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Research Article

Efficacy and Safety of a Combination of Remogliflozin Etabonate and Vildagliptin as Fixed Doses in Patients with Type-2 Diabetes Mellitus: A Randomized, Active-Controlled, Double-Blind Study. (FOREVER STUDY)

Paramesh Shamanna[1], FOREVER INVESTIGATORS[2], Brij Mohan[3], Sosale R Aravind[4], A R Balamurugan[5], Manoj Chawla[6], Arthur J Asirvatham[7], Keyur Bramhe[8], Sandeep K Gupta[9], Surendra K Sharma[10], Rahul Kodgule[11], Monika Tandon[11], Amol Pendse[11], Sumit Bhushan[11*], Abhishek Mane[11], Yash N Panchal[11], Wen Wu[11], Shabbir Rangwala[11], Hanmant Barkate[11]

[1]Bangalore Diabetes Centre, Bengaluru, India, [2]All FOREVER study investigators mentioned in acknowledgement section

[3]Brij Medical Centre Pvt. Ltd., Kanpur, India, [4]Diacon Hospital, Bengaluru, India

[5]Kovai Diabetes Speciality Centre & Hospital, Coimbatore, India, [6]BSES Municipal General Hospital, Mumbai, India

[7]Arthur Asirvatham Hospital, Madurai, India, [8]SSG Hospital, Vadodara, India

[9]M. V. Hospital and Research Centre, Lucknow, India, [10]Diabetes Thyroid & Endocrine Centre, Rajasthan, India

[11]Glenmark Pharmaceuticals Ltd, Mumbai, India,

[*]**Corresponding author:** Sumit Bhushan, Glenmark Pharmaceuticals Ltd, Mumbai, India

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Abstract

Aims: The study aimed at evaluating efficacy and safety of Remogliflozin etabonate and Vildagliptin fixed dose combination (FDC) compared to currently approved FDC of Empagliflozin and Linagliptin.

Methods: A randomized, double-dummy, double-blind, active-controlled, parallel-group, two-arm, multi-center study was conducted at 26 sites across India. Type-2 diabetes mellitus (T2DM) patients aged between 18-65 years on metformin ≥1500 mg were randomized to receive either Remogliflozin Etabonate and Vildagliptin (RV) or Empagliflozin and Linagliptin (EL) with matched placebo.

Results: A total of 400 study participants with T2DM who had inadequate glycemic control with stable metformin dose as monotherapy were enrolled. At end of study duration i.e. week 16, there was a statistically significant change from baseline in HbA1c levels in both the groups i.e. -1.38% in the RV group and -1.46% in the EL group ($p < 0.001$). The difference between the RV group and EL group was -0.08% (90% CI difference: -0.28, 0.13). Similarly, statistically significant changes from baseline to week 16 in fasting plasma glucose (FPG) and post prandial glucose (PPG) levels were seen in RV group and EL group ($p < 0.001$) with no statistically significant differences seen between the groups. The safety profile of both the FDC's were comparable.

Conclusion: The FDC of Remogliflozin and Vildagliptin was found to be non-inferior to FDC of Empagliflozin and Linagliptin in terms of efficacy and safety. This FDC of Remogliflozin and Vildagliptin provides an alternative to the management of Indian T2DM patients requiring SGLT2 inhibitor and DPP4 inhibitor combination.

Keywords: Remogliflozin; SGLT2 inhibitor; DPP-4 inhibitor; Fixed dose combination; Type-2 diabetes mellitus

Introduction

Diabetes mellitus is one of the fastest-growing health emergencies globally and a major public health concern in India [1]. As per the ICMR-INDIAB 17 study, the prevalence of Diabetes in India stands at 11.4% with 101 million people suffering from the condition. [2]. It is estimated that more than 50% of individuals with diabetes in India remain undiagnosed. Uncontrolled diabetes leads to increased risk of micro and macro vascular complication and significantly cause for increased premature morbidity and mortality [2]. Hence, to curb the epidemic of diabetes and its associated complications, there is a need for a multipronged strategy [2]. Multiple strategies are often required to effectively control hyperglycemia in patients with type 2 diabetes. The combinatory use of different anti-diabetic agents with complementary mechanisms of action enhances the glucose-lowering effect without compromising drug safety [3].

Newer anti-diabetic agents such as sodium glucose cotransporter 2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP4) inhibitors are very useful in managing T2DM and rarely cause common adverse effects of other oral hypoglycemic agents, such as weight gain and hypoglycemia [4]. SGLT2 inhibitors reduce hyperglycemia by increasing urinary glucose excretion independent of insulin secretion or action [4,5]. DPP4 inhibitors, which inhibit the breakdown of active incretin hormones, improve glucose homeostasis by increasing insulin secretion and decreasing glucagon secretion in a glucose-dependent manner [6,7]. In this regard, the combination of these two drugs could be effective and safe for the treatment of hyperglycemia in patients with sub-optimally controlled type 2 diabetes. Also, the ADA 2024 guidelines states that patients with levels ≥1.5% of glycated hemoglobin (HbA1c) above the glycemic target will require dual combination therapy to achieve their HbA1c level target [8].

SGLT2 inhibitor, Remogliflozin and DPP4 inhibitor, Vildagliptin, are twice- daily medications that are individually approved for T2DM management. A single pill fixed-dose combination (FDC) of Remogliflozin and Vildagliptin would not only offer beneficial pharmacologic effects and reduced pill burden, but also lead to a simplified treatment regimen with lesser cost of therapy and better treatment compliance [9]. In addition, Remogliflozin has promising efficacy in reducing Glycemic variability, an independent risk factor for cardiovascular complications in diabetic patients [10].

A similar SGLT2i-DPP4i FDC of Empagliflozin and Linagliptin was approved for use in India which has been demonstrated to have significant glycemic efficacy and safety in clinical trials [11]. This phase III clinical study evaluated the efficacy and safety of FDC of Remogliflozin etabonate 100 mg and Vildagliptin 50 mg given twice daily in comparison to FDC of Empagliflozin 25 mg and Linagliptin 5 mg once daily in study participants who have inadequately controlled T2DM with stable dose metformin.

Study Design

This phase-III clinical trial was a randomized, double-dummy, double-blind, active-controlled, two-arm, multi-center, parallel-group study that was conducted at 25 sites across India between February 2020 and October 2020. The study protocol and all documents related to the study were reviewed and then approved by an Institutional Ethics Committee (IEC) at each of the investigator's sites. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) according to the International Council for Harmonization (ICH) guidelines. An informed consent in compliance with the Declaration of Helsinki, ICH GCP, as well as local regulations, was obtained from each subject before entering into the trial.

Study Method

T2DM patients of either sex aged between 18 and 65 years receiving a stable dose of metformin ≥1500 mg/day as monotherapy for at least 10 weeks before screening, but having inadequate glycemic control at screening (defined as HbA1c levels ≥8% and ≤11%), and were willing to use a highly effective form of contraception if applicable for the study's duration were eligible to take part in the study. Patients who gave informed consent to follow all study procedures were enrolled in the study. Key exclusion criteria were a history of type 1 diabetes mellitus, secondary diabetes mellitus, diabetes insipidus, metabolic acidosis, or diabetic ketoacidosis; or who had fasting plasma glucose (FPG) >270 mg/dL and/or BMI ≥45.0 kg/m at screening.

Each eligible study participant was screened for a run-in period of at least 2 weeks before randomization, during which standard consultation for dietary and exercise modification were provided to all the study participants and background metformin dosage was switched to the nearest multiple of 500 mg. The study participants eligible after the run-in period were randomized 1:1 to receive either FDC of Remogliflozin 100 mg and Vildagliptin 50 mg group or FDC Empagliflozin 25 mg and Linagliptin 5 mg group for a total of 16 weeks. Study participants were followed up at 6, 12, and 16 weeks after randomization, as well as 2 weeks after treatment ended for a safety follow-up consultation. All study participants continued receiving metformin in an open-label fashion at the same ≥1500 mg dose that they received during run-in period throughout the study period, administered in 500 mg instant-release tablet form.

A medical history in detail was obtained from each subject at the screening visit which included a complete physical examination and measurements of body weight, height, waist circumference, body mass index (BMI), and vital signs (including supine blood pressure [BP], pulse rate, and oral temperature); a single 12-lead ECG; and laboratory assessment of HbA1c, FPG, eGFR, and

serum creatinine levels. Repeat examination was conducted at the 16th -week visit. At the 6th- and 12th-week visits, a brief physical exam was performed alongside vital sign measurements and laboratory tests.

Study Endpoints

The primary efficacy endpoint was a mean change in HbA1c levels from baseline after 16 weeks of treatment. Secondary efficacy endpoints included mean change from baseline in HbA1c levels at week 12, mean change in FPG, PPG and body weight from baseline at the end of treatment, percentage of patients achieving therapeutic glycemic response (defined as HbA1c <7%) at end of treatment, and percentage of study participants requiring rescue medications (open label anti-diabetic medications except GLP-1 analogs, other DPP4 inhibitors or SGLT2 inhibitors or their combinations) during study treatment. Safety was assessed by recording treatment-emergent adverse events (TEAEs) including special interest AEs such as hypoglycemia, urinary tract infections, and genital fungal infections, as well as by lipid pro le, vital signs, ECG, eGFR, other laboratory tests (hematology, blood chemistry, and urine values), and physical examination.

Statistical Analysis

For sample size, a total of 160 study participants in each treatment group was estimated to provide a power of 90% at one sided significance level of 2.5% (2 sided 5%), with assumed standard deviation of 1.1% of HbA1c, to demonstrate non-inferiority of FDC of Remogliflozin and Vildagliptin in comparison with FDC of Empagliflozin and Linagliptin, in HbA1c change from baseline at week 16, with a non-inferiority (NI) margin of 0.40. Assuming that 20% of randomized study participants were not included in the per- protocol set, 400 study participants (200 study participants per group) were planned for enrolment and randomization in the study. NI margin of 0.40 was selected based on the effect of the active comparator (i.e., FDC of Empagliflozin 25 mg and Linagliptin 5 mg) in placebo-controlled studies and is compliant with the international guidelines for anti-diabetic drugs

The per-protocol (PP) analysis set involved all study participants who were randomized, given at least a dose of study drug, completed the study, and did not have any major deviations from the protocol such as intake of prohibited medications or failure in meeting the study inclusion criteria. The modified intent-to-treat (mITT) analysis set involved all randomized patients who received at least a single dose of study medication, having a non-missing baseline measurement, and also having at least one post-baseline efficacy measurement for a primary efficacy variable. The safety analysis set involved all randomized patients who received at least one dose of the study medication.

The primary and secondary endpoints were analyzed using the PP and mITT sets. The comparison of RV versus EL in terms of HbA1c change from the baseline to week 16 was analyzed using a mixed-model repeated measure (MMRM) method. The MMRM model involved data from all the visits until week 16 and the following covariates: visit, treatment, HbA1c at baseline, eGFR at baseline, centre, and treatment by the visit interaction. An unstructured covariance matrix was used to allow correlations adjustment between the time points within study participants. Primary efficacy analysis was performed using the mITT population, and sensitivity analysis was performed using the PP population.

All numerical secondary efficacy endpoints were summarized by the treatment groups and analyzed using the MRMM method in the PP and mITT sets. Categorical variables were summarized by the treatment group and also compared using the chi-squared test. For comparison within treatment groups, a two-sided t-test was used, and comparability between the two treatment groups indicated no statistically significant difference between the two groups' means ($p \geq 0.05$).

The safety analysis set was used to analyze safety and tolerability. Safety data during the 16-week double-blind treatment period and safety follow- up period of 2 weeks were evaluated and summarized descriptively. The data was analyzed using the SAS® version 9.4 or above. Continuous variables were shown as means ± SD and categorical variables in the form of frequencies and percentages.

Results

Of the 647 study participants screened, 400 eligible were randomized, with 200 patients each assigned to each RV & EL treatment groups. Out of 400 study participants, 357 (89.3%) completed the study while 43 (10.8%) did not complete the study period. The most common reason for discontinuation was withdrawal by subject (24 [6%]), followed by lost to follow-up (7 [1.8%]). Data of 400 study participants (100%) were included in the safety population, 379 study participants (94.8%) were included in the modified intent to treat (mITT) population, and 357 study participants (89.3%) were included in the per-protocol (PP) population. The demographic and baseline characteristics were comparable between the two treatment groups. The mean age of study participants was 50.69 ± 9.07 years in EL group and 50.04 ± 9.08 years in RV group. The mean HbA1c level at screening was 9.32 ± 0.818% in the RV group and 9.34 ± 0.82% in the EL group. The mean body weight at screening was 70.48 ± 13.03 kg in the RV group and 67.97 ± 10.74 kg in the EL group. The disposition of study participants is depicted in Table 1. The demographic and baseline characteristics of the patient enrolled in each of the treatment is enlisted in Table 2**.**

Table 1: Subject disposition

Disposition/Reasons	EL group n (%)	RV group n (%)	Total n (%)
Randomized (N)	200 (100.0)	200 (100.0)	400 (100.0)
Completed Study	176 (88.0)	181 (90.5)	357 (89.3)
Subject Withdrawn	24 (12.0)	19 (9.5)	43 (10.8)
Analysis Population			
Safety Population	200 (100.0)	200 (100.0)	400 (100.0)
mITT Population	189 (94.5)	190 (95.0)	379 (94.8)
PP Population	176 (88.0)	181 (90.5)	357 (89.3)
Reason for Early Termination			
Withdrawal by subject	12 (6.0)	12 (6.0)	24 (6.0)
Adverse event	2 (1.0)	1 (0.5)	3 (0.8)
Lost to follow-up	3 (1.5)	4 (2.0)	7 (1.8)
Non-compliance with Study procedures	2 (1.0)	1 (0.5)	3 (0.8)
Other	5 (2.5)	1 (0.5)	6 (1.5)

Table 2: Baseline demographic characteristics. Data are presented as n (%) or mean ± standard deviation.

Parameter	Statistics	Empa/Lina (N=200)	Remo/Vilda (N=200)
Screening HbA1c (%)	Mean (SD)	9.34 (0.815)	9.32 (0.818)
Age (year)	Mean (SD)	50.69 (9.066)	50.04 (9.083)
Gender, n(%)	Male	113 (56.5%)	119 (59.5%)
	Female	87 (43.5%)	81 (40.5%)
Body Weight (kg)	Mean (SD)	67.97 (10.738)	70.48 (13.026)
Height (cm)	Mean (SD)	160.7 (8.75)	160.7 (9.38)
Screening eGFR (mL/min/1.73m^2)	Mean (SD)	94.1 (18.45)	96.2 (20.66)

Primary Efficacy endpoint

The mean HbA1c level reduction was seen in all visits in both the treatment groups (Figure 1) In mITT population, mean change from baseline in HbA1c levels at week 16 was -1.46% ± 0.01 in the RV group and -1.38% ± 0.1 in the EL group ($p < 0.001$) (Table 3). The mean difference between the two groups was -0.08% (90% CI difference: -0.28, 0.13). As the upper bound of the 90% CI i.e., 0.13 was less than the non-inferiority margin of 0.40, the RV treatment was found to be non-inferior to the EL treatment ($p < 0.001$). Similarly, there was no significant difference between the two groups in the PP ($p = 0.59$) populations analysis at 16 weeks. Non-inferiority of RV group in comparison with EL group was also demonstrated and confirmed in the sensitivity analyses in the PP population.

Figure 1: Mean Change in HbA1C levels from baseline over 16 weeks (LSM ± SE) in the mITT population.

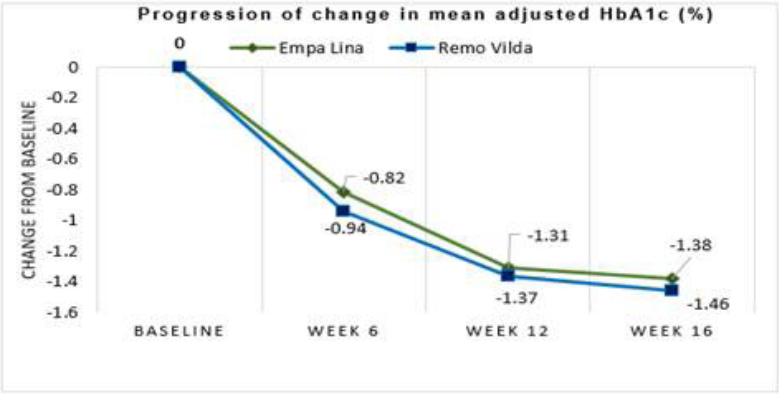


Table 3: Mean change in glycosylated haemoglobin (HbA1c %) levels in mITT and PP population (LSM ± SE): MMRM.

Mean Change from baseline	EL group	RV group
mITT population		
At week 6	-0.82 ± 0.10	-0.94 ± 0.10
At week 12	-1.31 ± 0.09	-1.37 ± 0.09
At week 16	-1.38 ± 0.10	-1.46 ± 0.10
PP population		
At week 6	-0.84 ± 0.10	-0.94 ± 0.10
At week 12	-1.34 ± 0.10	-1.38 ± 0.09
At week 16	-1.41 ± 0.10	-1.48 ± 0.10

Secondary efficacy endpoints

In both populations, mean change from baseline to week 12 in Hb1Ac levels was statistically significant in both the RV and EL groups. The mean difference between the two groups in change from baseline in Hb1Ac levels at 12 weeks was not statistically significant in the mITT population ($p = 0.63$) nor the PP population ($p = 0.74$) analysis, indicating that the mean improvement in Hb1Ac levels at week 12 was comparable between both groups. (Table 4). A statistically significant change from the baseline in FPG levels at week 16 was seen in both treatment groups. In the mITT population, the mean change from baseline in FPG levels was -32.01 ± 3.14 mg/dL in the RV group ($p < 0.001$) and -33.11 ± 3.20 mg/dL in the EL group ($p < 0.001$). The mean difference of 1.10 mg/dL (95% CI: -6.91, 9.12; $p = 0.79$) was not statistically significant. Similarly, these results were seen in the PP population (Figure 2).

A statistically significant change in PPG levels at week 16 was also observed in both the treatment groups in the mITT and PP populations analysis: the mean change from baseline in PPG levels was -48.95 ± 5.31 mg/dL in the RV group ($p < 0.001$) and -56.67 ± 5.4 mg/dL in the EL group ($p < 0.001$). The mean difference of 7.72 (95% CI: -5.93, 21.36) mg/dL between the two groups was found not statistically significant ($p = 0.267$)), indicating that the mean improvement in PPG levels at week 16 was comparable between the two treatment groups (**Figure 3**).

Figure 2: Mean Change in FPG concentrations from baseline to 16 weeks (LSM ± SE) in the mITT population.

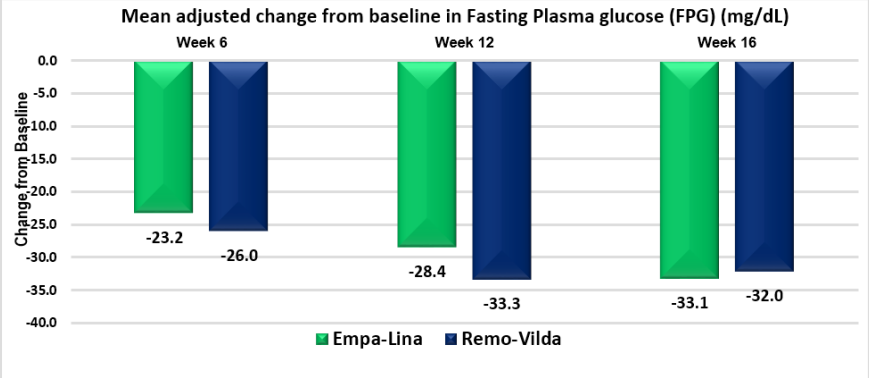
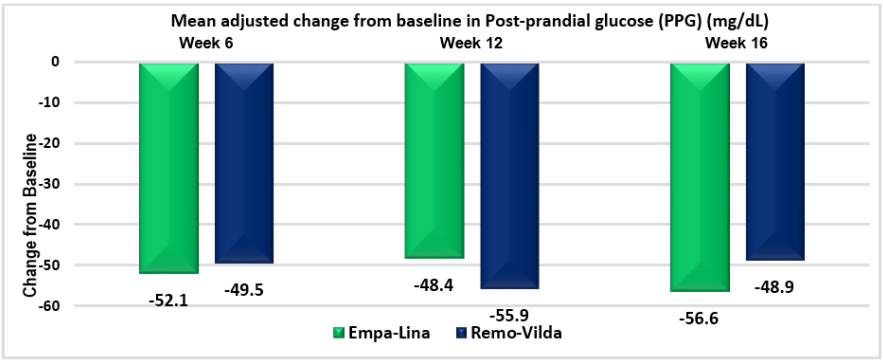


Figure 3: Mean Change in PPG concentrations from baseline to 16 weeks (LSM ± SE) in the mITT population.



The proportion of study participants who achieved the glycemic response of Hb1AC <7% at week 16 in the mITT population was 25.8% of the RV group and 31.7% of the EL group. No statistically significant (p = 0.20) difference in the proportion of study participants who achieved therapeutic response was found between the two treatment groups suggesting that the therapeutic response proportion was similar between the two groups. Similar observations were noted for study participants in the PP population at week 16 in which 57 (32.4%) of study participants in the Empa/Lina group and 47 (26.0%) of study participants in the RV group achieved therapeutic glycemic response (HbA1c <7%). Again, the difference in the proportion of study participants who achieved therapeutic glycemic response at week 16 between the RV group versus the EL group was found not statistically significant (p=0.182).

Three study participants (1.6%) in the RV group used rescue medication, and 8 (4.2%) study participants in the EL group used rescue medication. No statistically significant difference in the proportion of study participants using rescue medication between the two groups was found (p = 0.140), indicating that the use of rescue medication was comparable between the two groups. Similar observations were noted for study participants in the PP population. In the mITT population, the mean change from baseline in body weight was -1.27 ± 0.15 kg in the RV group and -1.56 ± 0.15 kg in the EL group. The mean difference of 0.28 (95% CI: -0.09, 0.66) kg was not statistically significant (p = 0.13) suggesting that the mean reduction in body weight was similar between the two groups.

Safety endpoints

A total of 58 of the 400 study participants (14.5%) in the safety population experienced treatment-emergent adverse events (TEAEs); all reported events were mild to moderate, with no severe adverse events or deaths reported. 24 (12.0%) study participants in the EL group had TEAEs of which 11 (5.5%) study participants had TEAEs which were considered related to study medication. 34 (17.0%) study participants in the RV group had TEAEs of which 9 (4.5%) study participants had TEAEs which were considered related to study medication. The TEAEs which were considered related to study medication and reported in ≥1.0% of study participants in the treatment groups were urinary tract infection (3; 1.5%) and hypoglycaemia (5; 2.5%) in the EL group and urinary tract infection (2; 1.0%) and hypoglycaemia (3; 1.5%) which were reported in the RV group (Table 4). One subject (0.5%) in the EL

group had TEAE (azotemia) which led to permanent discontinuation of the study drug whereas one subject (0.5%) in the RV group had TEAE (headache) leading to permanent discontinuation of the study drug.

The change from baseline in clinical & laboratory safety parameters were comparable between the two treatment groups with no treatment-related trends noted.

Table 4: Summary of Study participants with TEAE related to study drug (Safety population).

System Organ Class (SOC)	EL group (N=200) n (%)	RV group (N=200) n (%)
Any SOC		
Any Event (Total)	24 (12.0%)	34 (17.0%)
Any Event related to study drug	11 (5.5%)	9 (4.5%)
General Disorders and Administration Site Conditions	**2 (1.0%)**	**1 (0.5%)**
Asthenia	1 (0.5%)	1 (0.5%)
Chills	1 (0.5%)	0
Infections And Infestations	**3 (1.5%)**	**2 (1.0%)**
Genital infection fungal	1 (0.5%)	0
Urinary tract infection	3 (1.5%)	2 (1.0%)
Metabolism And Nutrition Disorders	**5 (2.5%)**	**4 (2.0%)**
Hyperglycaemia	0	1 (0.5%)
Hypoglycaemia	5 (2.5%)	3 (1.5%)
Nervous System Disorders	**0**	**1 (0.5%)**
Headache	0	1 (0.5%)
Reproductive System and Breast Disorders	**1 (0.5%)**	**1 (0.5%)**
Pruritus genital	1 (0.5%)	1 (0.5%)

Discussion

Many patients with type 2 diabetes mellitus (T2DM) have inadequate glycemic control on metformin monotherapy and require use of additional glucose lowering agents [12]. Combination of SGLT2i plus DPP-4i has the potential to produce a robust reduction in HbA1c. Owing to the differences in their adverse effects profile, the combination is less likely to increase the incidence of individual adverse effects. Remogliflozin being a twice daily SGLT2i has favorable pharmacokinetic profile when combined with twice daily DPP4i, Vildagliptin. In our study, their FDC has demonstrated significant reduction across all the glycemic parameters (HbA1c, FPG and PPG) in diabetic patients uncontrolled on higher doses of Metformin. In addition to its efficacy and safety, the FDC of Remogliflozin and Vildagliptin is a cost effective alternative to the current FDC of Empagliflozin and Linagliptin with reduced pill burden. A systematic review and meta-analysis of 14 randomized controlled trials demonstrated greater reduction in HbA1c with the combination compared to mono-components [13].

The mean change in HbA1c from baseline in the RV group was -1.41% over 16 weeks, a statistically significant value that translates to clinical relevance. The mean change in HbA1c from baseline in the EL group was -1.46%, a value consistent with previous reports from the phase III Empagliflozin/Linagliptin

clinical trial in which the mean change in HbA1c from baseline was -1.2% [14]. These differences are both larger than the reported response of -0.72% with Remogliflozin alone [15] and -0.80% with Empagliflozin alone [14], suggesting that the combination tablets support additional glucose-lowering activity. Additionally, these values are comparable to those found in a study of another SGLT2i-DPP4i combination tablet of saxagliptin plus dapagliflozin, which showed a mean change in HbA1c from baseline of -1.5% over 24 weeks [16]. Similarly, there was significant reduction in the FPG, PPG and body weight in the RV group comparable to that in the EL group. The mean change in FPG and PPG seen in this study is more than the reported response of Remogliflozin and Empagliflozin alone. Together with reduction seen in HbA1c, these findings support the efficacy of FDC of RV in T2DM patients.

The mean body weight reduction of 1.6 kg over 16 weeks in both the RV and EL groups was comparable to that in the placebo-controlled phase III study of EL, which observed a 3.1 kg reduction over 24 weeks [16]. The higher reduction observed in that study can probably be attributed to longer treatment duration & a higher mean baseline weight of participants (85.3 kgs vs 70.5 kgs). Similarly, patients in the clinical study of saxagliptin plus dapagliflozin lost over the 24-week period [16]. The percentage of study participants achieving therapeutic glycemic control, defined as HbA1c <7%, was also comparable between the two groups (25.8% in RV and 31.7% in EL). The saxagliptin/dapagliflozin study saw 41% of patients on the combined therapy reach HbA1c <7% over 24 weeks [16]. As different clinical trials studied different populations in terms of HbA1c% entry criteria (minimum HbA1c of 7% or 8%), had different proportions of patients in the baseline HbA1c strata of 7-8%, and involved different treatment durations (16 weeks to 24 weeks), the proportion of study participants achieving glycemic control varies widely among SGLT2 inhibitor/DPP4 inhibitor combination trials.

The FDC of Remogliflozin etabonate 100 mg and Vildagliptin 50 mg was also found to be safe and well-tolerated. The incidences of urinary tract infections, genital infections, and hypoglycemia were similar to the incidences reported in the Empagliflozin and Linagliptin phase III study [17]. Overall, this study establishes the safety and efficacy of the FDC of Remogliflozin etabonate 100 mg and Vildagliptin 50 mg administered twice daily in the treatment of study participants with T2DM having inadequate glycemic control while receiving a stable dose of metformin.

There are few limitations to this study such as inclusion of a controlled placebo arm which would have aided the treatment effect determination, but could not be done due to ethical concerns in regard to the denial of available standard of care to patients with hyperglycemia and therefore the tablet of Empagliflozin/Linagliptin was chosen as an active comparator so that non-inferiority between the two treatments could be determined. Also, the single clinical setting of the study compared to multiple settings would confirm more conclusively the efficacy and safety endpoints.

Conclusion

Remogliflozin etabonate and Vildagliptin given twice daily was found to be efficacious, safe, and well-tolerated in the treatment of study participants with T2DM and non-inferiority to FDC of Empagliflozin and Linagliptin. This SGLT2 inhibitor and DPP4 inhibitor combination provides a potential therapeutic option for management of Indian T2DM patients.

Data Sharing

All the clinically relevant data pertaining to results has been defined in the manuscript itself. However, any additional data can be provided by the corresponding author on reasonable request.

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References

1. Sahadevan P, Kamal VK, Sasidharan A, Bagepally BS, Kumari D, Pal A (2023) Prevalence and risk factors associated with undiagnosed diabetes in India: Insights from NFHS-5 national survey. Journal of Global Health 13: 04135.
2. ICMR-INDIAB Collaborative Study Group. Metabolic non-communicable disease health report of India: the ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17). Lancet Diabetes Endocrinol. 2023 Jul;11(7):474-489. doi: 10.1016/S2213-8587(23)00119-5. Epub 2023 Jun 7. PMID: 3730121
3. Min SH, Yoon JH, Moon SJ, Hahn S, Cho YM (2018) Combination of sodium-glucose cotransporter 2 inhibitor and dipeptidyl peptidase-4 inhibitor in type 2 diabetes: a systematic review with meta-analysis. Scientific Reports 8: 4466.

4. Abdul-Ghani MA, Norton L, DeFronzo RA (2011) Role of sodium-glucose cotransporter 2 (SGLT 2) inhibitors in the treatment of type 2 diabetes. Endocrine reviews 32: 515-31.

5. Tahrani AA, Barnett AH, Bailey CJ (2013) SGLT inhibitors in management of diabetes. The lancet Diabetes & endocrinology 1: 140-51.

6. Drucker DJ, Nauck MA (2006) The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. The Lancet 368: 1696-705.

7. Makrilakis K (2019) The role of DPP-4 inhibitors in the treatment algorithm of type 2 diabetes mellitus: when to select, what to expect. International journal of environmental research and public health 16: 2720.

8. American Diabetes Association Professional Practice Committee. Summary of revisions: Standards of Care in Diabetes–2024. Diabetes Care 2024;47(Suppl. 1):S5–S10

9. Scheen AJ (2016) DPP-4 inhibitor plus SGLT-2 inhibitor as combination therapy for type 2 diabetes: from rationale to clinical aspects. Expert opinion on drug metabolism & toxicology 12: 1407-17.

10. Sethi B, Modi KD, Srikanth K, Erande S, Khaladkar K, et al. (2022) A Prospective Multicenter Open-label Study to Assess the Effect of Remogliflozin on Glycemic Variability Compared to Dapagliflozin Using Continuous Glucose Monitoring (REMIT - GV study). J Diabetes Treat 7: 1099.

11. Mohan V, Mithal A, Joshi SR, et al. (2020) Remogliflozin Etabonate in the Treatment of Type 2 Diabetes: Design, Development, and Place in Therapy. Drug Des Devel Ther 14: 2487-2501.

12. Matthews DR, Paldánius PM, Proot P, et al. (2019) Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. The Lancet 394: 1519-1529.

13. Li D, Yang JY, Wang T, Shen S, Tang H (2018) Risks of diabetic foot syndrome and amputation associated with sodium glucose co-transporter 2 inhibitors: a meta-analysis of randomized controlled trials. Diabetes & metabolism 44: 410-414.

14. Chong WH (2015) Clinical Review and Cross-Discipline Team Leader Review: NDA-206073 (Empagliflozin/Linagliptin).

15. Dharmalingam M, Aravind S, Thacker H, et al. (2020) Efficacy and safety of remogliflozin etabonate, a new sodium glucose co-transporter-2 inhibitor, in patients with T2DM: a 24-week, randomized, double-blind, active-controlled trial. Drugs 80: 587-600.

16. Boehringer Ingleheim Pharmaceuticals, Inc. Jardiance Full Prescribing Information. 2020. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/204629s023lbl.pdf. Accessed 2 Feb. 2021.

17. Kovil R, Saboo B, Shah K, et al. (2020) Single-pill Combination of Empagliflozin and Linagliptin in Real World Indian Type 2 Diabetes Patient (GRID). The Journal of the Association of Physicians of India 68: 53-55.

Appendix I: Inclusion and Exclusion Criteria for the Study

Inclusion Criteria	
1.	Study participants must be willing and able to provide written informed consent.
2.	Male and female study participants ≥18 and ≤ 65 years of age, diagnosed with T2DM.
3.	Study participants who had received stable dose of metformin ≥1500 mg/day as monotherapy for at least 10 weeks prior to screening and had inadequate glycaemic control at screening defined as HbA1c levels of ≥8% to ≤11%.
4.	Willing and able to comply with all aspects of the protocol.
5.	Must be willing to use a highly effective form of contraception (with pearl index < 1%) e.g., double barrier method, for the duration of the study. Methods like periodic abstinence; post ovulation procedures and withdrawal are not considered adequate. Oral contraceptive pills are not allowed due to potential of drug interaction with investigational product. If the subject is a female of childbearing potential, the result of a urine pregnancy test at screening must be negative. Each female will be considered to have childbearing potential unless surgically sterilized by hysterectomy or has been post-menopausal for at least 2 years.

Exclusion Criteria	
1.	History of Type 1 diabetes mellitus or secondary diabetes mellitus or diabetes insipidus
2.	History of metabolic acidosis or diabetic ketoacidosis
3.	FPG >270 mg/dL at screening. If FPG is >270 mg/dL at screening, FPG will be repeated within 1 week. If repeat FPG is >270 mg/dL, subject will be excluded from the study.
4.	BMI ≥45.0 kg/m2 at screening
5.	Study participants with elevated thyroid stimulating hormone (TSH) level at screening with or without thyroid hormone replacement therapy as per the reference ranges of central laboratory manual*.

6.	Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m2 using the Modification of Diet in Renal Disease (MDRD) equation or serum creatinine level of > 1.5 mg/dL for male study participants and > 1.4 mg/dL for female study participants, at screening
7.	Severe hepatic insufficiency and/or significant abnormal liver function defined as aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 3X ULN or total serum bilirubin >2.0 mg/dL at screening
8.	Congestive heart failure defined as New York Heart Association (NYHA) class III/IV, unstable or acute congestive heart failure.
9.	Significant cardiovascular history defined as: myocardial infarction, unstable angina pectoris, transient ischemic attack, unstable or previously undiagnosed arrhythmia, cardiac surgery, or revascularization (coronary angioplasty or bypass grafts), or cerebrovascular accident.
10.	Study participants with uncontrolled hypertension with sitting systolic BP ≥ 160 mmHg and/or diastolic BP ≥ 100 mmHg at screening. Note: Study participants with SBP ≥ 160 mmHg and < 180 mmHg or a DBP ≥ 100 mmHg and < 110 mmHg will be able to enter the run-in period, provided their hypertension treatment is adjusted as deemed appropriate by the investigator. These study participants cannot be randomized if they meet the blood pressure exclusion criterion of SBP ≥ 160 mmHg or DBP ≥ 100 mmHg measured at randomization visit.
11.	Any abnormality on 12-lead ECG at screening that in the opinion of the investigator is clinically significant and is judged as potential risk for subject's participation in the study. For male study participants with mean QTcB ≥ 450 msec or female study participants with mean QTcB ≥ 470 msec, triplicate ECG will be performed. If mean QTcB is ≥ 450 msec in males or mean QTcB is ≥ 470 msec in females on triplicate ECG, subject will be excluded from the study.
12.	History of anaemia or haemoglobinopathy and/or serum haemoglobin <10 g/dL (<100 g/L) for men; haemoglobin <9 g/dL (<90 g/L) for women at screening
13.	Donation or transfusion of blood, plasma, or platelets within the past 3 months prior to enrolment
14.	History of malignancy within the last 5 years prior to enrolment, excluding non-melanoma skin cancer (e.g., basal or squamous cell skin carcinoma) or treated carcinoma-in-situ of cervix
15.	Intolerance, contraindication, or potential allergy/hypersensitivity to any of the ingredients of study medication or any other SGLT2 inhibitors or DPP4 inhibitors
16.	Study participants with symptomatic diarrhoea or any other medical condition which the investigators may judge to be a risk for dehydration and hypovolemia
17.	Study participants with symptomatic urinary tract infection or mycotic genital infection at screening or history of a recent symptomatic infection within 4 weeks prior to screening
18.	Subject with a positive result for hepatitis B surface antigen or hepatitis C antibody at screening.
19.	Subject is known to be seropositive for Human Immunodeficiency Virus (HIV).
20.	Subject not willing to comply with dietary and exercise plan provided at screening.
21.	Subject with any condition which, in the judgment of the Investigator, may render the subject unable to complete the study or which may pose a significant risk to the subject.
22.	Employee of the clinical study site or any other individuals involved with the conduct of the study, or immediate family members of such individuals.
23.	Concurrent enrolment in another interventional clinical study.
24.	Previous participation in another interventional clinical study within 3 months prior to screening or within 5 half-lives of the previous study drug.
25.	Pregnant or breastfeeding women
26.	Study participants with a history of substance abuse or dependence that in the opinion of the Investigator is considered to interfere with the subject's participation in the study.
*subject exclusion was based on additional testing (T3 & T4 at local laboratory) and investigator's opinion of significant abnormality	