blood donation, smoking, prescription medication use, alcohol and drug abuse, caffeine intake, and participation in other studies were applied. Subjects were also excluded if they had any clinically significant disorders; clinically significant abnormal findings from the laboratory evaluations; positive test results for hepatitis B surface antigen, hepatitis C antibody, HIV antibody, or positive VDRL result; recent history of urinary tract infection or dehydration; history of hypoglycemia, metabolic acidosis, or diabetic ketoacidosis; abnormal 12-lead ECG recording; or a creatinine clearance level <70 mg/dL. Subjects who were able to understand and comply with the study, including the ability to fast for at least 10 hours, were enrolled in the study.

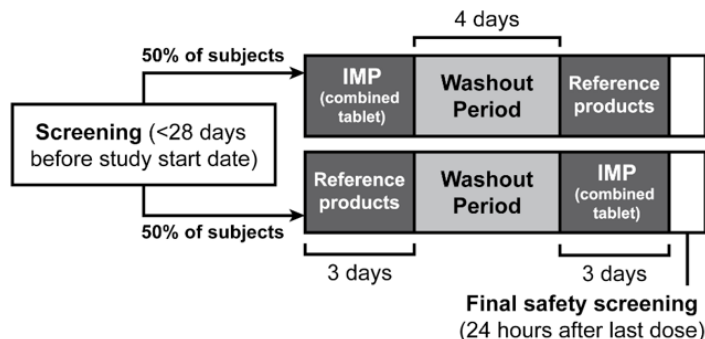
## Study Design

The study was designed and conducted as an open-label, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, two-way cross over oral bioequivalence study (Figure 1). Subjects were randomized to one of two sequences. Sequence 1 subjects received the IMP as a single dose fixed-combination tablet of remogliflozin etabonate 100 mg and vildagliptin 50 mg during the first three-day period and both of the two reference products, Remo<sup>®</sup> (remogliflozin etabonate) 100 mg and Galvus<sup>®</sup> (vildagliptin) 50 mg, as separate tablets in the second three-day period. Sequence 2 subjects received the reference products in the first period and the IMP in the second period. Analysts were blinded to the sequence of each individual subject until the completion of bio-analysis. The total subject participation duration was 10 days, including two three-day periods with a four-day washout period between the end of period 1 and the start of period 2. The washout period was calculated considering that the elimination half-life of the drugs is only 3-4 hours.

Screening was carried out within 28 days of the first study drug administration and included a medical history, physical examination, laboratory assessments, 12-lead ECG, and vital sign measurements (axillary temperature, radial pulse rate, sitting blood pressure and respiratory rate). Upon check-in at the start of each period, subjects underwent a physical examination, breath alcohol test, urine screen for drugs of abuse, blood glucose monitoring, and vital sign measurements.

Subjects were housed at the research facility for 11 hours before dose administration through 24 hours after administration. The study drugs were administered orally in a sitting posture with 240 mL of water at room temperature, preceded by an overnight fast of at least 10 hours and exactly 30 minutes after serving of a standard high-fat, high-calorie, non-veg breakfast, which was consumed within 30 minutes. Subjects were provided with

standard meals at 4-, 8-, and 12-hours post-dose.



**Figure 1:** Schematic of study design.

### Pharmacokinetic Evaluations

The direct measurements of this study were the plasma concentrations of remogliflozin, remogliflozin etabonate, GSK279782, and vildagliptin. A total of 21 blood samples of 6 mL each were collected from each subject: at pre-dose (0 hours) and at 0.16, 0.25, 0.5, 0.75, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 20.0 and 24.0 hours ( $\pm 2$  minutes) post-dose. These time-points were chosen to estimate primary parameters maximum concentration ( $C_{max}$ ), area under the plasma concentration–time curve (AUC) from time zero to the last measurable concentration ( $AUC_{0-t}$ ), and AUC from time zero to infinity ( $AUC_{0-\infty}$ ), and secondary parameters time to  $C_{max}$  ( $t_{max}$ ), elimination rate constant ( $k_{el}$ ), and half-life ( $t_{1/2}$ ) appropriately for remogliflozin and vildagliptin. The blood samples were collected in pre-labeled, pre-chilled potassium oxalate and sodium fluoride vacutainers and centrifuged within 60 minutes of collection at 3800 rpm and 4 °C for 10 minutes to separate the plasma. The separated plasma was separated into aliquots, flash-frozen, and stored at  $-70 \pm 10$  °C before and after analysis.

Concentrations of the drugs in plasma for all 28 subjects were measured by a validated analytical method using liquid chromatography–tandem mass spectrometry (LC-MS/MS). Two subjects were measured under each calibration curve and quality control samples were interspersed throughout each phase. The pharmacokinetic parameters were derived individually from each subject’s plasma concentration–time curve for remogliflozin, remogliflozin etabonate, GSK279782, and vildagliptin using NCA methods in Phoenix® WinNonlin® version 8.1.  $C_{max}$  and  $t_{max}$  were calculated directly from the concentration–time profile of each subject. The  $AUC_{0-t}$  (in ng\*h/ml) was calculated as an integral using the linear trapezoidal method. The  $AUC_{0-\infty}$  (in ng\*h/ml) was calculated as  $AUC_{0-t} + C_t/k_{el}$ , where  $C_t$  is the last measurable concentration. The  $AUC_{0-\infty}$  represents the sum of measurable and extrapolated parts.  $k_{el}$  is the first-order rate constant associated with the log-linear portion of the concentration–time curve and is calculated via linear least squares regression

analysis using at least three non-zero plasma concentration values. The terminal half-life  $t_{1/2}$  was calculated as  $t_{1/2} = 0.693/k_{el}$ . All concentration values below the limit of quantification were set to 0 for all calculations, and any missing or non-reportable values were documented and were not considered in the calculation of any parameters.

### Safety Evaluations

Safety was assessed throughout the screening and study process at periodic intervals. A medical officer and nursing staff were available at all times for examination of the subjects from check-in thorough the end of the second phase. A clinical examination and laboratory panel were performed at screening, enrollment, and after the second phase for post-trial safety. Laboratory tests included hematology, biochemistry, urine analysis, and serology. A 12-lead ECG was obtained at screening and post-study. Blood glucose level was monitored throughout the study at pre-dose and at 1.0, 1.67, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0 and 24.0 hours ( $\pm 15$  minutes) post-dose and additionally at investigator discretion. Vital signs including axillary temperature, sitting blood pressure, and radial pulse rate were recorded at 2.0, 4.0, 6.0, 8.0, and 12.0 hours ( $\pm 60$  minutes) post-dose during each study period. Subjects were monitored throughout the study and post-study for adverse events. CTCAE criteria was adopted for grading the adverse events (any unfavorable and unintended sign including an abnormal laboratory finding, symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.).

### Ethical Standards

The study was reviewed and approved by the Suraksha Ethics Committee and was conducted according to the approved protocol, the ICMR National Ethical Guidelines for Biomedical and Health Research, the ICH E6 R2, the CDSCO New Drugs and Clinical Trials Rules 2019 GSR 227(E), and the Declaration of Helsinki (Fortaleza 2013). All subjects provided written informed consent for the study procedures prior to screening.

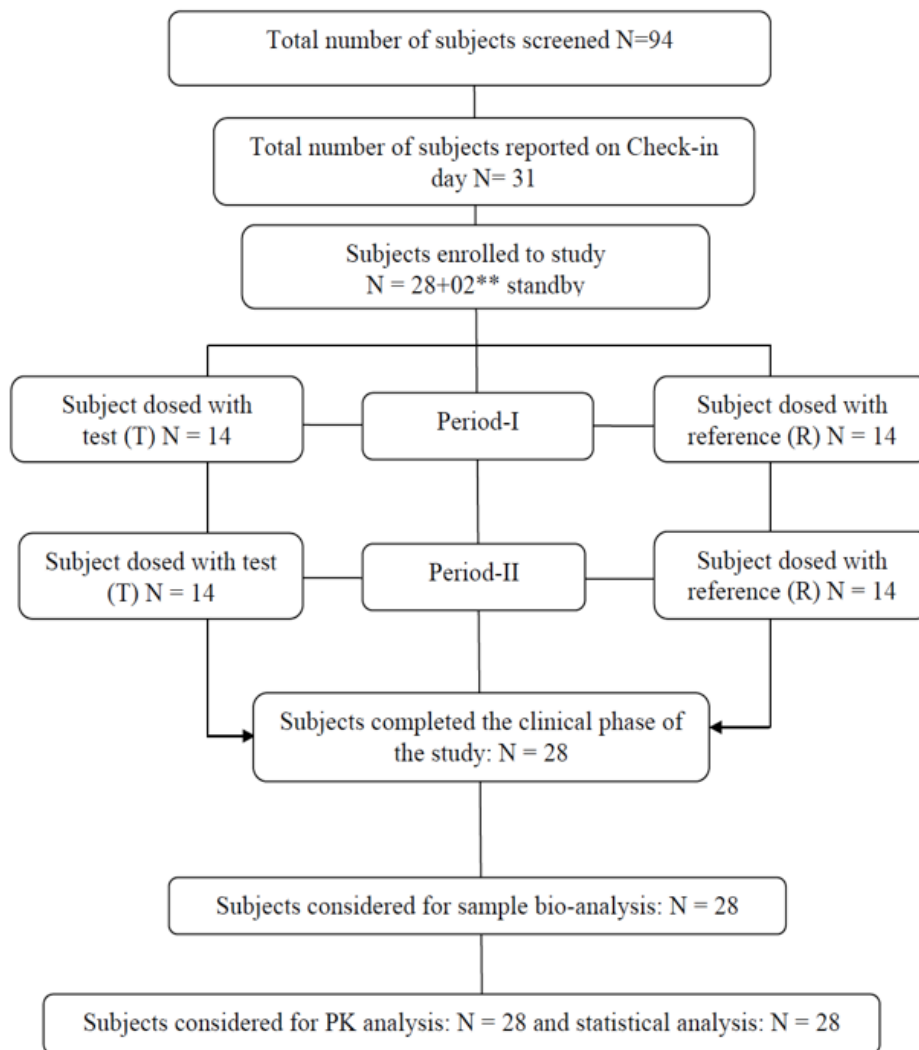
### Statistical Analysis

Based on available literature, the maximum intra-subject variability of vildagliptin was found to be 19.96%. Determination of the sample size was based on this intra-subject variability as well as a significance level of 5% and power  $\geq 80\%$ . A sample size of 24 subjects would be sufficient to establish bioequivalence with adequate power; 28 subjects were enrolled to accommodate potential dropouts. Descriptive statistics were calculated and reported for all pharmacokinetic parameters of remogliflozin, remogliflozin etabonate, GSK279782, and vildagliptin. Actual time of sample collection was used for all calculations. Statistical analysis for establishing bioequivalence was carried out using the

software SAS® version 9.4. ANOVA was performed for analyses of sequence, treatment, and period as fixed effects on  $C_{max}$ ,  $AUC_{0-12}$ , and  $AUC_{0-\infty}$  for remogliflozin and vildagliptin values.

## Results

All 28 subjects successfully completed the clinical study. Details on the screening and enrollment of subjects are shown in Figure 2. Subjects were healthy adult males with a mean age of  $31.11 \pm 5.65$  years (range 23-42 years), mean height of  $1.68 \pm 0.06$  meters (range 1.56-1.78 meters), mean weight of  $66.71 \pm 7.25$  kg (range 52-82 kg), and mean BMI of  $23.76 \pm 2.44$  kg/m<sup>2</sup> (range 19.3-28.8 kg/m<sup>2</sup>).



**Figure 2:** Subject disposition. \*\*indicates the two subjects who were enrolled as standbys in case any of the original 28 participants could not complete the study. These two subjects were not included in the final analysis.

The pharmacokinetic results of remogliflozin, vildagliptin, remogliflozin etabonate, and GSK279782 are presented in Tables 1 and 2. Assessment of bioequivalence for each analyte was done on the basis of 90% confidence intervals (CIs) for the ratio of geometric least-squares means for the natural log-transformed  $C_{max}$ ,  $AUC_{0-12}$ , and  $AUC_{0-\infty}$ , i.e.  $\ln(\text{IMP value})/\ln(\text{reference value})$ . Bioequivalence was confirmed if the entire confidence interval of this ratio was between 85.0%–125.0%.

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Pharmacokinetic Parameters (N=28)	Test	Reference
<b>Remogliflozin</b>		
$C_{max}$ (ng/mL)	483.5 ± 181.5 (37.5%)	455.1 ± 158.7 (34.9%)
$AUC_{0-t}$ (ng*hr/mL)	1697.6 ± 397.1 (23.4%)	1680.3 ± 414.7 (24.7%)
$AUC_{0-\infty}$ (ng*hr/mL)	1723.0 ± 412.6 (24.0%)	1690.8 ± 414.4 (24.5%)
$t_{max}$ (hr)	3.00 (0.75-8.00) (50.9%)	2.51 (0.50-5.00) (48.4%)
$K_{el}$ (1/hr)	0.400 ± 0.087 (21.7%)	0.404 ± 0.048 (11.97%)
$t_{1/2}$ (hr)	1.92 ± 1.02 (53.1%)	1.74 ± 0.22 (12.5%)
%AUC <sub>extrapolated</sub>	1.28 ± 3.43 (268.2%)	0.67 ± 0.37 (55.6%)
<b>GSK279782</b>		
$C_{max}$ (ng/mL)	90.00 ± 55.60 (61.8%)	82.10 ± 51.14 (62.3%)
$AUC_{0-t}$ (ng*hr/mL)	405.8 ± 175.1 (43.1%)	388.41 ± 181.93 (46.8%)
$AUC_{0-\infty}$ (ng*hr/mL)	413.6 ± 181.5 (43.9%)	391.49 ± 182.34 (46.6%)
$t_{max}$ (hr)	3.75 (1.33-8.00) (42.2%)	3.00 (1.00-5.00) (44.8%)
$K_{el}$ (1/hr)	0.237 ± 0.053 (22.3%)	0.258 ± 0.047 (18.1%)
$t_{1/2}$ (hr)	3.14 ± 1.04 (33.2%)	2.79 ± 0.59 (21.1%)
%AUC <sub>extrapolated</sub>	1.54 ± 3.32 (215.6%)	0.89 ± 0.33 (37.0%)
<b>Remogliflozin etabonate</b>		
$C_{max}$ (ng/mL)	14.74 ± 12.40 (84.2%)	14.79 ± 12.11 (81.9%)
$AUC_{0-t}$ (ng*hr/mL)	25.05 ± 14.35 (57.3%)	23.97 ± 13.64 (56.9%)
$AUC_{0-\infty}$ (ng*hr/mL)	26.94 ± 15.23 (56.5%)	24.34 ± 13.70 (56.3%)
$t_{max}$ (hr)	2.00 (0.50-5.00) (54.4%)	1.67 (0.25-3.50) (60.5%)
$K_{el}$ (1/hr)	1.21 ± 0.52 (42.7%)	1.16 ± 0.41 (35.2%)
$t_{1/2}$ (hr)	0.99 ± 1.51 (151.6%)	0.90 ± 1.15 (128.7%)
%AUC <sub>extrapolated</sub>	2.02 ± 4.55 (225.0%)	1.67 ± 2.02 (121.2%)
<b>Vildagliptin</b>		
$C_{max}$ (ng/mL)	245.9 ± 132.7 (54.0%)	217.5 ± 60.6 (27.9%)
$AUC_{0-t}$ (ng*hr/mL)	1205.1 ± 296.9 (24.6%)	1216.3 ± 350.1 (28.8%)
$AUC_{0-\infty}$ (ng*hr/mL)	1219.8 ± 297.8 (24.4%)	1230.2 ± 349.3 (28.4%)
$t_{max}$ (hr)	2.50 (0.75-6.00) (50.9%)	2.25 (1.00-5.00) (48.2%)
$K_{el}$ (1/hr)	0.325 ± 0.075 (23.1%)	0.32 ± 0.065 (20.1%)
$t_{1/2}$ (hr)	2.26 ± 0.59 (26.1%)	2.24 ± 0.60 (26.6%)
%AUC <sub>extrapolated</sub>	1.24 ± 0.58 (46.8%)	1.21 ± 0.66 (54.1%)



$C_{max}$  = maximum concentration,  $AUC_{0-t}$  = area under the plasma concentration–time curve from time zero to the last measurable concentration;  $AUC_{0-\infty}$  = area under the plasma concentration–time curve from time zero to infinity ( $AUC_{0-\infty}$ ),  $T_{max}$  = time to  $C_{max}$ ,  $K_{el}$  = elimination rate constant, and  $t_{1/2}$  = half-life.  $t_{max}$  is represented as reported median (minimum – maximum) (% coefficient of variation). All other values are reported as arithmetic mean  $\pm$  standard deviation (coefficient of variation).

**Table 1:** Pharmacokinetic parameters of remogliflozin, its active metabolite GSK279782, its precursor remogliflozin etabonate, and vildagliptin in test & reference products.

Remogliflozin demonstrated a  $C_{max}$  geometric least-squares mean ratio of 104.73 with a CI of 94.83–115.65, an  $AUC_{0-t}$  ratio of 101.30 with a CI of 98.36–104.33, and an  $AUC_{0-\infty}$  ratio of 101.99 with a CI of 98.54–105.56 (Table 2). Vildagliptin demonstrated a  $C_{max}$  ratio of 107.61 with a CI of 95.61–121.61, an  $AUC_{0-t}$  ratio of 99.83 with a CI of 97.29–102.44, and an  $AUC_{0-\infty}$  ratio of 99.86 with a CI of 97.41–102.36 (Table 3).

Pharmacokinetic Parameter	Geometric Least Squares Mean			90% CI	Intra-subject variability CV (%)	Power (%)
	Test	Reference	% Ratio (T/R)			
$C_{max}$ (ng/mL)	451.8	431.4	104.7	94.8 – 115.7	22.0	97.9
$AUC_{0-t}$ (ng*hr/mL)	1649.1	1628.0	101.3	98.4 – 104.3	6.47	100.0
$AUC_{0-\infty}$ (ng*hr/mL)	1671.6	1639.0	102.0	98.5 – 105.6	7.56	100.0

CI= Confidence Interval; CV= Coefficient of Variation

**Table 2:** Bioequivalence summary of remogliflozin (N = 28)

Geometric least-squares mean ratios for remogliflozin etabonate and GSK279782 were also calculated to provide supportive evidence of comparable therapeutic outcome.

Pharmacokinetic Parameter	Geometric Least Squares Mean			90% CI	Intra-subject variability CV (%)	Power (%)
	Test	Reference	% Ratio (T/R)			
$C_{max}$ (ng/mL)	226.3	210.3	107.6	95.6 – 121.1	26.4	92.9
$AUC_{0-t}$ (ng*hr/mL)	1178	1180.1	99.8	97.3 – 102.4	5.67	100
$AUC_{0-\infty}$ (ng*hr/mL)	1193	1194.6	99.9	97.4 – 102.4	5.44	100

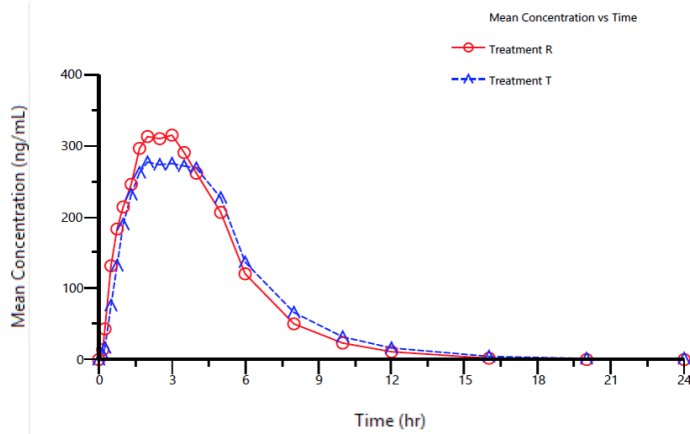
Remogliflozin etabonate demonstrated a  $C_{max}$  ratio of 100.20, an  $AUC_{0-t}$  ratio of 104.11, and an  $AUC_{0-\infty}$  ratio of 105.68 (Table 4). GSK279782 demonstrated a  $C_{max}$  ratio of 109.39, an  $AUC_{0-t}$  ratio of 105.33, and an  $AUC_{0-\infty}$  ratio of 106.09 (Table 4).

**Table 3:** Bioequivalence summary of Vildagliptin (N = 28).

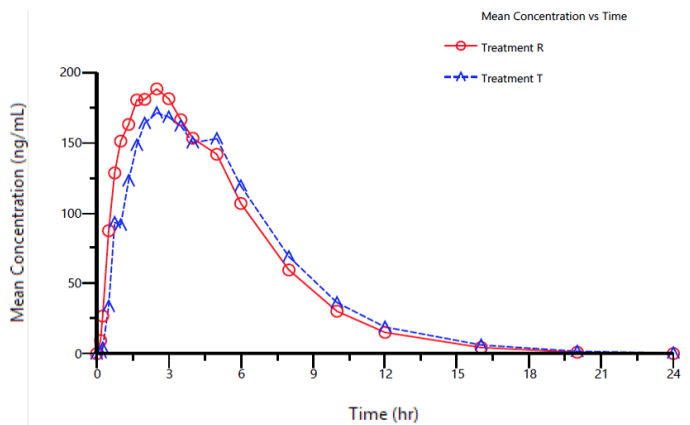
Pharmacokinetic Parameter	Remogliflozin Etabonate Geometric Least Squares Mean			GSK279782 Geometric Least Squares Mean		
	Test	Reference	% Ratio (T/R)	Test	Reference	% Ratio (T/R)
$C_{max}$ (ng/mL)	11.8	11.74	100.2	78.97	72.19	109.4
$AUC_{0-t}$ (ng*hr/mL)	22.5	21.57	104.1	372.4	353.5	105.3
$AUC_{0-\infty}$ (ng*hr/mL)	23.2	21.94	105.7	378.4	356.7	106.1

**Table 4:** Bioequivalence summary of remogliflozin etabonate and its derivative GSK279782 (N = 28)

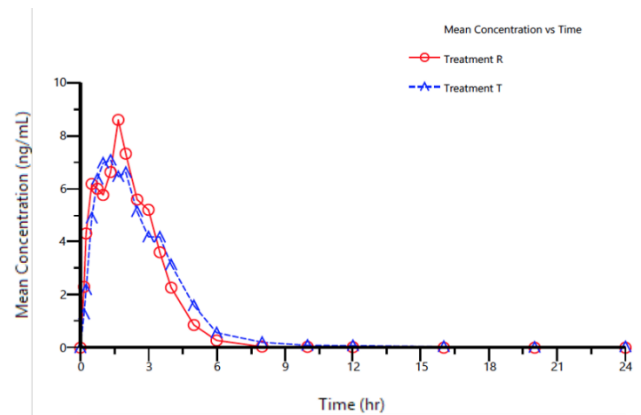
The plasma concentration–time curves for remogliflozin, vildagliptin, remogliflozin etabonate, and GSK279782 are shown in Figures 3, 4, 5, and 6 respectively. The similarity of the curves for the investigational product and reference product additionally verify bioequivalence between the two. As expected, both remogliflozin and vildagliptin are rapidly absorbed and gradually secreted from the body same as individual drugs. Combining the two drugs into one tablet does not appear to affect the pharmacokinetics of either drug.



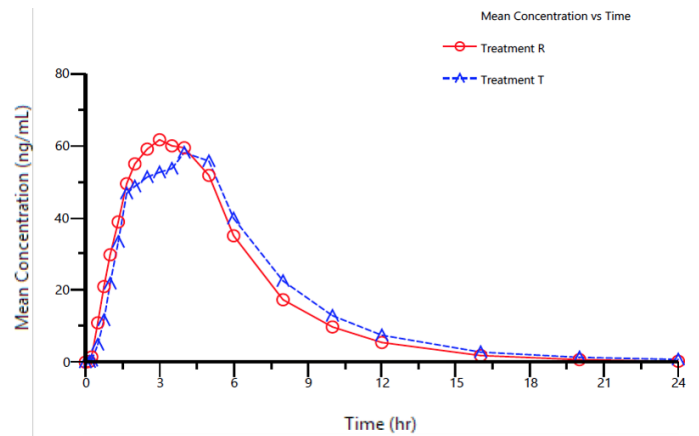
**Figure 3:** Plasma concentration–time curve for remogliflozin. Treatment R corresponds to the reference drugs and Treatment T is the investigational product.



**Figure 4:** Plasma concentration–time curve for vildagliptin. Treatment R corresponds to the reference drugs and Treatment T is the investigational product.



**Figure 5:** Plasma concentration–time curve for remogliflozin etabonate. Treatment R corresponds to the reference drugs and Treatment T is the investigational product.



**Figure 6:** Plasma concentration–time curve for GSK279782. Treatment R corresponds to the reference drugs and Treatment T is the investigational product.

The p-values obtained for sequence, treatment, and period effects on  $C_{max}$  for both remogliflozin and vildagliptin were all greater than 0.05, indicating no statistically significant effects. The p-values obtained for treatment and sequence effects on  $AUC_{0-12}$  and  $AUC_{0-\infty}$  for remogliflozin and for treatment and period effects on  $AUC_{0-12}$  and  $AUC_{0-\infty}$  for vildagliptin were also greater than 0.05. The p-values obtained for the period effect on  $AUC_{0-12}$  and  $AUC_{0-\infty}$  for remogliflozin and for the sequence effect on  $AUC_{0-12}$  and  $AUC_{0-\infty}$  for vildagliptin were less than 0.05, indicating that these two effects were statistically significant.

No adverse events were observed during the conduct of the study or in the post-study safety evaluation. No abnormalities were observed in any safety parameters (vital signs, blood glucose levels, physical examinations, and ECG) throughout the study or in the post-study evaluation.

## Discussion

TD2M patients typically take many prescription medications; combining two common and effective TD2M medications into one tablet can reduce the burden on patients and increase patient compliance by simplifying their medication regimen [9]. The aim of this study was to evaluate and compare pharmacokinetic variables ( $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$ ) of a single dose investigational product, a fixed-dose combination tablet of 100 mg remogliflozin etabonate and 50 mg vildagliptin (investigational product), to its individual mono-components, namely remogliflozin etabonate 100 mg and vildagliptin 50 mg tablets (reference products) in healthy, adult, male subjects under fed conditions.

The assessment of pharmacokinetic parameters for remogliflozin etabonate after administration of reference product is similar to a previous pharmacokinetic assessment of RE performed in healthy Indian male subjects in fasted and fed states [10]. The  $AUC_{0-\infty}$  for remogliflozin and GSK279782 is reported to be ranging from 1266.1 – 1546.6 ng\*h/mL and 323.6 – 651.1 ng\*h/mL after single dose of RE 100mg. This is in agreement with  $AUC_{0-\infty}$  of 1690.8 ng\*h/mL and 391.49 ng\*h/mL observed in reference arm. Similarly,  $AUC_{0-\infty}$  of RE reported prior (17.4 – 42.2 ng.h/mL) was comparable to observation in this study of 24.34 ng.h/mL. The observed  $C_{max}$  of remogliflozin & GSK279782 of 455.1 ng/mL & 82.10 ng/mL respectively in the reference arm is similar to reported  $C_{max}$  of 413.68 - 536.18 ng/mL for remogliflozin but lower compared to 96.63 - 138.64 ng/mL for GSK279782. Similarly, the  $C_{max}$  of RE (14.79 ng/mL) in this study was lower to reported  $C_{max}$  in the prior study. Considering wide variations due to multiple factors in absorption & metabolism of RE, these differences in  $C_{max}$  can be chance observations and are unlikely to have major clinical relevance. The shapes of the plasma–concentration time curves and the half-lives of the components were comparable between the two studies.

The pharmacokinetic parameters of vildagliptin, including  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$ , were very similar to results obtained from a previous study of healthy Chinese participants receiving a 50 mg tablet of vildagliptin once daily [11]. In that study, the average  $C_{max}$  of 50 mg vildagliptin was 308 ng/mL compared to 226 ng/mL in this study. The average  $AUC_{0-t}$  and  $AUC_{0-\infty}$  in that study were 1202 and 1209 ng\*hr/mL, respectively, compared to 1178.1 and 1192.9 ng\*hr/mL in this study. The marginal lower values observed can be potentially attributed to ethnic differences in study populations. The fairly rapid half-life of vildagliptin was observed in both studies, as was the overall shape of the plasma–

concentration time curve.

The analysis of effects of treatment, sequence, and period on  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  on vildagliptin and remogliflozin showed no statistically significant effects except for an effect of period on  $AUC_{0-t}$  and  $AUC_{0-\infty}$  for remogliflozin and an effect of sequence on  $AUC_{0-t}$  and  $AUC_{0-\infty}$  for vildagliptin. However, given that the study used an appropriate washout period and the resultant 90% CI were well within range of within regulatory limits, these effects were considered random and unlikely to have clinical implication.

The 90% confidence intervals of the geometric least-squares mean ratio of each parameter for both remogliflozin and vildagliptin fell in the regulatory limits of 85.0%–125.0%. The geometric least-squares mean ratios of remogliflozin etabonate and active metabolite GSK279782 were also approximately 100%, offering further support of bioequivalence between the products. This is also evident from the plasma–concentration time curves for remogliflozin & its metabolites as well as vildagliptin, wherein the plasma concentration profiles of all four analytes are practically identical between the combination investigational product and the separate reference products.

Safety was assessed throughout the study. There were no clinically significant findings in laboratory tests, vital signs assessments, clinical examinations, blood glucose levels, or ECG recordings found in any of the subjects at any point in the study. Additionally, no adverse effects were observed in the subjects during or after the study. This indicates that the combination investigational product was well-tolerated as a single oral dose in healthy adult men under fed conditions. Overall, the study data therefore demonstrates that combining the two drugs into a single tablet neither affects the plasma exposure to either drug nor has any additional safety concern. Thereby, the FDC is expected to potentially offer an equivalent biological response to independent drug administration of individual components.

## Conclusion

In this single-dose bioequivalence study, the pharmacokinetic data indicate that oral tablet of 100 mg remogliflozin etabonate and 50 mg vildagliptin FDC was bioequivalent to the reference products (remogliflozin etabonate 100 mg and vildagliptin 50 mg tablet). Also, the FDC was found to be well-tolerated.

## References

1. Bonora BM, Avogaro A, Fadini GP (2020) Extraglycemic effects of SGLT2 inhibitors: a review of the evidence. *Diabetes Metab Syndr Obes.* 13:161.
2. Tang H, Cui W, Li D, Wang T, Zhang J, Zhai S, et al. (2017) Sodium-glucose co-transporter 2 inhibitors in addition to insulin therapy for management of type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. *Diabetes Obes Metab.* 19(1):142-7.



3. Garcia-Ropero A, Badimon JJ, Santos-Gallego CG (2018) The pharmacokinetics and pharmacodynamics of SGLT2 inhibitors for type 2 diabetes mellitus: the latest developments. *Expert Opin Drug Metab Toxicol.* 14(12):1287-302.
4. Usman MS, Siddiqi TJ, Memon MM, Khan MS, Rawasia WF, et al. (2018) Sodium-glucose co-transporter 2 inhibitors and cardiovascular outcomes: a systematic review and meta-analysis. *Eur J Prev Cardiol.* 25(5):495-502.
5. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E et al (2015). Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 373(22):2117-28.
6. Cai X, Gao X, Yang W, Chen Y, Zhou L et al (2016) DPP-4 inhibitor treatment in Chinese type 2 diabetes patients: a meta-analysis. *Diabetes Technol Ther.* 18(12):784-93.
7. Wang X, Zheng P, Huang G, Yang L, Zhou Z (2018) Dipeptidyl peptidase-4 (DPP-4) inhibitors: promising new agents for autoimmune diabetes. *Clin Exp Med.* 18(4):473-80.
8. Li D, Shi W, Wang T, Tang H (2018) SGLT2 inhibitor plus DPP-4 inhibitor as combination therapy for type 2 diabetes: A systematic review and meta-analysis. *Diabetes Obes Metab.* 20(8):1972-6.
9. Scheen AJ (2016) DPP-4 inhibitor plus SGLT-2 inhibitor as combination therapy for type 2 diabetes: from rationale to clinical aspects. *Expert Opin Drug Metab Toxicol.* 12(12):1407-17.
10. Joshi S, Gudi G, Menon VC, Tandon M, Joshi V et al (2020) An Open-Label, Single-Period, Two-Stage, Single Oral Dose Pharmacokinetic Study of Remogliflozin Etabonate Tablet 100 and 250 mg in Healthy Asian Indian Male Subjects Under Fasting and Fed Conditions. *Clin Pharmacokinet.* 59(3):349-57.
11. Hu P, Yin Q, Deckert F, Jiang J, Liu D et al (2009) Pharmacokinetics and pharmacodynamics of vildagliptin in healthy Chinese volunteers. *Clin Pharmacol.* 49(1):39-49.