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Research Article

A Randomized, Double-blind, Active-controlled Study of Remogliflozin Etabonate 100 mg plus Teneligliptin 10 mg Twice-daily versus Teneligliptin 20 mg Once-daily as add-on to Metformin Monotherapy in Indian Diabetic Patients

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Abstract

Background: Fixed-dose combination (FDC) of sodium-glucose co-transporter-2 inhibitor (SGLT2i) and dipeptidyl peptidase-4 inhibitor (DPP4i) is a promising approach for type 2 diabetes (T2D) management due to their complementary mode of action. The present study evaluated efficacy and safety of FDC of remogliflozin etabonate (RE) and teneligliptin as add-on to metformin monotherapy in uncontrolled T2D patients compared to standard teneligliptin therapy. **Methods**: This 16-week, double-blind, double-dummy, active-controlled, parallel-group, multicentric study randomized 308 patients (glycated hemoglobin levels [HbA1c] 8-11%) who were on background metformin therapy (≥1500 mg/day) to receive add-on treatment of either RE 100 mg plus teneligliptin 10 mg twice-daily (RE+TE10) or teneligliptin 20 mg (TE20) once-daily. The primary endpoint was mean change in HbA1c from baseline to Week 16. Secondary endpoints were changes in fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and body weight from baseline to Week 16. Safety endpoints were assessed throughout the study. **Results**: At Week 16, significant reduction in HbA1c, FPG, PPG and body weight were noted in both the groups. The mean change in HbA1c from baseline to Week 16 was superior in the RE+TE10 (-1.23%) versus TE20 (-0.79%), whereas the mean change in FPG, PPG, body weight along with incidence of treatment-emergent adverse events (RE+T10: 11.8% vs. T20: 14.2%) were comparable between the two groups. **Conclusion**: FDC of remogliflozin/teneligliptin was superior to teneligliptin as an add-on to metformin in HbA1c reduction from baseline to Week 16 in Indian patients with uncontrolled T2DM on metformin therapy and was well-tolerated.

Keywords: Dipeptidyl peptidase-4 inhibitor; Fixed-dose combination; Metformin; Remogliflozin etabonate; Sodium-glucose co-transporter 2 inhibitor; Teneligliptin; Type 2 Diabetes Mellitus

Abbreviations: ADA: American Diabetes Association; AE: Adverse events; CI: Confidence Interval; CV: Cardiovascular; CYP3A4: Cytochrome P450 3A4; DPP4i: Dipeptidyl peptidase - 4 inhibitor; eGFR: Estimated glomerular filtration rate; ECG: Electrocardiogram; FDC: Fixed-dose combination; HbA1c: Glycated hemoglobin; LS: Least-square; mITT: Modified intent-to-treat; MMRM: Mixed model repeated measure; NYHA: New York Heart Association; OAD: Oral Antidiabetic; PP: Per protocol; PPG: Post-prandial plasma glucose; RE+TE10: Remogliflozin etabonate 100mg/Teneligliptin 10 mg; SAE: Serious adverse events; SGLT2i: Sodium-glucose co-transporter 2 inhibitors; D: Standard deviation; SE: Standard error; TE20: Teneligliptin 20 mg; TEAE: Treatment-emergent adverse events; T2DM: Type II diabetes mellitus

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is increasing globally, including India, with an estimated 1 in 7 adults (aged 20-79 years) living with diabetes as per the International Diabetes Federation Diabetes Atlas 2021. [1] Being a progressive disease, diabetic patients eventually require a multi-drug regimen to maintain glycemic control. [2] Dipeptidyl peptidase - 4 inhibitor (DPP4i), an antidiabetic agent available since 2006, is useful in lowering glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG) and post-prandial plasma glucose (PPG) with low risk of hypoglycemia. [3] Furthermore, this drug class has an established evidence of not increasing cardiovascular (CV) risk in patients with T2DM. [4] Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are a recently developed anti-hyperglycemic agent, and their usage is increasing due to their cardio-renal benefit. [5] SGLT2i helps in reducing body weight and lowers blood pressure, which in turn reduces cardiac afterload with subsequent improvement in ventricular arterial coupling and cardiac efficacy. [6] With these established clinical benefits, there exists a strong rationale for combining a DPP4i and a SGLT2i in patients with T2DM due to their different yet complementary glucose-lowering effects. [7] As a pharmacologic treatment for patients with T2DM, the American Diabetes Association (ADA) 2022 standard of care guidelines recommend other oral antidiabetic (OAD) agents with or without metformin therapy based on glycemic needs. [8] Moreover, the guidelines suggest dual combination therapies especially when HbA1c is ≥1.5% above glycemic target to achieve patients' target HbA1c. [9] Though the guidelines are applicable universally, there is a need to improvise the HbA1c management approach further in patients with T2DM in India uncontrolled on metformin monotherapy due to diverse population and management practices. One potential approach is utilizing fixed-dose combination (FDC) therapies to achieve better glycemic control and treatment compliance.

Expert opinion from International panel of clinicians on clinical approach to FDCs in the management of T2DM recommended a rational use of FDCs (double or triple) in managing such patients in India. [10] The panel aligned that adding a low-dose antidiabetic medication to monotherapy can enhance drug efficiency by 80%. Likewise, with the complementary mode of action, both DPP4i and SGLT2i have proven to be an adequate dual combination therapy to achieve target HbA1c levels in patients with inadequately controlled diabetes on high-dose metformin therapy. [7] In India, teneligliptin is one of the widely used DPP4i since 2015, [11] and is available as 20 mg once-daily dosage for the treatment of T2D as add-on therapy to metformin. Remogliflozin etabonate is a recently approved SGLT2i, [12] and is available as 100 mg twice-daily dosage regimen. In previous studies, teneligliptin combined with SGLT2i was shown to be well-tolerated and effective in improving glycemic control. [12,13] Also, due to its multiple elimination pathways, teneligliptin requires no dosage adjustment in patients with hepatic or renal impairment and have a low probability for drug-drug interactions. [14] FDC of teneligliptin and remogliflozin etabonate needs to be further evaluated in the Indian population with T2DM uncontrolled on metformin therapy.

In this study, we evaluated the FDC of remogliflozin etabonate (100 mg) and teneligliptin (10 mg) administered twice-daily in comparison to teneligliptin 20 mg administered once-daily in patients with inadequately controlled T2DM on a stable dose of metformin (≥1500 mg per day). Bioequivalence and comparable DPP4 inhibition of teneligliptin 10 mg twice-daily and 20 mg once-daily dosage regimen is already established. [15]

Materials And Methods

Study design and participants

This was a randomized, double-blind, double-dummy, active-controlled, two-arm, parallel-group, multicenter, phase III study conducted at 21 sites in India. Patients aged ≥18 and ≤65 years, diagnosed with T2DM, who had received a stable dose of metformin ≥1500 mg/day as monotherapy for at least 10 weeks before screening and had inadequate glycemic control at screening defined as HbA1c levels of ≥8% to ≤11%, and provided informed consent were enrolled in the study. Patients were excluded if they were diagnosed with Type 1 diabetes mellitus and diabetes insipidus, had a history of metabolic acidosis or diabetic ketoacidosis, had a body mass index of ≥45 kg/m^2 at screening and estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73

m^2, with presence or history of congestive heart failure defined as New York Heart Association (NYHA) class III/IV, and presented with unstable or acute congestive heart failure. The detailed list of inclusion and exclusion criteria is provided in Supplementary Table 1.

Inclusion criteria
• Patients must be willing and able to provide written informed consent. • Male and female patients (Age: ≥18 and ≤65 years) diagnosed with T2DM. • Patients who received stable dose of metformin ≥1500 mg/day as monotherapy for at least 10 weeks prior to screening with inadequate glycemic control (HbA1c: ≥8% to ≤11%). • Patients who are able to fulfill all aspects of the protocol. • Patients who agree to use a highly effective form of contraception for the study duration (with pearl index < 1%) e.g. double barrier method. Periodic abstinence, post ovulation procedures and withdrawal methods are considered inadequate. Oral contraceptive pills are not allowed due to potential for drug interaction with investigational product. Female patient of childbearing potential, must have a negative urine pregnancy test at the time of screening.
Exclusion criteria

- History of Type 1 diabetes mellitus or secondary diabetes mellitus or diabetes insipidus
- History of metabolic acidosis or diabetic ketoacidosis
- Fasting plasma glucose (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, patient will be excluded from the study
- Body mass index (BMI) ≥45.0 kg/m2 at screening
- Patients with elevated thyroid stimulating hormone (TSH) level at screening with or without thyroid hormone replacement therapy
- Estimated glomerular filtration rate (eGFR) 1.5 mg/dL for male patients and >1.4 mg/dL for female patients, at screening
- Severe hepatic insufficiency and/or significant abnormal liver function defined as aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 3 X upper limit of normal (ULN) or total serum bilirubin >2.0 mg/dL at screening
- Congestive heart failure (CHF) defined as New York Heart Association (NYHA) class III/IV, unstable or acute CHF
- 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
- Patients with uncontrolled hypertension with sitting systolic blood pressure (BP) ≥160 mmHg and/or diastolic BP ≥100 mmHg at screening. Note: Patients with systolic BP ≥160 mmHg and <180 mmHg or a diastolic ≥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 patients cannot be randomized if they meet the BP exclusion criterion of systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg measured at randomization visit
- Any abnormality on 12-lead electrocardiogram (ECG) at screening that in the opinion of the investigator is clinically significant and is judged as potential risk for patient's participation in the study. For male patients with mean (heart rate-corrected QC interval (QTcB) ≥450 msec or female patients 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, patient will be excluded from the study
- Patients with history of hereditary QT prolongation syndrome or patients having history of Torsades de pointes
- Patients with history of abdominal surgery or intestinal obstruction
- Patients with history of acute pancreatitis
- History of anemia or haemoglobinopathy and/or hemoglobin <10 g/dL (<100 g/L) for men; hemoglobin <9 g/dL (<90 g/L) for women at screening
- Donation or transfusion of blood, plasma, or platelets within the past 3 months prior to enrolment
- 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
- Intolerance, contraindication, or potential allergy/hypersensitivity to any of the ingredients of study medication or any other sodium glucose co-transporter 2 inhibitors (SGLT2is) or dipeptidyl peptidase-4 inhibitors (DPP4is)
- Patients with symptomatic diarrhea or any other medical condition which the investigators may judge to be a risk for dehydration and hypovolemia
- Patients with symptomatic urinary tract infection or mycotic genital infection at screening or history of a recent symptomatic urogenital infection within 4 weeks prior to screening
- Patient with a positive result for hepatitis B surface antigen or hepatitis C antibody at screening.
- Patient is known to be seropositive for human immunodeficiency virus (HIV).
- Patient not willing to comply with dietary and exercise plan provided at screening.
- Patient with any condition which, in the judgment of the investigator, may render the patient unable to complete the study or which may pose a significant risk to the patient.
- Employee of the clinical study site or any other individuals involved with the conduct of the study, or immediate family members of such individuals.
- Concurrent enrollment in another interventional clinical study.
- Previous participation in another interventional clinical study within 3 months prior to screening or within 5 half-lives of the previous study treatment.
- Pregnant or breastfeeding women.
- Patients with a history of substance abuse or dependence that in the opinion of the investigator is considered to interfere with the patient's participation in the study.

Supplementary Table 1: Inclusion and Exclusion criteria.

Treatment and interventions

Eligible patients were randomized (1:1) to receive one of the following treatments:

FDC of remogliflozin etabonate 100mg/teneligliptin 10 mg (RE+TE10) twice-daily or teneligliptin 20 mg (TE20) once-daily for 16 weeks as an add-on to the existing treatment with metformin. Metformin 1500 mg tablet was administered twice-daily along with the FDC of RE+TE10 twice-daily or TE20 once-daily at investigator discretion.

All the patients were screened at study entry and the screening period lasted for 3 weeks with a 2-week run-in period followed by treatment randomization (Figure 1). All patients received two tablets in the morning and one tablet in the evening, with food, preferably at the same time, including a double-blind matching placebo. Randomization was performed using a third-party interactive voice and web response system, and patients were stratified according to their HbA1c levels at screening (8%–8.9%, 9%–9.9%, and 10%–11%). Study visits were scheduled at Weeks 6, 12, and 16 after initiating treatment(s). A follow-up visit occurred two weeks post-last treatment dose for patients who completed the study. At screening, run-in and all treatment visits, standard dietary consultation and exercise modification information was provided to patients as per the applicable national/international guidelines.

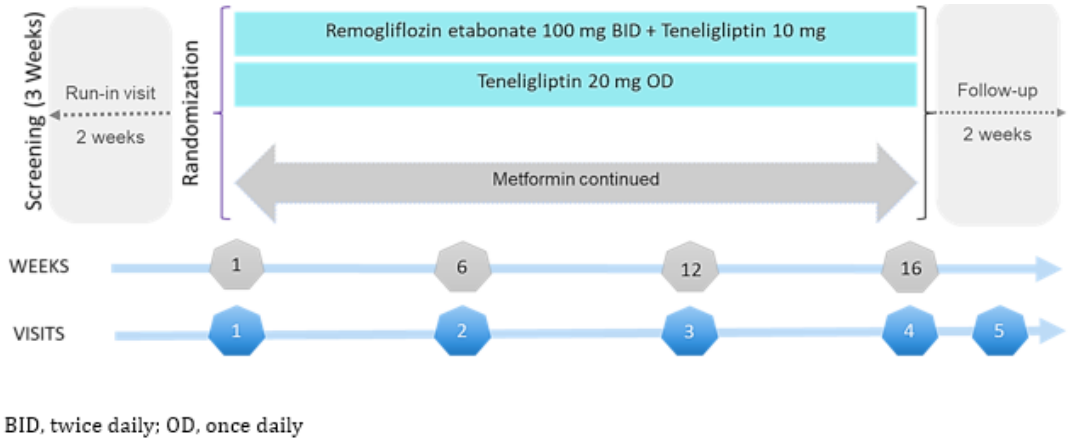


Figure 1: Study design.

Concomitant medications such as lipid-lowering agents/oral hypertensives were allowed, provided the drug/dose remained stable one month before and throughout the study period. Also, topical, inhaled, and intranasal corticosteroids were permitted. Oral corticosteroids were permitted if the daily dose was ≤20 mg of prednisone and it remained stable for at least three months before screening and throughout the treatment. Concomitant medications for weight loss, other antidiabetic agents, oral contraceptive pills, immunosuppressants, any medication that can interfere with blood glucose, and potent inducers of cytochrome P450 3A4 (CYP3A4) were prohibited.

Patients were eligible for an open-label rescue medication from Week 6 up to Week 16 if they had an FPG >240 mg/dL at Week 6 and FPG >200 mg/dL or HbA1c >9% at Week 12. The choice and dosage of rescue medication were at the investigator's discretion, but the use of DPP4i, Glucagon like receptor-1 analog, and SGLT2i was not permitted.

Endpoints and assessments

The primary efficacy endpoint was mean change in HbA1c from baseline to Week 16. The secondary efficacy endpoints were mean change from baseline to Week 12 in HbA1c levels; mean change from baseline in FPG, PPG, and body weight, the proportion of patients achieving a therapeutic glycemic response (HbA1c <7%) at Week 16, proportion of patients requiring rescue medication for hyperglycemia from Week 6 to Week 16, and safety and tolerability of the FDC throughout the study.

Safety was assessed by reporting treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), AEs of special interest (hypoglycemia, urinary tract infections, and genital fungal infections), lipid profile and other laboratory tests (hematology, blood chemistry, and urine parameters), vital signs, electrocardiogram (ECG), estimated glomerular filtration rate (eGFR) and physical examination.

Statistical analysis and sample size

A sample size of 123 patients per group was estimated to provide a power of 90% to detect a 0.5% treatment difference in HbA1c between RE+TE10 and TE20 groups, assuming a standard deviation (SD) of 1.2% and using a two-sided significance level of 5%.

The primary efficacy analysis was performed on the modified intent-to-treat (mITT) population. The mITT population included all randomized patients who received at least one study medication dose, who had a non-missing baseline measurement and at least one post-baseline efficacy measurement for primary efficacy variable. The differences between the FDC and TE groups were compared based on the Mixed Model Repeated Measure (MMRM) method, which included data from all visits until Week 16 and the following covariates: treatment, visit, HbA1c at baseline, baseline eGFR, center, and treatment by visit interaction. An unstructured covariance matrix was used, allowing adjustment for correlations between the time points within patients.

All secondary efficacy parameters were summarized by treatment groups and presented for mITT and per protocol (PP) populations. The PP population included all patients who were randomized, received at least one study medication dose, completed the study and did not have any major protocol deviations. The mean change from baseline in HbA1c levels at Week 12, the mean change from baseline in FPG, PPG and body weight at Week 16 were summarized and analyzed using the same model as for the primary endpoint, i.e., MMRM model to establish superiority of RE+TE10 vs. TE20. The proportion of patients achieving HbA1c <7% at Week 16 and the proportion of patients requiring rescue medication for hyperglycemia were summarized by treatment group and compared for RE+TE10 vs. TE20 using chi-square test.

All safety and tolerability analyses were performed on the safety population which included all patients who were randomized and received at least one dose of study medication. Safety findings were summarized descriptively. The severity of TEAEs were classified as mild, moderate, severe and life threatening.

All analyses were performed using SAS® software 9.4.

Ethics: The study was conducted following the Declaration of Helsinki, 2013 and in accordance with the International Council for Harmonization guidelines for Good Clinical Practice and New Drugs and Clinical Trials Rules, 2019 of Drugs and Cosmetics Act, 1940. The study was reviewed and approved by the Institutional Ethics Committee at each investigator site, and all participants provided written informed consent.

Results

Patient disposition, demographic and baseline characteristics

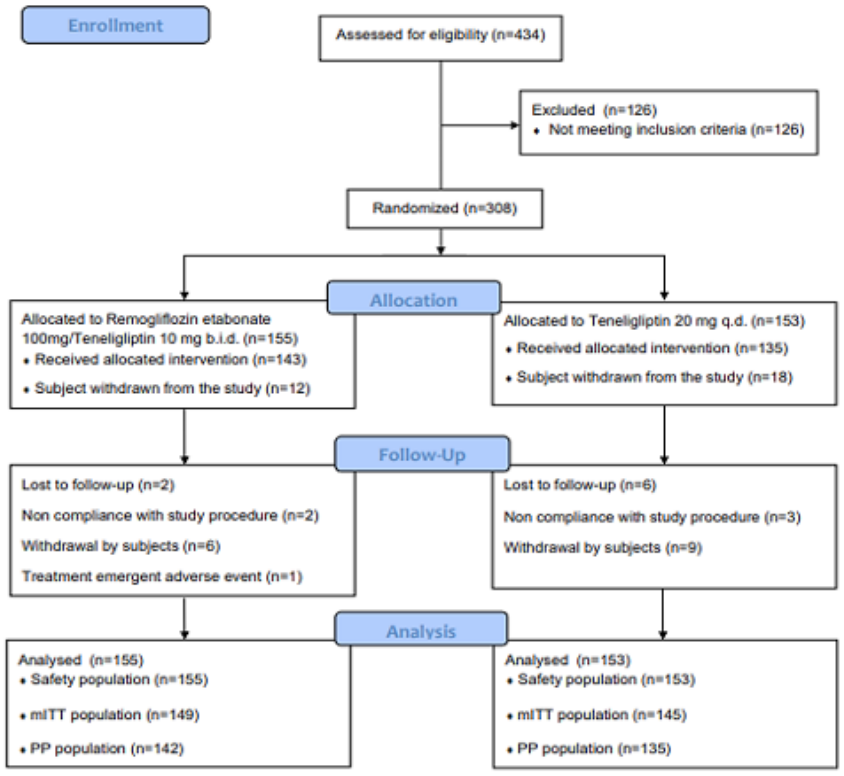
A total of 308 patients were randomized, of which 278 patients (90.3%; 143 in RE+TE10 and 135 in TE20 groups) completed the study. Thirty patients (9.7%) discontinued the study and the most common reason for discontinuation being patient unwilling to continue (4.9%), lost to follow-up (2.6%), and non-compliance with study procedures (1.6%). In total, 294 (95.5%) patients were included in the mITT population and 277 (89.9%) were included in the PP population. Patient disposition details is shown in Figure 2.

The demographic and baseline characteristics were comparable between the treatment groups. (Table 1) The mean ± SD age of patients was 50.72 ± 9.33 years in the RE+TE10 and 51.63 ± 8.15 years in the TE20 groups. The mean HbA1c level at screening was 9.24% ± 0.79% in the RE+TE10 and 9.25% ± 0.78% in the TE group.

Parameter	Statistics	Teneligliptin 20 mg (N=153)	Remogliflozin 100 mg/ Teneligliptin 10 mg (N=155)
Age, years	**n**	153	155
	Mean ± SD	51.63 ± 8.15	50.72 ± 9.33
Gender, n (%)	**Male**	95 (62.1%)	81 (52.3%)
	Female	58 (37.9%)	74 (47.7%)
Race, n (%)	**Asian**	153 (100 %)	155 (100 %)
Body Weight, kg	**n**	153	155
	Mean ± SD	70.80 ± 10.96	70.05 ± 9.83
Screening eGFR. mL/min/1.73m^2	**n**	153	154
	Mean ± SD	93.0 ± 21.09	96.1 ± 18.28

HbA1c (%)	**n**	153	155
	Mean ± SD	9.25 ± 0.78	9.24 ± 0.79
HbA1c (%): 8-8.9%	**n**	62	62
	Mean ± SD	8.47 ± 0.30	8.48 ± 0.26
HbA1c (%): 9-9.9%	**n**	59	59
	Mean ± SD	9.45 ± 0.29	9.37 ± 0.29
HbA1c (%): 10-11%	**n**	32	34
	Mean ± SD	10.37 ± 0.30	10.41 ± 0.32
HbA1c (%): metformin at stable doses of 1500 mg per day	**n**	97	92
	Mean ± SD	9.16 ± 0.77	9.12 ± 0.81
HbA1c (%): metformin at stable doses of >1500 mg per day	**n**	56	63
	Mean ± SD	9.40 ± 0.79	9.42 ± 0.74
eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; n, number of patients in the specific category; N, total number of patients; SD, standard deviation			

Table 1: Patient demographic and baseline characteristics.



BID, twice daily; n, number of patients; OD, once daily

Figure 2: Patient disposition.

Efficacy

Primary endpoints (mITT population)

The mean baseline HbA1c levels were comparable between groups in the mITT population and was 8.77% ± 1.01 and 8.86% ± 1.10 in the RE+TE10 and TE20 groups, respectively. The mean change from baseline in HbA1c at Week 16 was significantly higher in the RE+TE10 (-1.23% ± 0.13) when compared with TE (-0.79% ± 0.13) with a least-square (LS) mean difference of -0.44% (95% confidence interval [CI]: -0.75; -0.13; p=0.006) (Figure 3A and Table 2). The RE+TE10 group was superior compared to the TE20 group with respect to the mean change in HbA1c from baseline to Week 16 (p=0.006).

The mean change in HbA1c values at Week 16 in the HbA1c 8-8.9% subgroup and HbA1c 10-11% subgroups did not show a significant difference between RE+TE10 and TE20 (p=0.475 and 0.311, respectively). However, a significant difference between RE+TE10 and TE20 was observed for the mean change HbA1c at Week 16 for the HbA1c 9-9.9% subgroup (p=0.003). (Table 2)

Secondary endpoints (mITT population)

Mean change from baseline in HbA1c levels at Week 6 and 12 The RE+TE10 group was superior compared to the TE20 group with respect to mean change in HbA1c from baseline to Week 12. The LS mean (± standard error [SE]) change from baseline in HbA1c levels to Week 12 in the RE+TE10 and TE20 groups was -1.04% ± 0.11 and -0.69% ± 0.11 (both p<0.001), respectively. The mean reduction in HbA1c from baseline at Week 12 was significantly higher in the RE+TE10 than in the TE20 with a LS mean difference of -0.35% ± 0.12) (95% CI: -0.59, -0.11; p=0.004; Table 2).

Similarly, at Week 6, the LS mean reduction in HbA1c from baseline in the RE+TE10 group was statistically significant compared to the TE20 group (p=0.009).

Mean change from baseline in FPG and PPG levels at Week 16

At Week 16, a statistically significant reduction was observed in the FPG levels from baseline in the RE+TE10 and TE groups (p<0.001), respectively. (Figure 3B, Table 3). The LS mean change from baseline was -18.5 ± 4.32 mg/dL in RE+TE10 and -19.7 ± 4.46 mg/dLin TE20. However, the LS mean difference of 1.2 mg/dL (95% CI: -8.8, 11.2) was not statistically significant between the two groups (p=0.818).

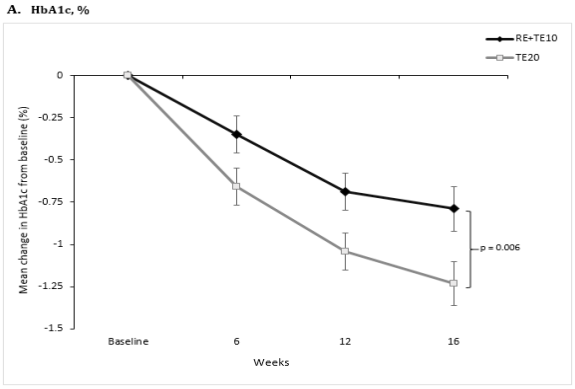
Similarly, a statistically significant reduction from baseline was observed for PPG at Week 16 (Figure 3C, Table 3). The LS mean change from baseline in PPG levels was -38.3 ± 6.13 mg/dL (p <0.001) and -24.5 ± 6.32 mg/dL in the RE+TE10 and TE groups, respectively. The mean reduction in PPG levels was numerically higher in the RE+TE10 than the TE group by 13.8 ± 7.09 mg/dL (95% CI: -27.8, 0.2; p=0.053) (Table 3).

Mean change in body weight from baseline at Week 16. At Week 16, a statistically significant reduction in body weight was observed in the RE+TE10 group whereas statistically significant increase in body weight was observed in TE20 group. The LS mean change from baseline in total body weight was -0.97 ± 0.14 kg in the RE+TE10 group and 0.76 ± 0.14 kg in the TE20 group, respectively (both p<0.001) (Table 3).

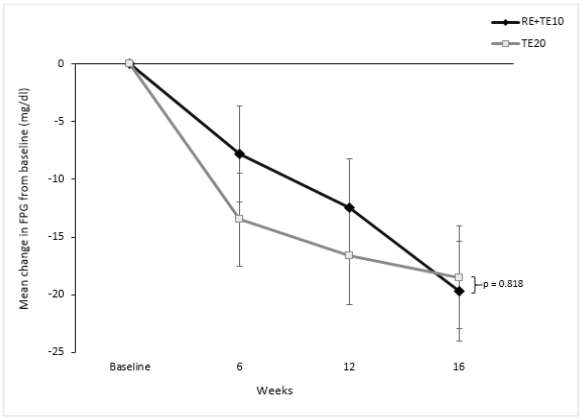
Proportion of patients achieving HbA1c <7%, at Week 16

At Week 16, numerically greater proportion of patients achieved a therapeutic glycemic response of HbA1c <7% in the RE+TE10 (53 [35.6%]) compared to the TE20 (39 [26.9%]) group. However, the difference between the two groups was not statistically significant (p=0.109).

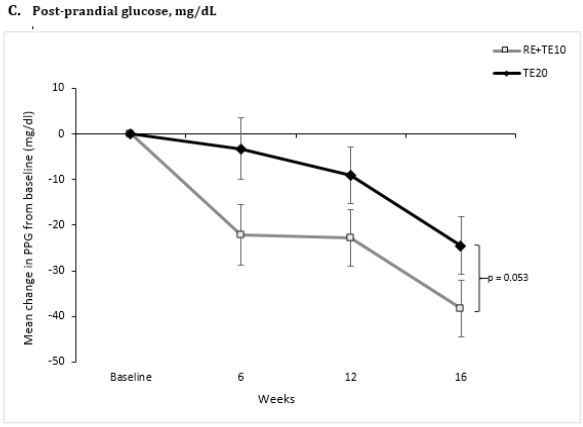
Proportion of patients requiring rescue medication for hyperglycemia during treatment by Week 16 Overall, by Week 16, significantly lesser proportion (p=0.039) of patients required rescue medication for hyperglycemia in the RE+TE10 group (6%; 9 patients) compared to the TE20 group (13.1%; 19 patients).



HbA1c, glycated hemoglobin; p-values for between group difference: Week 6, 0.009; Week 12, 0.004; Week 16, 0.006; RE+TE10, Remogliflozin 100 mg + Teneligliptin 10 mg; TE20, Teneligliptin 20 mg



FPG, fasting plasma glucose; p-values for between group difference: Week 6, 0.216; Week 12, 0.395; Week 16, 0.818; RE+TE10, Remogliflozin 100 mg + Teneligliptin 10 mg; TE20, Teneligliptin 20 mg



PPG, postprandial glucose; p-values for between group difference: Week 6, 0.019; Week 12, 0.059; Week 16, 0.053; RE+TE10, Remogliflozin 100 mg + Teneligliptin 10 mg; TE20, Teneligliptin 20 mg

Figure 3: Mean change from baseline at Week 16 (mITT Population).

Parameters	Visit	Statistics	Teneligliptin 20 mg (N=145)	Remogliflozin 100 mg/ Teneligliptin 10 mg (N=149)
HbA1c, %	Baseline	Mean ± SD	8.86 ± 1.1	8.77 ± 1.01
	Week 6	LS mean ± SE	-0.35 ± 0.11	-0.66 ± 0.11
		Mean ± SD	8.45 ± 1.22	8.06 ± 1.09
	Week 12	LS mean ± SE	-0.69 ± 0.11	-1.04 ± 0.11
		Mean ± SD	8.08 ± 1.20	7.66 ± 1.06
	Week 16	LS mean ± SE	-0.79 ± 0.13	-1.23 ± 0.13
		Mean ± SD	7.72 ± 1.18	7.37 ± 1.23
	Difference vs. Teneligliptin 20 mg (LS mean ± SE; 95% CI) at week 16			-0.44 ± 0.16
	p-value[1] at week 16			0.006
HbA1c (%): 8-8.9%	Baseline	Mean ± SD	8.17 ± 0.809	8.11 ± 0.610
	Week 6	LS mean ± SE	-0.22 ± 0.142	-0.43 ± 0.138
		Mean ± SD	7.86 ± 0.936	7.60 ± 0.944
	Week 12	LS mean ± SE	-0.39 ± 0.144	-0.61 ± 0.142
		Mean ± SD	7.66 ± 1.011	7.36 ± 0.941
	Week 16	LS mean ± SE	-0.37 ± 0.196	-0.55 ± 0.190
		Mean ± SD	7.58 ± 1.140	7.40 ± 1.473
	Difference vs. Teneligliptin 20 mg (LS mean ± SE; 95% CI) at week 16			-0.18 ± 0.25
	p-value[1] at week 16			0.475
HbA1c (%): 9-9.9%	Baseline	Mean ± SD	9.03 ± 0.988	8.83 ± 0.739
	Week 6	LS mean ± SE	-0.20 ± 0.152	-0.64 ± 0.165
		Mean ± SD	8.70 ± 1.198	8.15 ± 0.852
	Week 12	LS mean ± SE	-0.69 ± 0.161	-1.19 ± 0.169
		Mean ± SD	8.21 ± 1.237	7.60 ± 0.852
	Week 16	LS mean ± SE	-0.99 ± 0.170	-1.61 ± 0.168
		Mean ± SD	7.54 ± 0.990	7.18 ± 0.897
	Difference vs. Teneligliptin 20 mg (LS mean ± SE; 95% CI) at week 16			-0.62 ± 0.201
	p-value[1] at week 16			0.003

HbA1c (%): 10-11%	**Baseline**	**Mean ± SD**	9.94 ± 0.796	9.97 ± 0.932
	Week 6	**LS mean ± SE**	-0.56 ± 0.255	-0.85 ± 0.258
		Mean ± SD	9.19 ± 1.219	8.86 ± 1.294
	Week 12	**LS mean ± SE**	-0.98 ± 0.250	-1.33 ± 0.248
		Mean ± SD	8.75 ± 1.195	8.39 ± 1.308
	Week 16	**LS mean ± SE**	-1.03 ± 0.338	-1.50 ± 0.335
		Mean ± SD	8.43 ± 1.426	7.81 ± 1.206
	Difference vs. Teneligliptin 20 mg (LS mean ± SE; 95% CI) at week 16			-0.47 ± 0.456
	p-value[1] at week 16			0.311
CI, confidence interval; HbA1c, glycated hemoglobin; LS, least square; mITT, modified intent-to-treat; N, total number of patients; n, number of patients in a given category; p-value1 is the p-value for between-group change from baseline; SD, standard deviation; SE, standard error				

Table 2: Mean change from baseline in HbA1c%, stratified for screening HbA1c% (mITT Population).

Parameters	Visit	Statistics	Teneligliptin 20 mg (N=145)	Remogliflozin 100 mg/ Teneligliptin 10 mg (N=149)
FPG, mg/dL	**Baseline**	**Mean ± SD**	163.9 ± 50.53	160.8 ± 53.19
	Week 16	**LS mean ± SE**	-19.7 ± 4.46	-18.5 ± 4.32
		Mean ± SD	137.4 ± 40.45	135.8 ± 41.36
	Difference vs. Teneligliptin 20 mg (LS mean ± SE; 95% CI) at week 16			1.2 ± 5.08
	p-value[1] at week 16			0.818
PPG, mg/dL	**Baseline**	**Mean ± SD**	228.7 ± 69.93	224.4 ± 67.63
	Week 16	**LS mean ± SE**	-24.5 ± 6.32	-38.3 ± 6.13
		Mean ± SD	208.7 ± 61.41	187.9 ± 60.77
	Difference vs. Teneligliptin 20 mg (LS mean ± SE; 95% CI) at week 16			-13.8 ± 7.09
	p-value[1] at week 16			0.053
Body weight, kg	**Baseline**	**Mean ± SD**	70.85 ± 10.93	70.14 ± 9.95
	Week 16	**LS mean ± SE**	-0.76 ± 0.14	-0.97 ± 0.14
		Mean ± SD	69.47 ± 10.88	68.93 ± 10.20
	Difference vs. Teneligliptin 20 mg (LS mean ± SE; 95% CI) at week 16			-0.21 ± 0.17
	p-value[1] at week 16			0.201
CI, confidence interval; FPG, fasting plasma glucose; LS, least square; mITT, modified intent-to-treat; N, total number of patients; n, number of patients in a given category; PPG, postprandial glucose; p-value1 is the p-value for between-group change from baseline; SD, standard deviation; SE, standard error				

Table 3: Mean change from baseline FPG, PPG and body weight (mITT Population).

Safety and tolerability

Overall, TEAEs were reported in 40 patients (13%), the incidence was comparable between the two treatment groups (14.2% [n=22] in the RE+TE10 group and 11.8% [n=18] in the TE group). Only one patient (0.6%) in the RE+TE10 group with TEAEs (vomiting, diarrhea) discontinued from the study, and the event was considered related to the treatment by the investigator **(Table 4).**

The TEAEs reported in >1% of patients included diarrhea (n=3; 1.9%), urinary tract infection (n=3; 1.9%), dyslipidemia (n=2; 1.3%), hyperglycemia (n=2; 1.3%) and hypoglycemia (n=3; 1.9%), in the RE+TE10 group, while in the TE20 group, the reported TEAEs were urinary tract infection (n=2; 1.3%), hyperglycemia (n=4; 2.6%), and hypoglycemia (n=2; 1.3%).

All the TEAEs reported were mild-to-moderate in intensity. TEAEs of moderate intensity (gastritis, hyperglycemia, nocturia, vomiting, diarrhea, dyslipidemia) were reported in 1.3% (n=2) of patients in the RE+TE10 group and 3.9% (n=6) of patients in the TE20 group. The TEAEs of special interest of hypoglycemia and urinary tract infections were reported by 5 patients each; 3 (1.9%) in the RE+TE10 group and 2 (1.3%) in the TE20 group, respectively. There was only 1 (0.7%) patient in the TE20 group with symptomatic hypoglycemia and there were none in the RE+TE10 group. There were no reports of SAEs or deaths, or severe TEAEs throughout the study. **(Table 5)**

Clinical laboratory, vital signs and physical examination findings

There was no clinically relevant difference from baseline to Week 16 for the clinical biochemistry, 12-lead ECG, hematology, urine analysis, and vital signs in the RE+TE10 group compared to the TE20 group.

Treatment compliance

Patients who received ≥80% of prescribed treatment were considered drug compliant. Overall, the mean treament compliance was 98.7% ± 3.52 and 98.55% ± 2.99 in the RE+TE10 and TE20 groups, respectively. The mean metformin compliance was similar between the two groups (99.27% ± 1.98 in the RE+TE10 group and 99.05% ± 2.67 in the TE20 group).

System Organ Class Preferred Term	Teneligliptin 20 mg (N=153) n (%)	Remogliflozin 100 mg/ Teneligliptin 10 mg (N=155) n (%)
Any event	2 (1.3)	7 (4.5)
Gastrointestinal disorders	1 (0.7)	1 (0.6)
Diarrhea	0	1 (0.6)
Gastritis	1 (0.7)	0
Vomiting	0	1 (0.6)
Infections and Infestations	1 (0.7)	2 (1.3)
Urinary tract infections	1 (0.7)	2 (1.3)
Metabolism and nutrition disorder	0	3 (1.9)
Hyperglycemia	0	1 (0.6)
Hypoglycemia	0	2 (1.3)
Psychiatric disorders	0	1 (0.6)
Anxiety	0	1 (0.6)

Percentages are based on number of patients in safety population in the respective treatment group; System organ class and preferred terms are coded using MedDRA Version 22.0 or latest available dictionary; mITT, modified intent-to-treat; N, total number of patients; n, number of patients in a given category

Table 4: Patients with treatment-emergent adverse events related to treatment (Safety population).

System Organ Class Preferred Term	Teneligliptin 20 mg (N=153)	Remogliflozin 100 mg/ Teneligliptin 10 mg (N=155)
	n (%)	n (%)
Any event	18 (11.8)	22 (14.2)
Blood and lymphatic disorder	0	1 (0.6)
Anemia	0	1 (0.6)
Gastrointestinal disorders	2 (1.3)	3 (1.9)
Diarrhea	1 (0.7)	3 (1.9)
Gastritis	1 (0.7)	0
Vomiting	0	1 (0.6)
Infections and Infestations	3 (2.0)	5 (3.2)
COVID-19	0	1 (0.6)
Gastroenteritis	0	1 (0.6)
Pharyngitis bacterial	1 (0.7)	0
Urinary tract infection	2 (1.3%)	3 (1.9)
Investigations	1 (0.7)	1 (0.6)
Glomerular filtration rate decreased	0	1 (0.6)
Transaminases increased	1 (0.7)	0
Metabolism and nutrition disorder	7 (4.6)	9 (5.8)
Diabetes Mellitus	1 (0.7)	0
Dyslipidemia	0	2 (1.3)
Hyperglycemia	4 (2.6)	2 (1.3)
Hypertriglyceridemia	0	1 (0.6)
Hypoglycemia	2 (1.3)	3 (1.9)
Hyponatremia	0	1 (0.6)
Musculoskeletal and connective tissue disorder	1 (0.7)	1 (0.6)
Musculoskeletal pain	1 (0.7)	1 (0.6)
Nervous system disorders	1 (0.7)	1 (0.6)
Headache	1 (0.7)	1 (0.6)
Psychiatric disorder	1 (0.7)	1 (0.6)
Anxiety	0	1 (0.6)
Irritability	1 (0.7)	0
Renal and urinary disorders	2 (1.3)	1 (0.6)
Dysuria	0	1 (0.6)
Nocturia	1 (0.7)	0
Proteinuria	1 (0.7)	0
Respiratory, thoracic, and mediastinal disorders	1 (0.7)	0
Allergic rhinitis	1 (0.7)	0

Percentages are based on the number of patients in the safety population in the respective treatment group. System organ class and preferred terms are coded using MedDRA Version 22.0 or latest available dictionary. If a patient experienced more than one episode of an adverse event, the patient is counted once for that event. If a patient had more than one adverse event within a system organ class, the patient is counted once for each preferred term and once in that system organ class; COVID-19: coronavirus disease 2019; n (%), number (percentage) of patients in a given category; N, total number of patients

Table 5: Patients with treatment-emergent adverse events (Safety population).

Discussion

T2D is a complex and multifactorial disorder which generally requires a combination of several antidiabetic drugs to achieve optimal glycemic control. [7] Using FDC drug is a beneficial strategy that helps to achieve optimal therapeutic benefits and improves medication adherence in patients by minimizing pill burden. FDC drugs combine multiple active ingredients in a single dose product providing synergistic effects, better clinical outcomes, tolerability, and cost-effectiveness, which increases compliance and treatment adherence in patients. [10,16] Combining SGLT2i with DPP4i have shown to simplify the anti-diabetic therapy and improve the drug compliance. [7]

In the present study, we assessed the efficacy and safety of remogliflozin etabonate (100 mg) and teneligliptin (10 mg) twice-daily FDC therapy versus teneligliptin (20 mg) in patients with uncontrolled T2D on background therapy of metformin. The improvement in HbA1c in the RE+TE10 compared to TE20 was observed as early as Week 6 and was sustained over Week 12 and Week 16 confirming the superior efficacy of RE+TE10 compared to TE20 in terms of glycemic control. Also, the reduction observed in HbA1c from baseline to Week 16 in this study with RE+TE10 was similar to that reported in a clinical study with a combination of SGLT2i and DPP4i. [17] This proves that this RE+TE10 FDC has similar efficacy to other available SGLT2i and DPP4i combination.

Additionally, with rising HbA1c levels (HbA1c >8%), patients experience reduced functional independence. [18] The subgroup analysis based on baseline HbA1c levels between RE+TE10 and TE20 demonstrated a significant difference between two groups in HbA1c 9-9.9% subgroup (p=0.003), achieving HbA1c <7.5% with RE+TE10 at Week 16 from baseline, suggesting better outcomes for patients in this subgroup while for the other two subgroups (HbA1c 8-8.9% and 10-11%) difference was not statistically significant (**Table 2**). The reason of this findings could be the small no of patients in these subgroups. The results for FPG and PPG at Week 16 were not statistically significant between the two groups, however numerically higher reduction in the mean PPG levels were observed in the RE+TE10 than the TE20 group.

In our study, we found that addition of remogliflozin 100 mg and teneligliptin 10 mg to metformin resulted in numerically greater reduction in body weight than addition of teneligliptin 20 mg to metformin. Similar change in body weight was seen with teneligliptin and metformin. [19] Reduction in body weight and blood pressure with the use of SGLT2i in turn prevents the risk of CV death in patients with T2D. [6,20] In the TE20, patients who needed rescue medication were higher (13.1%) compared to the RE+TE10 (6%). Moreover, a significant proportion of patients in the RE+TE10 (35.6%) achieved HbA1c <7% compared to the TE20 (26.9%). As compared to TE20 statistically significant reductions in blood glucose and body weight in patients receiving RE+TE10 were observed from baseline to Week 16. Similar efficacy in providing glycemic and weight benefits was shown by other combinations of SGLT2is and DPP4is. [21-24] The greater percentage of patients attaining HbA1c <7% in RE+TE10 established the efficacy of FDC over TE20 in regulating blood glucose in patients with uncontrolled T2D. These findings support the overall clinical benefit of the FDC of remogliflozin/teneligliptin versus reducing hyperglycemia as an adjunct to metformin compared to the use of teneligliptin alone.

Both teneligliptin 10 mg and 20 mg dosages have shown efficacy in providing similar glycemic control and are well tolerated, with a low incidence of hypoglycemia. [26] Similar safety and tolerability of remogliflozin administered concomitantly with other OADs was observed in a real-world clinical study. [27,28] Of note, no ketoacidosis was reported in the RE+TE10 in the present study. SGLT2is, directly and indirectly, stimulates glucagon secretion, promoting the beta-oxidation of fatty acids and the formation of ketone bodies. [28] DPP4i suppresses SGLT2i-induced glucagon secretion by inactivating two incretin hormones, glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1, increasing insulin and reducing glucagon. [29] This combined mechanism of action of the combination therapy could explain the absence of ketoacidosis in this study. These findings further reinforce the benefits of combining anti-hyperglycemic therapies with different action mechanisms.

With improvement in multiple underlying pathophysiological defects associated with T2D, the FDC also needs to provide convenience to patients such as oral dosing and minimizing pill

burden, which will ultimately translate to improved adherence.[30] FDC of SGLT2i and DPP4i appears to be promising in meeting these criteria for improved medication adherence and treatment compliance among T2D patients. The overall drug compliance in our study was comparable between RE+TE10 and TE20 group and was >98% in both groups demonstrating good treatment adherence.

The strength of our study was the potential advantage of this FDC in increasing patient compliance and convenience. Our study was conducted at multiple centers spread across India thereby representing a wide range of patients from diverse bacgrounds which could be representative of larger population. Double-blind randomized treatment allocation eliminated the likely bias in the study, and the risk of confounding was well-controlled. A limitation of this study is that it reports 16-week results, thus not allowing the evaluation of long-term benefits of the FDC when compared to teneligliptin as an add-on to metformin. Overall, the FDC of remogliflozin etabonate 100 mg and teneligliptin 10 mg was effective and was shown to significantly reduce the HbA1c levels in this population and was well-tolerated. No SAE, death or cardiovascular events were reported in the study.

Conclusion

Remogliflozin 100 mg and teneligliptin 10 mg FDC achieved significantly greater improvements in glycemic control than with teneligliptin 20 mg as an add-on to metformin, with the benefit of body weight reduction and was also well tolerated. The findings from this study support initiating FDC of remogliflozin 100 mg and teneligliptin 10 mg as an effective treatment option in patients with uncontrolled T2D reducing pill burden resulting in improved improving patient's treatment compliance and medication adherence.

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