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Efficacy and safety of canagliflozin by baseline HbA_{1c} and known duration of type 2 diabetes mellitus

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ABSTRACT

Aims: Canagliflozin, a sodium glucose co-transporter 2 inhibitor, has demonstrated glycemic improvements across studies of patients with type 2 diabetes mellitus (T2DM). The impact of canagliflozin on HbA_{1c} lowering was assessed by baseline HbA_{1c} and known duration of T2DM.
Methods: This post hoc analysis pooled data from patients with T2DM enrolled in four 26-week, placebo-controlled, Phase 3 studies of canagliflozin (N = 2313). Change in HbA_{1c} from baseline to Week 26 was assessed in the overall population and in subgroups by baseline HbA_{1c} (<8.0%, 8.0%–<9.0%, and ≥9.0%) and known duration of T2DM (<5 years, 5–<10 years, and ≥10 years).
Results: Relative to placebo, canagliflozin 100 and 300 mg provided greater HbA_{1c} reductions in the overall population. Progressively larger placebo-subtracted reductions in HbA_{1c} with canagliflozin 100 and 300 mg were seen with increasing baseline HbA_{1c}. HbA_{1c} reductions were similar across subgroups based on known duration of T2DM. Both canagliflozin doses were generally well tolerated across subgroups, with a safety and tolerability profile consistent with that seen in Phase 3 studies.
Conclusions: Canagliflozin provided glycemic improvements in patients with T2DM across a range of baseline HbA_{1c} and known duration of T2DM.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic disease that develops as a result of defective insulin secretion and is frequently associated with obesity-related insulin resistance (Defronzo, 2010). T2DM is also characterized by progressively decreased beta-cell function over time (Inzucchi et al., 2012; Jabbour, 2008; Standl, 2007). Glucose-lowering agents are regularly implemented to manage hyperglycemia when lifestyle modifications (eg, diet and exercise) are insufficient (American Diabetes Association, 2014; Inzucchi et al., 2012). Underlying disease progression leads to treatment intensification with combination therapy, and ultimately insulin therapy is often initiated (Cook, Girman, Stein, & Alexander, 2007; Cook, Girman, Stein, Alexander, & Holman, 2005; Inzucchi et al., 2012). The efficacy of glucose-lowering treatments has been shown to be impacted by baseline HbA_{1c}, with greater reductions in HbA_{1c} generally observed in patients with higher baseline HbA_{1c} (Bloomgarden, Dodis, Viscoli, Holmboe, & Inzucchi, 2006).

In individuals with hyperglycemia, plasma glucose levels can be lowered by inhibiting sodium glucose co-transporter 2 (SGLT2), a low-affinity, high-capacity glucose transporter that is responsible for the majority of renal glucose reabsorption (Wright, Loo, & Hirayama, 2011). Canagliflozin is an SGLT2 inhibitor developed for the treatment of adults with T2DM (Janssen Pharmaceuticals, 2014). Canagliflozin lowers the renal threshold for glucose (RT_G), thereby promoting urinary glucose excretion (UGE; ~80–120 g/day) (Devineni et al., 2013; Devineni et al., 2012; Polidori et al., 2013; Rosenstock et al., 2012; Sha et al., 2014). Increased UGE leads to a mild osmotic diuresis and a net caloric loss that may lead to reductions in body weight and blood pressure. In addition, there is a low inherent risk of hypoglycemia with canagliflozin treatment, making it complementary

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to a range of other glucose-lowering agents. Across Phase 3 studies, canagliflozin improved glycemic control, reduced body weight and systolic blood pressure, and was generally well tolerated in a broad range of patients with T2DM inadequately controlled by their current treatment regimens (Bode, Stenlöf, Sullivan, Fung, & Usiskin, 2013; Cefalu et al., 2013; Forst et al., 2014; Lavalle-González et al., 2013; Leiter et al., 2014; Schernthaner et al., 2013; Stenlöf et al., 2013; Stenlöf et al., 2014; Wilding et al., 2013; Yale et al., 2013; Yale et al., 2014). Therefore, canagliflozin treatment may be beneficial for a broad range of patients across different stages of T2DM.

Baseline HbA_{1c} and duration of T2DM are patient disease characteristics known to potentially impact the efficacy of glucose-lowering treatments. In this analysis, the effects of canagliflozin on HbA_{1c}, by baseline HbA_{1c} and known duration of T2DM, were assessed based on pooled data from four 26-week, double-blind, placebo-controlled, Phase 3 studies in patients with T2DM (Forst et al., 2014; Lavalle-González et al., 2013; Stenlöf et al., 2013; Wilding et al., 2013).

2. Methods

2.1. Study design and patients

This post hoc analysis was based on pooled data from patients with T2DM (N = 2313) enrolled in four 26-week, double-blind, placebo-controlled, Phase 3 studies [monotherapy (Stenlöf et al., 2013), add-on to metformin (Lavalle-González et al., 2013), add-on to metformin plus sulfonylurea (Wilding et al., 2013), and add-on to metformin plus pioglitazone (Forst et al., 2014)]. Patients were randomized to receive canagliflozin 100 and 300 mg or placebo once daily during a 26-week core treatment period, followed by a 26-week extension period. Data from the 26-week core treatment periods of each study were included in this pooled analysis; the high glycemic subset (HbA_{1c} >10.0%–≤12.0%) of the monotherapy study, which was not placebo-controlled, and the sitagliptin arm of the add-on to metformin study, which was not prespecified for efficacy comparisons versus canagliflozin at Week 26, were excluded from this analysis.

Key inclusion and exclusion criteria are shown in Table 1. In each study, eligible patients who were on protocol-specified background glucose-lowering treatment entered into a 2-week, placebo run-in period. Patients who were not on the protocol-specified background glucose-lowering treatment (n = 821 [35.5%]) entered an 8- to 12-week adjustment/dose stabilization period prior to the placebo run-in period. Patients were required to remain on their stable diabetes treatment regimen throughout the entire double-blind period. Randomization (1:1:1) to study drug (canagliflozin 100 or 300 mg or placebo) was stratified using permuted blocks to ensure adequate distribution of patient characteristics relevant to each study (eg, whether a patient entered the adjustment/dose stabilization period, participation in a mixed-meal tolerance test, pioglitazone dose). After randomization, HbA_{1c} and fasting plasma glucose (FPG) values were masked to the study centers unless predefined criteria for glycemic rescue were met. Glycemic rescue therapy was initiated when FPG was >15.0 mmol/L after Day 1 to Week 6, >13.3 mmol/L after Week 6 to Week 12, and >11.1 mmol/L after Week 12 to Week 26 using a glucose-lowering agent selected to be complementary to the protocol-specified background therapy. In each study, the patients, study center, sponsor, and local sponsor personnel remained blinded throughout the 26-week treatment period.

These studies were conducted in accordance with the ethical principles originating in the Declaration of Helsinki and were consistent with Good Clinical Practices and applicable regulatory requirements. Approval was obtained from institutional review boards and independent ethics committees for participating centers, and written informed consent was provided by patients prior to participation.

Table 1
Study design and patient population[a].

Study	Inclusion criteria[b]			Patients contributing data to pooled analysis, n			
	Age, y	HbA_{1c}, %	eGFR, mL/min/1.73 m^2	PBO	CANA 100 mg	CANA 300 mg	Total
Monotherapy	18–80	7.0–10.0	≥50	192	195	197	584
Add-on to MET	18–80	7.0–10.5	≥55	183	368	367	918
Add-on to MET + SU	18–80	7.0–10.5	≥55	156	157	156	469
Add-on to MET + PIO	18–80	7.0–10.5	≥55	115	113	114	342
Overall total, N				**646**	**833**	**834**	**2313**

eGFR, estimated glomerular filtration rate; PBO, placebo; CANA, canagliflozin; MET, metformin; SU, sulfonylurea; PIO, pioglitazone; FPG, fasting plasma glucose; ULN, upper limit of normal.

[a] Data have been previously reported (Usiskin, Kline, Fung, Mayer, & Meininger, 2014).

[b] Key exclusion criteria common to the 4 studies included repeated FPG generally ≥15.0 mmol/L during the pretreatment phase; history of diabetic ketoacidosis or type 1 diabetes; history of myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident with 3 months of screening; uncontrolled hypertension; and alanine aminotransferase level >2 times the ULN or total bilirubin >1.5 times the ULN at screening.

2.2. Study endpoints and assessments

The primary endpoint of each study was the change from baseline in HbA_{1c} at Week 26. For this post hoc analysis, changes from baseline in HbA_{1c} at 26 weeks were evaluated in the overall pooled population and in subgroups of patients by baseline HbA_{1c} (<8.0% [n = 1218], 8.0%–<9.0% [n = 712], and ≥9.0% [n = 383]) and known duration of T2DM (<5 years [n = 936], 5–<10 years [n = 709], and ≥10 years [n = 668]). The proportion of patients with HbA_{1c} <7.0% at Week 26 was also assessed in subgroups by baseline HbA_{1c} and known duration of T2DM.

Safety and tolerability were assessed based on adverse event (AE) reports, safety laboratory tests, 12-lead electrocardiograms, vital sign measurements, physical examinations, and self-monitored blood glucose. The incidence of selected AEs, including genital mycotic infections, urinary tract infections, and AEs related to osmotic diuresis and volume depletion, was also evaluated. Documented hypoglycemia episodes included biochemically confirmed episodes (concurrent fingerstick or plasma glucose ≤3.9 mmol/L, with or without symptoms) and severe episodes (ie, those requiring the assistance of another individual or resulting in seizure or loss of consciousness).

2.3. Statistical analyses

Efficacy analyses were conducted using the modified intent-to-treat (mITT) population, consisting of all randomized patients who received ≥1 dose of double-blind study drug. The last observation carried forward (LOCF) approach was used to impute missing data at Week 26. For patients who received glycemic rescue therapy, the last post-baseline value prior to the initiation of rescue therapy was used for the efficacy analysis. Continuous endpoints were assessed using an analysis of covariance (ANCOVA) model, with treatment and study as factors and the respective baseline value as a covariate. Least squares (LS) means and 95% confidence intervals (CIs) were estimated for the comparisons of each canagliflozin dose with placebo. Odds ratios and 95% CIs were calculated for the proportion of patients achieving HbA_{1c} <7.0% with canagliflozin versus placebo in the subgroups by baseline HbA_{1c} and known duration of T2DM at Week 26. Statistical testing of canagliflozin versus placebo was not prespecified for analyses of efficacy parameters in these post hoc analyses. Therefore, no *P* values are reported; however, 95% CIs are reported for descriptive purposes.

3. Results

3.1. Patients

Of the 2313 patients in the mITT population, 1984 (85.8%) completed the 26-week treatment period. Baseline demographic and disease characteristics were generally similar across treatment groups in the overall population (Table 2) and in subgroups by baseline HbA_{1c} (Supplementary Table 1) and known duration of T2DM (Supplementary Table 2). Patients with higher baseline HbA_{1c} generally had longer known duration of T2DM. Patients with longer known duration of T2DM at baseline generally were older and had lower baseline eGFR values, but had similar baseline HbA_{1c} compared with patients with shorter known duration of T2DM.

3.2. Efficacy

At Week 26, canagliflozin 100 and 300 mg provided dose-related reductions from baseline in HbA_{1c} compared with placebo (Fig. 1). Across baseline HbA_{1c} subgroups, patients in both canagliflozin groups had larger dose-dependent reductions in HbA_{1c} compared with patients in the placebo group (Fig. 2A). Placebo-subtracted LS mean reductions at Week 26 with canagliflozin 100 and 300 mg were progressively larger with increasing baseline HbA_{1c}, with the largest reductions in HbA_{1c} observed in patients with the greatest degree of hyperglycemia at baseline. Compared with placebo, a greater proportion of patients achieved HbA_{1c} <7.0% with canagliflozin 100 and 300 mg across subgroups by baseline HbA_{1c}; the odds of achieving HbA_{1c} <7.0% favored both canagliflozin doses versus placebo across HbA_{1c} subgroups (Fig. 2B). The proportion of patients who achieved HbA_{1c} <7.0% with canagliflozin 100 and 300 mg versus placebo was highest in patients with baseline HbA_{1c} <8.0% compared with those who had baseline HbA_{1c} 8.0%–<9.0% and HbA_{1c} ≥9.0%.

Reductions in HbA_{1c} with canagliflozin 100 and 300 mg were similar across subgroups by known T2DM duration (Fig. 2C). The proportion of patients achieving HbA_{1c} <7.0% was greater with canagliflozin 100 and 300 mg compared with placebo across subgroups by known duration of T2DM; the odds of achieving HbA_{1c} <7.0% favored canagliflozin 100 and 300 mg versus placebo across subgroups by known T2DM duration (Fig. 2D).

Table 2
Baseline demographic and disease characteristics in the overall population[a,b].

Characteristic	PBO (n = 646)	CANA 100 mg (n = 833)	CANA 300 mg (n = 834)	Total (N = 2313)
Sex, n (%)[c]				
Male	334 (52)	408 (49)	404 (48)	1146 (50)
Female	312 (48)	425 (51)	430 (52)	1167 (51)
Age, y	56.3 (9.8)	55.9 (10.1)	55.7 (9.5)	56.0 (9.8)
Race, n (%)[c]				
White	470 (73)	591 (71)	610 (73)	1671 (72)
Black or African American	28 (4)	43 (5)	48 (6)	119 (5)
Asian	82 (13)	103 (12)	100 (12)	285 (12)
Other[d]	66 (10)	96 (12)	76 (9)	238 (10)
HbA_{1c}, %	8.0 (0.9)	8.0 (0.9)	8.0 (1.0)	8.0 (0.9)
BMI, kg/m^2	31.9 (6.4)	32.3 (6.4)	32.0 (6.5)	32.1 (6.4)
eGFR, mL/min/1.73 m^2	87.0 (19.8)	88.3 (19.0)	88.8 (18.9)	88.1 (19.2)
Duration of T2DM, y	7.5 (6.2)	7.2 (5.8)	7.4 (6.2)	7.3 (6.0)

PBO, placebo; CANA, canagliflozin; BMI, body mass index; eGFR, estimated glomerular filtration rate; T2DM, type 2 diabetes mellitus; SD, standard deviation.
[a] Data have been previously reported (Usiskin et al., 2014).
[b] Data are mean (SD) unless otherwise indicated.
[c] Percentages may not total 100% due to rounding.
[d] Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported.

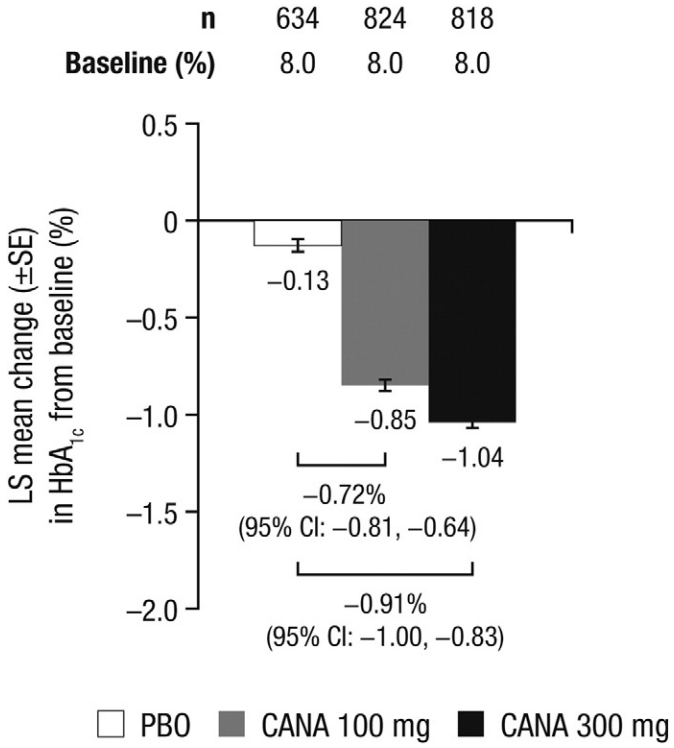

Fig. 1. Change in HbA_{1c} in the overall population (LOCF). LOCF, last observation carried forward; LS, least squares; SE, standard error; CI, confidence interval; PBO, placebo; CANA, canagliflozin.

3.3. Safety

The incidence of AEs was similar with canagliflozin 100 and 300 mg and placebo in the overall population; AE-related study discontinuations were low across groups, but slightly higher with canagliflozin compared with placebo (Supplementary Table 3) (Usiskin et al., 2014). Incidences of genital mycotic infections and AEs related to osmotic diuresis (eg, pollakiuria [increased urine frequency], polyuria [increased urine volume]) were higher with canagliflozin 100 and 300 mg relative to placebo, and incidences of volume depletion–related AEs (eg, orthostatic hypotension, postural dizziness) were low and similar across treatment groups. The incidence of urinary tract infections was similar across groups; 40.0% and 23.1% of patients who reported a urinary tract infection AE in the combined canagliflozin group and the placebo group, respectively, had confirmed diagnoses (Nicolle, Capuano, Fung, & Usiskin, 2014).

In subgroups by baseline HbA_{1c}, the incidence of AEs was generally similar to that seen in the overall population, with a low incidence of AE-related discontinuations (<5%) across treatment groups in all subgroups (Table 3). Across subgroups by baseline HbA_{1c}, the incidences of male and female genital mycotic infections were higher with canagliflozin 100 and 300 mg compared with placebo. There was no discernable trend in the incidence of male genital mycotic infections related to baseline HbA_{1c}; however, female genital mycotic infections were more common in patients with HbA_{1c} ≥9.0% versus those with lower baseline HbA_{1c}. The incidence of osmotic diuresis–related AEs was also higher in patients treated with canagliflozin versus placebo among those who had baseline HbA_{1c} ≥9.0% compared with those in the lower baseline HbA_{1c} subgroups. Consistent with the overall population, the incidence of volume depletion–related AEs was low and similar across subgroups. The incidence of documented hypoglycemia episodes (concurrent fingerstick or plasma glucose ≤3.9 mmol/L, with or without symptoms) was evaluated separately according to baseline use of glucose-lowering agents associated with hypoglycemia (ie, sulfonylurea). The incidence of documented hypoglycemia episodes

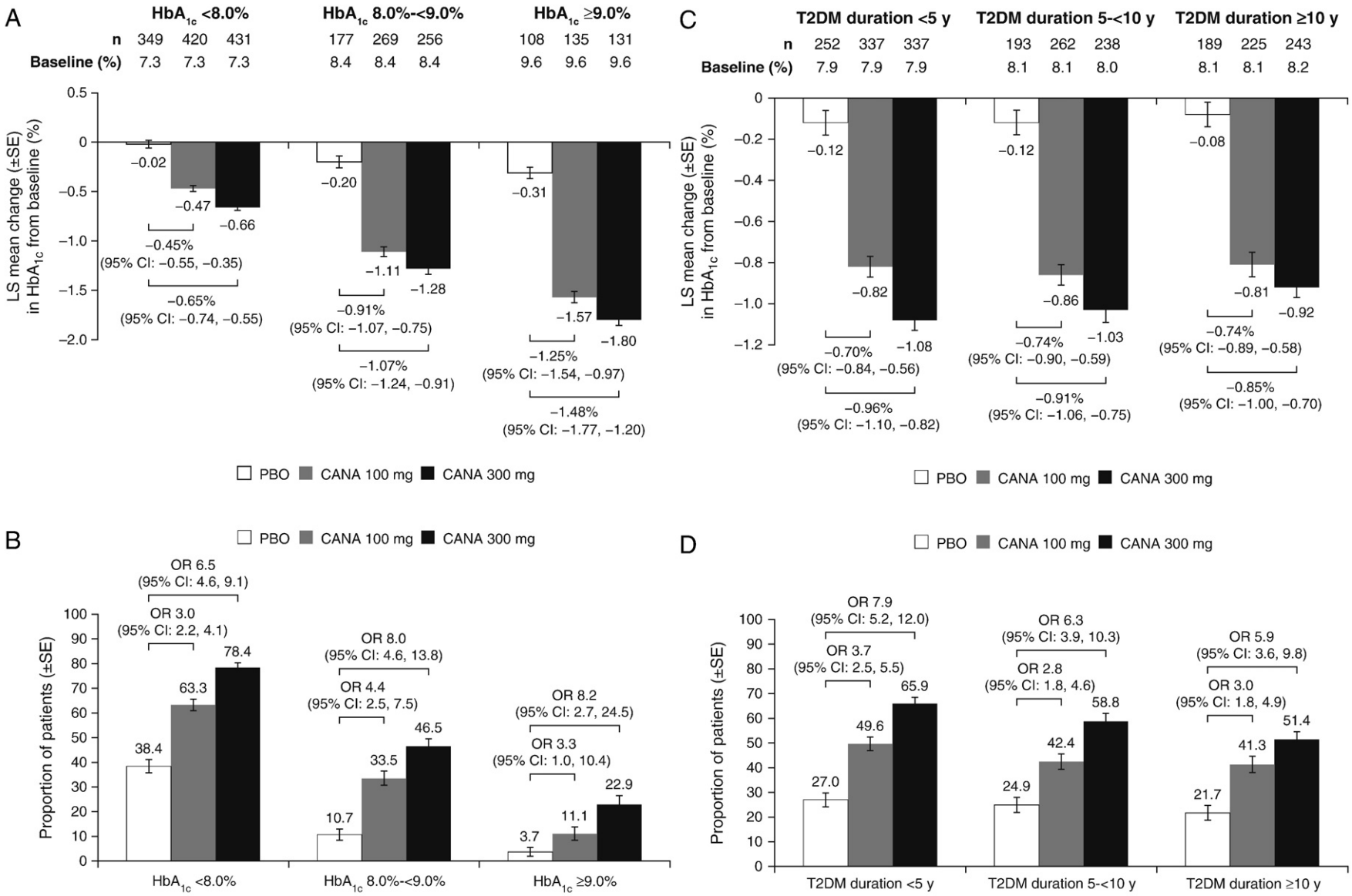

Fig. 2. Change in HbA_{1c} and proportion of patients with HbA_{1c} <7.0% at Week 26 in subgroups by baseline HbA_{1c} (A, B) and known duration of T2DM (C, D) (LOCF). T2DM, type 2 diabetes mellitus; LOCF, last observation carried forward; LS, least squares; SE, standard error; CI, confidence interval; PBO, placebo; CANA, canagliflozin; OR, odds ratio.

Table 3
Summary of overall safety and specific AEs in subgroups by baseline HbA_{1c}.

Patients, n (%)	HbA_{1c} <8.0%			HbA_{1c} 8.0%–<9.0%			HbA_{1c} ≥9.0%		
	PBO (n = 355)	CANA 100 mg (n = 425)	CANA 300 mg (n = 438)	PBO (n = 179)	CANA 100 mg (n = 272)	CANA 300 mg (n = 261)	PBO (n = 112)	CANA 100 mg (n = 136)	CANA 300 mg (n = 135)
Any AE	215 (60.6)	265 (62.4)	249 (56.8)	101 (56.4)	157 (57.7)	163 (62.5)	68 (60.7)	79 (58.1)	82 (60.7)
AEs leading to discontinuation	14 (3.9)	18 (4.2)	18 (4.1)	4 (2.2)	12 (4.4)	7 (2.7)	2 (1.8)	6 (4.4)	5 (3.7)
AEs related to study drug[a]	55 (15.5)	80 (18.8)	104 (23.7)	19 (10.6)	61 (22.4)	56 (21.5)	11 (9.8)	30 (22.1)	31 (23.0)
Serious AEs	13 (3.7)	11 (2.6)	11 (2.5)	5 (2.8)	12 (4.4)	8 (3.1)	4 (3.6)	5 (3.7)	3 (2.2)
Deaths	2 (0.6)	1 (0.2)	1 (0.2)	0	0	0	0	0	0
Genital mycotic infection									
Male[b,c]	0	6 (3.1)	7 (3.6)	1 (1.1)	8 (5.9)	5 (4.0)	1 (1.7)	3 (3.8)	3 (3.6)
Female[d,e]	6 (3.4)	22 (9.5)	28 (11.6)	2 (2.4)	13 (9.6)	12 (8.8)	2 (3.8)	9 (15.5)	9 (17.3)
UTI	17 (4.8)	26 (6.1)	17 (3.9)	6 (3.4)	17 (6.3)	14 (5.4)	3 (2.7)	6 (4.4)	5 (3.7)
Osmotic diuresis–related AEs[f]	5 (1.4)	24 (5.6)	19 (4.3)	0	19 (7.0)	18 (6.9)	0	13 (9.6)	10 (7.4)
Volume depletion–related AEs[g]	3 (0.8)	7 (1.6)	3 (0.7)	3 (1.7)	3 (1.1)	5 (1.9)	1 (0.9)	0	3 (2.2)

AE, adverse event; PBO, placebo; CANA, canagliflozin; UTI, urinary tract infection.
[a] Possibly, probably, or very likely related to study drug, as assessed by investigators.
[b] HbA_{1c} <8.0%: PBO, n = 180; CANA 100 mg, n = 194; CANA 300 mg, n = 197; HbA_{1c} 8.0%–<9.0%: PBO, n = 95; CANA 100 mg, n = 136; CANA 300 mg, n = 124; HbA_{1c} ≥9.0%: PBO, n = 59; CANA 100 mg, n = 78; CANA 300 mg, n = 83.
[c] Including balanitis, balanitis candida, balanoposthitis, and genital infection fungal.
[d] HbA_{1c} <8.0%: PBO, n = 175; CANA 100 mg, n = 231; CANA 300 mg, n = 241; HbA_{1c} 8.0%–<9.0%: PBO, n = 84; CANA 100 mg, n = 136; CANA 300 mg, n = 137; HbA_{1c} ≥9.0%: PBO, n = 53; CANA 100 mg, n = 58; CANA 300 mg, n = 52.
[e] Including genital infection fungal, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis.
[f] Including dry mouth, micturition urgency, nocturia, pollakiuria, polydipsia, polyuria, thirst, and urine output increased.
[g] Including blood pressure decreased, dehydration, dizziness postural, hypotension, orthostatic hypotension, orthostatic intolerance, presyncope, and syncope.

(≤3.9 mmol/L) was low across treatment groups by baseline HbA_{1c} among patients not on background sulfonylurea (HbA_{1c} <8.0%: 5.4%, 4.1%, and 3.6%; HbA_{1c} 8.0%–< 9.0%: 2.3%, 4.3%, and 0.8%; and HbA_{1c} ≥9.0%: 1.9%, 4.7%, and 0% with canagliflozin 100 and 300 mg and placebo, respectively). The overall incidence of documented hypoglycemia episodes was higher across HbA_{1c} subgroups in patients on background sulfonylurea, compared with patients not on background sulfonylurea (HbA_{1c} <8.0%: 35.1%, 42.1%, and 18.4%; HbA_{1c} 8.0%–<9.0%: 23.5%, 19.6%, and 16.0%; and HbA_{1c} ≥9.0%: 15.6%, 17.2%, and 6.7% with canagliflozin 100 and 300 mg and placebo, respectively).

The incidence of AEs was generally similar across subgroups by known T2DM duration, with slight differences in patients with longer versus shorter known duration of T2DM (Table 4). The incidence of AEs leading to discontinuation was slightly higher in patients receiving canagliflozin 300 mg in the 5–<10 year subgroup and with both canagliflozin doses in the ≥10 year subgroup compared with placebo; the incidence of AE-related discontinuations was low and similar across treatment groups in patients with known T2DM duration <5 years. A dose-dependent increase in the incidence of AEs related to the study drug was observed with canagliflozin 100 and 300 mg compared with placebo across subgroups by known T2DM duration. Across subgroups by known T2DM duration, an increased incidence of male and female genital mycotic infections was observed with canagliflozin 100 and 300 mg compared with placebo, respectively, and was highest in the patients with the longest known T2DM duration. Across subgroups by known T2DM duration, the incidence of osmotic diuresis–related AEs was higher in patients treated with canagliflozin 100 and 300 mg compared with placebo. A low and similar incidence of volume depletion–related AEs was seen across subgroups. In patients not on background sulfonylurea, the incidence of documented hypoglycemia episodes (≤3.9 mmol/L) was similar across treatment groups regardless of known T2DM duration

Table 4
Summary of overall safety and specific AEs in subgroups by known duration of T2DM.

Patients, n (%)	T2DM duration <5 y			T2DM duration 5–<10 y			T2DM duration ≥10 y		
	PBO (n = 253)	CANA 100 mg (n = 341)	CANA 300 mg (n = 342)	PBO (n = 200)	CANA 100 mg (n = 264)	CANA 300 mg (n = 245)	PBO (n = 193)	CANA 100 mg (n = 228)	CANA 300 mg (n = 247)
Any AE	143 (56.5)	204 (59.8)	179 (52.3)	125 (62.5)	158 (59.8)	148 (60.4)	116 (60.1)	139 (51.0)	167 (67.6)
AEs leading to discontinuation	7 (2.8)	13 (3.8)	5 (1.5)	6 (3.0)	9 (3.4)	13 (5.3)	7 (3.6)	14 (6.1)	12 (4.9)
AEs related to study drug[a]	26 (10.3)	68 (19.9)	63 (18.4)	28 (14.0)	50 (18.9)	61 (24.9)	31 (16.1)	53 (23.2)	67 (27.1)
Serious AEs	4 (1.6)	11 (3.2)	6 (1.8)	7 (3.5)	7 (2.7)	9 (3.7)	11 (5.7)	10 (4.4)	7 (2.8)
Deaths	1 (0.4)	1 (0.3)	1 (0.3)	0	0	0	1 (0.5)	0	0
Genital mycotic infection									
Male[b,c]	1 (0.8)	3 (1.8)	4 (2.4)	0	6 (4.5)	6 (4.8)	1 (1.0)	8 (7.1)	5 (4.3)
Female[d,e]	5 (4.1)	19 (10.7)	14 (7.9)	5 (5.1)	12 (9.1)	15 (12.4)	0	13 (11.2)	20 (15.3)
UTI	10 (4.0)	22 (6.5)	12 (3.5)	8 (4.0)	13 (4.9)	11 (4.5)	8 (4.1)	14 (6.1)	13 (5.3)
Osmotic diuresis–related AEs[f]	2 (0.8)	18 (5.3)	12 (3.5)	0	19 (7.2)	20 (8.2)	3 (1.6)	19 (8.3)	15 (6.1)
Volume depletion–related AEs[g]	0	2 (0.6)	2 (0.6)	1 (0.5)	2 (0.8)	2 (0.8)	6 (3.1)	6 (2.6)	7 (2.8)

AE, adverse event; PBO, placebo; CANA, canagliflozin; UTI, urinary tract infection.
[a] Possibly, probably, or very likely related to study drug, as assessed by investigators.
[b] T2DM duration <5 years: PBO, n = 130; CANA 100 mg, n = 164; CANA 300 mg, n = 164; T2DM duration 5–<10 years: PBO, n = 102; CANA 100 mg, n = 132; CANA 300 mg, n = 124; T2DM duration ≥10 years: PBO, n = 102; CANA 100 mg, n = 112; CANA 300 mg, n = 116.
[c] Including balanitis, balanitis candida, balanoposthitis, and genital infection fungal.
[d] T2DM duration <5 years: PBO, n = 123; CANA 100 mg, n = 177; CANA 300 mg, n = 178; T2DM duration 5–<10 years: PBO, n = 98; CANA 100 mg, n = 132; CANA 300 mg, n = 121; T2DM duration ≥10 years: PBO, n = 91; CANA 100 mg, n = 116; CANA 300 mg, n = 131.
[e] Including genital infection fungal, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis.
[f] Including dry mouth, micturition urgency, nocturia, pollakiuria, polydipsia, polyuria, thirst, and urine output increased.
[g] Including blood pressure decreased, dehydration, dizziness postural, hypotension, orthostatic hypotension, orthostatic intolerance, presyncope, and syncope.

(<5 years: 3.6%, 4.6%, and 1.8%; 5–<10 years: 3.9%, 1.5%, and 4.1%; and ≥10 years: 4.2%, 6.8%, and 0.8% with canagliflozin 100 and 300 mg and placebo, respectively). The incidence of documented hypoglycemia episodes was higher with canagliflozin 100 and 300 mg compared with placebo in patients on background sulfonylurea, with higher risk observed in all treatment groups as known duration of T2DM increased (<5 years: 17.9%, 17.5%, and 12.9%; 5–<10 years: 25.9%, 22.2%, and 15.4%; and ≥10 years: 35.0%, 42.3%, and 16.4% with canagliflozin 100 and 300 mg and placebo, respectively).

4. Discussion

Findings from this post hoc analysis demonstrated that canagliflozin improved glycemic control in patients with T2DM across a range of baseline HbA_{1c} and known duration of T2DM, including those with lower baseline HbA_{1c} and longer T2DM duration. Over 26 weeks, patients with higher baseline HbA_{1c} had larger reductions in HbA_{1c} with canagliflozin 100 and 300 mg than those with lower baseline HbA_{1c}. This is consistent with previous reports for canagliflozin and other non-insulin glucose-lowering agents, including sulfonylureas, metformin, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, and other SGLT2 inhibitors (Bloomgarden et al., 2006; Esposito et al., 2014; Zhang, Feng, List, Kasichayanula, & Pfister, 2010), that demonstrated a progressively greater HbA_{1c}-lowering effect as baseline HbA_{1c} increased. Furthermore, more patients had HbA_{1c} <7.0% at Week 26 with canagliflozin compared with placebo, particularly among those with a lower HbA_{1c} at baseline.

Canagliflozin 100 and 300 mg provided similar glycemic efficacy in patients regardless of known T2DM duration, which is representative of various stages of T2DM. This suggests that the likelihood of achieving glycemic goals with canagliflozin is similar across the spectrum of T2DM, even in those with longer duration of T2DM who may have greater impairment of beta-cell function. However, this is not surprising given the mechanism of action of canagliflozin, which is independent of beta-cell function, and a previous report that the glycemic efficacy of canagliflozin is largely independent of beta-cell function or insulin sensitivity (Matthews, Zinman, Tong, Meininger, & Polidori, 2014).

Canagliflozin was generally well tolerated across the baseline HbA_{1c} and known duration of T2DM subgroups, with a safety profile similar to that seen in the overall population (Usiskin et al., 2014). Of note, patients in the highest baseline HbA_{1c} subgroup who received canagliflozin 100 or 300 mg reported more female genital mycotic infections and osmotic diuresis–related AEs compared with those in the lower HbA_{1c} subgroups. The increase in genital mycotic infections with canagliflozin versus placebo was not strictly baseline HbA_{1c}- or dose-dependent, suggesting a threshold of UGE associated with genital mycotic infections. Other factors, such as prior history of genital mycotic infection or being uncircumcised, may be related to the increased incidence of genital mycotic infections with canagliflozin compared with placebo (Nyirjesy et al., 2014). Consistent with the overall population (Usiskin et al., 2014), the incidence of documented hypoglycemia episodes (≤3.9 mmol/L) was higher in patients on background sulfonylurea, with increases seen across groups with increasing known duration of T2DM.

This analysis is strengthened by the inclusion of a large, general population of patients with T2DM with diverse baseline characteristics. A limitation of this analysis was the lack of prespecified statistical testing across subgroups based on baseline HbA_{1c} and known duration of T2DM; however, the inclusion of 95% CIs provides descriptive comparisons for treatment with both canagliflozin doses and placebo. In addition, longer-term efficacy and safety analyses of canagliflozin in subgroups based on HbA_{1c} and known duration of T2DM would be beneficial to understand the durability of benefits and risks associated with canagliflozin treatment.

Because the efficacy of some T2DM treatments may be impacted by baseline patient characteristics, consideration of the potential impact of these factors may be beneficial as part of the shared decision-making process with patients regarding optimal T2DM treatment options. Findings from this analysis suggest that canagliflozin may be a therapeutic option in patients with T2DM across a range of baseline HbA_{1c} levels and different stages of T2DM.

Conflicts of interest

JPHW has served as a consultant for Astellas, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Janssen, and Novo Nordisk; has served as a speaker for AstraZeneca, Bristol-Myers Squibb, Janssen, Eli Lilly, and Novo Nordisk; and has received research support from AstraZeneca, Eli Lilly, Novo Nordisk, and Merck Sharpe & Dohme. LB has served as an investigator for Eli Lilly, Novo Nordisk, and Sanofi; has served as a speaker for Novo Nordisk, Sanofi, Merck, Janssen, and AstraZeneca; and has served as a consultant to Novo Nordisk, Sanofi, Merck, Janssen, Quest Diagnostics, AstraZeneca, and GlaxoSmithKline. LAL has received research funding from, has provided continuing medical education on behalf of, or has served as a consultant to AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Merck, Novo Nordisk, Sanofi, Servier, and Takeda. SC has no financial disclosures to declare. CT, JY, and GM are full-time employees of Janssen Research & Development, LLC.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jdiacomp.2014.12.016.

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