Fixed-Dose Combination of Canagliflozin and Metformin as an Adjunct to Diet and Exercise in Indian Adults with Type 2 Diabetes Mellitus: Results from a Multicentric, Open-Label, Single-Arm, Phase IV Study

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ABSTRACT
Background: Canagliflozin and metformin fixed-dose combination (CANA/MET FDC), an approved treatment for type 2 diabetes mellitus (T2DM) in India, effectively lowers glycated hemoglobin (HbA1c), promotes weight loss, and improves patient adherence. As a regulatory requirement, we aimed to evaluate the safety and efficacy of CANA/MET FDC in Indian patients with T2DM.

Research design and methods: This prospective, multicenter, open-label, single-arm, phase IV study included Indian patients with T2DM (aged 18–65 years) inadequately controlled on diet and exercise. Patients received CANA/MET (50/500 and 50/1000 mg) immediate-release (IR) FDC twice daily for 24 weeks. The primary endpoint was safety assessment, including adverse events (AEs) and serious AEs (SAEs). The secondary endpoint included a change in HbA1c from baseline to weeks 12 and 24. Descriptive statistics were used for all continuous safety variables and efficacy parameters.

Results: Of the 310 patients screened, 276 were enrolled. 114/274 (41.6%) patients had ≥1 treatment-emergent AE (treatment-emergent AEs (TEAEs), among which 29 (10.6%) were related to study intervention). The most common TEAEs were dyslipidemia (4.7%), pyrexia (4.7%), genital infections (3.3%), hypoglycemia (3.3%), and urinary tract infections (2.6%). Three (1.1%) patients had serious TEAEs, and all cases were resolved. No deaths were reported. The mean change in HbA1c from baseline was −0.92 and −0.93% at weeks 12 and 24, respectively.

Conclusion: The study demonstrates the safety and efficacy of CANA/MET FDC in Indian patients with T2DM, presenting a safe therapeutic option for diabetes management in India.

INTRODUCTION
The prevalence of type 2 diabetes mellitus (T2DM) has been steadily rising, with an estimated 537 million adults (20–79 years) living with T2DM across the globe.1 The trend remains similar in India, wherein 101 million people currently live with T2DM; the number is projected to reach 134 million by 2045, making India the diabetes capital of the world.1–3

Clinical and biochemical characteristics unique to the Indian population include high abdominal fat despite low body mass index (BMI), as well as high insulin resistance and triglycerides, resulting in a predisposition to T2DM.4 These characteristics together give rise to what is known as the “Asian Indian phenotype.” Along with urbanization and lifestyle changes, it is responsible for the rise of T2DM cases in India.4–6 Available data also suggest that the susceptibility of Asian Indians to the complications of DM differs from that of white populations.7 Asian Indians are at a higher risk of T2DM than individuals from other major ethnic groups.8 The younger age of onset, along with all the other factors associated with this phenotype, increases the probability of developing microvascular and macrovascular complications, which may lead to heart disease, kidney failure, blindness, and lower-limb amputations.6,9–11

Impaired glucose metabolism, the major pathophysiology of T2DM, is impacted by metabolic processes, including decreased insulin secretion, decreased incretin effect, increased lipolysis, increased glucon acid secretion, and increased glucose absorption. Thus, combining therapies with varying and complementary mechanisms of action might be beneficial in preventing complications, along with achieving glycemic control in patients with T2DM.12 Moreover, literature advocates that monotherapy cannot address the multiple defects of T2DM and often leads to failure to maintain glycemic control over time.13

The mainstay of T2DM treatment in India has been metformin (MET), which is known to reduce hepatic glucose production and intestinal glucose absorption, thereby reducing plasma glucose.13–15 Metformin is associated with a low risk of hypoglycemia and is weight-neutral or leads to weight loss.16,17 However, in the case of disease progression and unmet needs of glycemic control, additional antihyperglycemic agents are recommended.13,18,19 The combination of antihyperglycemic agents (AHAs) with complementary mechanisms of action may provide a more robust and durable glucose-lowering efficacy compared to a single agent.20

Canagliflozin (CANA), an active inhibitor of sodium-glucose cotransporter 2 (SGLT2),
Fixed-Dose Combination of Canagliflozin and Metformin in patients with T2DM. Previous studies have demonstrated that the addition of CANA to MET monotherapy significantly reduces glycated hemoglobin (HbA1c), along with weight loss in patients with T2DM. The American Diabetes Association (ADA) guideline recommends SGLT2i as first-line therapy with and without MET in patients with cardiovascular disease and T2DM. In August 2014, the United States Food and Drug Administration approved the CANA MET immediate-release fixed-dose combination (CANA/MET IR FDC) for the treatment of T2DM. The bioequivalence of CANA/MET IR FDC vs the individual components was established in pharmacokinetic studies in healthy participants. In general, FDCs have demonstrated that the addition of CANA to MET monotherapy significantly reduces glycated hemoglobin (HbA1c), along with weight loss in patients with T2DM.

The present study evaluated the safety and efficacy of the CANA/MET IR FDC marketed formulations (50/500 and 50/1000 mg) in Indian patients with T2DM to fulfill the postmarketing regulatory commitment in India.

**Research Design and Methods**

**Study Design and Patients**

This was a prospective, multicenter, open-label, single-arm, phase IV study conducted across 10 sites in different cities of India (Pune, Guwahati, Mohali, Trivandrum, Coimbatore, Bengaluru, Surat, Chandigarh, and Hyderabad) from December 2020 to July 2022. Patients with T2DM aged 18–65 years, following an inadequately controlled diet and exercise (as per investigator’s opinion), and able to receive the study drug as per prescribing information were included. Additionally, patients who were on stable AHA therapy for at least 12 weeks before screening and had HbA1c of ≥7.0 and ≤10.0% at screening were included.

Patients having a history of liver or renal insufficiency (estimated creatinine clearance <45 mL/minute); significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances; hereditary glucose-galactose malabsorption or primary renal glucosuria, history of diabetic ketoacidosis, type 1 DM, pancreas or β-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy, were excluded from the study. Patients were also deemed ineligible if they had a contraindication, any known allergies, hypersensitivity, or intolerance to CANA, MET, or CANA/MET IR FDC, or its excipients, or if they had used any other SGLT2i within 12 weeks before the screening visit. The study was carried out in three phases: a 7-day screening phase, a 24-week treatment phase, and a 28-day post-treatment phase. The study design is presented in Figure 1.

Patients received CANA/MET IR FDC (50/500 and 50/1000 mg) orally twice daily with meals, approximately at the same time each day. Wash-out from the previous treatment was not required. The study protocol was approved by local institutional review boards/ethics committees, and all the patients provided written informed consent prior to any study-related procedures. The study was conducted in compliance with the Declaration of Helsinki and the International Committee on Harmonization Good Clinical Practices and as per the New Drugs and Clinical Trials Rules, 2019—India and the Drug and Cosmetics Act and applicable regulatory requirements (Clinical Trials Registry CTRI/2020/07/026539).

**Statistical Analysis**

All the safety endpoints were assessed in the safety analysis set, comprising patients who received ≥1 dose of the study drug. Descriptive statistics were used for all continuous safety variables; categorical variables were summarized using frequency counts and percentages. All chemistry, hematologic, and urinalysis laboratory tests were summarized using descriptive statistics. All the efficacy endpoints were assessed in the efficacy analysis set, comprising patients who had taken ≥1 dose of study intervention.

**Study Assessment**

The primary endpoint was the determination of the incidence of adverse events (AEs), serious AEs (SAEs), unexpected AEs, or adverse drug reactions (ADRs) over the study period. Other safety assessments were also evaluated, including hypoglycemic episodes, safety laboratory parameters (including chemistry, hematology, and urinalysis), vital signs (systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse), and physical examinations.

All AEs were classified as per the Medical Dictionary for Regulatory Activities. Treatment-emergent AEs (TEAEs) were the AEs with onset during the treatment period that developed, worsened, or became serious from the initial administration of the study drug through the day of the last dose plus 28 days. The TEAEs that were not resolved or recovered, resolving, or recovering, or had an unknown status, were considered persistent TEAEs.

The secondary endpoint was the change in HbA1c from baseline to weeks 12 and 24. The exploratory endpoints were changes in fasting plasma glucose (FPG), 2-hour postprandial glucose (PPG), body weight, waist circumference, blood pressure (systolic and diastolic), and proportion of patients achieving HbA1c of <7.0% from baseline to weeks 12 and 24.

**Fig. 1:** Schematic representation of the study design; CANA, canagliflozin; FDC, fixed-dose combination; MET, metformin; IR, immediate-release
and had both baseline and at least 1 postbaseline efficacy assessment of HbA1c. All efficacy parameters were summarized using descriptive statistics.

**Results**

**Patient Demographics and Disposition**

Of the 310 patients screened, 276 were enrolled in this study as per inclusion and exclusion criteria and were treated with CANA/MET IR FDC. Two patients did not receive any dose of the study medication, resulting in 274 patients in the safety analysis set. The efficacy analysis set comprised 266 patients. The median age of the patients was 54 years, and the proportion of males (n = 169, 61.2%) was higher compared to females (n = 107, 38.8%). The mean ± standard deviation (SD) baseline weight, BMI, and waist circumference were 72.3 ± 11.67 kg, 26.6 ± 4.17 kg/m², and 98.4 ± 10.92 cm, respectively. The mean ± SD baseline FPG, PPG, and HbA1c values were 151.2 ± 50.67, 229.4 ± 67.46, and 8.5 ± 0.83 mg/dL, respectively (Table 1).

Overall, 180 (65.7%) and 94 (34.3%) patients received CANA/MET IR FDC with doses of 50/500 and 50/1000 mg, respectively. Two patients (0.7%) required modification of the study drug dose. The median duration of exposure to the study drug was 24.29 weeks (0.6–28.1 weeks). Overall, 265/274 (96.7%) patients showed ≥80% compliance to the study medication. In total, 263/274 (96%) patients showed ≥1 concomitant medication; the most commonly used were for diabetes (71.2%), general nutrients (48.2%), and lipid-modifying agents (45.6%). Of the 274 patients, 41 (15%) required rescue medications during the study. Rescue medication was defined as the new antidiabetic medication following the initiation of the study drug.

**Safety**

Overall, 41.6% (114/274) of the patients had ≥1 TEAE. Of these, 29 (10.6%) patients had TEAEs related to the study intervention. The most common TEAEs were dyslipidemia in 13/274 (4.7%), pyrexia in 13/274 (4.7%), genital infection in 9/274 (3.3%), and hypoglycemia in 9/274 (3.3%) patients. A total of 35 (12.8%) patients reported persistent TEAEs by the end of the study. Most of the TEAEs were mild or moderate in severity. The details of the TEAEs are presented in Table 2.

Overall, three (1.1%) patients reported ≥1 SAE during the study. Two (0.7%) patients reported SAE of severe urinary tract infection and were considered by the investigator to be possibly related to the study intervention. Of these two patients, one (0.4%) patient also had an SAE of diabetic ketoacidosis, which was assessed by the investigator as possibly related to study intervention. The same patient also had an SAE of prostatomegaly, which was severe and assessed by an investigator not related to the study intervention. One (0.4%) patient was hospitalized due to coronavirus disease of 2019 (COVID-19) infection with mild severity, which was assessed by the investigator as not related to study intervention. All the SAEs were resolved, and the patients recovered. Approximately, 262 (94.9%) patients had no hypoglycemic episodes, and eight (2.9%) patients had one hypoglycemic episode during the study. Two (0.7%) patients each had two, three, and four episodes of hypoglycemia, respectively. Of these 14 patients who had ≥1 hypoglycemic episode, the hypoglycemic events in five patients were not deemed clinically significant as per the investigator’s discretion. Overall, TEAEs leading to treatment discontinuation were low, that is, 6/274 (2.2%), anaemia (3 [1.1%] patients) being the most common (≥1%).

Other TEAEs leading to study discontinuation were pyrexia, gastroenteritis, urinary tract infection, decreased appetite, limb injury, diabetic ketoacidosis, and prostatomegaly reported in one patient each. No deaths were reported during the study.

In general, no clinically significant changes were observed in safety laboratory parameters at weeks 12 and 24. Clinically significant abnormal values for creatinine, potassium, and total cholesterol were reported in one (0.4%) patient each, whereas triglycerides and low-density lipoprotein (LDL) cholesterol were clinically abnormal in two (0.8%) and

### Table 1: Summary of demographics and baseline characteristics (all enrolled analysis set)

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>CANA/MET IR FDC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>Mean (SD) 52.2 (8.3)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 169 (61.2) Female 107 (38.8)</td>
</tr>
<tr>
<td>Weight (kg)*</td>
<td>Mean (SD) 72.3 (11.7)</td>
</tr>
<tr>
<td>BMI, kg/m², n (%)*</td>
<td>Mean (SD) &lt;25 26.6 (4.2) 25–30 92 (33.6) &gt;30 138 (50.4) 44 (16.1)</td>
</tr>
<tr>
<td>Waist circumference (cm)*</td>
<td>Mean (SD) 98.4 (10.9)</td>
</tr>
<tr>
<td>FPG (mg/dL)*</td>
<td>Mean (SD) 151.2 (50.7)</td>
</tr>
<tr>
<td>PPG (mg/dL)*</td>
<td>Mean (SD) 229.4 (67.5)</td>
</tr>
<tr>
<td>HbA1c (%)*</td>
<td>Mean (SD) 8.5 (0.83)</td>
</tr>
<tr>
<td>eGFR (mL/minute/1.73 m²), n (%)*</td>
<td>Mean (SD) 95.9 (15.3) 60–&lt;90 65 (23.7) ≥90 200 (73.0)</td>
</tr>
</tbody>
</table>

* N = 276, the total number of patients enrolled in the study; *N = 274; safety analysis set; patients who received at least one dose of the intervention; BMI, body mass index; CANA, canagliflozin; cm, centimeter; eGFR, estimated glomerular filtration rate; FDC, fixed-dose combination; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; IR, immediate release; MET, metformin hydrochloride; PPG, postprandial plasma glucose; SD, standard deviation.
four (1.5%) patients, respectively at week 12. Clinically significant abnormal values for creatinine persisted in one (0.4%) and two (0.8%) patients each for LDL cholesterol and triglycerides at week 24, respectively (Table 3).

None of the patients had clinically significantly abnormal values for any hematology parameter at week 24. For urinalysis, at week 12, one (0.4%) patient each had clinically significant abnormal values of urine albumin and urine creatinine, and two (0.8%) patients had a clinically abnormal urine albumin/creatinine ratio. At week 24, four (1.5%) patients had clinically significant abnormal urine albumin/creatinine ratio values (Table 3).

Table 2: Summary of TEAEs (safety analysis set)

<table>
<thead>
<tr>
<th>Safety analysis</th>
<th>CANA/MET IR FDC (N = 274), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with one or more TEAEs</td>
<td>114 (41.6)</td>
</tr>
<tr>
<td>Related to the study treatment</td>
<td>29 (10.6)</td>
</tr>
<tr>
<td>TEAEs leading to death</td>
<td>0</td>
</tr>
<tr>
<td>Serious TEAEs</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Related to the study treatment</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>TEAEs leading to discontinuation of study agent</td>
<td>6 (2.2)</td>
</tr>
<tr>
<td>TEAEs leading to termination of study participation</td>
<td>5 (1.8)</td>
</tr>
<tr>
<td>COVID-19 related TEAEs</td>
<td>5 (1.8)</td>
</tr>
<tr>
<td>Most common TEAEs</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>33 (12.0)</td>
</tr>
<tr>
<td>Genital infection</td>
<td>9 (3.3)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>7 (2.6)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>31 (11.3)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>13 (4.7)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>9 (3.3)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>22 (8.0)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13 (4.7)</td>
</tr>
<tr>
<td>One or more serious TEAEs</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>COVID-19</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Prostatomegaly</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

Safety analysis set, patients who received at least one dose of the intervention; CANA, canagliflozin; COVID, coronavirus disease; FDC, fixed-dose combination; IR, immediate-release; MET, metformin hydrochloride; TEAE, treatment-emergent AE

Table 3: Summary of patients with clinically significant abnormal laboratory parameters (safety analysis set)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline, n (%)</th>
<th>Week 12, n (%)</th>
<th>Week 24, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG (mg/dL)</td>
<td>75 (27.4)</td>
<td>46 (17.4)</td>
<td>35 (13.2)</td>
</tr>
<tr>
<td>PPG (mg/dL)</td>
<td>91 (33.2)</td>
<td>53 (20.2)</td>
<td>48 (18.3)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>57 (20.8)</td>
<td>28 (10.6)</td>
<td>23 (8.7)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>3 (1.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>5 (1.8)</td>
<td>4 (1.5)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>2 (0.7)</td>
<td>1 (0.4)</td>
<td>0</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>4 (1.5)</td>
<td>2 (0.8)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Urine albumin (mg/dL)</td>
<td>2 (0.7)</td>
<td>1 (0.4)</td>
<td>0</td>
</tr>
<tr>
<td>Urine creatinine (gm/dL)</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>0</td>
</tr>
<tr>
<td>UACR (mg/gm)</td>
<td>4 (1.5)</td>
<td>2 (0.8)</td>
<td>4 (1.5)</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>2 (0.7)</td>
<td>1 (0.4)</td>
<td>0</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>2 (0.7)</td>
<td>2 (0.8)</td>
<td>0</td>
</tr>
</tbody>
</table>

Safety analysis set, patients who received at least one dose of the intervention; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PPG, postprandial plasma glucose; SBP, systolic blood pressure; UACR, urine albumin-to-creatinine ratio

At week 12, very few patients had clinically significant abnormal vital signs for SBP, pulse (1 [0.4%] patient each), and DBP [two (0.8%) patients]. None of the patients had clinically significant abnormal vital signs at week 24. Overall incidences of abnormal flagged electrocardiogram values were low (n = 2).

Efficacy

The change in mean HbA1c levels from baseline was −0.92 (95% confidence interval [CI]: −1.055; −0.780) and −0.93% (95% CI: −1.084; −0.768) (at weeks 12 and 24, respectively (Fig. 2). Overall, 27.8% of the patients achieved an HbA1c <7% at week 12, which was increased to 34.2% at week 24 (Fig. 3).

The changes in the mean FPG from baseline were −20.13 mg/dL (95% CI: −26.97; −13.29) and −19.42 mg/dL (95% CI: −26.66; −12.19) at weeks 12 and 24, respectively. The changes in the mean 2-hour PPG from baseline were −34.65 mg/dL (95% CI: −43.82; −25.48) and −35.14 mg/dL (95% CI: −45.33; −24.96) at weeks 12 and 24, respectively (Fig. 2).

Mean changes in SBP and DBP from the baseline were −2.6 and −0.1 mm Hg at week 24, respectively. The mean body weight reduction was 2.10 kg, and the mean waist circumference reduction was 1.73 cm at the end of week 24. The results are presented in Figure 2.

Discussion

The present study evaluated the safety and efficacy of CANA/MET IR FDC (50/500 and 50/1000 mg) in Indian patients with T2DM who were inadequately controlled with diet and exercise and were eligible to receive the study drug as per prescribing information. It was also the first study conducted to evaluate the safety and efficacy of CANA/MET FDC in Indian patients with T2DM.

Safety assessments, including the determination of AEs, SAEs, and unexpected AEs, or ADRs over the study period was the primary endpoint of the study, and the safety profiles of CANA/MET IR FDC were found to be consistent with those reported in previous studies. Dyslipidemia, pyrexia, hypoglycemia, genital infection, and urinary tract infection were the most common TEAEs. No deaths were reported during the study. Improvements in HbA1c and FPG levels from the baseline were observed after 12 and 24 weeks of treatment with CANA/MET IR FDC. Overall, the study demonstrates the safety and efficacy of CANA/MET IR FDC and offers a safe therapeutic regimen in Indian patients with inadequately controlled T2DM.
The baseline demographics of the included patients (older adult age, overweight mean BMI, male dominance) were consistent with a phase IV study evaluating the safety and efficacy of SGLT2i in patients with T2DM. In the current analysis, the majority (96%) of patients were using one or more concomitant medications for comorbidities associated with diabetes. These findings concur with a cross-sectional survey from India, which reported that around 84% of patients with T2DM were suffering from one or more comorbid conditions associated with diabetes.

In this study, 41.6% of patients reported TEAEs, of which only 10.6% were related to the study drug, as assessed by the investigators. These results are in line with a phase II study in which treatment with CANA 50 mg twice daily wherein 35.5% of AE (11.8% related to the study drug) were reported. Additionally, in a dose-ranging study, 50% of patients reported at least one AE, with CANA 50 mg once daily added to background MET in patients with T2DM. Overall, only three (1.1%) patients reported SAEs in the current study, and most of the TEAEs were mild or moderate in severity, with minimal patient discontinuation (2.2%) in line with the previous CANA 50 mg study.

Safety data from six phase III studies on CANA showed 41.82% (CANA 100 mg) and...
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40.95% (CANA 300 mg) of patients reporting any AEs at week 26. Frequently occurring AEs were osmotic diuresis-related AEs, volume depletion AEs, urinary tract infections, and genital mycotic infections. As per the System Organ Class, infections and infestations were the most common AEs reported in 33 (12%) patients, including nine patients with genital infections (3.3%) and seven patients with urinary tract infections (2.6%). Not surprisingly, owing to its mechanism of action (SGLT2 inhibition), CANA is associated with a higher incidence of genital mycotic infections and urinary tract infections, as reported in the literature. The SGLT2 inhibitors increase urinary glucose concentration pharmacologically and provide favorable conditions for microbial growth, which results in an increased incidence of genital infections. Hence, clinicians should pay careful attention to the infections associated with SGLT2 inhibitors and personalize the treatment accordingly for patients with T2DM. Rosenstock et al. have reported genital infections in 4–6% of patients in the CANA/MET combination group, whereas 5–10% of patients in CANA alone. Similarly, 6% of patients suffered from genital infections, as reported in the post hoc analysis of pooled phase 3 studies of patients with T2DM from India treated with CANA (100 mg) on a range of background therapies.

In the present study, hypoglycemia was recorded in nine (3.3%) patients, consistent with the global study where 4.2 and 5.5% of patients had hypoglycemia in the CANA100/MET and CANA300/MET groups, respectively. In the post hoc analysis of Indian patients, fewer cases of hypoglycemia were reported in patients on CANA, not on a background AHA, compared to those on a background AHA. In general, fewer hypoglycemic episodes have been one of the key advantages associated with the use of SGLT2i. In studies wherein the patients were not on background AHA, the low risk of hypoglycemia observed with CANA, is by virtue of its mechanism of action, as the renal threshold for glucose is typically reduced to ~80–90 mg/dL above the hypoglycemia threshold in patients with T2DM. Incidences of hypoglycemia in our study might be associated with the concomitant AHAAs taken, along with the study medication. A phase II pooled analysis showed a higher incidence of documented hypoglycemia episodes in patients on a background of sulfonylurea compared to placebo, and this incidence was a dose-related increase as seen with CANA 100 and 300 mg. Our results are substantiated with other large trials, which have reported a safe and well-tolerated profile of CANA both alone and in combination of other AHAAs, including MET.

Approximately, 12.8% of patients reported persistent TEAEs that were not resolved or recovered or status unknown. Only one (0.4%) patient reported both severe DKA and pyrexia at very low level with the use of SGLT2 inhibitors. Dyslipidemia (4.7%) and pyrexia (4.7%) were the most common AE as per the preferred term reported in this study. A considerable number of patients (34.1%) had dyslipidemia at the time of study initiation, and this may have resulted in a higher incidence of AEs of dyslipidemia. Literature supports the potential beneficial effect of SGLT2 inhibitors on lipid metabolism at the cellular level to regulate lipoprotein concentration, fat storage, and substrate utilization. In this study, the abnormal values for creatinine, potassium, triglycerides, and LDL cholesterol were reported only in a small number of patients (~1%), which is consistent with published studies. Although the incidence of fever is reported to be very low in patients continuing CANA, the increase in the incidence of fever in this study might result from the higher incidence of infections.

The change in HbA1c levels from baseline were −0.92 and −0.93% at weeks 12 and 24, respectively. In a double-blind, placebo-controlled, parallel-group, multicenter, dose-ranging study including 451 subjects, CANA 50 mg once daily added to background MET therapy reduced HbA1c level by 0.79% at 12 weeks. However, another randomized, double-blind placebo-controlled study (N = 271) reported a decrease of 0.45% in HbA1c at 18 weeks with treatment of CANA 50 mg twice daily added to MET monotherapy. Rosenstock et al. reported HbA1c reductions of 1.77% for CANA100/MET and 1.78% for CANA300/MET at 26 weeks. As per the ADA and the European Association for the Study of Diabetes, the recommended target level of HbA1c is 7%. Nearly one-third of the patients (34%) achieved the target HbA1c level in our study compared with 43% of patients in a previous phase III study, evaluating the safety and efficacy of CANA/MET FDC. This difference might be due to the slight difference in the study duration. As SGLT2i acts by increasing the urinary glucose excretion, the differences in the baseline estimated glomerular filtration rate (eGFR) and potentially some other characteristics could influence the HbA1c responses across different ethnicities. In a phase II study of 279 patients evaluating 50 and 150 mg of CANA, significantly higher proportions of patients achieved HbA1c <7.0% at week 18 with 50 (47.8%) and 150 mg (57.1%) compared with placebo.

The FPG reductions (~20.13 mg/dL) in this study are nearly consistent with the findings of the previous CANA studies. Rosenstock et al. reported a decline of −65.77, 66.37, and −52.32 mg/dL in CANA 100/MET vs CANA 300/MET vs MET at week 26. Similarly, in a real-world study, there was a significant reduction in the FPG (~35.8 mg/dL; p < 0.005) at week 26 after switching from sitagliptin to CANA (100 mg). The mean PPG levels also showed a decline from the baseline at weeks 12 and 24, in line with CANA studies. Moreover, the changes in body weight, waist circumference, SBP, and DBP reported in this study are consistent with the published studies.

The main strengths of our study were the low dropout rates and the inclusion of a considerable number of patients in the real-world setting. Among the 276 patients enrolled, 265 (96.7%) patients completed the study. This might be due to the adherence and compliance associated with FDC. The limitation of the current study is that it is a single-arm, real-world, postmarketing study without a comparator arm as this was a real-world, post-marketing study with safety assessment as the primary endpoint. Further, efficacy endpoints could have been impacted by concomitant medications and comorbidities. The efficacy endpoints assessed changes from the baseline, and there was no direct comparison with a comparator arm.

Overall, results from this study have demonstrated that CANA/METIR FDC (50/500 and 50/1000 mg) have an acceptable safety profile to be prescribed in Indian patients since all reported AEs were manageable without any new safety signals, and no deaths were reported. The CANA/MET FDC could effectively reduce the HbA1c, FPG, and PPG levels in Indian patients with T2DM. Additionally, the reduction in body weight, waist circumference, and vital parameters was consistent with previous studies. Thus, CANA/MET IR FDC could be an acceptable and effective therapeutic option in Indian patients with T2DM.

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Fixed-Dose Combination of Canagliflozin and Metformin

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All authors contributed to data analysis, drafting, or revising of the article, provided final approval for the version to be published, and agreed to be accountable for all aspects of the work.

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