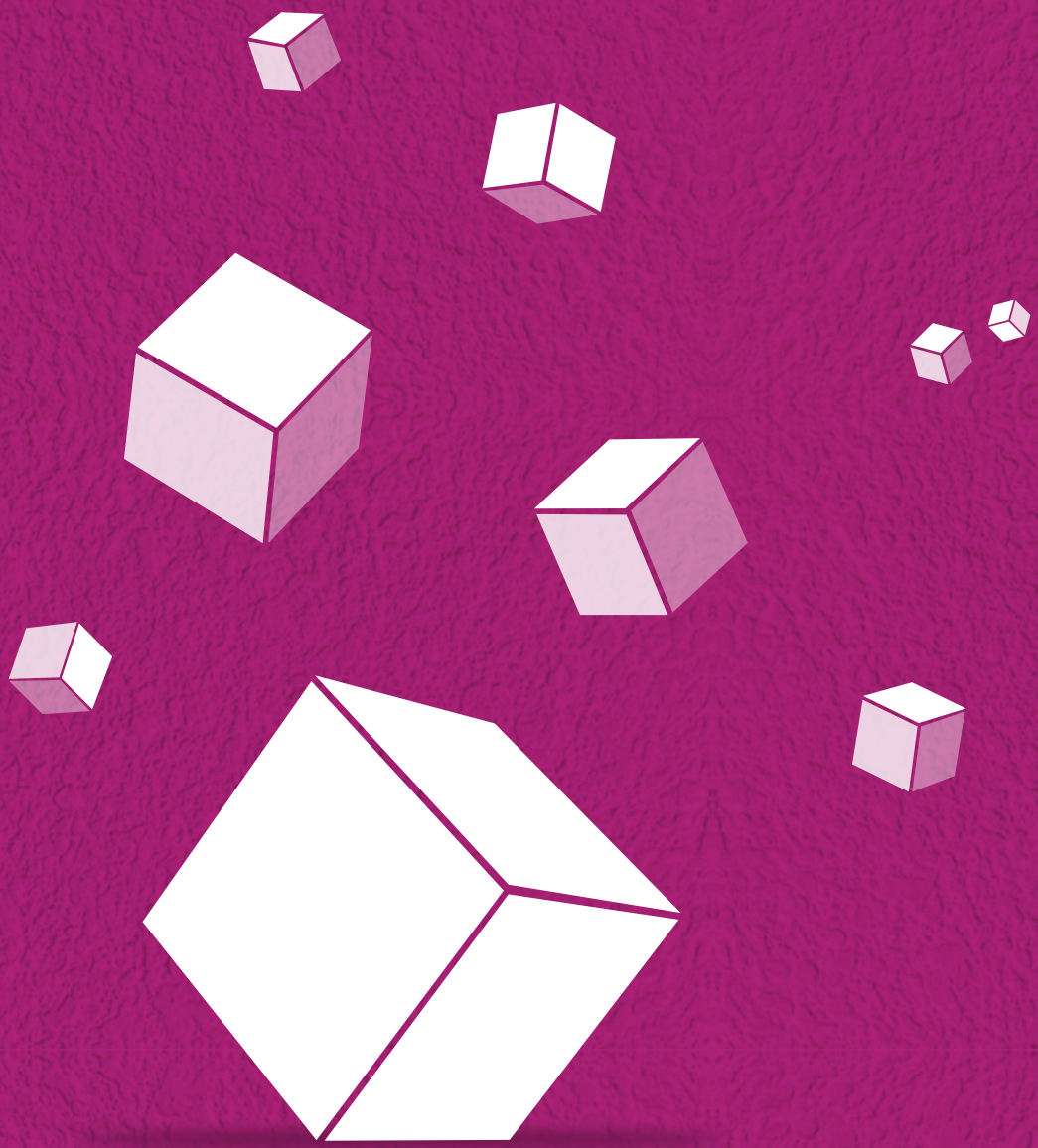
Reniva

Remogliflozin Etabonate 100 mg Tablets

The *Cardiometabolic OAD*



Product Monograph

Prevalence of Co-morbid conditions with T2DM

Hypertension

60% of T2DM patients[1]

CVDs*

68% of T2DM patients[3]

Obesity

86% of T2DM patients[2]

Need a *"Cardiometabolic OAD"*

1. World J Diabetes. 2015 Oct 10; 6(13): 1246–1258. 2. Postgrad Med J. 2006 Apr; 82(966): 280–284
3. Circ Res. 2016 May 27; 118(11): 1723–1735. *** CVD:** Cardio Vascular Diseases

Reniva

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PART I: HEALTH PROFESSIONAL INFORMATION
SUMMARY OF PRODUCT CHARACTERISTICS

Remogliflozin etabonate 100 mg Tablets

1. NAME OF THE MEDICINAL PRODUCT

Remogliflozin etabonate 100 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Remogliflozin etabonate 100 mg Tablets
Each film coated tablet contains:
Remogliflozin Etabonate .... 100 mg
Excipients q.s
Colour: Titanium Dioxide USP.

3. PHARMACEUTICAL FORM

Film coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Remogliflozin etabonate is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycemic control as:

- Monotherapy when diet and exercise alone do not provide adequate glycaemic control.
- Add on therapy with Metformin, when these, together with diet and exercise, do not provide adequate glycaemic control.

4.2 Posology and Method of Administration

Posology

The recommended dose of Remogliflozin etabonate (GSK189075) is 100 mg twice daily for monotherapy and add-on therapy with Metformin. As observed with other sodium-dependent glucose co-transporter member 2 (SGLT2) inhibitors, when Remogliflozin etabonate (GSK189075) is used in addition to insulin or an insulin secretagogue, such as a sulphonylurea, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia.

Special populations

Renal impairment

In a single dose study with subjects having mild and moderate renal impairment, there was no clinically meaningful impact on the plasma exposure or elimination t1/2 of Remogliflozin etabonate (GSK189075), Remogliflozin (GSK189074) and metabolite GSK279782. Renal impairment also did not affect extent of plasma protein binding. However, Remogliflozin etabonate (GSK189075) has not been studied in patients with severe renal impairment (eGFR < 30 ml/min/1.73m2). No dosage adjustment is indicated in patients with mild to moderate renal impairment.

In Phase IIb studies, Serum creatinine and estimated glomerular filtration rate (eGFR) changes were variable and showed no consistent changes over time. The change from baseline in renal function parameters was clinically insignificant & comparable to active-control group in Phase 3 study.

Remogliflozin (GSK189074) is not recommended to be initiated in patients with GFR < 60 mL/min and recommended to be discontinued at GFR <45 mL/min.

Hepatic impairment

The safety, efficacy and pharmacokinetic of Remogliflozin (GSK189074) in patients with hepatic impairment has not been established. In contrast, 90% of elimination happens through metabolism by Cytochrome P450 (CYPs) and glucuronidation. Hepatic impairment can impact the pharmacokinetic (PK) of Remogliflozin (GSK189074). Remogliflozin (GSK189074) is not recommended for use in patients with moderate to severe hepatic impairment.

Elderly (≥ 65 years)

In general, no dosage adjustment is recommended based on age. Renal function and risk of volume depletion should be taken into account. Due to the limited therapeutic experience in patients 75 years and older, initiation of Remogliflozin (GSK189074) therapy is not recommended.

Paediatric population

The safety and efficacy of Remogliflozin etabonate (GSK189075) in children aged 0 to <18 years have not yet been established.

Method of administration

There was no clinically relevant impact of food on the pharmacokinetics of Remogliflozin etabonate (GSK189075). Remogliflozin etabonate (GSK189075) can be taken orally twice daily with or without food. Tablets are to be swallowed as a whole.

No sex or age related effect was identified in glucose lowering effect of Remogliflozin etabonate (GSK189075).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special Warnings and Precautions for Use

Remogliflozin (GSK189074) is not recommended to be initiated in patients with moderate to severe renal impairment (glomerular filtration rate [GFR] <60 mL/min) and is recommended to be discontinued at GFR <45 mL/min.

The safety and efficacy of Remogliflozin (GSK189074) in patients with hepatic impairment has not been established. Remogliflozin (GSK189074) is not recommended for use in patients with moderate to severe hepatic impairment.

Due to its mechanism of action, Remogliflozin etabonate (GSK189075) produces glycosuria and osmotic diuresis. Consequently, there may be a decrease in intravascular volume that could result in hypotension, hemoconcentration, or electrolyte abnormalities. Initiation of Remogliflozin etabonate (GSK189075) in patients receiving concomitant diuretics should be undertaken cautiously and, where appropriate, dose reduction of diuretics should be considered based upon clinical presentation or laboratory results.

Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors. No moderate to severe events of diabetic ketoacidosis (DKA) were reported in clinical studies with Remogliflozin (GSK189074).

The risk of diabetic ketoacidosis (DKA) must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

In patients where diabetic ketoacidosis (DKA) is suspected or diagnosed, treatment with Remogliflozin (GSK189074) should be discontinued immediately.

Urinary tract infections were reported for Remogliflozin (GSK189074) up to 24 weeks. Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of Remogliflozin (GSK189074) should be considered when treating urinary tract infections.

There is no experience in clinical studies with Remogliflozin (GSK189074) in patients with cardiac failure.

An increase in cases of lower limb amputation (primarily of the toe) has been observed in ongoing long-term, clinical studies with another sodium-glucose co-transporter 2 (SGLT2) inhibitor. No event of limb amputation has been reported in clinical studies with Remogliflozin (GSK189074). Like for all diabetic patients it is important to counsel patients on routine preventative foot care.

In patients with diabetes mellitus receiving other SGLT2 inhibitors, reports of necrotizing fasciitis of the perineum (Fournier's Gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in post-marketing surveillance. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death. Patients treated with Remogliflozin presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue Remogliflozin, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Caution should be exercised in patients who have potential for complex metabolic abnormalities with intercurrent illnesses and who experience significant volume depletion or significant hypoglycaemia.

Patients on oral contraceptives should be advised to use alternative, non-hormonal methods of birth control during treatment with Remogliflozin etabonate (GSK189075).

4.5 Interaction with other medicinal products and other forms of interactions

No clinically meaningful effect of food on the exposures of either Remogliflozin etabonate (GSK189075), Remogliflozin (GSK189074), or metabolites (i.e. GSK279782, GSK333081) has been observed.

The risk of drug interactions with cytochrome P450 (CYP) inhibitors is low due to the multiple pathways (CYP and non-CYP) of elimination. Following co-administration of Remogliflozin etabonate (GSK189075) with ketoconazole, a potent CYP3A4 inhibitor, clinically meaningful effect was not observed on the systemic exposure of Remogliflozin (GSK189074) and its metabolites. (1)

There is a potential for CYP inducers to alter the pharmacokinetics of Remogliflozin (GSK189074) and its metabolites.

In a clinical pharmacology study, low levels of ethinylestradiol and norethindrone were observed probably due to sporadic lack of absorption in women receiving the oral contraceptive (Brevicon) in combination with Remogliflozin etabonate (GSK189075). As the effectiveness of oral contraceptives may be negatively impacted, patients on oral contraceptives should be advised to use alternative, non-hormonal methods of birth control during treatment with Remogliflozin etabonate (GSK189075).

Both Remogliflozin etabonate (GSK189075) and Remogliflozin (GSK189074) are P-glycoprotein (P-gp) substrates whereas neither are P-gp inhibitors. It is unlikely that P-gp inhibitors will have a clinically relevant effect as more than 90% of the dose is absorbed in humans.

In a clinical study, serum concentrations of metformin were not altered by co-administration of Remogliflozin etabonate (GSK189075) and similarly, serum levels of Remogliflozin etabonate (GSK189075), Remogliflozin (GSK189074), and metabolite (GSK279782) were not affected by co-administration of metformin. No significant rise in serum lactic acid was seen when Remogliflozin etabonate (GSK189075) was co-administered with metformin. (2)

Co-administration of Remogliflozin etabonate (GSK189075) and diuretic increases urinary glucose excretion but has no appreciable effects on urine & Serum electrolyte concentrations. The creatinine clearance decreases slightly more than with placebo, when Remogliflozin etabonate (GSK189075) is added to background diuretic regimens with trend of increase serum creatinine and urea indicating possible volume depletion with the Remogliflozin (GSK189074) diuretic combination.

Initiation of Remogliflozin etabonate (GSK189075) in patients receiving concomitant diuretics should be undertaken cautiously and where appropriate dose reduction of diuretics considered based upon clinical presentation or laboratory results.

Concomitant administration of Remogliflozin etabonate (GSK189075) and bupropion does not affect the steady state pharmacokinetic (PK) of Remogliflozin (GSK189074) or bupropion and has no impact on urine glucose excretion.

Increased risk of hypoglycaemia is known when sulfonylurea such as glimepiride is co-administered with sodium-glucose co-transporter 2 (SGLT2) inhibitors. However, in 24-week phase III clinical trial in subjects with type 2 diabetes mellitus, no adverse event of hypoglycaemia was reported in 36 patients when sulfonylurea was concomitantly administered with Remogliflozin etabonate (GSK189075) and metformin.

Single-dose study of Remogliflozin etabonate (GSK189075) when co-administered with basal insulin in Type 1 DM were generally well tolerated with no safety issues identified. (3) However, patients should be alerted to the risk of hypoglycaemia when Remogliflozin (GSK189074) is used in combination with insulin.

Paediatric population

No interaction studies have been performed in paediatric population.

4.6 Fertility, pregnancy and lactation

Pregnancy and Lactation

No clinical studies with Remogliflozin etabonate (GSK189075) have been conducted in pregnant or lactating women and it is not known if Remogliflozin etabonate or Remogliflozin (active moiety) is secreted in human breast milk. Remogliflozin etabonate (GSK189075) is not recommended during pregnancy and breastfeeding. Pregnancy should be excluded prior to administration of Remogliflozin etabonate (GSK189075) and appropriate contraceptive measures should be followed by women of childbearing potential. Due to a potential effect of Remogliflozin etabonate (GSK189075) on absorption, oral hormonal contraceptives may not provide effective contraception and an appropriate alternative method for avoiding pregnancy should be utilized (see section 4.5).

Fertility

Remogliflozin etabonate had no effect on male (200, 600 and 1200 mg/kg/day; oral) and female (200, 600 and 1000 mg/kg/day; oral) fertility in rats and the no-observed-adverse-effect level

(NOAEL) were 1200 mg/kg/day (approximately 2358 times the maximum recommended human daily dose (MRHDD) of 100250 mg twice daily (500200 mg/day) on body surface area [mg/m2] basis) and 1000 mg/kg/day (approximately 2049 times the MRHDD of 500200 mg/day on mg/m2 basis), respectively. Remogliflozin etabonate was not teratogenic in rats (200, 600 and 1000 mg/kg/day) and rabbits (125, 250 and 500 mg/kg/day) at oral doses of 1000 and 500 mg/kg/day (approximately 2049 times the MRHDD of 500200 mg/day on mg/m2 basis), respectively. In pre- and post-natal developmental study in rats (200, 600 and 1000 mg/kg/day; oral), Remogliflozin etabonate was administered orally to parental pregnant females (from Day 15 of presumed gestation to lactation) and selected F1 generation males (from weaning through their periods of growth to sexual maturity and during pairing) and females (from weaning through their periods of growth to sexual maturity, during pairing, gestation, lactation and until weaning of F2 litres) at daily doses of 200, 600 and 1000 mg/kg/day. No treatment-related effects were noted in pregnant/lactating females and on development of the conceptus and the offspring following exposure up to 1000 mg/kg/day (approximately 2049 times the MRHDD of 500200 mg/day on mg/m2 basis).

4.7 Effects on ability to drive and use machines

Currently, there is no information available to assess any possible effect of Remogliflozin (GSK189074) on the ability to drive or use machinery. Patients should be alerted to the risk of hypoglycaemia when Remogliflozin (GSK189074) is used in combination with a sulphonylurea or insulin.

4.8 Undesirable effects

Summary of the safety profile

In a 24-week, randomised, double-blind, double-dummy parallel-group, multi-centre, active-controlled (Dapagliflozin 10 mg) phase III study, 465 subjects with type 2 diabetes mellitus were treated with Remogliflozin etabonate (GSK189075) in addition to ongoing metformin treatment with doses ≥1500 mg (≥1000 mg per day in subjects not tolerating higher doses of metformin).

Commonly reported adverse reaction (>1% incidence) were urinary tract infection (4.9%), pyrexia (2.7%), headache (2.5%), bacteriuria (2.3%), constipation (1.7%), diarrhoea (1.7%), glomerular filtration rate decreased (1.7%), ketonuria (1.7%), cough (1.5%), dyslipidaemia (1.5%), asthenia (1.0%), viral upper respiratory tract infection (1.0%), hypoglycaemia (1.0%), and orthostatic hypotension (1.0%).

Tabulated list of adverse reactions

The following adverse reactions have been identified in the active-controlled clinical trial.

Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data).

Table 1: Summary of Frequency Categories of TEAEs for Remogliflozin etabonate (GSK189075) (Safety Population)

System Organ Class	Common	Uncommon
Blood and lymphatic system disorders		Anaemia Eosinophilia Iron deficiency anaemia, Microcytic anaemia, Thrombocytopenia Thrombocytosis
Ear and labyrinth disorders		Vertigo
Eye disorders Eye pain		Lacrimation increased
Gastrointestinal disorders	Constipation Diarrhoea	Abdominal discomfort Abdominal pain Abdominal pain upper Gastritis Gastrooesophageal reflux disease Hyperchlorhydria Stomatitis Vomiting
General disorders and administration site conditions	Asthenia Pyrexia	Fatigue Pain
Hepatobiliary disorders		Hyperbilirubinemia
Infections and infestations	Bacteriuria, Urinary tract infection Viral upper respiratory tract infection	Gastroenteritis Genital infection fungal Herpes zoster Lower respiratory tract infection Periodontitis Pharyngitis Pulpitis dental Pyuria Upper respiratory tract infection Vaginal infection Viral infection Vulvovaginal candidiasis Vulvovaginitis
Investigations	Glomerular filtration rate decreased	Blood bicarbonate abnormal Blood cholesterol increased Blood creatinine increased Blood lactic acid increased Blood pressure increased Blood triglycerides increased Electrocardiogram QT prolonged Gamma-glutamyltransferase increased Hepatic enzyme increased Low density lipoprotein increased Weight decreased

System Organ Class	Common	Uncommon
Metabolism and nutrition disorders	Dyslipidaemia Hypoglycaemia	Decreased appetite Diabetic ketoacidosis Hypercholesterolemia Hypertriglyceridemia Hypocalcaemia Lactic acidosis Polydipsia
Musculoskeletal and connective tissue disorders		Arthralgia Back pain Costochondritis Musculoskeletal pain Myalgia Pain in extremity
Nervous system disorders	Headache	Dizziness Hypoesthesia
Psychiatric disorders		Anxiety Insomnia
Renal and urinary disorders	Ketonuria	Dysuria Pollakiuria Polyuria
Reproductive system and breast disorders		Balanoposthitis Pruritus genital Vulvovaginal pruritus
Respiratory, thoracic and mediastinal disorders	Cough	Oropharyngeal pain Rhinitis allergic
Skin and subcutaneous tissue disorders		Rash Skin lesion Urticaria
Vascular disorders	Orthostatic hypotension	Hypertension

Note:

(1) Remogliflozin etabonate (GSK189075) 100 mg and 250 mg are pooled to have TEAE frequencies only for Remogliflozin etabonate (GSK189075), not for Dapagliflozin. Percentages are based on the total number of subjects in safety population in both Remogliflozin etabonate (GSK189075) groups, irrespective of relationship to the study drug.

(2) System organ class and preferred terms are coded using the MedDRA Version 20.0 or latest available dictionary.

Description of selected adverse reactions

Hypoglycemia

In the randomized controlled study of Remogliflozin etabonate (GSK189075) as add-on to metformin, the frequency of adverse events of hypoglycaemia was similar (<2%) between treatment groups. Major events of hypoglycaemia were comparable between the groups treated with Remogliflozin etabonate (GSK189075) or control arm treatment.

Vulvovaginitis, balanitis and related genital infections

Vulvovaginitis, balanitis and related genital infections were reported in 1.8% and 1.2% of subjects who received Remogliflozin etabonate (GSK189075) 100 mg and Remogliflozin etabonate

(GSK189075) 250 mg, respectively and 2.7% in subjects who received control arm treatment. All the infections were mild to moderate, and subjects responded to an initial course of standard treatment and did not result in discontinuation from Remogliflozin etabonate (GSK189075) treatment. These infections were similarly frequent in males and females.

Urinary tract infections

Urinary tract infections were reported in 3.1% and 6.6% of subjects who received Remogliflozin etabonate (GSK189075) 100 mg and Remogliflozin etabonate (GSK189075) 250 mg, respectively and 2.1% in subjects who received control arm treatment. All the infections were mild to moderate, and subjects responded to an initial course of standard treatment and did not result in discontinuation from Remogliflozin etabonate (GSK189075) treatment. These infections were more frequent in females.

Increased creatinine

Increased creatinine was reported in one subject receiving Remogliflozin etabonate (GSK189075) 250 mg. No adverse event of increased creatinine was reported in subjects receiving Remogliflozin etabonate (GSK189075) 100 mg.

Glomerular filtration rate decreased was reported in 0.4% and 2.9% of subjects who received Remogliflozin etabonate (GSK189075) 100 mg and Remogliflozin etabonate (GSK189075) 250 mg, respectively. The decreases in glomerular filtration rate were generally transient during continuous treatment or reversible.

Volume depletion

No event of dehydration or hypovolaemia was reported. Orthostatic hypotension was reported in 1.3% and 0.8% of subjects who received Remogliflozin etabonate (GSK189075) 100 mg and Remogliflozin etabonate (GSK189075) 250 mg, respectively. All the events of postural hypotension were mild to moderate.

4.9 Overdose

There is no specific antidote for an overdose of Remogliflozin etabonate (GSK189075). Inhibition of SGLT2 is reversible and the half-life of the active serum metabolite is 1.4 to 2.9 hours in human. Supportive care (e.g., fluids, electrolyte replacement, and glucose) should be provided as appropriate based on the subject's clinical status. Supra-therapeutic doses of 4000 mg Remogliflozin etabonate (GSK189075) have been administered for up to 3 days to healthy volunteers. Gastro-intestinal complaints (e.g., nausea, vomiting, abdominal pain, diarrhoea, flatulence) and dizziness were among the more commonly reported events at this dose and were reported at a higher incidence than with comparator.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Consistent with inhibition of SGLT2, a dose-dependent increase in urine glucose excretion has been observed with a plateau of ~400 mmols/day in healthy subjects (equating to 72 g/day or 288 kcal/day). The maximal filtered glucose excreted in the urine is ~45%. In subjects with T2DM following 2 weeks of dosing, there were statistically significant decreases from baseline in the weighted mean 24-hour plasma glucose concentrations in Remogliflozin etabonate (GSK189075) twice daily (BID) dosing groups compared to placebo. In the 12-week dose range finding studies in subjects with T2DM, Remogliflozin etabonate (GSK189075) demonstrated a clinically significant lowering of HbA1c (up to 1.07% from baseline versus placebo) and plasma glucose (up to 2.07 mmol/L from baseline versus placebo). The number of reported hypoglycemic episodes was low

(One subject each in the 50 mg and 500 mg groups). Following 12 weeks of dosing in subjects with T2DM, significant weight loss was observed in the Remogliflozin etabonate (GSK189075) group compared to placebo (up to 3.51 kg from baseline versus placebo). (4)

Clinical efficacy and safety

Efficacy and safety of Remogliflozin etabonate (GSK189075) 100 mg and Remogliflozin etabonate (GSK189075) 250 mg twice daily as add-on to metformin therapy, was evaluated in a randomized, double blind controlled clinical trial in 612 subjects with type 2 diabetes mellitus, in comparison with Dapagliflozin 10 mg once daily. 224 subjects received Remogliflozin etabonate (GSK189075) 100mg and 241 subjects received Remogliflozin etabonate (GSK189075) 250 mg and were treated for 24 weeks.

Glycaemic control

Treatment with Remogliflozin etabonate (GSK189075) 100 mg and Remogliflozin etabonate (GSK189075) 250 mg reduced HbA1c by 0.72% and 0.77%, respectively compared to a reduction in HbA1c by 0.58% in the control arm treatment, at 24 weeks.

Table 2: Analysis of Mean Change in Glycosylated Haemoglobin (HbA1c%) Levels (PP Population): MMRM

Visit	Remogliflozin etabonate (GSK189075) 100mg (N=163)	Remogliflozin etabonate (GSK189075) 250mg (N=166)	Dapagliflozin 10mg (N=101)
HbA1c (Mean±SE)	-0.72 (0.093)	-0.77 (0.090)	-0.58 (0.116)
p value[1] (90% CI)	<0.001 [-0.38, 0.10]	<0.001 [-0.42, 0.05]	

CI= confidence interval; HbA1c= glycosylated haemoglobin; LSM= least mean square; PP= per protocol; MMRM= mixed model repeated measures; SE= standard error.
The 90% CI for the LSM difference in HbA1c% levels between arms are calculated for Remogliflozin etabonate (GSK189075) 100 mg or Remogliflozin etabonate (GSK189075) 25 mg minus dapagliflozin 10 mg.
P value[1] is calculated for the 1-sided non-inferior test with non-inferiority margin 0.35

Fasting plasma glucose

Treatment with Remogliflozin etabonate (GSK189075) 100 mg and Remogliflozin etabonate (GSK189075) 250 mg reduced fasting plasma glucose by 17.86 mg/dL and 20.94 mg/dL, respectively compared to a reduction in fasting plasma glucose by 20.23 mg/dL in the control arm treatment, at 24 weeks.

Post prandial plasma glucose

Treatment with Remogliflozin etabonate (GSK189075) 100 mg and Remogliflozin etabonate (GSK189075) 250 mg reduced post prandial plasma glucose by 39.2 mg/dL and 41.5 mg/dL, respectively compared to a reduction in post prandial plasma glucose by 32.4 mg/dL in the control arm treatment, at 24 weeks.

Proportion of subjects achieving glycemic control defined as HbA1c <7% at 24 weeks was 36.4% in the Remogliflozin (GSK189074) 100 mg group and 37.1% in the Remogliflozin (GSK189074) 250 mg group and 30.3% in control arm treatment.

At 24 weeks, a reduction in body weight by around 3 kgs was observed in Remogliflozin (GSK189074) treatment arms which was comparable to weight reduction observed in control arm.

At 24 weeks, a small reduction in blood pressure was observed in Remogliflozin (GSK189074) treatment arms which was comparable to blood pressure reduction observed in control arm.

5.2 Pharmacokinetic properties

Absorption

Remogliflozin etabonate (GSK189075) was rapidly & completely absorbed and extensively converted to Remogliflozin (GSK189074), and then further to metabolite (GSK279782). Administration with standard breakfast slightly delayed the Tmax by approximately 1.0-1.5 hour, however there were no considerable difference in the Cmax or AUC relative to fasted state. Hence Remogliflozin etabonate (GSK189075) can be administered with or without food. The steady state mean Cmax and AUC0-tau of Remogliflozin (GSK189074) in type 2 diabetic mellitus patients of Indian origin was 559 ng/mL and 1798 ng.h/mL at 100 mg dose and 1370 ng/mL and 4610 ng.h/mL at 250mg dose, respectively. The single dose mass balance study in humans indicated > 93 % of [14C] Remogliflozin etabonate (GSK189075) was absorbed. (1) Both Remogliflozin etabonate (GSK189075) and Remogliflozin (GSK189074) were P-gp substrates and not P-gp inhibitors.

Distribution

The plasma protein binding of Remogliflozin (GSK189074) was around 65%. Remogliflozin (GSK189074) was not preferentially distributed to blood cells and no selective association with melanin containing tissues.

Metabolism

Remogliflozin etabonate (GSK189075) is extensively metabolized, leading to loss of ethyl hydrogen carbonate, N-dealkylation, O-dealkylation, oxidation, loss of glucose and glucuronidation. In vitro studies have demonstrated that CYP3A4 is the primary enzyme involved in the metabolism of Remogliflozin (GSK189074) in human hepatic microsomes with minor contribution from CYP2C19. A clinical study with ketoconazole (a potent CYP3A4 inhibitor) resulted in <2-fold increase (suggestive of weak interaction) in Remogliflozin (GSK189074) exposure. (1)

Elimination

The mean plasma elimination half-life of Remogliflozin (GSK189074) and metabolite (GSK279782) were 1.5 to 1.9 hours and 2.3 to 3.8 hours respectively, in healthy volunteers after a single dose of Remogliflozin etabonate (GSK189075) at 100 mg or 250 mg. In the same study the mean plasma half-life of prodrug was

0.4 to 0.7 hours. In radiolabelled Absorption, Metabolism and Excretion (AME) study, approximately 93% was excreted in urine of which about 11% of the dose was recovered as Remogliflozin (GSK189074) in urine; the majority of drug-related material is eliminated via the urine as inactive glucuronide metabolites.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The clinical formulation of Remogliflozin etabonate (GSK189075) tablets contains the following excipients:

Crosscarmellose (Ac-di-sol)

Crosscarmellose Sodium

Microcrystalline Cellulose (Avicel PH 101 and PH 102) Povidone/Plasdone K29/32

Opadry White YS-1-18202-A (containing Hypromellose, Titanium Dioxide and Polyethylene Glycol/Macrogol)

Magnesium Stearate

6.2 Incompatibilities

No drug substance-excipient incompatibility found.

6.3 Shelf Life

Proposed Shelf life is 24 months.

6.4 Special Precautions for Storage

The recommended storage condition is: Store in a dry place at a temperature not exceeding 30°C. The recommended storage conditions, and expiry date where required, are stated on the product label.

6.5 Nature and Contents of the Container

Tablets are packed in Alu-alu Blister

PART II: SCIENTIFIC INFORMATION

1. PHARMACEUTICAL INFORMATION

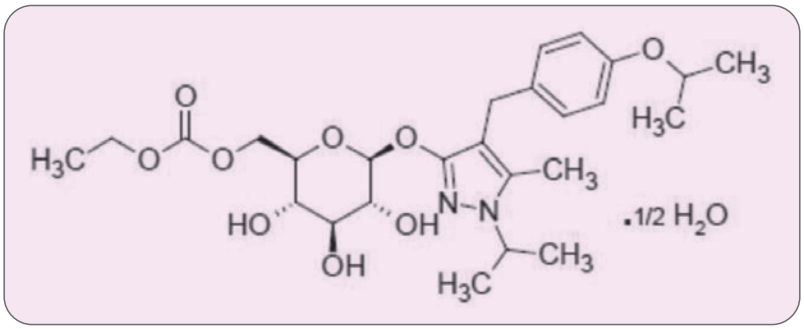
Drug Substance

Common Name : Remogliflozin etabonate (GSK189075)

Chemical Name : 5-methyl-1-(propan-2-yl)-4- [4-(propan-2 yloxy) benzyl]1Hpyrazol-3-yl6-O-(ethoxycarbonyl)-b-D glucopyranoside Hemihydrate.

Molecular Formula and Molecular Mass : C26H38N2O9 and 522.586 g/mol

Structural Formula :



Physicochemical Properties :

Remogliflozin etabonate (GSK189075) is presented as film Coated tablets and clinical formulation of Remogliflozin etabonate (GSK189075) tablets contains the following excipients:

Crosscarmellose (Ac-di-sol)

Crosscarmellose Sodium

Microcrystalline Cellulose (Avicel PH 101 and PH 102)

Povidone/Plasdone K29/32

Opadry White YS-1-18202-A (containing Hypromellose,

Titanium Dioxide and Polyethylene Glycol/Macrogol)

Magnesium Stearate

2. CLINICAL TRIALS

Clinical Development program included 26 clinical studies with Remogliflozin etabonate (GSK189075) tablets involving 2036 subjects. Remogliflozin etabonate (GSK189075) was studied as monotherapy and add on drug with metformin and insulin. RE was also studied in patients with type 2 diabetes mellitus (T2DM), type 1 diabetes mellitus (T1DM), and in patients with mild to moderate renal impairment.

Treatment with Remogliflozin etabonate (GSK189075) as monotherapy and add on with metformin produced clinically relevant and statistically significant improvements in HbA1c, fasting plasma glucose (FPG), and 2-hour postprandial plasma glucose (PPG) at Week 24, compared to placebo or control.

2.1. Clinical Studies and designs

Table 3: Listing of clinical studies

S.N	Trial design	Objective of the study	Dosage, route of administration and Duration	Total No. of Subjects/ No. exposed to Remogliflozin etabonate
1.	**GPL/CT/2016/009/III** Randomised,Multi-centre double-blind, double-dummy, active- controlled	Efficacy and Safety with stable dose of Metfomin as monotherapy	Remogliflozin etabonate (GSK189075) 100 mg, 250 mg, Dapagliflozin 10 mg Oral, 24 weeks	612/466
2.	**0637-17** Open label, two-stage, single-period	PK, Efficacy and safety under fasting and/or fed condition	Remogliflozin etabonate (GSK189075) 100 mg Remogliflozin etabonate (GSK189075) 250 mg Oral, 28 days	66/65
3.	**0355-17** Open label, single period, single dose	PK in adult subjects under fasting condition	Remogliflozin etabonate (GSK189075) Tablets 250 mg, Oral, Single dose	28/28
4.	**BHV20200** Randomized, multicenter, doubleblind, parallel group, dose ranging study, Placebo-controlled	Efficacy, Safety, Tolerability and QD Dose Ranging Study with Biphasic Release Formulation	Remogliflozin etabonate (GSK189075) 150 mg, 250 mg, 450 mg QD, placebo; oral; 12 Wks	171/134
5.	**KG2110375** [5] Randomized, multicenter, double blind, parallel group, dose ranging study, Placebo- and active controlled	Efficacy, Safety, Tolerability and QD; Dose Ranging Study	Remogliflozin etabonate (GSK189075) 100 mg, 250 mg, 500 mg, 1000 mg QD, 250 mg BID, Pioglitazone 30 mg QD or placebo; oral; 12 Wks	252/179
6.	**KG2105255** Randomized, multicenter, double blind, parallel group, dose ranging study Placebo and active controlled	Efficacy, Safety, Tolerability and BID Dose Ranging Study	Remogliflozin etabonate (GSK189075) 50 mg 100 mg, 250 mg, 500mg 1000 mg BID Pioglitazone 30 mg QD Placebo; oral; 12 Wks	336/238
7.	**KG2105246** [2] Open label, Randomized, Crossover	PK interaction with Metformin	Remogliflozin etabonate (GSK189075) 500 mg; q12h for; oral 3 days	13/13

S.N	Trial design	Objective of the study	Dosage, route of administration and Duration	Total No. of Subjects/ No. exposed to Remogliflozin etabonate
8.	**KG2108197** [1] Open label single-sequence	PK interaction with Ketoconazole	Remogliflozin etabonate (GSK189075) 250 mg; SD; Oral	20/20
9.	**KG2107494** Open label, Single sequence	PK interaction with Oral Contraceptive	Remogliflozin etabonate (GSK189075) 500 mg; BID; Oral 28 Days	21/17
10.	**KGW111083** Double-blind, Randomized, Crossover	PK interaction with Bupropion	Remogliflozin etabonate (GSK189075) 250 mg; BID; 2 weeks, oral	27/27
11.	**KG2105253** [6] Open label, Single dose, parallel group	Safety, PK and PD in renal insufficiency	Remogliflozin etabonate (GSK189075) 250 mg; SD; Oral	Renally impaired 19/19 Matched control 12/12
12.	**KG2109799** Double-blind Randomized Rising dose Placebo controlled	Safety, tolerability, PK or Supra-therapeutic doses	Remogliflozin etabonate (GSK189075) 2000 mg and 4000 mg; oral; 3 days	12/12
13.	**KG2110243** Double-blind Randomized Escalating Dose Placebo controlled	Safety, PK, PD with Metformin	Remogliflozin etabonate (GSK189075) 500 mg BID or 750 mg BID; oral, 2 weeks	50/33
14.	**KG2104940** [7] Double-blind Randomized Placebo controlled Escalating dose	Safety, tolerability, PK/PD, glucose lowering agent	Remogliflozin etabonate (GSK189075) 100 mg BID, 1000 mg QD; 1000 mg BID GW869682 1000 mg QD Placebo, oral; 12 days	46/27
15.	**KG2105251** Double-blind Randomized Placebo controlled	PD when added to a diuretic	Remogliflozin etabonate (GSK189075) 500 mg BID, oral (added to either furosemide or hydrochlorthiazide; 6 days	54/24
16.	**KGI107465** [3] Double-blind Randomized Placebo controlled Crossover Single dose	Safety, tolerability, PK and PD (with insulin)	Remogliflozin etabonate (GSK189075) 50 mg, 150 mg and 500 mg; SD; Oral Single dose	10/10

S.N	Trial design	Objective of the study	Dosage, route of administration and Duration	Total No. of Subjects/ No. exposed to Remogliflozin etabonate
17.	**KGT-1101** Double-blind, Randomized, Escalating dose, Placebo controlled	Safety, PK, PD	Remogliflozin etabonate (GSK189075) 50, 100, 200, 400, 800, 1000 mg; SD; Oral Single dose	59/44
18.	**KGT-1102** Double-blind, Placebo controlled, Randomized	Safety, PK, PD	Remogliflozin etabonate (GSK189075) 200 mg or 600 mg once daily or BID Oral; 12 days	20/16
19.	**BHV010020** Open label, Randomized, Single dose, Crossover	PK, PD, safety and tolerabilityof biphasic formulation	Remogliflozin etabonate (GSK189075)150, 200, 250, 450, 500 mg; SD, Oral; Single dose	12
20.	**KG2105217** Open label Randomized, Single dose, Crossover	Safety, tolerability, PK/PD of bio-enhanced formulations, effect of food on PK	Remogliflozin etabonate (GSK189075) 100 mg; SD; oral; Single dose	12/12
22.	**KG2107489** Double-blind Randomized Placebo controlled Active control	Effect on cardiac repolarization	Remogliflozin etabonate (GSK189075) 500 mg and 4000 mg; oral. Moxifloxacin:400mg SD; oral, 3 days	78/71
23.	**KGW108201**[8] Double-blind Randomized Placebo controlled	Weight loss and body Composition	Remogliflozin etabonate (GSK189075) 250 mg TID; oral 8 weeks	30/9
24.	**KG2105259** Open label, Randomized, Crossover	Evaluate regional gastrointestinal absorption	Remogliflozin etabonate (GSK189075) 100 mg; SD; oral solution or suspension; Single dose	8/8
25.	**KG2105264**[1] Open label single-dose	Mass balance	Remogliflozin etabonate (GSK189075) 400 mg; SD; Oral; Single dose	8/8
26.	**KG219017**[9] Double-blind, Randomized, Parallel Group, Dose escalation, Crossover	PK first time in man (Healthy volunteers & T2DM)	Remogliflozin etabonate (GSK189075) 20-1000mg; SD Oral; Single dose	Healthy : 10/10 T2DM: 6/6

2.2. Study Results

Remogliflozin etabonate (GSK189075) is a prodrug that rapidly gets converted to moiety Remogliflozin (GSK189074), which then further metabolize to metabolite (GSK279782). The Remogliflozin (GSK189074) showed the highest plasma exposure and is most important from safety and efficacy perspective, followed by metabolite (GSK279782) which showed relatively lower plasma exposure and less important from safety and efficacy perspective. The inactive prodrug Remogliflozin etabonate (GSK189075) has very low serum exposure and is not anticipated to contribute towards efficacy or safety.

Remogliflozin etabonate (GSK189075) in comparision with Dapagliflozin in type 2 diabetes mellitus patients as an add on to Metformin (phase III)

A phase 3 randomized, double-blind, double-dummy parallel group, multicentre, active controlled study was conducted in 612 patients. The study enrolled subjects with type 2 diabetes mellitus (T2DM) who had inadequate glycaemic control with stable dose of metformin as monotherapy. Efficacy and safety of Remogliflozin etabonate (GSK189075) 100 mg and Remogliflozin etabonate (GSK189075) 250 mg twice daily was evaluated in comparison with dapagliflozin 10 mg once daily. 224 subjects received Remogliflozin etabonate (GSK189075) 100 mg and 241 subjects received Remogliflozin etabonate (GSK189075) 250 mg and were treated for 24 weeks.

The primary efficacy endpoint of mean change from baseline in HbA1c levels at Week 24 was analysed using the MMRM method in the PP population. Mean baseline levels of HbA1c were generally comparable across the treatment arms and ranged from 8.14% to 8.24%. Reduction in the mean HbA1c levels was seen at all visits and in all the treatment arms. The primary endpoint assessment, least squares mean (LSM) change from baseline in HbA1c levels at Week 24 was -0.77% in the Remogliflozin etabonate (GSK189075) 250 mg arm, -0.72% in the Remogliflozin etabonate (GSK189075) 100 mg arm, and -0.58% in the dapagliflozin 10 mg arm. The difference in change from baseline in HbA1c level at Week 24, between Remogliflozin etabonate (GSK189075) 100 mg and dapagliflozin 10 mg arms was -0.14% (90% CI: -0.38, 0.10) and was NI to dapagliflozin with high statistical significance (P<0.001). The difference in change from baseline in HbA1c level at Week 24 between Remogliflozin etabonate (GSK189075) 250 mg and dapagliflozin 10 mg arms was -0.19% (90% CI: -0.42, 0.05) and was NI to dapagliflozin with high significance (P<0.001). Thus, the primary endpoint was achieved with both doses: Remogliflozin etabonate (GSK189075) 250 mg and Remogliflozin etabonate (GSK189075) 100 mg demonstrating NI to dapagliflozin 10 mg. Details are provided in Table 4.

Table 4: Analysis of Mean Change in Glycosylated Haemoglobin (HbA1c%) Levels (PP Population)

Remogliflozin etabonate Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of subjects in Study (total exposed Remogliflozin Etabonate	Primary Endpoints	Secondary Endpoints
Remogliflozin etabonate (GSK189075) 100 mg, 250 mg BID Dapagliflozin 10 mg QD, Dapagliflozin placebo; Oral; 24 weeks	612/466	**Change in HbA1c (%) from baseline to Week 24: Diff from placebo (90% CI, p value)** 100 mg: -0.14 (-0.38,0.10; <0.001) 250 mg: -0.19 (-0.42, 0.05; <0.001)	**Change from baseline in HbA1c (%) at week 12 (90% CI, p value)** 100 mg: -0.09 (-0.30, 0.12; <0.001) 250 mg: -0.23 (-.44, 0.02; <0.001)

HbA1c: Glycosylated Haemoglobin; BID: Twice daily; QD: once daily

The diagrammatic representation of HbA1c levels at Week 12 and week 24 is given in Figure 1. While the visit-wise decrease in glycated haemoglobin for test and control arm are detailed in Figure 2. It is shown that both 100 mg and 250 mg doses of Remogliflozin etabonate (GSK189075) had higher reduction in HbA1c at all the visits compared to Dapagliflozin 10 mg. In the per protocol (PP) population, the least square mean (LSM) difference in change from baseline HbA1c levels at week 24 between Remogliflozin etabonate (GSK189075) 250mg and Remogliflozin etabonate (GSK189075) 100 mg stratified for screening HbA1c levels (7% to 7.9%, 8% to 8.9%, and 9% to 10%) was not statistically significant.

Figure 1: Change in HbA1c at Week 12 and 24

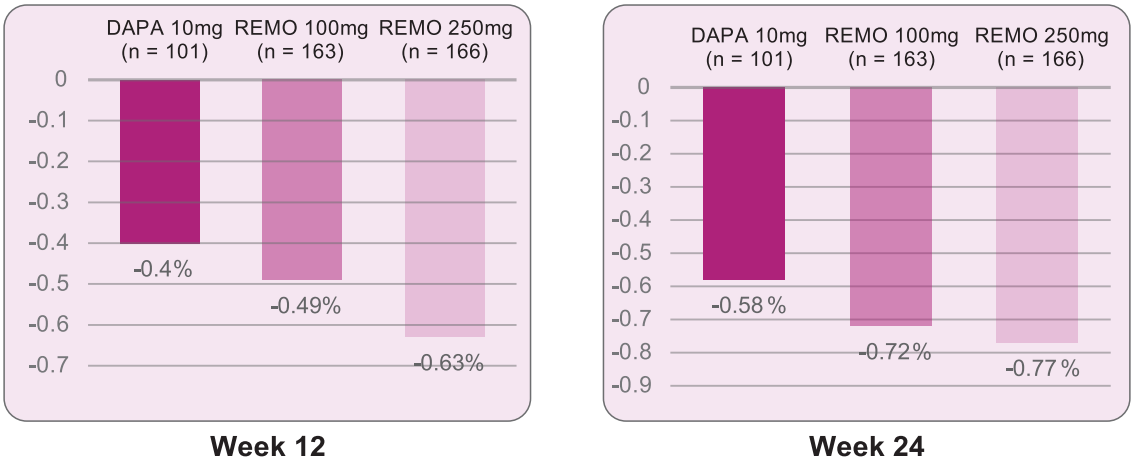
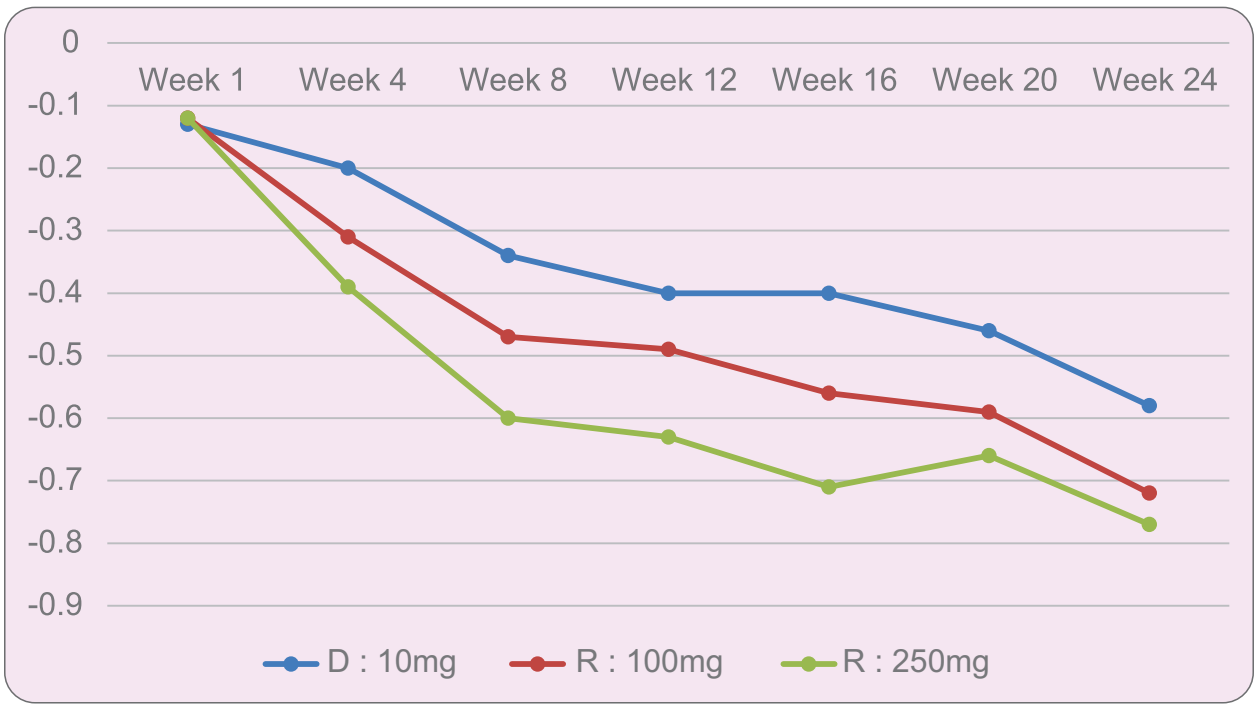


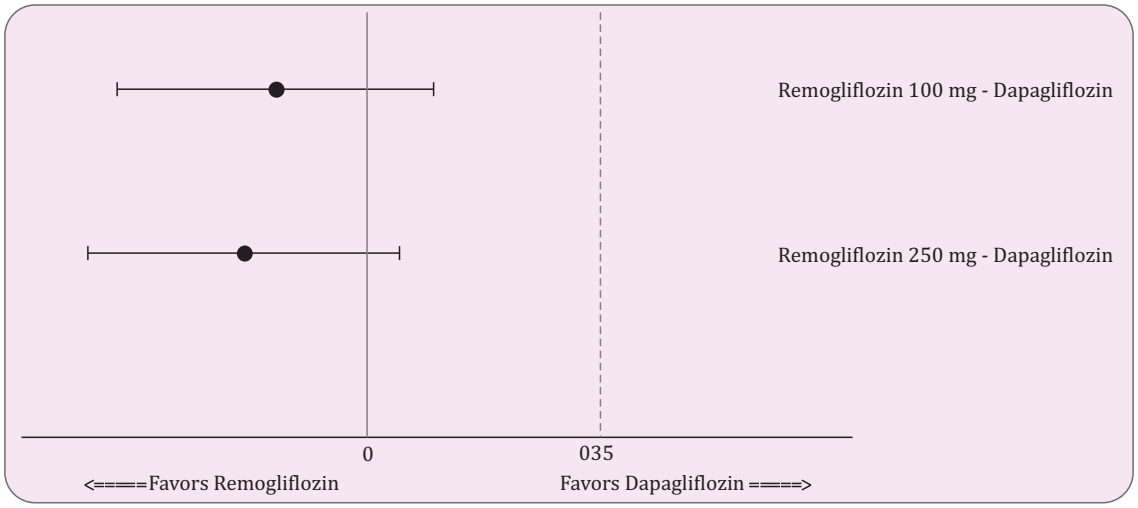
Figure 2: Visit-wise change in HbA1c levels



D = Dapagliflozin R = Remogliflozin

Both 100 mg & 250 mg doses of Remogliflozin etabonate (GSK189075) were statistically non-inferior to Dapagliflozin 10 mg in HbA1c reduction. (Figure 3)

Figure 3: Change from Baseline in HbA1c %: Primary Endpoint Results – Non-inferiority



The mean reduction in fating plasma glucose (FPG) and post prandial glucose (PPG) concentrations from baseline was observed at Week 1, Week 12, and Week 24 in all the treatment arms. (Table 5)

Table 5 presents the reduction in Fasting Plasma Glucose (FPG) and Postprandial Plasma Glucose (PPG) concentrations from baseline was observed at Week 12, and Week 24 in all the treatment arms. No statistically significant difference was observed between Remogliflozin etabonate (GSK189075) 100 mg or Remogliflozin etabonate (GSK189075) 250 mg and Dapagliflozin 10 mg arms at Week 1, Week 12, and Week 24 in change from baseline in FPG and PPG concentrations. Both FPG and PPG reductions were comparable in Remogliflozin etabonate (GSK189075) 100 mg and 250 mg arms to Dapagliflozin arm (difference was not statistically significant)

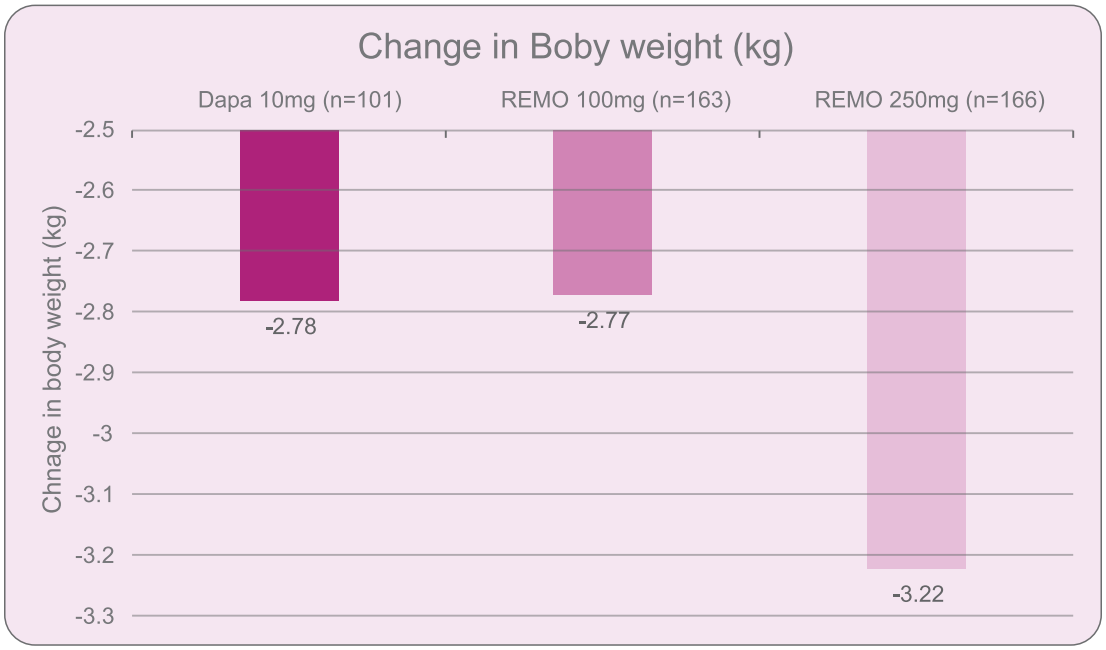
Table 5: Analysis of Mean Change in Fasting Plasma Glucose (FPG) and Postprandial Plasma Glucose (PPG) Concentrations, mg/dL (PP Population)

Visit	Intervention	Mean Change in FPG from	Mean Change in PPG from baseline
Week 12	Remogliflozin etabonate (GSK189075) 100 mg (N=163)	-9.01 (2.99)	-21.5 (5.60)
	Remogliflozin etabonate (GSK189075) 250 mg (N=166)	-14.53 (2.97)	-34.4 (5.55)
	Dapagliflozin 10 mg (N=101)	-10.38 (3.67)	-21.6 (6.86)
Week 24	Remogliflozin etabonate (GSK189075) 100 mg (N=163)	-17.86 (2.95)	-39.2 (5.36)
	Remogliflozin etabonate (GSK189075) 250 mg (N=166)	-20.94 (2.93)	-41.5 (5.28)
	Dapagliflozin 10 mg (N=101)	-20.23 (3.59)	-32.4 (6.54)

CI = confidence interval; MMRM = mixed model repeated measures; PP = per protocol; SE = standard error

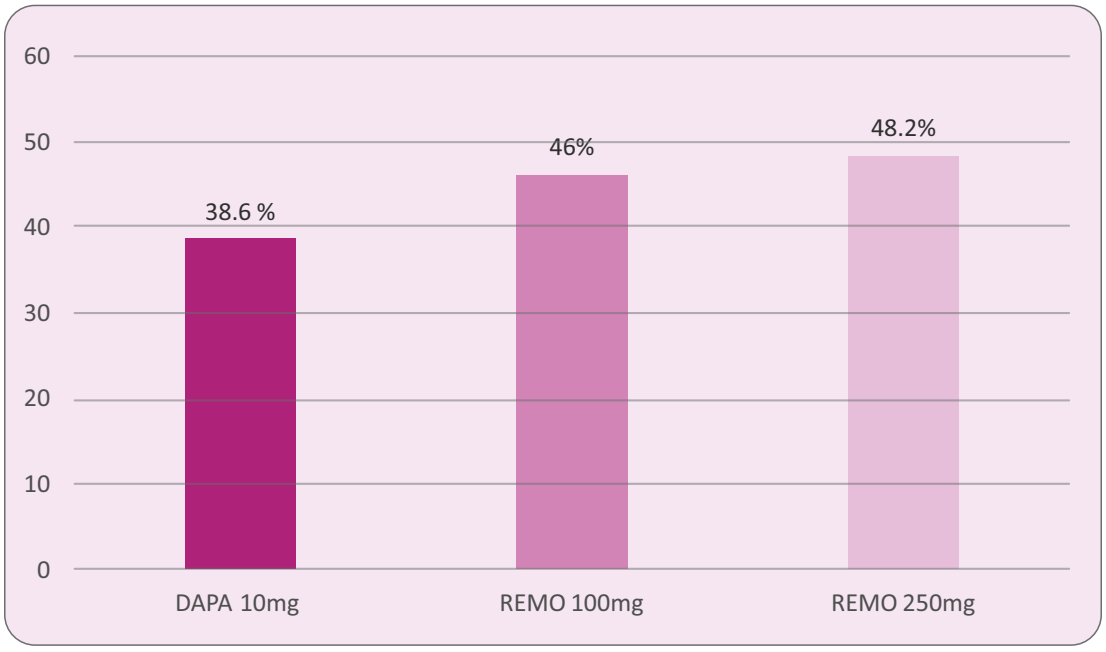
There was also body weight reduction reported in a similar manner in all the treatment arms. Body weight reduction (~3 kgs) with Remogliflozin etabonate (GSK189075) 100 and 250 mg was comparable to Dapagliflozin 10 mg. (Figure 4)

Figure 4: Change in Body Weight (Kgs) from baseline at week 24



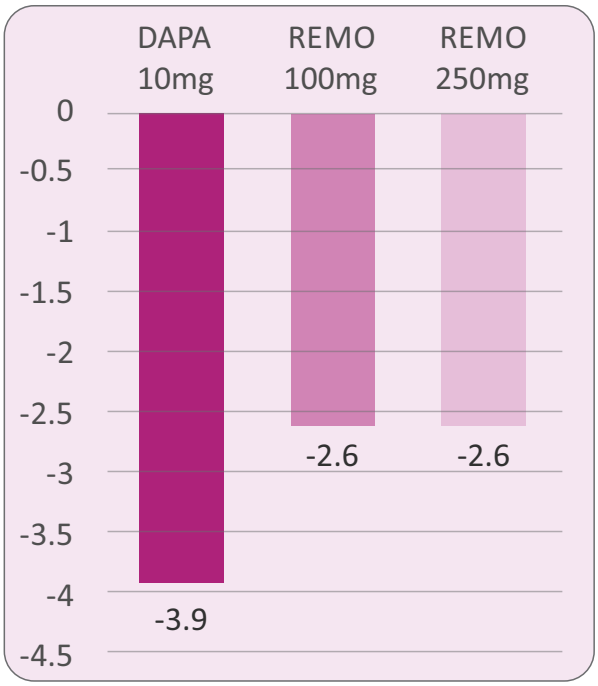
In the per protocol (PP) population, the least square mean (LSM) difference in change from baseline HbA1c levels at week 24 between Remogliflozin etabonate (GSK189075) 250 mg and Remogliflozin etabonate (GSK189075) 100mg stratified for screening HbA1c levels (7% to 7.9%, 8% to 8.9%, and 9% to 10%) was not statistically significant. A higher proportion of subjects achieved glycaemic response in the Remogliflozin etabonate (GSK189075) 100 mg and 250 mg arms compared with the dapagliflozin 10 mg arm. However, the difference between the treatment arms was not statistically significant. (Figure 5)

Figure 5: Subjects Achieving Target HbA1c (<7%): Secondary Endpoint Results – 24 weeks

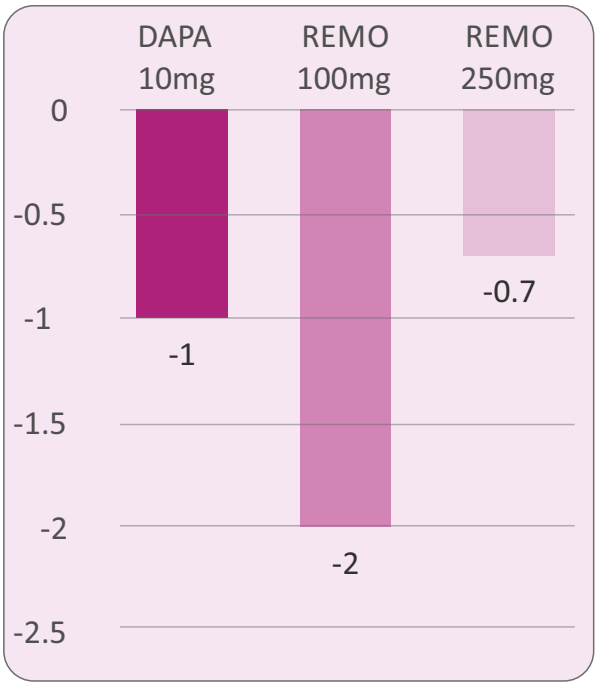


BP reduction in Remogliflozin etabonate (GSK189075) 100 and 250 mg was non-inferior to Dapagliflozin 10 mg. (Figure 6)

Figure 6: Change in Blood Pressure (mmHg) from BL at week 24



Change in SBP (mmHg)



Change in DBP (mmHg)

3. DETAILED PHARMACOLOGY

Several compounds have been developed to pharmacologically inhibit sodium-dependent glucose co-transporter member 2 (SGLT2) alone or along with sodium-dependent glucose co-transporter member 1(SGLT1). This mechanism of action is dependent on blood glucose levels and is independent of the actions of insulin.

Remogliflozin (GSK189074) is one such molecule that inhibits sodium-dependent glucose co- transporter member (SGLT2) with high selectivity and affinity. Remogliflozin etabonate (GSK189075) is the ester prodrug of Remogliflozin (GSK189074), which in turn selectively inhibits sodium- dependent glucose co-transporter member (SGLT2). It has high solute translocation capacity and low substrate affinity and is considered to be a primary pathway for renal glucose re-absorption. Inhibiting this pathway has been shown to inhibit re-absorption of glucose and enhance urinary glucose excretion and thus reduce the blood glucose levels. The net effect is the lowering of blood glucose levels and calorific loss through urine. (10) Remogliflozin (GSK189074) showed a dose dependent effect on plasma glucose concentrations. (7)

Various phase I, and phase II studies evaluated the pharmacokinetic (PK) and pharmacodynamics (PD) profile of Remogliflozin etabonate (GSK189075).

3.1 Controlled Phase 2b Clinical studies in Type 2 diabetes mellitus

The clinical dosing regimens & Clinical efficacy data of Remogliflozin etabonate (GSK189075) is derived from three 12-week randomized, double-blind, active-controlled, placebo-controlled phase IIb dose-ranging studies in type 2 diabetes mellitus (T2DM) subjects conducted as part of the clinical development program.

Study KG2105255: Pioglitazone & placebo controlled, Monotherapy in BID regimen (4)

This multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study evaluated the efficacy, safety and tolerability of a BID doses of Remogliflozin etabonate (GSK189075) (50 mg, 100 mg, 250 mg, 500 mg, or 1000 mg) and 30 mg pioglitazone (PIO), compared with placebo, administered as monotherapy over 12 weeks in T2DM patients.

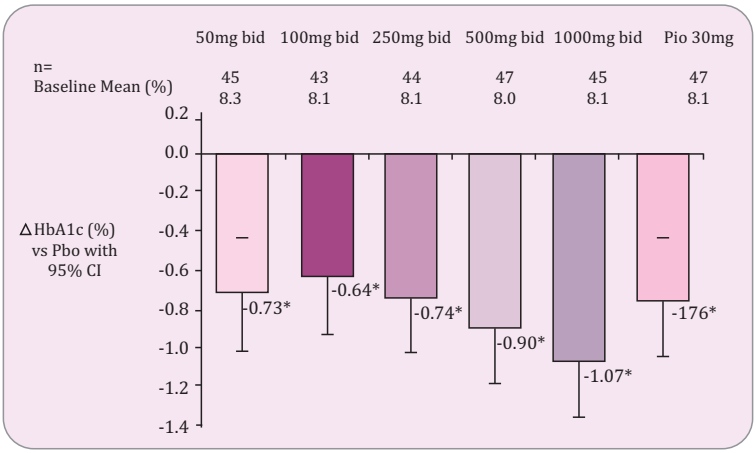
A total of 336 type 2 diabetes mellitus (T2DM) patients (HbA1c ≥7.0% to ≤9.5%) across 18 countries were randomized equally to either five Remogliflozin etabonate (GSK189075) doses BID, pioglitazone, or placebo. The baseline characteristics were generally well balanced across the treatment groups. The majority of subjects were male (58%), White/Caucasian (86%), of European heritage (86%) (24% were of Hispanic/Latino ethnicity) with a mean age of 55 years (17% subjects were ≥65 years of age) and a mean body weight and body mass index (BMI) of 87.3 kg and 31 kg/m2, respectively. The mean baseline HbA1c ranged from 8.0% to 8.2% across treatment groups and the mean duration of T2DM ranged from 1.7 to 2.7 years. All Remogliflozin etabonate (GSK189075) doses produced a statistically significant trend in dose response for change from baseline in HbA1c at Week 12 ($p<0.001$). Additionally, clinically and statistically significant decreases in HbA1c versus placebo ($p<0.001$) were observed at each Remogliflozin etabonate (GSK189075) dose.

Study KG2105255: Efficacy results from 12-week Phase 2b study

Remogliflozin etabonate Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of subjects in Study (total Exposed to Remogliflozin etabonate	Primary Endpoints	Secondary Endpoints
Remogliflozin etabonate (GSK189075), 50 mg, 100 mg, 250 mg, 500 mg, and 1000 mg BID, pioglitazone 30 mg QD or placebo ; oral; 12 Wks	336 (238)	**Change in HbA1c (%) from baseline to Week 12: Diff from placebo (95% CI, p value)** 50 mg: -0.73 (-1.02, -0.44; <0.001) 100 mg: -0.64 (-0.94, -0.35; <0.001) 250 mg: -0.74 (-1.03, -0.44; <0.001) 500 mg: -0.90 (-1.19, -0.61; <0.001) 1000 mg: -1.07 (-1.36, -0.77; <0.001) PIO 30 mg: -0.76 (-1.05, -0.47; <0.001)	**Change from baseline in HbA1c (%) at week 4 and 8: mean (SD)** **Group — Week 4 — Week 8** 50 mg -0.77 (0.54) -0.98 (0.71) 100 mg -0.69 (0.58) -0.96 (0.83) 250 mg -0.64 (0.54) -0.99 (0.75) 500 mg -0.83 (0.64) -1.07 (0.75) 1000 mg -0.84 (0.55) -1.28 (0.64) PIO 30 mg -0.39 (0.56) -0.88(0.71) Placebo -0.30 (0.54) -0.41(0.69) **Change from baseline in FPG, fructosamine and fasting insulin at week 12: mean difference from Placebo** **Group FPG Fructosamine Fasting insulin** 50 mg -0.87 -40.0 -7.8 100 mg -1.43 -39.6 -11.9 250 mg -1.60 -46.0 -12.7 500 mg -1.77 -45.2 -21.7 1000 mg -2.07 -56.6 - 17.1 PIO 30 mg -1.59 -37.9 -12.4

HbA1c: Glycosylated Haemoglobin; FPG: Fasting Plasma Glucose; BID: Twice daily; PIO: Pioglitazone; QD: once daily; SD: Standard deviation

Figure: Change in HbA1c (Percentage) From Baseline to Week 12 (ITT Population with LOCF [Study KG2105255]



ANCOVA adjusted for baseline. Excludes 1 extreme outlier in the placebo group withdrawn due to Lack of Efficacy; * p < 0.001 vs placebo; Bid: Twice daily; Pio: Pioglitazone; HbA1c: Glycosylated haemoglobin; ITT: Intention-to-treat; LOCF: Last observation carried forward

An increase from placebo in LDL-cholesterol (LDL-c) of 4.9 to 13.2% at Week 12 was observed for Remogliflozin etabonate (GSK189075) groups compared to a 4.7% decrease on pioglitazone. This was accompanied by an increase in HDL-cholesterol (HDL-c) and a trend for a decrease in triglycerides (TG). The response for lipid parameters was not dose ordered.

Statistically significant decreases in body weight from baseline compared with placebo were observed across all of the Remogliflozin etabonate (GSK189075) treatment groups at Week 12 (1.36 to 3.51 kg), and were generally dose-related, with an increase of 1.26 kg in the pioglitazone group.

Study KG2110375: Pioglitazone & placebo controlled, Monotherapy in QD regimen (5)

This study was designed to evaluate the efficacy, safety and tolerability of a range of QD doses of Remogliflozin etabonate (GSK189075), a BID dose of Remogliflozin etabonate (GSK189075) and 30 mg PIO QD, compared with placebo, administered as monotherapy over 12 weeks in T2DM patients.

There was significant evidence of a trend in HbA1c above 100 mg once daily, with significant reductions in HbA1c compared to placebo for the 250 mg once daily, 1000 mg once daily and 250 mg BID treatment groups. There were non-significant reductions in HbA1c for the 100 mg once daily, 500 mg once daily and pioglitazone groups. The decreases in HbA1c were rapid for the once daily and BID dosing, and were seen as early as Week 4 and continuing through to Week 12

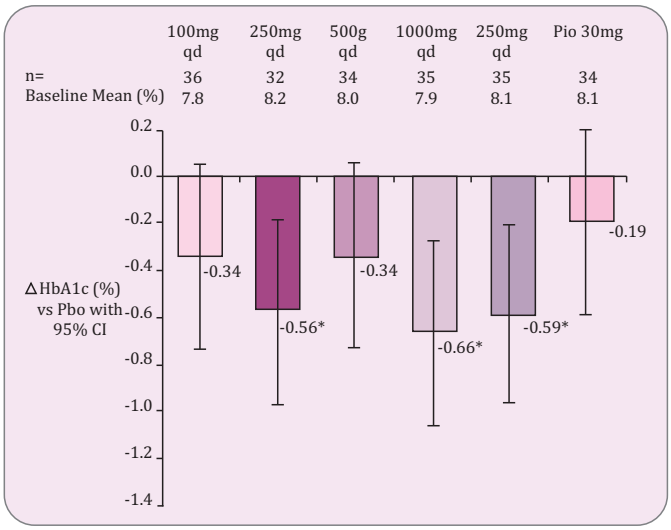
Clinically and statistically significant decreases from baseline in fasting plasma glucose (FPG) (0.85 to1.06 mmol/L) were observed at Week 12 compared with placebo in all Remogliflozin etabonate (GSK189075) once daily doses except for the 500 mg once daily (0.64 mmol/L) and 250 mg BID (1.13 mmol/L) treatment groups. Changes in FPG were seen as early as Week 2 and were maintained throughout to Week 12. In addition, the 24-hour urine glucose excretion (UGE) level increased from baseline in all Remogliflozin etabonate (GSK189075) treatment groups (ranging from 108 to 388 mmol/24h).

Study KG2110375: Efficacy results from 12-week Phase 2b study

Remogliflozin etabonate Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of subjects in Study (total exposed to Remogliflozin etabonate	Primary Endpoints	Secondary Endpoints
Remogliflozin etabonate (GSK189075), 100 mg, 250 mg, 500 mg and 1000 mg QD, Remogliflozi netabonate (GSK189075), 250 mg BID, pioglitazone 30 mg once daily or placebo; oral; 12 Wks	252 (179)	**Change in HbA1c (%) from baseline to Week 12: Diff from placebo (95% CI, p value)** 100 mg QD: -0.34 (-0.73, -0.05;0.085) 250 mg QD: -0.56 (-0.95, -0.16;0.006) 500 mg QD: -0.34 (-0.73, -0.05;0.084) 1000 mg QD: -0.66 (-1.05, -0.28;0.001) 250 mg BID: -0.59 (-0.97, -0.20;0.003) PIO 30 mg: -0.19 (-0.58, -0.20; 0.337)	**Change from baseline in HbA1c (%) at week 4 and 8: mean (SD)** **Group Week 4 Week 8** 100 mg QD -0.37 (0.44) -0.42 (0.72) 250 mg QD -0.57 (0.64) -0.76 (0.67) 500 mg QD -0.40 (0.53) -0.60 (0.83) 1000 mg QD -0.45 (0.60) -0.77 (0.66) 250 mg BID -0.31 (0.54) -0.67 (0.65) PIO 30 mg -0.07 (0.58) -0.25 (0.82) Placebo -0.18 (0.52) -0.08 (0.94) **Change from baseline in FPG and fructosamine at week 12: mean diff from placebo** **Group FPG Fructosamine** 100 mg QD -0.85 -24.1 250 mg QD -1.06 -35.0 500 mg QD -0.64 -29.8 1000 mg QD -0.95 -36.5 250 mg BID -1.13 -29.5 PIO 30 mg -0.51 -13.8

HbA1c: Glycosylated Haemoglobin; FPG: Fasting Plasma Glucose; BID: Twice daily; PIO: Pioglitazone; QD: once daily; SD: Standard deviation

Study KG2110375: Change in HbA1c (Percentage) From Baseline to Week 12



Adjusted for baseline; *P<0.01

BID: Twice daily; qd: Qnce daily; Pio: Pioglitazone; HbA1c: Glycosylated haemoglobin; ITT: Intention-to-treat; LOCF: Last observation carried forward

3.2 Pharmacokinetic studies

Pharmacokinetic in Indian T2DM patients from subset of patients of Phase 3 study

In the ongoing study Phase 3 study, a subset of patients receiving Remogliflozin etabonate (GSK189075) 100 mg or 250 mg twice-daily were consented and included in PK subset for analysis of pharmacokinetics in type 2 diabetic patients the concentration of Remogliflozin etabonate (GSK189075), Remogliflozin (GSK189074) and metabolite GSK279782 using validated LC-MS/MS method.

Among the three analytes, the active moiety (Remogliflozin) showed the highest Cmax and AUC, followed by the metabolite GSK279782. The lowest Cmax and AUC was observed for the prodrug (Remogliflozin etabonate), suggesting rapid conversion of the prodrug to the active moiety. The metabolite GSK279782 exposures were about 22-25% of the Remogliflozin exposure. The Cmax and AUC of both the active moiety and metabolite appear to be nearly proportional between 100 mg and 250 mg on both days. The geometric mean t1/2 was shortest for the prodrug (0.581 to 0.975 hr), followed by Remogliflozin (1.44 to 1.66 hr), and the longest t1/2 was observed for metabolite (1.97 to 2.34 hr). Consistent with the overall short half-lives, none of the analytes showed considerable accumulation in plasma exposure. The lack of considerable accumulation on day 8 also suggests the plasma concentrations are at steady state.

Summary of PK parameters in PK subset of Phase 3 study

		Day 1 (N=15)			Day 8 (N=14)		
100 mg	**Unit**	**Metabolite GSK279782**	**Remogliflozin (GSK189074)**	**Remogliflozin etabonate (GSK189075)**	**Metabolite GSK279782**	**Remogliflozin (GSK189074)**	**Remogliflozin etabonate (GSK189075)**
Tmax[a]	**(hr)**	2.0 (1.0-4.0)	1.50 (0.5-4.0)	1.0 (0.25-3.0)	2.5 (0.25-4.0)	2.5 (0.25-4.0)	1.5 (0.25-4.0)
Cmax	**(ng/mL)**	92.8 (48.9)	533 (30.6)	20.0 (103)	105 (43.0)	559 (33.3)	18.3 (77.8)
AUC0-tau	**(ng*hr/mL)**	393 (49.6)	1738 (28.6)	25.9 (78.8)	444 (47.4)	1798 (23.9)	27.3 (85.4)
t1/2	**(hr)**	2.10 (17.6)	1.59 (26.0)	0.883 (27.5)	2.26 (27.0)	1.64 (24.3)	0.581 (82.2)

		Day 1 (N=10)			Day 8 (N=10)		
250 mg	**Unit**	**Metabolite GSK279782**	**Remoglif lozin (GSK189074)**	**Remoglif lozin etabonate (GSK189075)**	**Metabolite GSK279782**	**Remoglif lozin (GSK189074)**	**Remoglif lozin etabonate (GSK189075)**
Tmaxa	(hr)	3.0 (1.0-8.0)	2.5 (0.5-8.0)	1.25 (0.25-6.0)	3.0 (1.0-4.0)	2.0 (0.5-8.0)	2.0 (0.25-4.0)
Cmax	(ng/mL)	205 (40.8)	1145 (34.0)	57.1 (88.6)	230 (48.8)	1370 (44.3)	62.9 (88.5)
AUC0-tau	(ng*hr/mL)	968 (42.9)	4374 (16.5)	b97.9 (69.9)	1025 (45.0)	4610 (23.1)	100 (41.6)
t1/2	(hr)	1.97 (16.0)	1.44 (18.4)	0.975 (120)	2.34 (17.2)	1.66 (20.6)	0.881 (70.2)

Geometric mean (%CV geometric mean) is provided for all PK parameters except for Tmax; a: Median

Study No. 0637-17: Pharmacokinetics in Healthy Indian subjects & effect of food

An open label, two stage, single period, single oral dose PK study of Remogliflozin etabonate (GSK189075) Tablet 100 mg & 250 mg of Glenmark Pharmaceuticals Ltd., India was conducted in 65 normal, healthy, adult, Indian mal subjects under fasting and/or fed condition.

In general, under fasted state, the maximum plasma concentrations were achieved rapidly for all 3 analytes with median Tmax ranging between 0.5 to 1.5 hours. With food, there was a slight delay in the Tmax (1.50 to 3.00 hours) for all 3 analytes. In general, the Cmax was generally comparable for all 3 analytes between fasted and fed state across both the dose levels. The AUC was largely comparable for the Remogliflozin (GSK189074) between fasted and fed state, and were slightly higher under fed state for the inactive prodrug and the metabolite GSK279782. The observed difference in Cmax or AUC of the Remogliflozin (GSK189074), metabolite or the inactive prodrug between fasted and fed state is not anticipated to be of clinical significance.

When a 250 mg of Remogliflozin etabonate tablet was administered in presence of glucose solution, the plasma concentration profiles showed considerably prolonged absorption, indicating glucose solution could be impacting the absorption probably by interfering with solubility of the prodrug. The dose proportional increase in Cmax and AUC, and similar half-lives at 100 mg and 250 mg indicate linear pharmacokinetics. Across dose levels and diet conditions, the Remogliflozin (GSK189074) showed the highest exposures, followed by metabolite GSK279782 (~ 25 to 42% of Remogliflozin). Inactive prodrug Remogliflozin etabonate (GSK189075) had the lowest exposure (≤3% of Remogliflozin), across the treatments. The elimination half-lives remained consistent for each analyte between the doses and diet conditions, with the shortest half-life for the Remogliflozin etabonate (GSK189075) prodrug (~ 0.5 hours) and the longest for the metabolite GSK279782 (~ 3.8 hours).

The pharmacokinetic parameters of Remogliflozin etabonate (GSK189075), Remogliflozin (GSK189074), & metabolite GSK279782 summarized in the following tables.

Pharmacokinetic Parameters following single doses of 100 mg and 250 mg of Remogliflozin Etabonate under fasting Conditions

PK Parameters (Units)	Fasted State (100 mg); N=15			Fasted State (250 mg); N=15		
	Remogliflozin etabonate (GSK189075)	Remogliflozin (GSK189074)	Metabolite GSK279782	Remogliflozin etabonate (GSK189075)	Remogliflozin (GSK189074)	Metabolite GSK279782
Tmax (h) #	0.50 (0.25-1.50)	0.75 (0.50-2.0)	1.00 (0.75-2.00)	0.50 (0.25-2.00)	0.75 (0.25-4.00)	1.500 (0.50-4.50)
Cmax (ng/mL)	20.88 (82.0)	536.18 (29.3)	96.63(50.2)	49.57(89.5)	1275.35(51.1)	286.31(49.0)
AUC0-t (ng.h/mL)	15.50(66.5)	1259.54 (25.8)	316.31 (49.5)	43.52 (76.0)	3168.83 (34.5)	1028.41 (41.3)
AUC0- inf (ng.h/mL)	17.40(68.9)*	1266.61 (25.7)	323.60 (48.5)	49.72(72.4)*	3178.13 (34.4)	1037.10 (14.0)
t1/2 (h)	0.44(84.7)*	1.54(13.1)	2.37(13.1)	0.45(44.6)*	1.79(15.4)	3.31 (15.6)

#Tmax is represented in median (min-max) value.

PK Parameters (Units)	Fed State (100 mg); N=15			Fed State (250 mg); N=15		
	Remogliflozin etabonate (GSK189075)	Remogliflozin (GSK189074)	Metabolite GSK279782	Remogliflozin etabonate (GSK189075)	Remogliflozin (GSK189074)	Metabolite GSK279782
aTmax (h)#	1.50 (0.25-3.00)	2.50 (0.50-3.00)	3.00 (1.50-4.00)	1.517 (0.250-3.000)	2.500 (1.50-4.00)	3.00 (2.50-4.51)
Cmax (ng/mL)	20.92 (60.6)	413.68 (32.7)	138.64 (31.1)	38.98 (53.1)	1037.11 (16.1)	319.58 (41.4)
AUC0-t (ng.h/mL)	38.47(46.9)	1536.81(19.2)	642.51(35.8)	87.43 (46.6)	4286.94 (22.5)	1606.73(36.2)
AUC0-inf (ng.h/mL)	42.20(41.8)	1546.58(19.1)	651.09(35.3)	89.03 (45.7)	4294.85 (22.5)	1617.26 (36.0)
t1/2 (h)	0.69(41.0)*	1.53(15.8)	2.80(12.4)	0.55(30.5)*	1.90(28.1)	3.77(14.9)

#Tmax is represented in median (min-max) value.

Study KG2105264: Metabolic Disposition using Mass Balance Study (radioactive isotope) to investigate Absorption, Distribution, Metabolism and Excretion:

Following oral tablet administration, Remogliflozin etabonate (GSK189075) is rapidly converted to the Remogliflozin (GSK189074); Tmax generally occurs within an hour. Remogliflozin (GSK189074) is further metabolized to metabolite GSK279782, with the elimination half-life (t½) of Remogliflozin (GSK189074) being approximately 02 hours. Absolute bioavailability of Remogliflozin (GSK189074) from prodrug administration has not yet been determined in humans. The mean terminal half-lives were 0.39, 1.57, and 2.68 hours for

Remogliflozin etabonate (GSK189075), Remogliflozin (GSK189074), and metabolite GSK279782, respectively. Remogliflozin (GSK189074) is extensively metabolized with approximately 15% of the oral Remogliflozin etabonate (GSK189075) dose recovered in urine as Remogliflozin etabonate (GSK189075), Remogliflozin (GSK189074) and metabolite GSK278782. Only about 11% of the dose was recovered in urine as Remogliflozin (GSK189074). Approximately 93% of the total radioactivity was excreted in the urine and 3% eliminated in the faeces. The mean total recovery was approximately 96%.

KG2105253 study: Pharmacokinetics in Renal insufficiency (6)

This study was performed in non-diabetic subjects with mild or moderate renal insufficiency compared to matched healthy subjects with single dose of RE 250mg. Apart from quantification of Remogliflozin etabonate (GSK189075), Remogliflozin (GSK189074), & metabolite GSK279782, Plasma protein binding measurements were carried out to determine the free (unbound) fraction of Remogliflozin (GSK189074), & metabolite GSK279782 in plasma.

Plasma concentration-time data for Remogliflozin etabonate (GSK189075) and its metabolites from 12 subjects with mild renal impairment, 7 subjects with moderate renal function & 12 subjects with normal renal function. Key comparison of PK parameters of Remogliflozin etabonate (GSK189075) its metabolites in each renal function group are summarized as follows.

Results of statistical analysis to compare PK parameters of GSK189075 and its metabolites (KG2105253 study)

	Mild Renal Impairment / Matched Normal	Moderate Renal Impairment / Matched Normal
Remogliflozin etabonate (GSK189075)		
AUC(0-t)	1.20 (0.749-1.92)	1.18 (0.677, 2.04)
Cmax	1.56 (0.841, 2.90)	0.753 (0.365, 1.55)
T1/2	1.11 (0.678, 1.83)	1.76 (0.990, 3.12)
Remogliflozin (GSK189074)		
AUC(0-∞)	1.08 (0.798, 1.47)	1.14 (0.800, 1.64)
Cmax	1.35 (0.836, 2.18)	0.933 (0.533, 1.63)
t1/2	1.09 (0.998, 1.20)	1.17 (1.05, 1.31)
Metabolite GSK279782		
AUC(0-∞)	1.51 (0.930, 2.45)	1.34 (0.763, 2.37)
Cmax	1.69 (0.959, 2.99)	1.02 (0.524, 1.99)
t1/2	1.09 (0.955, 1.25)	1.15 (0.980, 1.34)

In general, plasma profiles and PK parameter estimates of Remogliflozin etabonate (GSK189075) and Remogliflozin (GSK189074) were comparable between subjects with varying degrees of renal insufficiency and subjects with normal renal function. The plasma protein binding measurements for Remogliflozin (GSK189074) and metabolite GSK279782 were also comparable.

As expected, the % dose recovered and renal clearances of Remogliflozin (GSK189074) and metabolite GSK279782 were reduced in subjects with renal impairment, and the extent of reduction was greater in subjects with moderate renal impairment. The magnitude of increase in the AUC of metabolite GSK279782 was consistent with reduced renal clearance.

3.3 Drug Drug interaction studies

Study KG2105246 (2) & KG2110243: Metformin in combination with Remogliflozin etabonate (GSK189075) in Type 2 diabetic patients

Two studies have been conducted in subjects with T2DM to evaluate the combination of Remogliflozin etabonate (GSK189075) and metformin. There was no effect of Remogliflozin etabonate (GSK189075) on metformin PK parameters in either study; metformin area under the plasma concentration versus time curve at steady state, Cmax and Tmax were similar when given alone or when given with Remogliflozin etabonate (GSK189075). In Study KG2105246, there was no effect of metformin on the PK parameters of Remogliflozin etabonate (GSK189075) and its metabolites. In study KG2110243, no significant rise in serum lactic acid was seen when Remogliflozin etabonate (GSK189075) was co-administered with metformin (≥2000 mg/day) for 12 days.

Drug-drug Interaction Studies in Healthy Subjects

Diuretic interaction study (Study KG2105251) with furosemide or hydrochlorothiazide:

Results from repeat dose administration of Diuretic with RE study show that addition of RE to furosemide or HCTZ does not significantly reduce serum sodium or potassium concentrations compared with the administration of these diuretics alone nor does it pose any significant electrolyte abnormalities. The primary pharmacodynamic effect (urine glucose excretion) of Remogliflozin etabonate (GSK189075) is consistent with that observed in previous studies of Remogliflozin etabonate (GSK189075) and does not appear to be affected by its co-administration with furosemide or HCTZ. A potential safety issue identified in this study is a risk of complications such as postural dizziness/orthostasis resulting from volume contraction.

Ketoconazole interaction (1) (Study KG2108197): Pharmacokinetic results show that ketoconazole increases the remogliflozin (GSK189074) AUC by 1.75-fold and prolongs the t½ by approximately 1 hour. Exposure of metabolite GSK279782 decreased by approximately 15% and exposure of GSK333081 decreased about 3-fold. A <2-fold increase by a potent inhibitor such as ketoconazole is considered to be a weak interaction. These data demonstrate that CYP3A4 is not the only important metabolic pathway for

remogliflozin (GSK189074) metabolism. Given the wide therapeutic index observed to date with Remogliflozin etabonate (GSK189075), and the weak interaction observed in this study, no dose- adjustment is needed when Remogliflozin etabonate (GSK189075) is administered with a CYP3A4 inhibitor.

Oral contraceptive interaction (Study KG2107494): The results of the study suggested that, there appears to be a potential for a sporadic lack of absorption of Brevicon [0.5 mg norethindrone/35 µg ethinylestradiol tablet] when co-administered with GSK189075. As the effectiveness of the oral contraceptive may be negatively impacted, it is recommended that an appropriate alternative method for avoiding pregnancy should be utilized

Bupropion interaction (Study KGW111083): This study was conducted to rule out an effect of Remogliflozin etabonate (GSK189075) on the PK of bupropion. Concomitant administration of WELLBUTRIN SR [Bupropion 150 mg (sustained release)] with Remogliflozin etabonate (GSK189075) also did not affect the plasma profiles and PK of remogliflozin (GSK189074), the active entity of Remogliflozin etabonate (GSK189075). The lack of PK interactions between Remogliflozin etabonate (GSK189075) and WELLBUTRIN SR is expected based on the knowledge that GSK189074 and bupropion are metabolized by multiple CYP and non-CYP pathways, show low inhibitory potential towards most CYP enzymes except for bupropion for CYP2D6, and have no known induction potential clinically.

3.4 Early development studies:

KG219017: First-time-in-human Study in Healthy Subjects and Subjects with T2DM (9)

Following single doses of Remogliflozin etabonate (GSK189075) in healthy subjects (20 to 1000 mg) and in subjects with type 2 diabetes mellitus (T2DM) (50 and 500 mg), there was a dose-dependent increase in Urine Glucose Excretion (UGE). Twenty-four hour UGE increased less than proportionally with increasing exposure to Remogliflozin (GSK189074); the largest effect was observed with 500 mg dose in healthy subjects. The Urine Glucose Excretion (UGE) in subjects with type 2 diabetes mellitus (T2DM) was higher compared to the healthy subjects for the same dose of Remogliflozin etabonate (GSK189075). Drug exposures were proportional to the dose administered in healthy volunteers.

Pharmacokinetic Parameters after Oral Administration of GSK189075 in Healthy Subjects

Healthy Subjects (n=8)				
Dose (mg)	**Cmax (ng/mL)**	**Tmax (hr)**	**AUC(0-∞)* (ng.hr/mL)**	**t½ (hr)**
Remogliflozin etabonate (GSK189075)				
20	1.89 (1.01-3.51)	0.63 (0.33-2.0)	1.61 (0.66-3.89)	NQ
50	4.98 (2.91-8.51)	0.63 (0.17-1.5)	3.56 (2.21-5.74)	0.35 (0.19-0.64)
150	17.6 (11.3-27.4)	0.52 (0.17-1.5)	9.51 (6.98-13)	0.26 (0.18-0.36)
500	41.6 (20.5-84.3)	1.3 (0.33-2.5)	35.4 (19.5-64)	0.26 (0.18-0.39)
1000	144 (72.3-287)	0.63 (0.33-2.5)	107 (61.9-185)	0.71 (0.45-1.1)
Remogliflozin (GSK189074)				
20	61 (37.8-98.3)	0.89 (0.50-1.5)	133 (90.7-196)	1.4 (1.2-1.6)
50	158 (104-240)	1.1 (0.5-1.5)	324 (245-429)	1.5 (1.3-1.7)
150	515 (362-731)	0.66 (0.33-2.1)	991 (785-1252)	1.6 (1.4-1.8)
500	1703 (1163-2493)	1.5 (0.5-3)	3721 (2876-4814)	2.6 (2-3.3)
1000	4822 (3485-6672)	1.3 (0.5-3)	10257 (8892-11832)	2.9 (2.5-3.3)
Metabolite GSK279782				
20	17.5 (10.9-28.2)	1.26 (0.75-2.5)	51.8 (33.8-79.4)	1.5 (1.4-1.7)
50	50.2 (28.1-89.5)	1.4 (1-2)	146 (90.3-235)	2.2 (1.9-2.5)
150	155 (102-235)	1 (0.75-2)	447 (305-654)	2.3 (2-2.6)
500	498 (340-730)	1.5 (1-4)	1523 (1085-2139)	3.1 (2.7-3.5)
1000	1286 (1003-1650)	1.3 (0.75-3)	3995 (3367-4740)	3.5 (3.2-3.9)

*AUClast reported for GSK189075 as AUC\ (0-∞) not always quantifiable due to lack of t 1/2 estimates in some subjects; NQ

= not quantifiable; Cmax, AUC and t 1/2 are presented as geometric mean and (95% confidence interval); Tmax presented as median and range.

Subjects with T2DM

Following single doses of Remogliflozin etabonate (GSK189075), ranging from 50 and 500 mg in subjects with type 2 diabetes mellitus (T2DM), Remogliflozin etabonate (GSK189075) was rapidly absorbed and then rapidly and extensively converted to Remogliflozin (GSK189074). Drug exposures were proportional to the dose administered in type 2 diabetes mellitus (T2DM) patients.

Pharmacokinetic Parameters after Oral Administration of Remogliflozin etabonate (GSK189075) in Subjects with T2DM

Type 2 Diabetic Subjects (n=6)				
Dose (mg)	**C_{max} (ng/mL)**	**T_{max} (hr)**	**$AUC_{(0-\infty)}$* (ng.hr/mL)**	**$t_{½}$ (hr)**
Remogliflozin etabonate (GSK189075)				
50	9.56 (5.82-15.7)	0.58 (0.33-0.78)	8 (3.7-17.5)	0.61 (0.39-0.95)
500	83.9 (40-176)	0.75 (0.33-2.5)	91.9 (51.2-165)	NQ (n<2)
Remogliflozin (GSK189074)				
50	195 (119-320)	1.5 (0.33-2)	523 (372-736)	1.6 (1.2-2.1)
500	1891 (1049-3408)	2.5 (0.33-4)	5176 (3424-7824)	3.9 (3.1-5.0)
Metabolite GSK279782				
50	34.6 (19.9-60.4)	1.7 (0.75-4)	130 (65.2-260)	2.1 (1.5-2.8)
500	314 (189-522)	2.8 (0.75-4)	1293 (725-2307)	3.3 (2.5-4.3)

*AUC last reported for GSK189075 as AUC\ (0-∞) not always quantifiable due to lack of t 1/2 estimates in some subjects; NQ = not quantifiable; Cmax, AUC and t 1/2 are presented as geometric mean and (95% confidence interval); Tmax presented as median and range.

Study KG2109799: Multiple-dose pharmacokinetic studies

A multiple-dose study (was conducted in 12 healthy subjects in order to evaluate pharmacokinetic (PK) of supra-therapeutic doses of Remogliflozin etabonate (GSK189075) prior to formal evaluation of the effect of these doses on cardiac repolarization (QTc interval). There were dose-related increases in the steady-state plasma exposure to Remogliflozin etabonate (GSK189075) and its metabolites when doses of 2000 mg once daily and 4000 mg once daily were administered for 3 days, even though the increases were slightly less than dose proportional. The steady state plasma exposure to Remogliflozin etabonate (GSK189075) and its metabolites following 2000 mg or 4000 mg once daily regimens achieved at least 2-fold higher levels than those observed in previous clinical studies (e.g., 1000 mg once daily). Pharmacokinetic parameters are summarized in Table below.

Pharmacokinetic Parameters Following Multiple Dose Administration of GSK189075 2000 mg and 4000 mg

PK	2000 mg QD (n=12)		
Parameter	**Remogliflozin etabonate**	**Remogliflozin (GSK189074)**	**Metabolite GSK27978**
$AUC_{(0-24)}$ (ng.hr/mL)	272 (61)	20844 (20)	6337 (20)
C_{max} (ng/mL)	243 (66)	7460 (29)	1820 (28)
$t_{½}$ (hr)	0.507 (28)	2.24 (6.1)	2.99 (8.9)
T_{max} (hr)	0.5 (0.50-0.57)	0.75 (0.5-2.0)	1.5 (1.0-4.1)
PK	**4000 mg QD (n=11)**		
$AUC_{(0-24)}$ (ng.hr/mL)	532 (26)	33693 (26)	8188 (25)
C_{max} (ng/mL)	328 (45)	10170 (23)	2044 (25)
$t_{½}$ (hr)	0.587 (32)	2.22 (5.8)	2.96 (7.7)
T_{max} (hr)	1 (0.5-2.0)	2 (1.0-3.1)	1.5 (1.0-3.1)

Values are geometric mean (%CVb) for each parameter, except for T_{max} which are median (range).

Study KG2107489: In a randomized, double-blind, 3-day, repeat-dose, four-period, cross-over design study (formal QTc evaluation), Pharmacokinetic parameters were evaluated at doses of 500 mg once daily and 4000 mg once daily for 3 days in 67 healthy subjects, these have been presented below table.

Summary of Remogliflozin (GSK189074), Remogliflozin etabonate (GSK189075) Pharmacokinetic Parameters

Remogliflozin etabonate (GSK189075), dose	N	AUC(0-24) (ng.h/mL)	AUC(0-t) (ng.h/mL)	Cmax (ng/mL)	tmax (h)	t1/2 (h)	Cmin (ng/mL)	AUC Ratio
Remogliflozin (GSK189074)								
500 mg	66	3495 (33.3)	3486 (33.4)	1567 (42.2)	1.00(0.50-4.02)	1.55 (18.4)	0.00 (0.00-11.31)	104 (76.8)
4000 mg	64	34591 (35.8)	33992 (36.9)	10231 (30.0)	2.00(0.50-4.07)	2.08 (16.6)	7.07(0.00-59.8)	91.0 (53.2)
Remogliflozin etabonate (GSK189075)								
500 mg	66	41.9(50.3)	39.5(56.8)	48.5 (55.7)	0.500(0.50-3.00)	0.396 (84.7)	0.00(0.00-0.00)	NA
4000 mg	64	471 (51.8)	447 (53.6)	272 (53.6)	1.00(0.50-4.07)	0.721 (53.9)	0.00(0.00-0.99)	NA

Values are geometric mean (%CVb) for each parameter, except for Tmax which are median (range).

Remogliflozin etabonate (GSK189075) was readily absorbed following oral administration of both doses 500 mg (high therapeutic) and 4000 mg (supra-therapeutic) with median peak plasma Remogliflozin etabonate (GSK189075) concentrations occurring between 0.5-1.0-hour post dose. Plasma AUC ratio between Remogliflozin (GSK189074) and Remogliflozin etabonate (GSK189075) were 104 and 91 following oral administration of therapeutic and supra-therapeutic dose levels of Remogliflozin etabonate (GSK189075), respectively. Plasma AUC exposure of Remogliflozin (GSK189074) and Remogliflozin etabonate (GSK189075) higher than dose proportional following administration of supra-therapeutic dose (4000mg) compared to those following administration of therapeutic dose suggesting nonlinearity when comparing therapeutic to supra-therapeutic overdose.

Study KG2104940: Multiple Dose Pharmacokinetics in Type 2 diabetes mellitus7)

The pharmacokinetic (PK) of repeat doses of 100 mg BID, 1000 mg BID and 1000 mg QD of Remogliflozin etabonate (GSK189075) taken 15 minutes before a meal have been investigated in subjects with type 2 diabetes mellitus (T2DM) following multiple dosing. No accumulation or time-dependent changes were observed. Calculated pharmacokinetic (PK) parameters are listed in Table below.

Pharmacokinetic Parameters Following Multiple Dosing in Subjects with T2DM

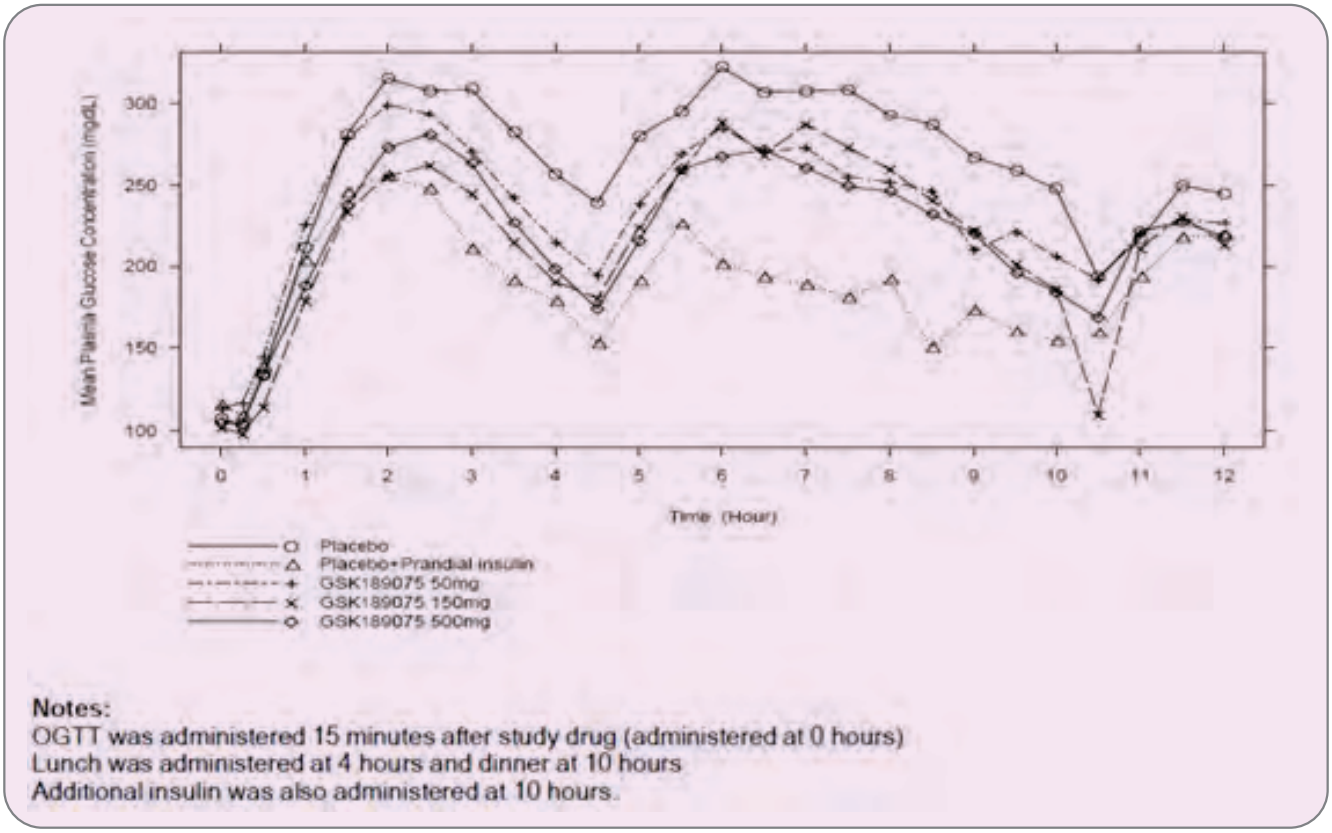
PK Parameter	100 mg BID (Day 1) n=9	100 mg BID (Day 11) n=9	1000 mg BID (Day 1) n=9	1000 mg BID (Day 11) n=9	1000 mg QD (Day 1) n=9	1000 mg QD (Day 11) n=9
Remogliflozin etabonate (GSK189075)						
AUC (ng.hr/mL)	23.0 (17.3)	14.7 (39.0)	141 (36.5)	167 (42.8)	134 (47.5)	179 (38.1)
Cmax (ng/mL)	16.9 (97.8)	16.3 (66.8)	226 (60.5)	255 (88.8)	219 (59.4)	247 (52.4)
Tmax	0.320 (0.25, 1)	0.5 (0.25, 0.77)	0.5 (0.25, 0.75)	0.5 (0.25, 0.75)	0.5 (0.25, 0.75)	0.5 (0.25, 0.75)
t½ (hr)	0.709 (169)	0.404 (54)	0.631 (43)	0.496 (66)	0.507 (50)	0.636 (80)
Remogliflozin (GSK189074)						
AUC(0-12) (ng.hr/mL)	699 (45.4)	783 (33.7)	9270 (31.7)	8936 (32.0)	7888 (27.2)	8745 (28.5)
AUC(0-24) (ng.hr/mL)	NA	NA	NA	NA	7888 (27.2)	8745 (28.5)
Cmax (ng/mL)	363 (36.3)	427 (32.0)	6436 (56.8)	5754 (62.7)	4830 (32.3)	6088 (32.3)
Tmax (hr)	0.55 (0.25,3)	0.75 (0.5, 0.78)	0.75 (0.5, 1.0)	0.75 (0.5, 1.5)	0.73 (0.5, 0.83)	0.75 (0.5, 0.92)
t½(hr)	1.42 (11)	1.39 (7.3)	1.47 (7.0)	1.52 (4.8)	1.43 (6.9)	1.45 (6.1)
CLr (mL/min)	177 (29)	187 (39)	147 (48)	174 (33)	187 (31)	173 (31)
Metabolite GSK279782						
AUC(0-12) (ng.hr/mL)	127 (56.3)	159 (49.7)	1514 (36.0)	1395 (39.3)	1721 (50.4)	1795 (38.1)
AUC(0-24) (ng.hr/mL)	NA	NA	NA	NA	1722 (50.4)	1795 (38.1)
Cmax (ng/mL)	43.4 (48.0)	54.8 (35.8)	646 (53.3)	552 (42.5)	648 (41.9)	723 (33.5)
Tmax (hr)	0.78 (0.52, 3)	1.0 (0.75, 1.5)	0.7 (0.75, 1.5)	0.7 (0.75, 2)	1.0 (0.75, 1.0)	1.0 (0.75, 1.0)
t½(hr)	1.93 (19.3)	2.05 (10.7)	2.01 (11.3)	2.09 (8.26)	1.95 (7.91)	2.00 (9.95)
CLr (mL/min)	138 (24)	155 (40)	142 (42)	166 (32)	166 (29)	166 (35)

Values are geometric mean (%CV), except for Tmax which are median (range); NA = not applicable

Study KGI107465: Single-dose Study in Subjects with T1DM (3)

Based on available preliminary results in 10 subjects with type 1 diabetes mellitus (T1DM), the increase in plasma glucose concentrations following oral glucose (75 g) at breakfast, as well as a mixed meal at lunchtime, was blunted compared to placebo, with single Remogliflozin etabonate (GSK189075) doses of 50 mg, 150 mg and 500 mg administered prior to the oral glucose. No dose-response was apparent. The effect on mean glucose concentration was less with Remogliflozin etabonate (GSK189075) than with bolus insulin.

Figure: Plasma Glucose Profiles in Subjects with T1DM



Notes:
OGTT was administered 15 minutes after study drug (administered at 0 hours)
Lunch was administered at 4 hours and dinner at 10 hours
Additional insulin was also administered at 10 hours.

Study KGW108201: Multiple-dose Study in Healthy Obese Subjects (8)

Remogliflozin etabonate (GSK189075) 250 mg TID was administered for 8 weeks to 9 healthy obese subjects in this study to evaluate the effect of Remogliflozin etabonate (GSK189075) on body weight and body composition. With this dose regimen, the mean urine glucose excretion (UGE) was 400 mmol/24hr (or 238 kcal/24h) at 8 weeks. Weight loss was observed in the Remogliflozin etabonate (GSK189075) group compared to placebo (–2.5 kg from baseline versus placebo), although the difference did not achieve statistical significance in this small study. The treatment-related increase in calorie excretion was associated with a similar measurable treatment-related change in fat mass assessed by both QMR Echo-MRI (Quantitative magnetic resonance Echo-magnetic resonance imaging) and 4-compartment model modalities. Statistically significant ($p<0.001$) decreases from baseline values to Week 8 for body fat mass and weight were observed (–4.8 kg and –7.6 kg, respectively, for Remogliflozin etabonate (GSK189075), but these findings were not significantly different than the placebo response (–4.6 kg and – 5.1 kg, respectively, for placebo), which may be explained by the protocol-required reduction of caloric intake.

A range of in vitro and in vivo studies has been conducted to investigate the primary, secondary and safety pharmacology of Remogliflozin etabonate (GSK189075) (prodrug).

In vitro assays using cell lines transfected with either rat or human sodium-dependent glucose co-transporter member 1 or 2 (SGLT1 or SGLT2), based on Ki values, Remogliflozin (GSK189074) has

~100 to 1000-fold selective for SGLT2 inhibition than SGLT1, with weak inhibitory effects on human

SGLT1. Remogliflozin etabonate (GSK189075) (single oral dose) induced a concentration-dependent

increase in urinary glucose excretion in normal mice (fasted: 1-100 mg/kg), rats (fed and fasted: 1-10 mg/kg) and dogs (fed: 1-10 mg/kg). Oral administration with pharmacological doses of Remogliflozin etabonate (GSK189075) reduced post-prandial glucose excursions in normal animals, without inducing

hypoglycaemia. In diabetic animal models, plasma glucose and glycosylated haemoglobin (HbA1c) levels were reduced although the insulin response varied depending on the model studied.

In secondary pharmacology in vitro assays, Remogliflozin etabonate (GSK189075) and Remogliflozin (GSK189074) showed no marked inhibition for various receptors, ion channels or transporters and had no effects on glucose uptake in human erythrocytes. In the vivo studies, Remogliflozin etabonate (GSK189075) showed no potential for gastrointestinal malabsorption of carbohydrates and low risk for hypoglycaemia. Remogliflozin etabonate (GSK189075) was shown to have intrinsic anti-oxidant activity. Remogliflozin etabonate (GSK189075), Remogliflozin (GSK189074), dapagliflozin, and canagliflozin were assayed for anti-oxidant activity using the ORAC (oxygen radical antioxidant capacity) assay. Only Remogliflozin (GSK189074) demonstrated significant activity compared to Remogliflozin etabonate (GSK189075), dapagliflozin, and canagliflozin.

4. TOXICOLOGY Acute Toxicity

No mortality was noted in rats and dogs after a single oral dose of 2000 mg/kg Remogliflozin etabonate (GSK189075). In dogs, clinical signs such as soft stools/diarrhoea, glycosuria and decreased rectal body temperature were noted on the day of dosing.

In mice mortality was observed with the administration of the metabolite (GSK279782) at doses of 200,

≥600 or 1000 mg/kg when given intravenously, intraperitoneally or subcutaneously, respectively. No mortality or adverse events were observed in a 13-week study in mice when Remogliflozin etabonate (GSK189075) was orally administered up to 2000 mg/kg/day.

Sub-chronic and Chronic Toxicity

Repeat dose toxicity studies with Remogliflozin etabonate (GSK189075) have been performed in the (ICR) mice (up to 13 weeks), Sprague Dawley rats (up to 26 weeks) and Beagle dogs (up to 52 weeks). All the pivotal toxicity studies included recovery groups and satellite groups for toxicokinetic evaluation. The list of the pivotal and non-pivotal (dose range finding studies) are mentioned in the table below.

Table: Toxicology Studies Conducted with Remogliflozin etabonate (GSK189075)

Type of Study	Species	Route	Compound	Doses (mg/kg/day)
Single-Dose Toxicity				
Single dose study	Mouse	Intraperitoneal	Metabolite GSK279782	60, 200, 600 and 2000
		Subcutaneous	Metabolite GSK279782	60, 200, 600 and 2000
		Intravenous	Metabolite GSK279782	60 and 200
Single dose study	Rat	Oral (gavage)	Remogliflozin etabonate (GSK189075)	1000 and 2000
Single dose study	Dog	Oral (gavage)	Remogliflozin etabonate (GSK189075)	1000 and 2000
Single dose study	Rat	Oral (gavage)	GSK1132678 (ametabolite)	2000
Repeat-Dose Toxicity				
2-Week toxicity study			Remogliflozin etabonate (GSK189075)	200, 600, 1200 and 2000
13-Week toxicity study			Remogliflozin etabonate (GSK189075)	250, 500, 1000 and 2000
2-Week toxicity study			Remogliflozin etabonate (GSK189075)	30, 100, 300 and 1000

Type of Study	Species	Route	Compound	Doses (mg/kg/da
4-Week toxicity study	Rat	Oral (gavage)	Remogliflozin etabonate (GSK189075)	100, 300 and 1000
4-Week toxicity study	Rat	Oral (gavage)	Remogliflozin etabonate (GSK189075)	200, 600 and 1200
13-Week toxicity study	Rat	Oral (gavage)	Remogliflozin etabonate (GSK189075)	200, 600 and 1200
26-Week toxicity study	Rat	Oral (gavage)	Remogliflozin etabonate (GSK189075)	200, 600 and 1200
4-Week toxicity study	Rabbit	Oral (gavage)	Remogliflozin etabonate (GSK189075)	30, 100 and 300
2-Week toxicity study	Dog	Oral (gavage)	Remogliflozin etabonate (GSK189075)	100 and 300
4-Week toxicity study	Dog	Oral (gavage)	Remogliflozin etabonate (GSK189075)	60, 250 and 1000
13-Week toxicity study	Dog	Oral (gavage)	Remogliflozin etabonate (GSK189075)	100, 300 and 1000/650
52-Week toxicity study	Dog	Oral (gavage)	Remogliflozin etabonate (GSK189075)	100, 300 and 650

The no-observed-adverse effect levels (NOAEL) established in 13-, 26- and 52-week oral toxicity studies in mice, rats and dogs were 2000, 1200 and 650 mg/kg/day, respectively (the highest dose tested in each species). The systemic exposure (AUC) obtained at the no-observed-adverse effect levels (NOAEL) dose (650 mg/kg/day) in 52-week dog (most sensitive species) study are ~315 to 366-fold for Remogliflozin etabonate (GSK189075) (prodrug), ~14 to 17-fold for Remogliflozin (GSK189074) and ~4 to 5-fold for metabolite (GSK279782) when compared to human AUC0-24hr values for Remogliflozin etabonate (GSK189075), Remogliflozin (GSK189074) and metabolite (GSK279782) achieved at maximum recommended clinical dose of 500 mg/day (250 mg BID) in a 24-week clinical study with Remogliflozin etabonate (GSK189075) in type 2 diabetes mellitus patients (GPL/CT/2016/009/III).

The systemic exposure obtained at the no observed adverse effect levels (NOAEL) dose (1200 mg/kg/day) in 26-week rat study are ~31 to 53-fold for Remogliflozin etabonate (GSK189075) (prodrug), ~14 to 16-fold for Remogliflozin (GSK189074) and ~28 to 43-fold for metabolite (GSK279782) when compared to human AUC0-24hr values for Remogliflozin etabonate (GSK189075), Remogliflozin (GSK189074) and metabolite (GSK279782) achieved at maximum recommended clinical dose of 500 mg/day (250 mg BID) in a 24-week clinical study with Remogliflozin etabonate (GSK189075) in type 2 diabetes mellitus patients (GPL/CT/2016/009/III).

The no observed adverse effect levels (NOAELs) doses established in animal toxicity studies, provides sufficient safety margins to support the clinical safety of Remogliflozin etabonate (GSK189075) at doses up to 500 mg/day (250 mg twice daily).

Carcinogenicity

A 2-year carcinogenicity study with Remogliflozin etabonate (GSK189075) was conducted in Sprague Dawley rats with oral gavage doses of 0, 60, 200, 600 or 1200 mg/kg/day and in mice with oral doses of 300, 600 and 1000 mg/kg/day. There was no drug related effects on survival. Exposure multiples for Remogliflozin (GSK189074) greater than 5 to 8-fold human AUC exposures were obtained with 600 mg/kg/day in rats and mice in the carcinogenicity studies. The neoplastic findings observed in the carcinogenicity studies do not appear to have direct relevance to humans, based on observations of the species/sex selectivity and type of tumours observed. Thus Remogliflozin etabonate (GSK189075) was non-carcinogenic in a 2-year oral (gavage) carcinogenicity study conducted in rats (60, 200, 600 or 1200 mg/kg/day) and mice (300, 600 and 1000 mg/kg/day).

Genotoxicity

Remogliflozin etabonate (GSK189075) (prodrug) and Remogliflozin (GSK189074) were non-mutagenic in separate Ames tests (bacterial reverse mutation test) and showed no evidence of in vitro clastogenicity in Chinese hamster lung cells and mouse lymphoma cells (Remogliflozin etabonate (GSK189075) only). In an in vivo rat micronucleus study, Remogliflozin etabonate (GSK189075) did not increase the incidence of micronucleated polychromatic erythrocytes at doses up to 2000 mg/kg. Overall, these data indicate that Remogliflozin etabonate (GSK189075) did not pose a genotoxic risk to humans

Reproductive Toxicity

Remogliflozin etabonate (GSK189075) had no effect on male (200, 600, and 1200 mg/kg/day) and female (200, 600 or 1000 mg/kg/day) fertility in rats and the NOAEL were 1200 mg/kg/day (~23 times the MRHDD of 500 mg/day on body surface area [mg/m2] basis) and 1000 mg/kg/day (~20 times the MRHDD of 500 mg/day on mg/m2 basis), respectively.

Remogliflozin etabonate (GSK189075) was not teratogenic in rats (200, 600 and 1000 mg/kg/day) and rabbits (125, 250 and 500 mg/kg/day) at oral doses of 1000 and 500 mg/kg/day (~20 times the MRHDD of 500 mg/day on mg/m2 basis), respectively.

In pre- and post-natal developmental study in rats (200, 600 and 1000 mg/kg/day), no treatment-related effects were noted in pregnant/lactating females and on development of the conceptus and the offspring following exposure up to 1000 mg/kg/day (~20 times the MRHDD of 500 mg/day on mg/m2 basis).

Local Tolerance Studies

Remogliflozin etabonate (GSK189075) did not produce anaphylactic reactions in the active systemic anaphylaxis (ASA) test or in the homologous passive cutaneous anaphylaxis (PSA) test in guinea pigs.

Based on in vitro assays, Remogliflozin etabonate (GSK189075) was found non-irritant to skin and eye. Further in local lymph node assay both Remogliflozin etabonate (GSK189075) was determined to be non-sensitizer.

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Remogliflozin Etabonate 100 mg Tablets

Reniva ABPI Abbreviated Prescribing Information – Reniva Active ingredient: Each film coated tablet of Reniva contains Remogliflozin Etabonate 100 mg. Indication: In adults with Type 2 diabetes Mellitus as Monotherapy, when diet & exercise do not provide adequate glycemic control, or add on therapy with Metformin, together with diet & exercise do not provide adequate glycemic control. **Dosage and Administration:** The recommended dose of Remogliflozin Etabonate is 100 mg twice daily. Remogliflozin can be taken with or without food. **Contraindications:** Hypersensitivity to the active substance or to any of its excipients. **Warnings & Precautions:** Remogliflozin should not be initiated in patients with moderate to severe renal impairment (glomerular filtration rate [GFR] < 60 mL/min). Remogliflozin is not recommended for use in patients with moderate to severe hepatic impairment. Remogliflozin can cause hypotension, hemoconcentration, or electrolyte abnormalities. Initiation of Remogliflozin in patients receiving concomitant diuretics should be undertaken cautiously. Rare cases of diabetic ketoacidosis (DKA), including lite-threatening and fatal cases, have been reported in patients treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors. No moderate to severe events of DKA were reported in clinical studies with Remogliflozin. Urinary tract infections were reported for Remogliflozin. Patients on oral contraceptives should be advised to use alternative, non-hormonal methods of birth control during treatment with Remogliflozin. Cases of a rare but serious infection of the genitals and area around the genitals have been reported with this class of Type 2 diabetes medicines i.e. Sodium Glucose Cotransporter-2 (SGLT2) inhibitors. This serious rare infection, called necrotizing fasciitis of the perineum, is also referred to as Fournier's gangrene. **Use in specific population:** Safety and efficacy of Remogliflozin in children less than 18 years have not been established. No clinical studies with Remogliflozin Etabonate have been conducted in pregnant or lactating women. **Adverse Reactions:** Urinary tract infection, pyrexia, headache, bacteriuria, constipation, diarrhea, Glomerular filtration rate decreased, ketonuria, cough, dyslipidemia, asthenia, viral upper respiratory tract infection, hypoglycemia, and orthostatic hypotension. **Over dosage:** There is no specific antidote for an overdose of Remogliflozin Etabonate. Inhibition of SGLT2 is reversible. (Please refer complete prescribing information for further details, before prescribing) It is recommended to refer to the full prescribing information before prescribing. Version: 31stJan 2020. If you require further information, please contact us on below given address.

Reniva-M 500 1000

Remogliflozin Etabonate 100 mg + Metformin Hydrochloride IP 500/1000 mg Tablets

Reniva M ABPI : Abbreviated Prescribing Information – Reniva M
Active ingredient: Each film coated tablet of Reniva contains Remogliflozin Etabonate 100 mg and Metformin Hydrochloride I.P. 500 mg/1000 mg **Indication:** Indicated in adults aged 18 years and olderwith type 2 diabetes mellitus as an adjunctto dietand exercise to improve glycemic control: - in patients insufficiently controlled on their maximally tolerated dose of metformin alone- In patients already being treated with the combination of Remogliflozin and metformin as separate tablets. **Dosage and Administration:** Adults with normal renal function (GFR >90 ml/min). The recommended dose is one tablet twice daily. **Contraindications:** Hypersensitivity to the active substance or to any of its excipients. Any type of acute metabolic acidosis. Diabetic pre-coma. Severe renal failure (GFR <30 ml/min). Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock.Hepatic impairment, acute alcohol intoxication, alcoholism. Disease which may cause tissue hypoxia. **Warnings & Precautions:** Remogliflozin should not be initiated in patients with moderate to severe renal impairment (glomerular filtration rate [GFR] < 60 mL/min). This medicinal product must not be used in patients with hepatic impairment. Remogliflozin can cause hypotension, hemoconcentration, or electrolyte abnormalities. Initiation of Remogliflozin in patients receiving concomitant diuretics should be undertaken cautiously. Rare cases of diabetic ketoacidosis (DKA), including lite-threatening and fatal cases, have been reported in patients treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors. No moderate to severe events of DKA were reported in clinical studies with Remogliflozin. Urinary tract infections were reported forRemogliflozin. Patients on oral contraceptives should be advised to use alternative, non-hormonal methods of birth control during treatment with Remogliflozin. Cases of a rare but serious infection of the genitals and area around the genitals have been reported with this class of Type 2 diabetes medicines i.e. Sodium Glucose Cotransporter-2 (SGLT2) inhibitors. This serious rare infection, called necrotizing fasciitis of the perineum, is also referred to as Fournier's gangrene. intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis.For patients with acute and unstable heart failure, Remogliflozin and Metformin is contraindicated due to the metformin component.As Remogliflozin and Metformin contains metformin, Remogliflozin and Metformin must be discontinued at the time of surgery under general, spinal, or epidural anaesthesia. **Use in specific population:** Safety and efficacy of Remogliflozin in children less than 18 years have not been established. No clinical studies have been conducted in pregnant or lactating women. **Adverse Reactions:** Remogliflozin - Urinary tract infection, pyrexia, headache, bacteriuria, constipation, diarrhea, Glomerular filtration rate decreased, ketonuria, cough, dyslipidemia, asthenia, viral upper respiratory tract infection, hypoglycemia, and orthostatic hypotension. Metformin- Lactic acidosis, Decrease of vitamin B12 absorption, Taste disturbance, Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. Skin reactions such as erythema, pruritus, urticarial. **Over dosage:** Remogliflozin- There is no specific antidote for an overdose of Remogliflozin Etabonate. Inhibition of SGLT2 is reversible. (Please refer complete prescribing information for further details, before prescribing). Metformin- Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin or concomitant risks maylead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis. It is recommended to refer to the full prescribing information before prescribing. Version: 31stJan 2020. If you require further information, please contact us on below given address.

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