Initial Combination Therapy With Canagliflozin Plus Metformin Versus Each Component as Monotherapy for Drug-Naïve Type 2 Diabetes

Julio Rosenstock,[1] Leonard Chuck,[2] Manuel González-Ortiz,[3] Kate Merton,[4] Jagriti Craig,[4] George Capuano,[4] and Rong Qiu[4]

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OBJECTIVE

This study assessed the efficacy/safety of canagliflozin (CANA), a sodium–glucose cotransporter 2 (SGLT2) inhibitor, plus metformin extended-release (MET) initial therapy in drug-naïve type 2 diabetes.

RESEARCH DESIGN AND METHODS

This 26-week, double-blind, phase 3 study randomized 1,186 patients to CANA 100 mg (CANA100)/MET, CANA 300 mg (CANA300)/MET, CANA100, CANA300, or MET. Primary end point was change in HbA_{1c} at week 26 for combinations versus monotherapies. Secondary end points included noninferiority in HbA_{1c} lowering with CANA monotherapy versus MET; changes in fasting plasma glucose, body weight, and blood pressure; and proportion of patients achieving HbA_{1c} <7.0% (<53 mmol/mol).

RESULTS

From mean baseline HbA_{1c} of 8.8% (73 mmol/mol), CANA100/MET and CANA300/MET significantly lowered HbA_{1c} versus MET (median dose, 2,000 mg/day) by −1.77%, −1.78%, and −1.30% (−19.3, −19.5, and −14.2 mmol/mol; differences of −0.46% and −0.48% [−5.0 and −5.2 mmol/mol]; *P* = 0.001) and versus CANA100 and CANA300 by −1.37% and −1.42% (−15.0 and −15.5 mmol/mol; differences of −0.40% and −0.36% [−4.4 and −3.9 mmol/mol]; *P* = 0.001). CANA100 and CANA300 monotherapy met noninferiority for HbA_{1c} lowering and had significantly more weight loss versus MET (−2.8, −3.7, and −1.9 kg [−3.0%, −3.9%, and −2.1%]; *P* = 0.016 and *P* = 0.002). Greater attainment of HbA_{1c} <7.0% (50%, 57%, and 43%) and significantly more weight loss (−3.2, −3.9, and −1.9 kg [−3.5%, −4.2%, and −2.1%]; *P* = 0.001) occurred with CANA100/MET and CANA300/MET versus MET. The incidence of adverse events (AEs) related to SGLT2 inhibition (genital mycotic infections, osmotic diuresis– and volume depletion–related AEs) was higher in the CANA arms (0.4–4.4%) versus MET (0–0.8%). AE-related discontinuation rates were 1.3–3.0% across groups. The incidence of hypoglycemia was 3.0–5.5% in the CANA arms and 4.6% with MET.

CONCLUSIONS

Initial therapy with CANA plus MET was more effective and generally well tolerated versus each monotherapy in drug-naïve type 2 diabetes. CANA monotherapy demonstrated noninferior HbA_{1c} lowering versus MET.

[1]Dallas Diabetes and Endocrine Center at Medical City, Dallas, TX
[2]Diablo Clinical Research, Walnut Creek, CA
[3]Institute of Experimental and Clinical Therapeutics, Physiology Department, Health Science University Center, University of Guadalajara, Guadalajara, Mexico
[4]Janssen Research & Development, LLC, Raritan, NJ

Corresponding author: Julio Rosenstock, juliorosenstock@dallasdiabetes.com.

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The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend individualized HbA_{1c} targets of approximately <7.0% (<53 mmol/mol) for patients with type 2 diabetes (1,2) if this target can be achieved safely without unwanted side effects, as glycemic control can lower the risk of diabetes-related complications (3,4). A range of antihyperglycemic agents (AHAs) is available to manage hyperglycemia in patients with type 2 diabetes (1). Metformin (MET) monotherapy is the standard first-line AHA; however, its use is limited in some patients due to poor gastrointestinal tolerability (1). In addition, patients with elevated baseline HbA_{1c} may have difficulty meeting glycemic targets with a single AHA (5,6). Thus, many people will require combination therapy with two or three AHAs to achieve individualized glycemic targets (1).

Early intervention with combination therapy has been successful in the management of chronic conditions such as hypertension, and a similar approach is recommended for patients with type 2 diabetes (7). Physicians are increasingly initiating dual therapy as the preliminary treatment strategy in patients who would benefit from a more proactive approach to glycemic control (i.e., those with HbA_{1c} ≥9.0% [≥75 mmol/mol]). The ADA/EASD support initiation of dual therapy in newly diagnosed patients with type 2 diabetes and HbA_{1c} ≥9.0% (≥75 mmol/mol) (1). Similarly, combination therapy is recommended in Canada for patients with HbA_{1c} ≥8.5% (≥69 mmol/mol) (8). In contrast, the American Association of Clinical Endocrinologists supports initiation of dual therapy in patients with a lower baseline HbA_{1c} (i.e., ≥7.5% [≥58 mmol/mol]) (9), but there are no randomized controlled studies at that early stage to substantiate such an aggressive approach for relatively mild HbA_{1c} elevations that can be potentially controlled by a single agent. Therefore, an evaluation of the efficacy and safety of initial combinations of newer AHA classes with established therapies, such as MET, is important.

The recently revised ADA/EASD recommendations include sodium–glucose cotransporter 2 (SGLT2) inhibitors as another suitable add-on option for combination therapy due to their favorable efficacy and safety profile (1). Canagliflozin (CANA) is an SGLT2 inhibitor developed for the treatment of adults with type 2 diabetes (10–23). CANA lowers the renal threshold for glucose, thereby increasing urinary glucose excretion (UGE); increased UGE results in insulin-independent glucose-lowering effects, as well as a mild osmotic diuresis and net caloric loss that can lead to weight loss and blood pressure (BP) reductions (24,25). Across phase 3 studies in a broad range of patients with type 2 diabetes, CANA provided reductions in HbA_{1c}, body weight, and BP and was generally well tolerated as monotherapy and in combination with other AHAs, including MET (11–23). This study evaluated the efficacy and safety of initial combination therapy with CANA 100 mg (CANA100) or CANA 300 mg (CANA300) plus MET in drug-naïve patients with type 2 diabetes over 26 weeks. In addition, changes in HbA_{1c} and body weight with CANA monotherapy versus MET monotherapy were assessed with sufficient statistical power.

RESEARCH DESIGN AND METHODS

Study Design and Patients

This double-blind, five-arm, parallel-group, phase 3 study was conducted at 158 centers in 12 countries from 16 May 2013 to 1 December 2014. The study consisted of a 2-week, single-blind, placebo run-in period, followed by a 26-week, double-blind treatment phase and 4 weeks of follow-up for all patients.

Eligible patients were ≥18 and <75 years of age with drug-naïve type 2 diabetes (i.e., not on AHA therapy or off for ≥12 weeks before screening) that was inadequately controlled with diet and exercise (HbA_{1c} ≥7.5% and ≤12.0% [≥58 and ≤108 mmol/mol] at screening). Patients were excluded if they had a history of type 1 diabetes; repeated fasting self-monitored blood glucose >300 mg/dL (>16.7 mmol/L); myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident ≤12 weeks before screening; history of New York Heart Association Functional Classification III and/or IV cardiac disease; uncontrolled hypertension; estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or serum creatinine ≥1.4 mg/dL (≥124 μmol/L) for men and ≥1.3 mg/dL (≥115 μmol/L) for women; or were taking any AHA within 12 weeks before screening or during the placebo run-in period. Patients were discontinued from the study if they had fasting plasma glucose (FPG) values meeting prespecified glycemic withdrawal criteria (FPG >270 mg/dL [>15.0 mmol/L] after day 1 through week 6; >240 mg/dL [>13.3 mmol/L] after week 6 through week 12; >200 mg/dL [>11.1 mmol/L] after week 12 through week 26), serum creatinine ≥1.5 mg/dL (≥133 μmol/L) for men or ≥1.4 mg/dL (≥124 μmol/L) for women, or eGFR <50 mL/min/1.73 m^2.

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practice and applicable regulatory requirements. Regulatory approval for the conduct of the trial was obtained in each country, and ethics approval was received at every site before initiation. Patients provided written informed consent before participation.

Randomization and Blinding

Patients were randomized (1:1:1:1:1) to receive CANA100/MET extended-release (XR), CANA300/MET XR, CANA100, CANA300, or MET XR over 26 weeks using a computer-generated randomization schedule that was prepared by the sponsor before the study. Randomization was balanced using permuted blocks and stratified by HbA_{1c} values at screening (i.e., <9.0% or ≥9.0% [<75 or ≥75 mmol/mol]). FPG and HbA_{1c} values were masked to the study sites and to the sponsor, unless an FPG value met glycemic discontinuation criteria.

At week −2, all patients received placebo tablets matching MET XR 500 mg and placebo capsules matching CANA. Patients were instructed to take three pills each day during the 2-week, single-blind, placebo run-in period: one placebo capsule matching CANA before the morning meal, then one placebo capsule matching CANA and one placebo tablet matching MET XR 500 mg with the evening meal. MET XR was administered in the evening to minimize adverse gastrointestinal effects. During the double-blind treatment period, patients in all treatment groups were instructed to take two capsules of CANA or matching placebo each day to maintain blinding, with one capsule taken before the morning meal and one capsule taken with the

evening meal. The doses of CANA were not titrated.

Patients randomly assigned to the treatment groups with MET XR (as monotherapy or coadministered with CANA) received 500 mg tablets or matching placebo that were administered with the evening meal and titrated as follows: one tablet (500 mg/day) from day 1 through week 1; two tablets (1,000 mg/day) from week 1 through week 3; three tablets (1,500 mg/day) from week 3 through week 6; and four tablets (2,000 mg/day) from week 6 through week 9. At week 9, patients meeting protocol-specified glycemic criteria who did not previously uptitrate MET XR to 2,000 mg/day or matching placebo for reasons other than tolerability were allowed to uptitrate with MET XR 500 mg (or matching placebo) up to 2,000 mg/day.

End Points and Assessments

The prespecified primary efficacy end point was the change from baseline in HbA_{1c} at week 26. Key secondary end points included the change from baseline in FPG and systolic BP (SBP), percent change from baseline in body weight and fasting plasma lipids, and the proportion of patients with HbA_{1c} $<$7.0% ($<$53 mmol/mol) at week 26. Overall safety and tolerability were assessed based on adverse event (AE) reports, safety laboratory tests, vital signs measurements, and physical examinations. The incidence of documented hypoglycemia (i.e., fingerstick or plasma glucose $\leq$70 mg/dL [$\leq$3.9 mmol/L], with or without symptoms or severe episodes [i.e., requiring assistance or resulting in seizure, loss of consciousness, or cognitive dysfunction]) was also assessed.

Statistical Analyses

The primary hypothesis for this study was that each CANA/MET combination provides statistically superior HbA_{1c} lowering compared with their respective monotherapies. Key secondary hypotheses included demonstrating that CANA100 and CANA300 provide noninferior HbA_{1c} reductions (based on the prespecified margin of 0.35% for the between-group difference) and greater reductions in body weight versus MET and that coadministration of CANA and MET provides greater reductions in body weight, greater proportions of patients achieving HbA_{1c} $<$7.0% (53 mmol/mol), greater reductions in SBP, greater increases in HDL cholesterol (HDL-C), and greater decreases in triglycerides compared with MET.

The sample size was determined based on demonstrating the statistical superiority of each dose of CANA in combination with MET to their respective monotherapies in HbA_{1c} lowering, as well as demonstrating the noninferiority of each dose of CANA compared with MET. A total of 216 patients per group were estimated to be required to achieve 90% power for both comparisons, with an assumed minimum group difference of 0.4% and an assumed SD of 1.15% using a two-sample, two-sided *t* test, with a type I error rate of 0.05. To provide 90% power to demonstrate the noninferiority of either CANA dose compared with MET (assuming a difference of 0.0% and a common SD of 1.15% using a two-sample, one-sided *t* test, with a type I error rate of 0.025), 240 patients were required per group, assuming 5% of patients would have missing HbA_{1c} values at week 26.

Efficacy analyses were conducted using the modified intent-to-treat (mITT) population (i.e., all patients who were randomized and received $\geq$1 dose of the double-blind study drug). Safety analyses were performed in the mITT population according to the predominant treatment received. The primary efficacy end point of change from baseline in HbA_{1c} was analyzed with a mixed model for repeated measures (MMRM) using a restricted maximum likelihood approach. This analysis was based on observed data that included treatment, stratification factor (i.e., HbA_{1c} $<$9.0 or $\geq$9.0% [$<$75 or $\geq$75 mmol/mol] at screening), visit, and treatment-by-visit interaction as fixed categorical effects, and baseline and baseline-by-visit interaction as continuous fixed covariates. Least squares (LS) mean differences and 95% CIs were estimated at week 26 for each combination versus MET and versus their respective CANA monotherapy, as well as for CANA100 and CANA300 versus MET.

Continuous secondary end points (e.g., FPG, body weight, BP) were analyzed with an MMRM similar to the primary efficacy end point. Percent changes from baseline in lipids were analyzed using an ANCOVA, with treatment and the stratification factor as fixed effects and the corresponding baseline value as a covariate. Given the skewed nature of the distribution of the percent change in triglycerides, the Wilcoxon rank sum test was used to evaluate treatment comparisons. Missing lipids data were imputed using the last observation carried forward approach, as longitudinal analysis was not possible due to the collection schedule for lipids in the study. The binary secondary end point of the proportion of patients with HbA_{1c} $<$7.0% ($<$53 mmol/mol) was analyzed longitudinally using a generalized linear mixed model, with similar terms as the primary efficacy analysis.

A prespecified hierarchical testing procedure was used to control the overall type I error rate (two-sided α = 0.05) based on the mixture methodology developed by Dmitrienko and Tamhane (26). Hochberg-type procedures were used for testing the hypotheses, and Hochberg-adjusted *P* values are reported for the prespecified comparisons only.

RESULTS

Patients

A total of 1,186 patients were randomized and received $\geq$1 dose of the study drug, comprising the mITT analysis set; of these, 1,069 (90.1%) completed 26 weeks of treatment (Supplementary Fig. 1). Discontinuations were reported in 5.1%, 10.5%, 11.0%, 9.2%, and 13.5% of patients who received CANA100/MET, CANA300/MET, CANA100, CANA300, and MET, respectively; overall, the most common reasons for discontinuation were meeting glycemic withdrawal criteria (2.3%) and AEs (2.2%). Baseline demographic and disease characteristics were generally similar across treatment groups (Table 1). Patients had a mean baseline HbA_{1c} of 8.8% (73 mmol/mol) and a mean eGFR of 88 mL/min/1.73 m^2; 48% of participants were male, mean age was 54.9 years, and mean duration of type 2 diabetes was 3.3 years. At week 26, the mean dose of MET was 1,924, 1,909, and 1,930 mg/day in the CANA100/MET, CANA300/MET, and MET groups, respectively.

Table 1—Baseline demographic and disease characteristics

	CANA100/MET (*n* = 237)	CANA300/MET (*n* = 237)	CANA100 (*n* = 237)	CANA300 (*n* = 238)	MET (*n* = 237)	Total (*N* = 1,186)
Sex, *n* (%)						
Male	108 (45.6)	115 (48.5)	105 (44.3)	125 (52.5)	116 (48.9)	569 (48.0)
Female	129 (54.4)	122 (51.5)	132 (55.7)	113 (47.5)	121 (51.1)	617 (52.0)
Age, years	54.2 ± 9.6	55.4 ± 9.8	54.0 ± 10.7	55.8 ± 9.6	55.2 ± 9.8	54.9 ± 9.9
Race, *n* (%)†						
White	189 (79.7)	187 (78.9)	192 (81.0)	208 (87.4)	192 (81.0)	968 (81.6)
Black/African American	6 (2.5)	8 (3.4)	12 (5.1)	8 (3.4)	9 (3.8)	43 (3.6)
Asian	6 (2.5)	5 (2.1)	4 (1.7)	4 (1.7)	9 (3.8)	28 (2.4)
Other‡	36 (15.2)	37 (15.6)	29 (12.2)	18 (7.6)	27 (11.4)	147 (12.4)
HbA_{1c}, %	8.8 ± 1.1	8.9 ± 1.2	8.8 ± 1.2	8.8 ± 1.2	8.8 ± 1.2	8.8 ± 1.2
HbA_{1c}, mmol/mol	73 ± 12	74 ± 13	73 ± 13	73 ± 13	73 ± 13	73 ± 13
Baseline HbA_{1c}, *n* (%)						
<9.0% (<75 mmol/mol)	135 (57.0)	137 (57.8)	144 (60.8)	142 (59.7)	146 (61.6)	704 (59.4)
≥9.0% (≥75 mmol/mol)	102 (43.0)	100 (42.2)	93 (39.2)	96 (40.3)	91 (38.4)	482 (40.6)
FPG, mg/dL	191 ± 51	202 ± 56	196 ± 54	193 ± 52	191 ± 49	195 ± 52
FPG, mmol/L	10.6 ± 2.8	11.2 ± 3.1	10.9 ± 3.0	10.7 ± 2.9	10.6 ± 2.7	10.8 ± 2.9
Body weight, kg	88.3 ± 17.6	91.4 ± 21.4	90.2 ± 18.6	93.0 ± 19.9	92.1 ± 20.1	91.0 ± 19.6
BMI, kg/m^2	31.9 ± 5.3	32.8 ± 6.5	32.4 ± 5.4	32.6 ± 5.8	33.0 ± 6.0	32.5 ± 5.8
eGFR, mL/min/1.73 m^2	89 ± 19	87 ± 19	90 ± 19	85 ± 18	87 ± 19	88 ± 19
Type 2 diabetes duration, years	2.9 ± 3.3	3.3 ± 3.9	3.5 ± 4.4	3.3 ± 4.4	3.3 ± 4.5	3.3 ± 4.1

Data are mean ± SD unless otherwise indicated. †Percentages may not total 100.0% due to rounding. ‡Includes American Indian or Alaskan Native, multiple, other, unknown, and not reported.

Efficacy

Glycemic Efficacy

At week 26, reductions from baseline in HbA_{1c} were seen with CANA100/MET, CANA300/MET, CANA100, CANA300, and MET (–1.77%, −1.78%, –1.37%, –1.42%, and –1.30% [–19.3, –19.5, –15.0, –15.5, and –14.2 mmol/mol], respectively), resulting in final mean HbA_{1c} values of 7.0%, 7.0%, 7.4%, 7.3%, and 7.4% (53, 53, 57, 56, and 57 mmol/mol), respectively (Fig. 1*A* and Table 2). Reductions in HbA_{1c} with CANA100/MET and CANA300/MET were statistically significant versus MET (LS mean differences of –0.46% and –0.48% [–5.0 and –5.2 mmol/mol], respectively; $P = 0.001$ for both) and versus CANA100 and CANA300 (LS mean differences of –0.40% and –0.36% [–4.4 and –3.9 mmol/mol], respectively; $P = 0.001$ for both). Noninferiority of HbA_{1c} lowering was also demonstrated with CANA100 and CANA300 versus MET (LS mean differences of –0.06% and –0.11% [–0.7 and –1.2 mmol/mol], respectively; noninferiority $P = 0.001$ for both). At week 26, significant differences in the proportion of patients who achieved HbA_{1c} <7.0% (<53 mmol/mol) were observed with CANA100/MET and CANA300/MET versus MET ($P = 0.027$ and $P = 0.016$, respectively); 49.6%, 56.8%, 38.8%, 42.8%, and 43.0% of patients achieved HbA_{1c} <7.0% (<53 mmol/mol) with CANA100/MET, CANA300/MET, CANA100, CANA300, and MET, respectively (Fig. 1*B*). A subgroup analysis showed greater HbA_{1c} reductions with CANA100/MET, CANA300/MET, CANA100, and CANA300 compared with MET in patients with baseline HbA_{1c} ≥9.0% (≥75 mmol/mol) (–2.43%, −2.44%, –1.94%, –2.03%, and –1.79% [–26.6, –26.7, –21.2, –22.2, and –19.6 mmol/mol], respectively) versus those with baseline HbA_{1c} <9.0% (<75 mmol/mol) (–1.32%, –1.31%, –0.97%, –0.99%, and –0.94% [–14.4, –14.3, –10.6, –10.8, and –10.3 mmol/mol], respectively) (Fig. 1*C*).

Dose-related reductions in FPG were observed with CANA100/MET and CANA300/MET that were greater compared with their respective monotherapies (Fig. 1*D* and Table 2). Across groups, FPG appeared to reach the nadir at week 6 and then remained stable through week 26 with each treatment.

Body Weight and BP

At week 26, reductions in body weight from baseline were observed across groups (–3.2, –3.9, –2.8, –3.7, and –1.9 kg [−3.5%, –4.2%, –3.0%, –3.9%, and –2.1%] with CANA100/MET, CANA300/MET, CANA100, CANA300, and MET, respectively) (Fig. 1*E* and Table 2). Body weight reductions were largest from baseline to week 6 and decreased steadily, with no apparent plateau through week 26. Statistically significant reductions in body weight were seen with CANA100/MET and CANA300/MET versus MET (LS mean differences of –1.2 and –2.0 kg [–1.4% and –2.1%], respectively; $P = 0.001$ for both). CANA100 and CANA300 also provided significant reductions in body weight relative to MET (LS mean differences of –0.9 and –1.8 kg [–0.9% and –1.8%], respectively; $P = 0.016$ and $P = 0.002$, respectively).

CANA100/MET, CANA300/MET, CANA100, and CANA300 provided modest reductions in SBP compared with MET (–2.2, –1.7, –2.2, –2.4, and –0.3 mmHg, respectively) (Table 2 and Supplementary Fig. 2). Reductions in SBP with CANA100/MET and CANA300/MET were not statistically significant versus MET (LS mean differences of –1.9 and –1.3 mmHg, respectively). Modest reductions in diastolic BP (DBP) were observed at week 26 that were greater in all CANA arms compared with MET (Table 2).

Fasting Plasma Lipids

Changes from baseline in fasting plasma lipids are summarized in Table 2. Increases in HDL-C were seen with CANA100/MET,

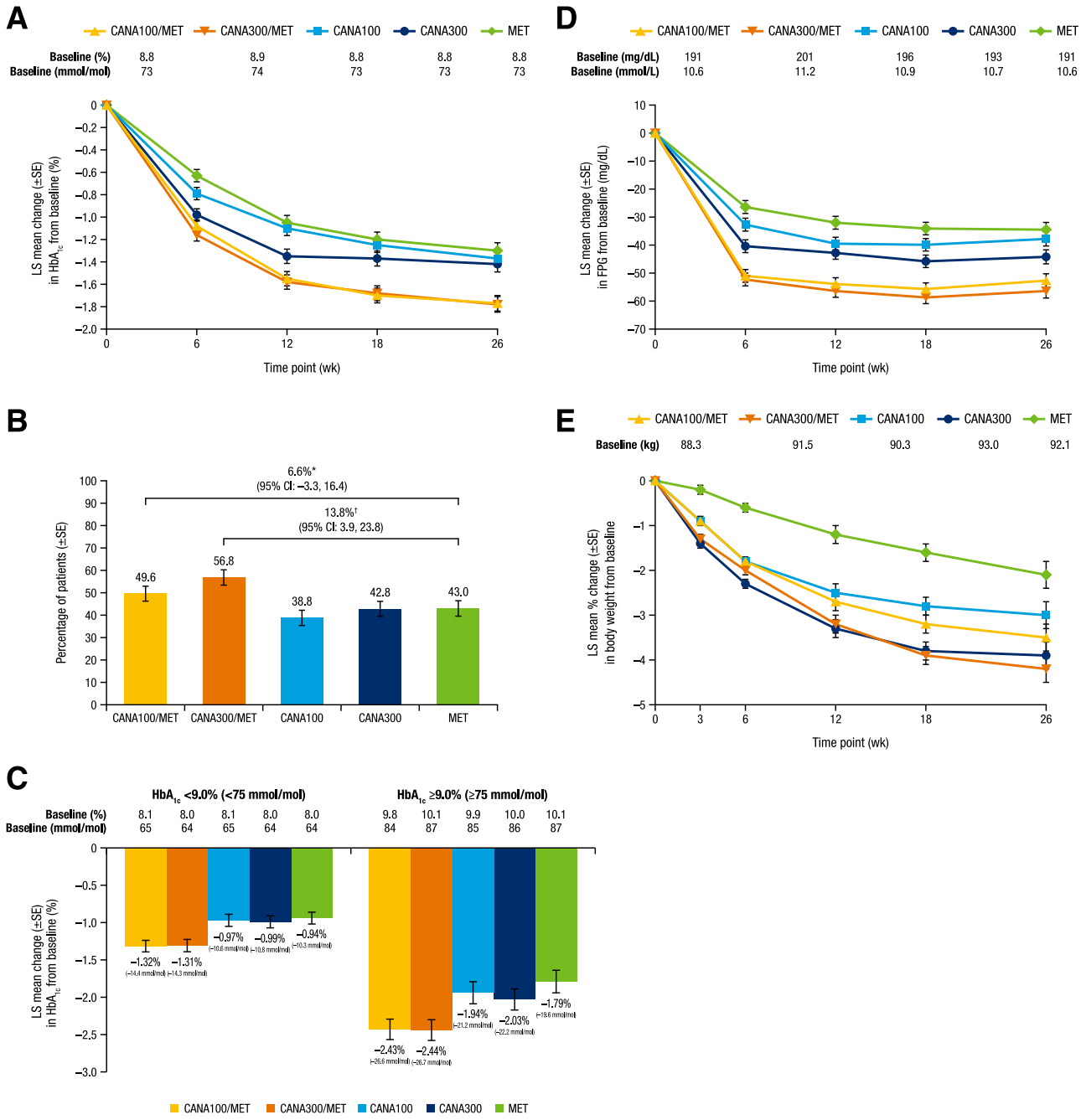

Figure 1—Effects on efficacy parameters. *A*: Change from baseline in HbA_{1c} over 26 weeks. *B*: Proportion of patients with HbA_{1c} <7.0% (<53 mmol/mol) at week 26. *C*: Change from baseline in HbA_{1c} in subgroups with baseline HbA_{1c} <9.0% (<75 mmol/mol) or ≥9.0% (≥75 mmol/mol) at week 26. *D*: Change from baseline in FPG over 26 weeks. *E*: Percent change from baseline in body weight over 26 weeks. *P = 0.027 vs. MET. †P = 0.016 vs. MET.

CANA300/MET, CANA100, and CANA300 compared with MET (15.5%, 14.5%, 17.6%, 16.6%, and 10.2%, respectively); LS mean differences for CANA100/MET, CANA300/MET, CANA100, and CANA300 versus MET were 5.3%, 4.3%, 7.4%, and 6.5%, respectively. Median percent changes from baseline in triglycerides were 2.9%, 7.8%, −8.7%, −7.3%, and 4.2% with CANA100/MET, CANA300/MET, CANA100, CANA300, and MET, respectively. Owing to the lack of significance of testing SBP in the prior step of the hypothesis testing sequence, statistical testing of HDL-C and triglycerides was not performed. CANA100/MET and CANA300/MET provided similar increases in LDL cholesterol (LDL-C) versus MET (LS mean differences of –0.2% and 1.2%, respectively), but increases in LDL-C were greater with CANA100 and CANA300 versus MET (LS mean differences of 10.3% and 7.4%, respectively).

Safety and Tolerability

The overall incidence of AEs was 41.8%, 44.3%, 37.1%, 39.9%, and 37.6% with CANA100/MET, CANA300/MET, CANA100, CANA300, and MET, respectively, over 26 weeks (Table 3). AEs leading to discontinuation were reported in 1.3–3.0% of patients across groups. The incidence of serious AEs was low across groups (≤3.0%), with no discernible trend across treatment groups. One death occurred in

Table 2—Summary of efficacy findings at week 26*

Parameter	CANA100/MET	CANA300/MET	CANA100	CANA300	MET
HbA_{1c}, *n*	235	236	230	234	230
Mean ± SD baseline, % (mmol/mol)	8.8 ± 1.1 (73 ± 12)	8.9 ± 1.2 (74 ± 13)	8.8 ± 1.2 (73 ± 13)	8.8 ± 1.2 (73 ± 13)	8.8 ± 1.2 (73 ± 13)
LS mean ± SE change, % (mmol/mol)	−1.77 ± 0.07 (−19.3 ± 0.8)	−1.78 ± 0.07 (−19.5 ± 0.8)	−1.37 ± 0.07 (−15.0 ± 0.8)	−1.42 ± 0.07 (−15.5 ± 0.8)	−1.30 ± 0.07 (−14.2 ± 0.8)
Difference vs. MET (95% CI), % [mmol/mol]	−0.46 (−0.66, −0.27)† [−5.0 (−7.2, −3.0)]	−0.48 (−0.67, −0.28)† [−5.2 (−7.3, −3.1)]	−0.06 (−0.26, 0.13)‡ [−0.7 (−2.8, 1.4)]	−0.11 (−0.31, 0.08)‡ [−1.2 (−3.4, 0.9)]	
Difference vs. CANA100 (95% CI), % [mmol/mol]	−0.40 (−0.59, −0.21)§ [−4.4 (−6.4, −2.3)]				
Difference vs. CANA300 (95% CI), % [mmol/mol]		−0.36 (−0.56, −0.17)‖ [−3.9 (−6.1, −1.9)]			
FPG, *n*	235	236	230	234	230
Mean ± SD baseline, mg/dL (mmol/L)	191 ± 51 (10.6 ± 2.8)	201 ± 56 (11.2 ± 3.1)	196 ± 54 (10.9 ± 3.0)	193 ± 52 (10.7 ± 2.9)	191 ± 49 (10.6 ± 2.7)
LS mean ± SE change, mg/dL (mmol/L)	−53 ± 3 (−2.9 ± 0.1)	−56 ± 3 (−3.1 ± 0.1)	−38 ± 3 (−2.1 ± 0.1)	−44 ± 3 (−2.5 ± 0.1)	−35 ± 3 (−1.9 ± 0.1)
Difference vs. MET (95% CI), mg/dL [mmol/L]	−18 (−25, −11) [−1.0 (−1.4, −0.6)]	−22 (−29, −15) [−1.2 (−1.6, −0.8)]	−3 (−10, 4) [−0.2 (−0.6, 0.2)]	−10 (−17, −3) [−0.5 (−0.9, −0.1)]	
Difference vs. CANA100 (95% CI), mg/dL [mmol/L]	−15 (−22, −8) [−0.8 (−1.2, −0.4)]				
Difference vs. CANA300 (95% CI), mg/dL [mmol/L]		−12 (−19, −5) [−0.7 (−1.1, −0.3)]			
Body weight, *n*	237	236	236	236	237
Mean ± SD baseline, kg	88.3 ± 17.6	91.5 ± 21.4	90.3 ± 18.6	93.0 ± 20.0	92.1 ± 20.1
LS mean change ± SE, % (kg)	−3.5 ± 0.3 (−3.2 ± 0.2)	−4.2 ± 0.3 (−3.9 ± 0.2)	−3.0 ± 0.3 (−2.8 ± 0.2)	−3.9 ± 0.3 (−3.7 ± 0.2)	−2.1 ± 0.3 (−1.9 ± 0.2)
Difference vs. MET (95% CI), % [kg]	−1.4 (−2.1, −0.6)† [−1.2 (−1.9, −0.6)]	−2.1 (−2.9, −1.4)† [−2.0 (−2.6, −1.3)]	−0.9 (−1.6, −0.2)¶ [−0.9 (−1.6, −0.2)]	−1.8 (−2.6, −1.1)# [−1.8 (−2.4, −1.1)]	
SBP, *n*	237	236	236	236	237
Mean ± SD baseline, mmHg	127.6 ± 11.5	128.1 ± 12.2	128.9 ± 11.7	130.1 ± 11.5	129.4 ± 12.0
LS mean ± SE change, mmHg	−2.2 ± 0.6	−1.7 ± 0.6	−2.2 ± 0.6	−2.4 ± 0.6	−0.3 ± 0.6
Difference vs. MET (95% CI)	−1.9 (−3.6, −0.2)**	−1.3 (−3.1, 0.4)**			
DBP, *n*	237	236	236	236	237
Mean ± SD baseline, mmHg	78.4 ± 7.7	78.1 ± 8.3	79.0 ± 7.8	78.5 ± 7.8	78.3 ± 7.8
LS mean ± SE change, mmHg	−1.5 ± 0.4	−1.02 ± 0.4	−1.1 ± 0.4	−1.7 ± 0.4	−0.5 ± 0.4
Difference vs. MET (95% CI)	−1.1 (−2.3, 0.1)††	−0.6 (−1.8, 0.6)††	−0.7 (−1.9, 0.6)††	−1.3 (−2.5, −0.1)††	
HDL-C, *n*	227	225	225	228	222
Mean ± SD baseline, mg/dL (mmol/L)	44.4 ± 10.9 (1.2 ± 0.3)	43.5 ± 10.3 (1.1 ± 0.3)	43.1 ± 9.1 (1.1 ± 0.2)	44.0 ± 11.9 (1.1 ± 0.3)	43.7 ± 10.6 (1.1 ± 0.3)
LS mean ± SE change, mg/dL (mmol/L)	6.4 ± 0.6 (0.16 ± 0.02)	5.5 ± 0.7 (0.14 ± 0.02)	6.9 ± 0.7 (0.18 ± 0.02)	6.8 ± 0.6 (0.17 ± 0.02)	3.9 ± 0.7 (0.10 ± 0.02)

Continued on p. 359

Table 2—Continued

Parameter	CANA100/MET	CANA300/MET	CANA100	CANA300	MET
LS mean ± SE percent change	15.5 ± 1.5	14.5 ± 1.5	17.6 ± 1.5	16.6 ± 1.5	10.2 ± 1.5
Difference vs. MET (95% CI)	5.3 (1.2, 9.5)‡‡	4.3 (0.2, 8.5)‡‡	7.4 (3.2, 11.6)††	6.5 (2.3, 10.6)††	
Triglycerides, *n*	229	225	225	229	223
Mean ± SD baseline, mg/dL (mmol/L)	166.6 ± 84.1	179.0 ± 105.1	187.1 ± 118.8	173.4 ± 108.7	188.6 ± 126.6
	(1.9 ± 0.9)	(2.0 ± 1.2)	(2.1 ± 1.3)	(2.0 ± 1.2)	(2.1 ± 1.4)
LS mean ± SE change, mg/dL (mmol/L)	−1.4 ± 6.7	15.5 ± 6.8	−15.9 ± 6.8	−17.4 ± 6.7	15.2 ± 6.8
	(−0.02 ± 0.08)	(0.17 ± 0.08)	(−0.18 ± 0.08)	(−0.20 ± 0.08)	(0.17 ± 0.08)
Median percent change (range)	2.9 (−82.2, 1,022.6)	7.8 (−81.4, 415.1)	−8.7 (−81.2, 268.2)	−7.3 (−76.9, 620.8)	4.2 (−83.1, 278.6)
Hodges-Lehmann estimate (95% CI)	−3.7 (−11.1, 3.4)‡‡	1.3 (−7.3, 10.0)‡‡			
LDL-C, *n*	225	223	222	228	222
Mean ± SD baseline, mg/dL (mmol/L)	118.6 ± 37.6	118.8 ± 41.2	116.0 ± 38.1	122.5 ± 38.0	115.5 ± 36.3
	(3.1 ± 1.0)	(3.1 ± 1.1)	(3.0 ± 1.0)	(3.2 ± 1.0)	(3.0 ± 0.9)
LS mean ± SE change, mg/dL (mmol/L)	−1.1 ± 2.1	−0.4 ± 2.1	9.8 ± 2.1	9.0 ± 2.1	−0.6 ± 2.1
	(−0.03 ± 0.05)	(−0.01 ± 0.05)	(0.25 ± 0.05)	(0.23 ± 0.05)	(−0.02 ± 0.05)
LS mean ± SE percent change	3.8 ± 2.2	5.2 ± 2.2	14.3 ± 2.2	11.4 ± 2.2	4.0 ± 2.2
Difference vs. MET (95% CI)	−0.2 (−6.2, 5.9)††	1.2 (−4.8, 7.3)††	10.3 (4.2, 16.4)††	7.4 (1.4, 13.4)††	

*Changes in HbA_{1c}, FPG, body weight, and BP were analyzed with an MMRM using a restricted maximum likelihood approach using observed data. Changes in lipids were analyzed using an ANCOVA, with missing data imputed using the last observation carried forward; given the skewed nature of the distribution of the percent change in triglycerides, this secondary end point was analyzed using nonparametric methods. †P = 0.001 vs. MET. ‡Noninferiority P = 0.001 vs. MET. §P = 0.001 vs. CANA100. ‖P = 0.001 vs. CANA300. ¶P = 0.016 vs. MET. #P = 0.002 vs. MET. **P = NS vs. MET. ††Statistical testing not performed (not prespecified). ‡‡Statistical testing not performed due to the hierarchical testing sequence.

the MET group during the 26-week treatment period that was not considered to be related to study drug by the investigator.

Across treatment groups, no specific AE had an incidence ≥5%. Overall, the most commonly reported AE was diarrhea, with the highest incidence seen in the CANA/MET groups (4.2% for each dose) compared with CANA100 (1.3%), CANA300 (1.7%), and MET (1.3%). The overall incidence of gastrointestinal-related AEs (i.e., diarrhea, nausea, vomiting), which are commonly associated with MET, ranged from 1.7 to 4.6% across groups.

The incidence of AEs related to the mechanism of SGLT2 inhibition was generally higher in the CANA/MET and CANA monotherapy arms. Incidences of genital mycotic infections were ≤4.0% in men and ≤4.4% in women in the CANA arms and 0% in the MET group. All genital mycotic infections were reported as mild or moderate in intensity, and none led to discontinuation. Urinary tract infections (UTIs) were reported in 1.3–3.0% of patients across groups. No upper UTIs were reported. One UTI was reported as a serious AE with CANA300, but the patient remained in the study. Only one UTI in the CANA300/MET group led to discontinuation. Incidences of AEs related to osmotic diuresis (e.g., pollakiuria [increased urine frequency], polyuria [increased urine volume]), volume depletion (e.g., postural dizziness, hypotension), and renal function (e.g., glomerular filtration rate decreased, blood creatinine increased) were low across groups, but higher in all CANA groups versus MET.

The incidence of documented hypoglycemia episodes was 4.2%, 5.5%, 3.0%, 3.8%, and 4.6% with CANA100/MET, CANA300/MET, CANA100, CANA300, and MET, respectively. One patient experienced two episodes of severe hypoglycemia while taking MET. No hypoglycemia episodes with glucose values <36 mg/dL (<2.0 mmol/L) were reported in any treatment group.

Overall, no clinically meaningful differences in safety laboratory parameters were observed (Supplementary Table 1). Modest increases in hemoglobin were observed with CANA100/MET, CANA300/MET, CANA100, and CANA300 compared with MET (1.6%, 2.9%, 4.4%, 4.2%, and −1.5%, respectively). Increases in blood urea nitrogen were also seen in

Table 3—Summary of overall safety and selected AEs over 26 weeks

Patients, *n* (%)	CANA100/MET (*n* = 237)	CANA300/MET (*n* = 237)	CANA100 (*n* = 237)	CANA300 (*n* = 238)	MET (*n* = 237)
Any AE	99 (41.8)	105 (44.3)	88 (37.1)	95 (39.9)	89 (37.6)
AEs leading to discontinuation	4 (1.7)	7 (3.0)	3 (1.3)	7 (2.9)	4 (1.7)
AEs related to the study drug*	15 (6.3)	35 (14.8)	24 (10.1)	22 (9.2)	17 (7.2)
Serious AEs	7 (3.0)	4 (1.7)	4 (1.7)	7 (2.9)	7 (3.0)
Deaths	0	0	0	0	1 (0.4)
UTIs	3 (1.3)	7 (3.0)	3 (1.3)	5 (2.1)	3 (1.3)
Genital mycotic infections					
Male†‡	1 (0.9)	2 (1.7)	2 (1.9)	5 (4.0)	0
Female§‖	3 (2.3)	4 (3.3)	3 (2.3)	5 (4.4)	0
Osmotic diuresis–related AEs¶	2 (0.8)	6 (2.5)	5 (2.1)	4 (1.7)	2 (0.8)
Volume depletion–related AEs#	4 (1.7)	2 (0.8)	1 (0.4)	3 (1.3)	1 (0.4)
Renal-related AEs**	1 (0.4)	3 (1.3)	7 (3.0)	3 (1.3)	0
Gastrointestinal-related AEs††	11 (4.6)	11 (4.6)	4 (1.7)	7 (2.9)	10 (4.2)
Hypoglycemia episodes					
Documented hypoglycemia‡‡	10 (4.2)	13 (5.5)	7 (3.0)	9 (3.8)	11 (4.6)
Severe hypoglycemia	0	0	0	0	1 (0.4)

*Possibly, probably, or very likely related to study drug, as assessed by investigators. †CANA100/MET, *n* = 108; CANA300/MET, *n* = 115; CANA100, *n* = 105; CANA300, *n* = 125; MET, *n* = 116. ‡Includes balanoposthitis, genital candidiasis, and genital fungal infection. §CANA100/MET, *n* = 129; CANA300/MET, *n* = 122; CANA100, *n* = 132; CANA300, *n* = 113; MET, *n* = 121. ‖Includes genital infection female, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis. ¶Includes dry mouth, pollakiuria, polyuria, and thirst. #Includes dehydration, dizziness postural, hypotension, orthostatic hypotension, and syncope. **Includes blood creatinine increased, glomerular filtration rate decreased, and renal impairment. ††Includes diarrhea, nausea, and vomiting. ‡‡Includes biochemically documented episodes (fingerstick or plasma glucose ≤70 mg/dL [≤3.9 mmol/L]), with or without symptoms, and severe episodes (i.e., requiring the assistance of another individual or resulting in seizure, loss of consciousness, or cognitive dysfunction).

patients who received CANA. Reductions from baseline in alanine aminotransferase and serum urate were observed in the CANA groups compared with MET. Consistent with previous studies of CANA (11–23), all CANA groups experienced early reductions in eGFR and commensurate increases in serum creatinine that attenuated over 26 weeks (Supplementary Fig. 3).

CONCLUSIONS

Initial combination therapy consisting of CANA100 or CANA300 plus MET was associated with glycemic improvements and body weight reductions and was generally well tolerated compared with CANA alone and MET alone in drug-naïve patients with type 2 diabetes over 26 weeks. Relative to MET and CANA monotherapy, CANA100/MET and CANA300/MET provided statistically significant greater reductions in HbA_{1c} and body weight. CANA100/MET and CANA300/MET were also associated with a significantly higher proportion of patients who achieved HbA_{1c} <7.0% (<53 mmol/mol) versus MET monotherapy. In addition, noninferiority in HbA_{1c} lowering and greater reductions in body weight were demonstrated with CANA100 and CANA300 as monotherapy than with MET, suggesting that CANA may provide an alternative to standard first-line antihyperglycemic therapy in newly diagnosed patients with type 2 diabetes, especially in those who cannot tolerate MET. Across groups, greater reductions in HbA_{1c} were seen in patients with baseline HbA_{1c} ≥9.0% (≥75 mmol/mol) versus those with baseline HbA_{1c} <9.0% (<75 mmol/mol). The patterns of HbA_{1c} reductions with CANA100/MET and CANA300/MET versus their respective monotherapies and with CANA100 and CANA300 versus MET were consistent in both baseline HbA_{1c} subgroups.

Consistent with the current study, greater reductions in HbA_{1c} have been observed in studies with combinations that included other SGLT2 inhibitors (i.e., dapagliflozin/MET, dapagliflozin/saxagliptin, and empagliflozin/linagliptin) versus their respective monotherapies (27–29). However, a lack of additivity in the HbA_{1c} response, based on HbA_{1c} changes with the respective monotherapies, was reported in these studies. Of note, subadditive HbA_{1c} lowering was observed with the combinations of SGLT2 inhibitors and dipeptidyl peptidase 4 inhibitors (i.e., dapagliflozin/saxagliptin, empagliflozin/linagliptin), even though dipeptidyl peptidase 4 inhibition might be expected to attenuate SGLT2 inhibition–mediated glucagon increases, thereby preventing endogenous glucose production (EGP) (27,29). Less than additive HbA_{1c}-lowering effects were also observed in the current study with the CANA/MET combinations and have been observed in studies of other combination treatments (27–35), with few exceptions (36), even when the individual agents have complementary mechanisms. The less than additive efficacy commonly observed with combination treatments may be at least partly due to a "floor effect," as the efficacy of each individual agent depends on baseline HbA_{1c}. Conceptually, when given in combination, one AHA would lower HbA_{1c} more rapidly than the other due to the differential time to onset of action for each drug, thereby resulting in a smaller "effective baseline HbA_{1c}" for the second AHA. Thus, the second AHA would then have a smaller incremental reduction in HbA_{1c} compared with its use in monotherapy, given the lower starting HbA_{1c}. An alternative explanation for the subadditive HbA_{1c} lowering observed in the CANA/MET combination arms may be related to the mechanism of action of the individual components. MET has been shown to improve glycemic

control in patients with type 2 diabetes, in part, by decreasing EGP (37). In contrast, dapagliflozin and empagliflozin have both been associated with an increase in EGP that has been attributed to increased plasma glucagon levels (38,39). Therefore, the effects of SGLT2 inhibition on EGP may partially counteract those of MET, thereby resulting in decreased efficacy for the combination. Nevertheless, initial combination therapy with CANA plus MET significantly improves glycemic control compared with each component in monotherapy.

Smaller differences in HbA_{1c} were seen between treatment arms containing CANA100 and CANA300 in this study compared with previous studies where a dose response had been observed (11–23). However, HbA_{1c} lowering with CANA has been observed to be less dose-dependent as baseline HbA_{1c} increases (40). The small observed difference in HbA_{1c} lowering between CANA100 and CANA300 in this study is consistent with expectations of a proportionally smaller between-dose difference in UGE as baseline plasma glucose increases. Because the renal threshold for glucose lowering is greater with the higher dose of CANA, a patient whose plasma glucose is, for example, 140 mg/dL (7.8 mmol/L) would be expected to have 25% more overnight UGE with CANA300 versus CANA100; however, a patient whose plasma glucose is, for example, 200 mg/dL (11.1 mmol/L) would only be expected to have 10% more UGE with CANA300 (Janssen Research & Development, LLC, unpublished observation). Interestingly, a dose response was seen for the proportion of patients achieving an HbA_{1c} <7.0% (<53 mmol/mol) in the CANA/MET and CANA-alone arms, which is also clinically meaningful because it was associated with weight loss and no increased risk of hypoglycemia, and it is highly relevant for patients and clinicians because such improved glycemic control has been associated with a decreased risk of diabetes-related complications (3,4).

In addition to glycemic improvements, weight loss was seen across groups; however, differences in body weight in the CANA groups versus MET were smaller than anticipated, likely due to the large response with MET. CANA100/MET and CANA300/MET were associated with modest increases in HDL-C and triglycerides. Increases in LDL-C with both combinations were similar to those seen with MET monotherapy.

Both CANA/MET combinations were generally well tolerated compared with their respective monotherapies, consistent with the observed low rate of discontinuations in the study. The overall incidence of AEs was lower across groups in this study compared with previous studies (11–23); the reason for this observation, which has been seen with other AHAs (41,42), is not known but may be related to the characteristics of the study population. The pattern of specific AEs observed with CANA in this study was consistent with previous reports (11–23), with a higher incidence of AEs related to the mechanism of SGLT2 inhibition (e.g., genital mycotic infections, volume depletion–related AEs, osmotic diuresis–related AEs) observed in all CANA treatment arms versus MET. No differences in gastrointestinal-related AEs were observed with combination therapy compared with MET monotherapy. No new safety signals were observed from the coadministration of CANA and MET compared with the monotherapies.

This study demonstrates that drug-naïve patients with type 2 diabetes respond well to treatment with an initial combination of CANA plus MET. A study of longer duration may be beneficial to assess the potential long-term impact of combination therapy with CANA/MET on patient outcomes.

In summary, CANA100 and CANA300 in combination with MET provided significantly greater reductions in HbA_{1c} and body weight compared with monotherapy with MET, CANA100, or CANA300, with a tolerability profile consistent with the respective monotherapies. In addition, CANA100 and CANA300 monotherapy provided comparable HbA_{1c} reductions and greater weight loss compared with MET monotherapy. Overall, these findings support the efficacy and safety of initial combination therapy with CANA100 or CANA300 and MET in drug-naïve patients with type 2 diabetes, particularly for patients with baseline HbA_{1c} >8.5% (>69 mmol/mol), and suggest that CANA may also be used as an alternative to MET in this population.

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