Original Report:
Diabetes

Efficacy and Safety of Canagliflozin in Type 2 Diabetes Patients of Different Ethnicity

Jaime A. Davidson, MD[1]; Richard Aguilar, MD[2]; Fernando J. Lavalle González, MD[3]; Angelina Trujillo, MD[4]; Maria Alba, MD[5]; Ujjwala Vijapurkar, PhD[5]; Gary Meininger, MD[5]

Objective: To assess the efficacy and safety of the sodium glucose co-transporter 2 (SGLT2) inhibitor canagliflozin in patients of different ethnicities.

Design, Setting, and Patients: Post hoc analysis of data pooled from four randomized, placebo-controlled, phase 3 studies of adults with inadequately controlled type 2 diabetes mellitus (T2DM).

Interventions: Once daily oral canagliflozin 100 mg or 300 mg, or placebo.

Main Outcome Measures: Efficacy endpoints included change from baseline in HbA1c, body weight (BW), systolic blood pressure (SBP), and lipids at week 26; safety and tolerability were assessed by adverse event reports.

Results: Of the 2,313 patients included in this pooled analysis, 609 self-identified as Hispanic/Latino. Hispanic/Latino patients had a mean age of 54 years, mean duration of T2DM of 7 years, mean HbA1c of 8.1%, mean body mass index of 31.2 kg/m^2, and mean SBP of 126.1 mm Hg. There were more women in the non-Hispanic/Latino cohort (63%) compared with the Hispanic/Latino cohort. Placebo-subtracted changes in HbA1c were −.82% with canagliflozin 100 mg and −.94% with canagliflozin 300 mg in the Hispanic/Latino cohort, which were similar to reductions observed in the non-Hispanic/Latino cohort. Significantly greater dose-related reductions in HbA1c, BW, and SBP were observed with both canagliflozin doses compared with placebo. Canagliflozin was generally well-tolerated. Genital mycotic infections were less frequent in Hispanic/Latino women than in non-Hispanic/Latino women.

Conclusions: The SGLT2 inhibitor canagliflozin was generally well-tolerated and was associated with clinically meaningful reductions in HbA1c, BW, and SBP in both Hispanic/Latino and non-Hispanic/Latino patients with T2DM. *Ethn Dis*. 2016;26(1):221-228; doi:10.18865/ed.26.2.221

Key Words: Canagliflozin; Glucose Co-transporter Inhibitor; Type 2 Diabetes Mellitus; Hispanic; Latino; Efficacy; Safety

Introduction

Individuals of Hispanic/Latino ethnicity are at increased risk of developing type 2 diabetes mellitus (T2DM) compared with people of non-Hispanic origin.[1] American Hispanics/Latinos have a 1.7-times greater risk of diabetes[2] compared with non-Hispanic Whites, and face one of the highest lifetime risks to be diagnosed with diabetes, exceeding 50%.[3] According to a recent survey, nearly 1 in 5 (19%) Hispanics/Latinos in the US reported that diabetes is the largest health problem facing their families,[4] which accentuates the impact of diabetes in this population.

The management and treatment of diabetes in the Hispanic/Latino population represents a significant health care challenge. In the United States, patients of Hispanic/Latino ethnicity have higher rates of severely elevated HbA1c, have more diabetes-related chronic complications, and are more unaware of their glycemic status compared with patients of non-Hispanic/Latino origin.[5-9] The reasons for this ethnic disparity can be partially explained by a higher level of insulin resistance, which has been shown to correlate with ethnicity after adjusting for body mass index, age, and presence of T2DM.[10] Insulin resistance has been reported to account for a large and significant proportion of the excess diabetes risk.[11] Additionally, many Hispanic/Latino patients with T2DM are reluctant to initiate insulin therapy or increase insulin dosage in order to achieve glycemic control, mostly due to socioeconomic

[1]Touchstone Diabetes Center, University of Texas Southwestern Medical School
[2]Seville Medical Center, Downey, CA
[3]Universidad Autónoma de Nuevo León, Nuevo León, Mexico
[4]Janssen Scientific Affairs, LLC, Raritan, NJ
[5]Janssen Research and Development, LLC, Raritan, NJ

Address correspondence to Jaime Davidson; Clinical Professor of Medicine, Touchstone Diabetes Center, Endocrinology and Internal Medicine Department, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, K5.246, Dallas, TX 75390-4854; 214.648.3756; jaime.davidson@UTSouthwestern.edu

(eg, costs, lack of health insurance), educational (eg, lack of English language, literacy), and cultural issues.[12]

Differences in metabolic responses to glucose-lowering agents (eg, insulin, metformin, dipeptidyl peptidase-4 inhibitors) have been observed across racial and ethnic groups.[13-15] Most currently available therapies for T2DM have an insulin-dependent mode of action. Sodium glucose cotransporter 2 (SGLT2) inhibitors are a novel class of drugs that treat T2DM through an insulin-independent mechanism.[16] SGLT2 is found in the proximal renal tubules and is responsible for the majority of renal glucose reabsorption. SGLT2 inhibitors lower the renal threshold for glucose, resulting in enhanced urinary glucose excretion.[17] This effect is independent of beta-cell function and insulin sensitivity.[18] Therefore, the mechanism of action of SGLT2 inhibitors is complementary to that of other classes of antihyperglycemic agents (AHAs) including insulin, and may be particularly beneficial for Hispanic/Latino patients. SGLT2 inhibitors were recently included in the American Diabetes Association (ADA) Standards of Medical Care as an additional treatment option for T2DM to be used as second- or third-line therapy.[19]

Our analysis evaluated the efficacy and safety of the SGLT2 inhibitor canagliflozin in Hispanic/Latino patients with T2DM, one of the larger populations with T2DM.

SGLT2 inhibitors have been shown to improve glycemic control, reduce body weight (BW), and lower systolic blood pressure (SBP), with a low risk of hypoglycemia when used alone or combined with antihyperglycemic therapies not associated with hypoglycemia.[16] Our analysis evaluated the efficacy and safety of the SGLT2 inhibitor canagliflozin in Hispanic/Latino patients with T2DM, one of the larger populations with T2DM.

Methods

Study Design and Population

A post hoc analysis was conducted using data from four randomized, double-blind, placebo-controlled phase 3 clinical studies of canagliflozin in the general T2DM patient population (ClinicalTrials.gov identifiers: NCT01081834, NCT01106677, NCT01106625, NCT01106690).[20-23] All studies had a similar study design and differed mainly in their use of background AHAs. Briefly, adult patients with T2DM inadequately controlled with diet and exercise,[20] metformin,[21] metformin, and a sulfonylurea (SU),[22] or metformin and pioglitazone,[23] were included.

Enrolled patients were randomly assigned to receive daily oral doses of canagliflozin 100 mg or 300 mg, or placebo (1:1:1 randomization ratio);[20,22,23] or canagliflozin 100 mg or 300 mg, sitagliptin 100 mg, or placebo (2:2:2:1).[21] To allow robust data comparisons, canagliflozin and placebo data from the 26-week core treatment periods of each study were included in this pooled analysis; data from patients in the high glycemic subset (HbA1c >10.0% and ≤12.0%) of the monotherapy study,[19] which was not placebo controlled, and patients in the sitagliptin arm of the add-on to metformin study (predefined comparison between canagliflozin and sitagliptin at 52 weeks)[21] were excluded.

The primary efficacy endpoint was change from baseline in HbA1c at week 26. Secondary endpoints included change from baseline in SBP, and percentage change from baseline in BW and fasting plasma lipids (ie, high-density lipoprotein cholesterol [HDL-C], and triglycerides) at week 26. All studies were approved by relevant institutional review boards and conducted according to the guidelines of the Declaration of Helsinki.

Statistical Analysis

The efficacy outcomes are presented according to self-identified Hispanic/Latino and non-Hispanic/Latino subgroups. Safety analyses included a summary of clinical adverse events (AEs) over 26 weeks. Selected AEs associated with the mode of action of SGLT2 inhibitors include genital mycotic infections (GMIs), urinary tract infections (UTIs), and osmotic diuresis and volume-related events.

Efficacy and safety analyses were evaluated according to the following two ethnic subgroups: Hispanic/Latino and non-Hispanic/Latino. Demographic and baseline disease characteristics were summarized descriptively.

Last observation carried forward

Table 1. Baseline demographic and disease characteristics according to self-reported ethnicity, N=2,304

Characteristics[a]	Hispanic/Latino, N=609			Non-Hispanic/Latino, N=1,695		
	Placebo n=175	CANA 100 mg n=213	CANA 300 mg n=221	Placebo n=471	CANA 100 mg n=615	CANA 300 mg n=609
Age, years	54.7 (9.7)	54.2 (10.4)	53.3 (9.5)	56.9 (9.8)	56.5 (9.9)	56.6 (9.4)
Duration of T2DM, years	7.6 (6.3)	7.4 (6.1)	7.2 (5.6)	7.4 (6.1)	7.1 (5.7)	7.4 (6.4)
Male sex, *n* (%)	76 (43.4)	73 (34.3)	76 (34.4)	258 (54.8)	332 (54.0)	324 (53.2)
Circumcision status, yes[a,b]	13 (17.1)	10 (13.7)	22 (28.9)	102 (39.5)	125 (37.7)	130 (40.1)
History of balanitis, yes[b,c]	1 (1.3)	2 (2.7)	2 (2.6)	4 (1.6)	13 (3.9)	9 (2.8)
HbA1c, %	8.1 (1.0)	8.1 (1.0)	8.1 (1.0)	8.0 (.9)	8.0 (.9)	7.9 (.9)
Body weight, kg	81.2 (19.1)	80.2 (18.8)	80.2 (18.9)	92.2 (21.9)	93.1 (22.5)	91.5 (22.4)
BMI, kg/m^2	31.3 (6.1)	31.2 (5.6)	31.0 (6.1)	32.1 (6.5)	32.7 (6.6)	32.3 (6.6)
SBP, mm Hg	127.7 (12.5)	125.0 (13.0)	125.8 (13.3)	128.8 (13.6)	129.0 (12.6)	129.8 (12.5)
HDL-C, mg/dL	45.3 (9.9)	45.5 (11.5)	47.3 (11.7)	45.7 (11.4)	45.8 (11.9)	46.0 (11.5)
LDL-C, mg/dL	115.0 (33.3)	110.6 (32.7)	111.0 (33.0)	106.2 (40.0)	104.9 (36.6)	102.4 (35.9)
Triglycerides, mg/dL	214.9 (126.0)	208.2 (131.6)	194.8 (138.3)	175.2 (108.7)	173.6 (124.2)	176.8 (115.6)
eGFR, mL/min/1.73 m^2	92.7 (18.7)	94.4 (18.5)	95.5 (20.1)	84.9 (19.9)	86.2 (18.6)	86.4 (17.8)

All values are mean (standard deviation) unless stated otherwise.
a. Among male Hispanic/Latino patients, the circumcision status was not known for 1 patient who received placebo, 2 patients who received CANA 100 mg, and 4 patients who received CANA 300 mg; among male non-Hispanic/Latino patients, the circumcision status was unknown for 6, 13, and 6 patients in these treatment groups, respectively.
b. For circumcision status and history of balanitis, percentages were calculated with the number of male subjects in each group as denominator.
c. Status was not known for 1, 2, and 4 Hispanic/Latino patients and for 6, 14, and 6 male non-Hispanic/Latino patients receiving placebo, CANA 100 mg, and CANA 300 mg, respectively.
BMI, body mass index; CANA, canagliflozin; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.

methods were applied to impute any missing data. Least squares mean or mean percentage changes from baseline were calculated for each of the efficacy measures for each treatment group in both cohorts. Placebo-subtracted differences are reported with 95% confidence intervals.

Results

Patient Characteristics

Of the 2,313 patients in the pooled population, 609 (26.3%) patients self-identified as Hispanic/Latino; the ethnicity of 9 patients was unknown and so these patients were not included in this analysis. The Hispanic/Latino group included more women (63% vs 46%), had lower mean SBP, higher mean

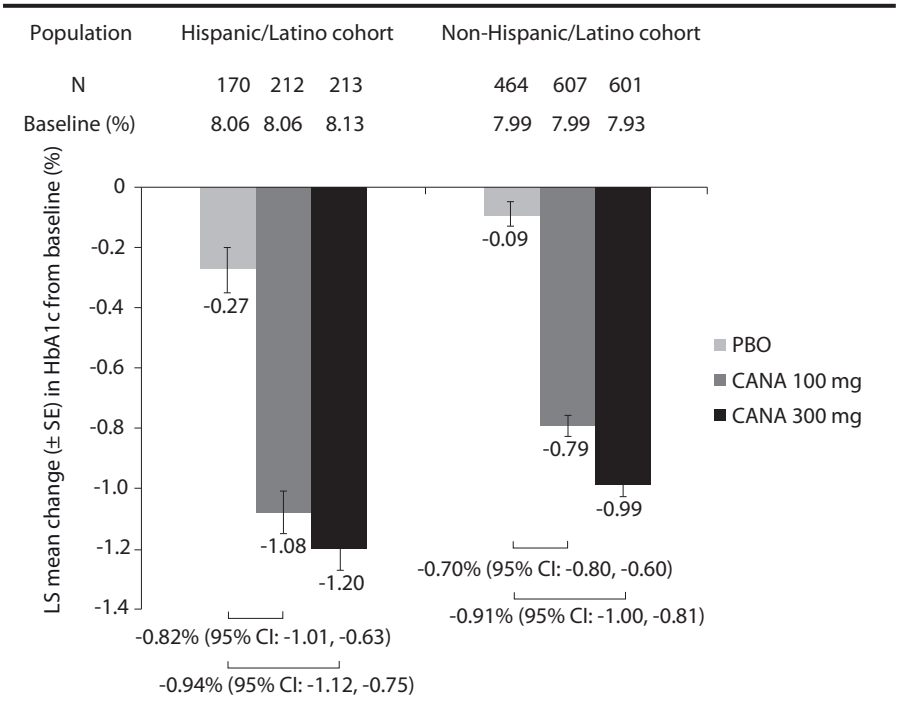

Figure 1. Change from baseline in HbA1c at week 26
CANA, canagliflozin; CI, confidence interval; LS, least squares; PBO, placebo; SE, standard error.

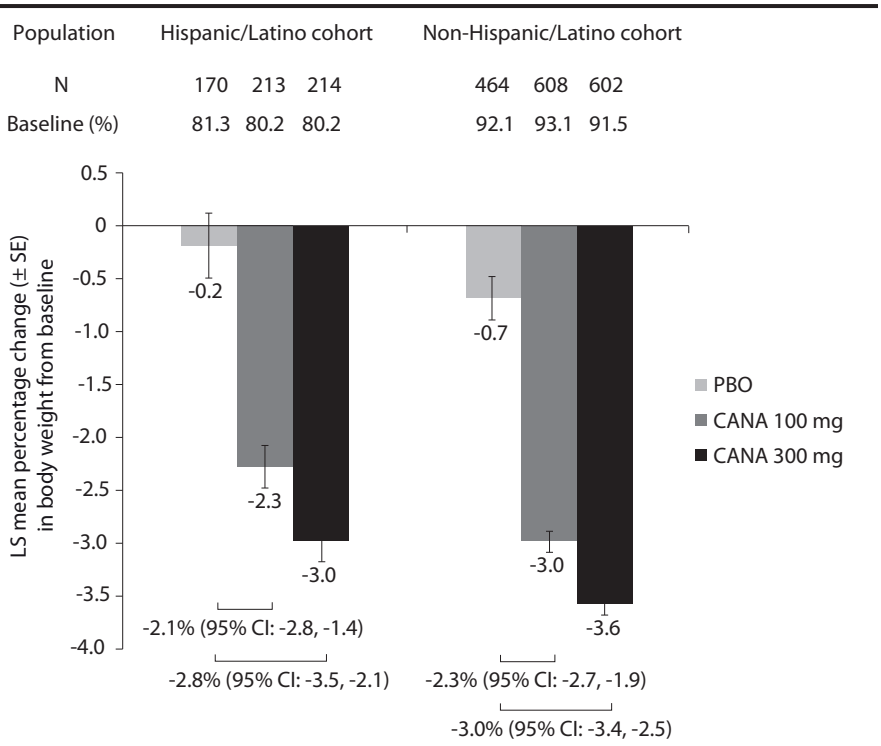

Figure 2. Percentage change from baseline in body weight at week 26
CANA, canagliflozin; CI, confidence interval; LS, least squares; PBO, placebo; SE, standard error.

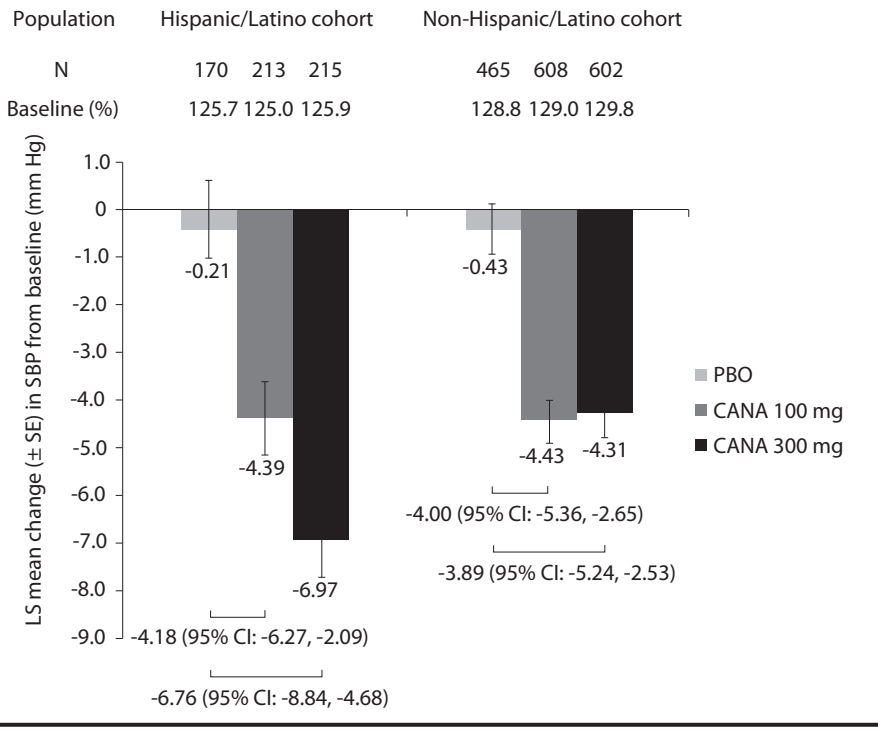

Figure 3. Change from baseline in SBP at week 26
CANA, canagliflozin; CI, confidence interval; LS, least squares; PBO, placebo; SBP, systolic blood pressure; SE, standard error.

LDL-C and triglycerides levels, and higher mean estimated glomerular filtration rate than the non-Hispanic/Latino group. In addition, male circumcision was less common in Hispanic/Latinos than in non-Hispanic/Latinos (20% vs 39%) (Table 1).

Efficacy

Treatment with canagliflozin 100 mg and 300 mg significantly lowered HbA1c in a dose-related manner compared with placebo in both cohorts (Figure 1). There were no differences in changes in HbA1c between the Hispanic/Latino and non-Hispanic/Latino cohorts. Canagliflozin 100 mg and 300 mg was also associated with large reductions in BW (of up to 3%) and SBP compared with placebo in both cohorts (Figures 2 and 3). Changes in SBP were dose-dependent only in the Hispanic/Latino cohort (–4.2 mm Hg and –6.8 mm Hg with canagliflozin 100 mg and 300 mg, respectively), whereas dose-related reductions in BW were observed in both cohorts.

An increase in HDL-C and LDL-C was observed with canagliflozin treatment in both cohorts compared with placebo (Table 2). However, this did not significantly impact the LDL-C/HDL-C ratio (Hispanic/Latino cohort: –2.4% and –.4% with canagliflozin 100 mg and 300 mg vs +1.7% with placebo; non-Hispanic/Latino cohort: –1.0% and +1.8% with canagliflozin 100 mg and 300 mg vs –1.3% with placebo). A decrease in triglycerides was observed with canagliflozin 300 mg but not with canagliflozin 100 mg or placebo in the Hispanic/Latino cohort; the percent change from baseline in

triglycerides was +3.6%, –2.1%, and +3.2% with canagliflozin 100 mg, canagliflozin 300 mg, and placebo.

Safety

Canagliflozin was generally well-tolerated in both Hispanic/Latino and non-Hispanic/Latino patients. As expected, an increase in drug-related AEs was observed with canagliflozin 100 mg and 300 mg compared with placebo in both cohorts (Table 3). However, the incidence of AEs leading to study discontinuation and serious AEs was lower in the Hispanic/Latino cohort than in the non-Hispanic/Latino cohort. Overall, the incidence of hypoglycemia tended to increase with canagliflozin treatment and depended on whether patients were on background SU. In patients not on background SU, incidence of hypoglycemia was higher with canagliflozin 100 mg and 300 mg versus placebo in Hispanic/Latinos (5.5% and 7.4% vs 1.5%, respectively) compared with the non-Hispanic/Latino cohort (2.5% and 3.3% vs 2.9%). The incidence of severe hypoglycemia was low and limited to 1 patient with canagliflozin 100 mg (Hispanic/Latino cohort) and 1 patient with canagliflozin 300 mg (non-Hispanic/Latino cohort). In patients on background SU, the overall incidence of hypoglycemia was higher across treatment groups. In the Hispanic/Latino cohort, the incidence was higher with canagliflozin 100 mg vs canagliflozin 300 mg and placebo (37.5% vs 21.2% and 20.5%, respectively), whereas increased incidence with both canagliflozin 100 mg and 300 mg versus placebo was observed in the non-Hispanic/Latino cohort (25.0% and 32.5% vs 13.4%). Severe hypoglycemia was reported only in 1 patient with canagliflozin 100 mg (non-Hispanic/Latino cohort) and 1 patient with placebo (Hispanic/Latino cohort).

Regardless of ethnicity, canagliflozin treatment was associated with a higher incidence of GMIs compared with placebo. There was no difference in the incidence of GMIs between Hispanic/Latino and non-Hispanic/Latino men treated with canagliflozin (2.7% vs 4.5% and 3.9% vs 3.4% with canagliflozin 100

Table 2. Percentage changes in fasting plasma lipids at week 26

	Hispanic/Latino			Non-Hispanic/Latino		
	Placebo	CANA 100 mg	CANA 300 mg	Placebo	CANA 100 mg	CANA 300 mg
HDL-C[a]						
Baseline, mean (SD), mg/dL	44.9 (10.0)	45.7 (11.7)	47.4 (11.9)	45.7 (11.4)	45.9 (11.9)	46.0 (11.5)
LS mean % change from baseline (SE)	.9 (1.3)	8.9 (1.2)	10.3 (1.2)	4.6 (.8)	8.9 (.7)	9.9 (.7)
LDL-C[b]						
Baseline, mean (SD), mg/dL	114.2 (34.0)	110.6 (32.7)	110.6 (32.6)	106.8 (40.7)	105.2 (36.8)	102.2 (35.7)
LS mean % change from baseline (SE)	1.5 (2.2)	4.7 (2.1)	8.3 (2.0)	1.0 (1.4)	5.9 (1.2)	9.9 (1.2)
LDL-C/HDL-C[c]						
Baseline, mean (SD), mg/dL	2.63 (.9)	2.53 (.9)	2.45 (.9)	2.48 (1.2)	2.43 (1.0)	2.32 (.9)
LS mean % change from baseline (SE)	1.7 (2.1)	−2.4 (2.0)	−.4 (1.9)	−1.3 (1.4)	−1.0 (1.2)	1.8 (1.2)
Non-HDL-C[d]						
Baseline, mean (SD), mg/dL	157.3 (38.8)	151.7 (38.5)	148.4 (39.1)	141.4 (46.4)	139.5 (44.4)	136.6 (41.0)
LS mean % change from baseline (SE)	−.2 (1.5)	1.0 (1.4)	2.2 (1.4)	1.6 (1.1)	2.9 (1.0)	5.4 (1.0)
Triglycerides[e]						
Baseline, mean (SD), mg/dL	217.4 (124.9)	206.0 (129.9)	192.1 (140.1)	173.0 (107.5)	171.9 (120.4)	177.1 (117.6)
LS mean % change from baseline (SE)	3.2 (3.4)	3.6 (3.2)	−2.1 (3.1)	10.8 (2.2)	3.4 (1.9)	1.6 (1.9)

a. Number of patients with available data at baseline and week 26; placebo, CANA 100 mg, and CANA 300 mg: Hispanic/Latino, 160, 200, and 199; non-Hispanic/Latino, 421, 586, and 566.
b. Number of patients with available data at baseline and week 26; placebo, CANA 100 mg, and CANA 300 mg: Hispanic/Latino, 160, 199, and 198; non-Hispanic/Latino, 418, 582, and 562.
c. Number of patients with available data at baseline and week 26; placebo, CANA 100 mg, and CANA 300 mg: Hispanic/Latino, 160, 199, and 198; non-Hispanic/Latino, 418, 582, and 562.
d. Number of patients with available data at baseline and week 26; placebo, CANA 100 mg, and CANA 300 mg: Hispanic/Latino, 160, 200, and 199; non-Hispanic/Latino, 419, 583, and 560.
e. Number of patients with available data at baseline and week 26; placebo, CANA 100 mg, and CANA 300 mg: Hispanic/Latino, 161, 201, and 199; non-Hispanic/Latino, 420, 588, and 572.
CANA, canagliflozin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LS, least squares; SD, standard deviation; SE, standard error.

Table 3. Summary of overall safety and selected adverse events by ethnicity

	Hispanic/Latino			Non-Hispanic/Latino		
	Placebo n=175	CANA 100 mg n=213	CANA 300 mg n=221	Placebo n=471	CANA 100 mg n=615	CANA 300 mg n=609
Any AE	98 (56.0)	126 (59.2)	126 (57.0)	286 (60.7)	370 (60.2)	364 (59.8)
AEs leading to discontinuation	3 (1.7)	3 (1.4)	6 (2.7)	17 (3.6)	32 (5.2)	24 (3.9)
AEs related to study drug[a]	19 (10.9)	36 (16.9)	40 (18.1)	66 (14.0)	132 (21.5)	150 (24.6)
Serious AEs	3 (1.7)	4 (1.9)	4 (1.8)	19 (4.0)	23 (3.7)	18 (3.0)
Deaths	0	0	0	2 (.4)	1 (.2)	1 (.2)
Genital mycotic infection	3 (1.7)	14 (6.6)	16 (7.2)	9 (1.9)	47 (7.6)	47 (7.7)
Female[b]	3 (3.0)	12 (8.6)	13 (9.0)	7 (3.3)	32 (11.3)	36 (12.6)
Male[c]	0	2 (2.7)	3 (3.9)	2 (.8)	15 (4.5)	11 (3.4)
Urinary tract infection	12 (6.9)	18 (8.5)	15 (6.8)	14 (3.0)	30 (4.9)	21 (3.4)
Female[b]	11 (11.1)	18 (12.9)	13 (9.0)	13 (6.1)	28 (9.9)	14 (4.9)
Male[c]	1 (1.3)	0	2 (2.6)	1 (.4)	2 (.6)	7 (2.2)
Osmotic diuresis-related AEs	1 (.6)	11 (5.2)	5 (2.3)	4 (.8)	44 (7.2)	42 (6.9)
Volume depletion-related AEs	0	1 (.5)	3 (1.4)	7 (1.5)	9 (1.5)	8 (1.3)

All values are *n* (%).
Percentages are calculated by the number of patients in each group as the denominator and the number of subjects experiencing ≥1 AE regardless of use of rescue medication as the numerator.
a. Possibly, probably, or very likely related to study drug, as assessed by investigators.
b. Number of female patients, placebo, CANA 100 mg, and CANA 300 mg: Hispanic/Latino, 99, 140, and 145; non-Hispanic/Latino, 213, 283, and 285.
c. Number of male patients, placebo, CANA 100 mg, and CANA 300 mg: Hispanic/Latino, 76, 73, and 76; non-Hispanic/Latino, 258, 332, and 324.
AE, adverse event; CANA, canagliflozin.

mg and 300 mg, respectively), even though Hispanic/Latino men had a lower circumcision rate than the non-Hispanic/Latino men (13.7% vs 37.7% with canagliflozin 100 mg and 28.9% vs 40.1% with canagliflozin 300 mg, respectively). In women, the incidence of GMIs associated with canagliflozin treatment was lower in Hispanic/Latino than in non-Hispanic/Latino women (8.6% vs 11.3% and 9.0% vs 12.6% with canagliflozin 100 mg and 300 mg, respectively). GMIs were generally mild or moderate in severity, and responded to conventional treatment.

The incidence of UTIs was higher in the Hispanic/Latino cohort versus the non-Hispanic/Latino cohort across treatment groups. Compared with placebo, treatment-related increases in UTIs were observed only with canagliflozin 100 mg in both cohorts. In addition, upper UTIs occurred in the non-Hispanic/Latino cohort (1 case [.2%] in each canagliflozin 100 mg and 300 mg treatment groups), whereas none was reported in the Hispanic/Latino cohort.

In both cohorts, incidence of osmotic diuresis-related AEs was higher with canagliflozin compared with placebo. However, the overall incidence tended to be lower in Hispanic/Latino than in non-Hispanic/Latino patients (5.2% vs 7.2% and 2.3% vs 6.9% with canagliflozin 100 mg and 300 mg, respectively). The incidence of volume depletion-related AEs was similar across cohorts. Of note, use of loop diuretics was lower in both canagliflozin groups compared with placebo, and lower in the Hispanic/Latino patients (Hispanic/Latinos: .9% and 0% in the canagliflozin 100 mg and 300 mg treatment groups, respectively, vs 1.7% with placebo; non-Hispanic/Latinos: 3.4% and 2.3% in the canagliflozin 100 mg and 300 mg treatment groups vs 4.2% with placebo).

Discussion

Although Hispanics/Latinos with T2DM are less likely to achieve measures of glycemic and metabolic control, our current analysis demonstrated that the SGLT2 inhibitor canagliflozin was effective and generally well-tolerated in Hispanic/Latino patients with T2DM. Clinically important reductions in HbA1c compared with placebo were observed with both doses of canagliflozin. The findings in Hispanic/Latino patients were generally comparable to those observed in non-Hispanic/Latino patients, indicating that canagliflozin is equally effective in Hispanic/Latino patients.

In addition to lowering HbA1c,

SGLT2 inhibitors reduce BW and SBP.[21,24-26] This has been attributed to their mode of action — by increasing glucose excretion in the urine, SGLT2 inhibitors lower blood glucose and increase urinary caloric loss resulting in weight loss,[27] whereas osmotic diuresis effects due to inhibition of glucose and sodium reabsorption are thought to lead to initial reductions in blood pressure.[17] In this analysis, similar, clinically relevant dose-related BW reductions were observed with canagliflozin in both Hispanic/Latino and non-Hispanic/Latino patients, suggesting that this ethnic background does not affect the weight loss associated with canagliflozin. Canagliflozin-related SBP reductions were also recorded in both cohorts.

…our current analysis demonstrated that the SGLT2 inhibitor canagliflozin was effective and generally well-tolerated in Hispanic/Latino patients with T2DM.

Changes in plasma lipids were observed in both cohorts. However, greater numeric increases in HDL-C and small numeric changes in triglycerides were recorded in the Hispanic/Latino patients. Since the US Hispanic/Latino population tends to have low HDL-C and high triglycerides levels,[28] the changes in lipid profile observed with canagliflozin may help improve the distinct profiles of this ethnic group.

Overall, canagliflozin was generally well-tolerated, and the safety and tolerability profile of canagliflozin in Hispanic/Latino patients was similar to that in non-Hispanic/Latino patients. The incidence of selected AEs (GMIs, UTIs, osmotic diuresis-related AEs, and volume depletion-related AEs) was increased with use of canagliflozin compared with placebo, and was generally similar in the Hispanic/Latino cohort as previously reported for SGLT2 inhibitors in the general population.[29]

Increased incidence of GMIs was seen with canagliflozin; GMIs were generally mild or moderate in severity, and responded to conventional treatment. Hispanic/Latino women reported fewer GMIs than non-Hispanic/Latino women. Incidence of GMIs in men has been associated with circumcision status;[30] however, in our analysis, the incidence of GMIs in Hispanic/Latino men was not higher than in non-Hispanic/Latino men, only 21% of them were circumcised compared with 39% of non-Hispanic/Latinos. Overall, the incidence of UTIs was higher in the Hispanic/Latino patients than non-Hispanic/Latino patients. However, treatment-related increase in incidence of UTIs was observed only with the lower dose of canagliflozin compared with placebo.

Previous analyses have indicated that the majority of patients who experienced volume-depletion related AEs were on antihypertensive therapy with diuretics.[29] In our study population, Hispanics/Latinos used loop diuretics less frequently than non-Hispanics/Latinos, but no differences in volume depletion-related AEs were observed.

Conclusion

In conclusion, treatment with canagliflozin was associated with clinically meaningful reductions in HbA1c, BW, and SBP and was generally well-tolerated in Hispanic/Latino patients with T2DM. These findings were similar to those observed in non-Hispanic/Latino patients. Canagliflozin has a unique insulin-independent mode of action and, as such, it can potentially be used in patients with impaired insulin secretion or high incidence of insulin resistance, such as Hispanic/Latino patients, and can be combined with all other classes of antihyperglycemic agents.

Acknowledgments

This analysis was supported by Janssen Scientific Affairs, LLC. Editorial support was provided by Elaine Santiago, PharmD, and Sandrine Buisson, PhD, of Excerpta Medica, and was funded by Janssen Scientific Affairs, LLC.

Disclaimer

This analysis was supported by Janssen Scientific Affairs, LLC, Raritan, NJ (JAD).

Author Contributions

Research concept and design: Davidson, Lavalle González, Trujillo, Alba, Meininger. Acquisition of data: Alba, Meininger. Data analysis and interpretation: Davidson, Aguilar, Lavalle González, Trujillo, Alba, Vijapurkar, Meininger. Manuscript draft: Davidson, Aguilar, Lavalle González, Alba, Vijapurkar, Meininger. Statistical expertise: Vijapurkar. Administrative: Davidson, Aguilar, Trujillo. Supervision: Davidson, Aguilar, Lavalle González, Alba, Meininger.

References

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2014: Estimates of Diabetes and Its Burden in the United

States. Available from: http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf. Accessed January 12, 2015.
2. American Diabetes Association. Fast Facts: Data and Statistics about Diabetes, revised 7/2014. Available from: http://professional.diabetes.org/admin/UserFiles/0%20-%20Sean/14_fast_facts_june2014_final3.pdf. Accessed January 12, 2015.
3. Gregg EW, Zhuo X, Cheng YJ, Albright AL, Narayan KM, Thompson TJ. Trends in lifetime risk and years of life lost due to diabetes in the USA, 1985-2011: a modelling study. *Lancet Diabetes Endocrinol*. 2014;2(11):867-874. http://dx.doi.org/10.1016/S2213-8587(14)70161-5. PMID:25128274.
4. Drug Store News. Johnsen M. Survey: Latinos see diabetes as biggest health concern for their families, January 22, 2014. Available from: http://www.drugstorenews.com/article/survey-latinos-see-diabetes-biggest-health-concern-their-families. Accessed January 12, 2015.
5. Hunt KJ, Williams K, Resendez RG, Hazuda HP, Haffner SM, Stern MP. All-cause and cardiovascular mortality among diabetic participants in the San Antonio Heart Study: evidence against the "Hispanic Paradox". *Diabetes Care*. 2002;25(9):1557-1563. http://dx.doi.org/10.2337/diacare.25.9.1557. PMID:12196427.
6. Caballero AE. Type 2 diabetes in the Hispanic or Latino population: challenges and opportunities. *Curr Opin Endocrinol Diabetes Obes*. 2007;14(2):151-157. http://dx.doi.org/10.1097/MED.0b013e32809f9531. PMID:17940434.
7. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004;27(5):1047-1053. http://dx.doi.org/10.2337/diacare.27.5.1047. PMID:15111519.
8. Boltri JM, Okosun IS, Davis-Smith M, Vogel RL. Hemoglobin A1c levels in diagnosed and undiagnosed black, Hispanic, and white persons with diabetes: results from NHANES 1999-2000. *Ethn Dis*. 2005;15(4):562-567. PMID:16259477.
9. Lopez JM, Bailey RA, Rupnow MF, Annunziata K. Characterization of type 2 diabetes mellitus burden by age and ethnic groups based on a nationwide survey. *Clin Ther*. 2014;36(4):494-506. http://dx.doi.org/10.1016/j.clinthera.2013.12.016. PMID:24508418.
10. Ferrannini E, Gastaldelli A, Matsuda M, et al. Influence of ethnicity and familial diabetes on glucose tolerance and insulin action: a physiological analysis. *J Clin Endocrinol Metab*. 2003;88(7):3251-3257. http://dx.doi.org/10.1210/jc.2002-021864. PMID:12843172.
11. Lorenzo C, Hazuda HP, Haffner SM. Insulin resistance and excess risk of diabetes in Mexican-Americans: the San Antonio Heart Study. *J Clin Endocrinol Metab*. 2012;97(3):793-799. http://dx.doi.org/10.1210/jc.2011-2272. PMID:22174423.
12. Campos C. Addressing cultural barriers to the successful use of insulin in Hispanics with type 2 diabetes. *South Med J*. 2007;100(8):812-820. http://dx.doi.org/10.1097/SMJ.0b013e3180f609c4. PMID:17713308.
13. Davidson JA, Lacaya LB, Jiang H, et al. Impact of race/ethnicity on the efficacy and safety of commonly used insulin regimens: a post hoc analysis of clinical trials in type 2 diabetes mellitus. *Endocr Pract*. 2010;16(5):818-828. http://dx.doi.org/10.4158/EP09285.OR. PMID:20439249.
14. Zeitler P, Hirst K, Pyle L, et al; TODAY Study Group. A clinical trial to maintain glycemic control in youth with type 2 diabetes. *N Engl J Med*. 2012;366(24):2247-2256. http://dx.doi.org/10.1056/NEJMoa1109333. PMID:22540912.
15. Kim YG, Hahn S, Oh TJ, Kwak SH, Park KS, Cho YM. Differences in the glucose-lowering efficacy of dipeptidyl peptidase-4 inhibitors between Asians and non-Asians: a systematic review and meta-analysis. *Diabetologia*. 2013;56(4):696-708. http://dx.doi.org/10.1007/s00125-012-2827-3. PMID:23344728.
16. Musso G, Gambino R, Cassader M, Pagano G. A novel approach to control hyperglycemia in type 2 diabetes: sodium glucose co-transport (SGLT) inhibitors: systematic review and meta-analysis of randomized trials. *Ann Med*. 2012;44(4):375-393. http://dx.doi.org/10.3109/07853890.2011.560181. PMID:21495788.
17. Rosenwasser RF, Sultan S, Sutton D, Choksi R, Epstein BJ. SGLT-2 inhibitors and their potential in the treatment of diabetes. *Diabetes Metab Syndr Obes*. 2013;6:453-467. PMID:24348059.
18. Matthews D, Zinman B, Tong C, Meininger G, Polidori D. Glycemic efficacy of canagliflozin (CANA) is largely independent of baseline beta-cell function or insulin sensitivity. [abstract 1096-P]. *Diabetes*. 2014;63(suppl 1):A285.
19. American Diabetes Association. Standards of Medical Care in Diabetes. (7) Approaches to Glycemic Treatment. *Diabetes Care*. 2015;38(suppl 1):S41-S48. http://dx.doi.org/10.2337/dc15-S010. PMID:25537707.
20. Stenlöf K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab*. 2013;15(4):372-382. http://dx.doi.org/10.1111/dom.12054. PMID:23279307.
21. Lavalle-González FJ, Januszewicz A, Davidson J, et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. *Diabetologia*. 2013;56(12):2582-2592. http://dx.doi.org/10.1007/s00125-013-3039-1. PMID:24026211.
22. Wilding JP, Charpentier G, Hollander P, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea: a randomised trial. *Int J Clin Pract*. 2013;67(12):1267-1282. http://dx.doi.org/10.1111/ijcp.12322. PMID:24118688.
23. Forst T, Guthrie R, Goldenberg R, et al. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes on background metformin and pioglitazone. *Diabetes Obes Metab*. 2014;16(5):467-477. http://dx.doi.org/10.1111/dom.12273. PMID:24528605.
24. Cefalu WT, Leiter LA, Yoon KH, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. *Lancet*. 2013;382(9896):941-950. http://dx.doi.org/10.1016/S0140-6736(13)60683-2. PMID:23850055.
25. Nauck MA, Del Prato S, Meier JJ, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. *Diabetes Care*. 2011;34(9):2015-2022. http://dx.doi.org/10.2337/dc11-0606. PMID:21816980.
26. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med*. 2013;159(4):262-274. http://dx.doi.org/10.7326/0003-4819-159-4-201308200-00007. PMID:24026259.
27. Fujita Y, Inagaki N. Renal sodium glucose cotransporter 2 inhibitors as a novel therapeutic approach to treatment of type 2 diabetes: Clinical data and mechanism of action. *J Diabetes Investig*. 2014;4;5(3):265-75.
28. Rodriguez CJ, Daviglus ML, Swett K, et al. Dyslipidemia patterns among Hispanics/Latinos of diverse background in the United States. *Am J Med*. 2014;127(12):1186-94.e1. http://dx.doi.org/10.1016/j.amjmed.2014.07.026. PMID:25195188.
29. Usiskin K, Kline I, Fung A, Mayer C, Meininger G. Safety and tolerability of canagliflozin in patients with type 2 diabetes mellitus: pooled analysis of phase 3 study results. *Postgrad Med*. 2014;126(3):16-34. http://dx.doi.org/10.3810/pgm.2014.05.2753. PMID:24918789.
30. Nyirjesy P, Sobel JD. Genital mycotic infections in patients with diabetes. *Postgrad Med*. 2013;125(3):33-46. http://dx.doi.org/10.3810/pgm.2013.05.2650. PMID:23748505.