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Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus living in hot climates

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Summary

Aims: Patients with type 2 diabetes mellitus (T2DM) have increased risk of adverse events (AEs; e.g. dehydration, hypoglycaemia) in hot weather. This analysis assessed the efficacy and safety of canagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, in patients with T2DM who live in hot climates.

Methods: This post hoc analysis evaluated patients with T2DM using pooled data from four 26-week, placebo-controlled studies (N=2,313) and data from a 104-week, active-controlled study (add-on to metformin vs glimepiride; N=1,450). Changes in HbA1c, fasting plasma glucose (FPG), body weight and blood pressure (BP) were assessed in subsets of patients living in hot climates (pooled, placebo-controlled studies, n=611; active-controlled study, n=307) and those living in other climates (i.e. other climate subset; pooled, placebo-controlled studies, n=1,702; active-controlled study, n=1,143). Safety was assessed based on AE reports.

Results: Canagliflozin 100 and 300 mg lowered HbA1c, FPG, body weight and BP vs placebo over 26 weeks and glimepiride over 104 weeks in the hot climate subsets. Canagliflozin was generally well tolerated in the hot climate subsets, with a higher incidence of AEs related to the mechanism of SGLT2 inhibition (i.e. genital mycotic infections). Volume depletion–related AEs were low across groups.

Conclusion: Canagliflozin improved glycaemic control, lowered body weight and BP, and was generally well tolerated in patients with T2DM living in hot climates compared with placebo over 26 weeks or glimepiride over 104 weeks.

Clinical Trials registration: ClinicalTrials.gov NCT01081834, NCT01106677, NCT01106625, NCT01106690, NCT00968812.

1 | INTRODUCTION

People with diabetes are at increased risk of dehydration and hypoglycaemia in hot weather, which may be related to impairment of thermoregulatory mechanisms and orthostatic responses.[1] In addition, diabetes medications (e.g. insulin) and devices (e.g. test strips for blood glucose monitoring systems) are susceptible to damage in hot weather.[1] In regions that typically have warm weather year-round (e.g. Middle East/North Africa, South and Central America, Southeast Asia), the prevalence of diabetes in 2014 was 9.7%, 8.1% and 8.3%, respectively, compared with 8.3% worldwide.[2] However, despite the relatively high prevalence of diabetes in these regions and the potential impact of heat exposure on diabetes management, healthcare resources allocated for the care of diabetes and its complications

are limited in these areas.[3] Therefore, patients must find ways to adapt their disease management in warmer weather conditions to avoid potentially serious complications, adverse events (AEs) and hospitalisations.[1]

Approximately, 90% of people with diabetes have type 2 diabetes mellitus (T2DM), which is characterised by hyperglycaemia, insulin resistance, and impaired beta-cell function.[3] Because uncontrolled hyperglycaemia can lead to microvascular and macrovascular complications of T2DM,[4] many organisations recommend that patients with T2DM implement lifestyle changes and/or begin treatment with antihyperglycaemic agents (AHAs) in order to lower their blood glucose levels.[5] Metformin is the first-line AHA recommended when diet and exercise are insufficient to control hyperglycaemia; selection of additional AHAs is usually at the discretion of the clinician, whose recommendations may vary depending on individual patient characteristics and the risk/benefit profiles of available agents.[5] However, there remains a large contingency of patients with T2DM who are unable to control their disease with currently available treatment options.[6]

Canagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, is an oral AHA that is approved in many countries for the treatment of adults with T2DM.[7–21] Canagliflozin lowers plasma glucose by increasing urinary glucose excretion, which also results in a mild osmotic diuresis and a net caloric loss.[22–25] Across Phase 3 studies, canagliflozin has been associated with reductions in HbA1c, body weight and blood pressure (BP), and was generally well tolerated, with an increased incidence of AEs related to the mechanism of SGLT2 inhibition (e.g. genital mycotic infections, osmotic diuresis–related AEs) and low incidence of volume depletion–related AEs.[7–21] Canagliflozin has also demonstrated a low risk of hypoglycaemia when not used in conjunction with AHAs associated with hypoglycaemia (e.g. insulin, sulphonylureas).[7–21]

The mild osmotic diuresis associated with the SGLT2 inhibitor mechanism of action may increase the risk of volume depletion in some patients. This manuscript reports the efficacy and safety of canagliflozin in two populations of patients with T2DM who live in countries with hot climates, including a pooled data set representative of the general T2DM population and a long-term data set from an active-controlled study that enrolled a large number of patients from countries with hot climates.

What's known

- Patients with type 2 diabetes mellitus (T2DM) have increased risk of dehydration and hypoglycaemia in hot weather.
- Canagliflozin, a sodium glucose co-transporter 2 inhibitor, lowers plasma glucose in patients with T2DM by increasing urinary glucose excretion, which results in a mild osmotic diuresis and net caloric loss.
- Canagliflozin was generally well tolerated across Phase 3 studies, with low rates of volume depletions-related adverse events.

What's new

- Efficacy and safety of canagliflozin were evaluated in patients with T2DM living in hot climates using pooled data from placebo-controlled studies and data from an active–controlled study.
- Canagliflozin 100 and 300 mg improved glycaemic control and lowered body weight and blood pressure in patients living in hot climates.
- Canagliflozin was generally well tolerated in patients living in hot climates, with low incidences of volume depletion–related AEs.

2 | MATERIALS AND METHODS

2.1 | Patients and study design

Post hoc efficacy and safety analyses were conducted in two populations of patients with T2DM who were enrolled in study centres that are located in countries with hot climates (i.e. defined as being located predominantly between the Tropics of Cancer and Capricorn, including Colombia, Costa Rica, Guatemala, India, Malaysia, Mexico, Peru, the Philippines, Singapore, and Thailand) vs those who were enrolled in study centres in other countries (i.e. Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Israel, Italy, Latvia, Lithuania, Norway, Poland, Portugal, Romania, Russia, Slovakia, South Africa, South Korea, Spain, Sweden, Turkey, Ukraine, the United Kingdom, and the United States). The pooled, placebo-controlled studies included pooled data from patients with T2DM from four 26-week, randomised, double-blind, placebo-controlled studies of canagliflozin 100 and 300 mg (monotherapy,[7] add-on to metformin,[8] add-on to metformin plus sulphonylurea,[9] and add-on to metformin plus pioglitazone[10]; N=2313); of these, 611 patients were living in countries with hot climates and 1702 patients were living in other countries. The active-controlled study included data from the 104-week, randomised, double-blind, active-controlled study of canagliflozin 100 and 300 mg vs glimepiride as add-on to metformin (N=1450)[14]; of these, 307 patients were living in countries with hot climates and 1143 were living in other countries.

Details of individual study designs, including randomisation and blinding, have been reported for the placebo-controlled studies[7–10] and the active-controlled study.[14] Briefly, the placebo-controlled studies consisted of a 26-week core treatment period, followed by a 26-week extension treatment period; data from the core treatment periods were included in this analysis. Patients who were eligible for the placebo-controlled studies generally included adults with T2DM who were 18–80 years of age and were inadequately controlled (HbA1c ≥7.0% and ≤10.5%) on protocol-specified background therapy. The active-controlled study consisted of a 52-week core treatment period, followed by a 52-week extension treatment period. Patients who were eligible for the active-controlled study included adults with T2DM who were 18–80 years of age and were inadequately controlled

(HbA1c ≥7.0% and ≤9.5%) on metformin ≥2000 mg (or ≥1500 mg if higher doses were not tolerated). Glimepiride was uptitrated from 1 to 6 or 8 mg (based on maximum approved dose in the country of the investigational site; mean dose, 6.8 mg) if patients met protocol-specified glycaemic criteria. In all studies, glycaemic rescue therapy complementary to the protocol-specified background AHA was initiated using protocol-specified glycaemic criteria.

Approval was obtained from institutional review boards and independent ethics committees for participating centres in each study, in accordance with the ethical principles originating in the Declaration of Helsinki and consistent with Good Clinical Practices and applicable regulatory requirements. Patients provided informed written consent prior to participation.

2.2 | Study outcomes

Efficacy and safety analyses were conducted in the hot climate and other climate subsets for each population. Efficacy endpoints evaluated at week 26 in the pooled, placebo-controlled studies and at week 104 in the active-controlled study included changes from baseline in HbA1c, fasting plasma glucose (FPG), body weight and BP. Safety and tolerability were assessed based on AE reports, safety laboratory tests, 12-lead electrocardiograms, vital sign measurements, physical examinations and self-monitored blood glucose. AEs were reported spontaneously by patients or in response to non-directed questioning. Additional information was prespecified to be collected for urinary tract infections (UTIs), genital mycotic infections (e.g. yeast infections) and hypoglycaemia via a supplemental electronic case report form. Additional AEs of interest included osmotic diuresis–related AEs [e.g. pollakiuria (increased urine frequency), polyuria (increased urine volume)] and volume depletion–related AEs (e.g. dehydration, hypotension). Documented hypoglycaemia episodes included biochemically confirmed episodes [concurrent fingerstick or plasma glucose ≤3.9 mmol/L (70 mg/dL), with or without symptoms] and severe episodes (i.e. those requiring the assistance of another individual or resulting in seizure or loss of consciousness).

2.3 | Statistical analyses

These post hoc analyses were conducted using the modified intent-to-treat population, which comprised all randomised patients who received ≥1 dose of double-blind study drug. The last observation carried forward approach was used to impute missing efficacy data at week 26 in the pooled, placebo-controlled studies and at week 104 in the active-controlled study. Data from the hot climate and other climate subsets were analysed using separate models. Changes in HbA1c, FPG, body weight, and BP were analysed using analysis of covariance models, with treatment and study as fixed effects and the corresponding baseline value as a covariate. Differences in least squares (LS) means and two-sided 95% confidence intervals (CIs) were calculated. Statistical testing of canagliflozin vs either placebo or glimepiride was not prespecified for these post hoc analyses; therefore, *P*-values are not reported.

3 | RESULTS

3.1 | Patients

In the pooled, placebo-controlled studies, the hot climate subset included patients living in Colombia, Guatemala, India, Malaysia, Mexico, Peru, the Philippines, Singapore and Thailand. In the active-controlled study, the hot climate subset included patients living in Costa Rica, India, Mexico and the Philippines. Patient enrolment by country was generally balanced across treatment groups in the hot climate subset of each population (Table 1). Baseline characteristics were generally similar across groups in the hot climate subset of the

TABLE 1 Enrolment by country in the hot climate subsets

	Pooled, PBO-controlled studies			Active-controlled study		
Country, n (%)[a]	PBO (n=163)	CANA 100 mg (n=222)	CANA 300 mg (n=226)	GLIM (n=102)	CANA 100 mg (n=103)	CANA 300 mg (n=102)
Colombia	12 (7.4)	23 (10.4)	14 (6.2)	0	0	0
Costa Rica	0	0	0	9 (8.8)	10 (9.7)	9 (8.8)
Guatemala	25 (15.3)	22 (9.9)	29 (12.8)	0	0	0
India	31 (19.0)	49 (22.1)	44 (19.5)	56 (54.9)	55 (53.4)	55 (53.9)
Malaysia	15 (9.2)	9 (4.1)	18 (8.0)	0	0	0
Mexico	49 (30.1)	57 (25.7)	67 (29.6)	24 (23.5)	24 (23.3)	25 (24.5)
Peru	16 (9.8)	36 (16.2)	30 (13.3)	0	0	0
Philippines	3 (1.8)	4 (1.8)	6 (2.7)	13 (12.7)	14 (13.6)	13 (12.7)
Singapore	3 (1.8)	5 (2.3)	3 (1.3)	0	0	0
Thailand	9 (5.5)	17 (7.7)	15 (6.6)	0	0	0

PBO, placebo; CANA, canagliflozin; GLIM, glimepiride.

[a]Percentages may not total 100.0% because of rounding.

TABLE 2 Baseline demographic and disease characteristics in the pooled, PBO-controlled studies[a]

	Hot climate subset			Other climate subset		
	PBO (n=163)	CANA 100 mg (n=222)	CANA 300 mg (n=226)	PBO (n=483)	CANA 100 mg (n=611)	CANA 300 mg (n=608)
Sex, n (%)[b]						
Male	71 (43.6)	81 (36.5)	78 (34.5)	263 (54.5)	327 (53.5)	326 (53.6)
Female	92 (56.4)	141 (63.5)	148 (65.5)	220 (45.5)	284 (46.5)	282 (46.4)
Age (years)	53.0±10.0	53.4±9.7	53.3±9.8	57.4±9.5	56.8±10.1	56.6±9.3
Race, n (%)[b]						
White	54 (33.1)	54 (24.3)	77 (34.1)	416 (86.1)	537 (87.9)	533 (87.7)
Black/African American	0	0	1 (0.4)	28 (5.8)	43 (7.0)	47 (7.7)
Asian	61 (37.4)	83 (37.4)	87 (38.5)	21 (4.3)	20 (3.3)	13 (2.1)
Other[c]	48 (29.4)	85 (38.3)	61 (27.0)	18 (3.7)	11 (1.8)	15 (2.5)
HbA1c (%)	8.1±1.0	8.0±0.9	8.0±1.0	8.0±0.9	8.0±0.9	8.0±0.9
BMI (kg/m^2)	29.1±5.5	29.0±5.0	28.6±5.3	32.9±6.4	33.5±6.5	33.2±6.5
eGFR (mL/min/1.73 m^2)	93.0±21.5	93.2±18.4	93.9±20.4	85.0±18.8	86.5±18.9	86.9±17.9
Duration of T2DM (years)	6.5±6.1	6.5±5.1	6.8±6.0	7.8±6.2	7.4±6.0	7.6±6.3

PBO, placebo; CANA, canagliflozin; BMI, body mass index; eGFR, estimated glomerular filtration rate; T2DM, type 2 diabetes mellitus; SD, standard deviation.

[a]Data are mean±SD unless otherwise indicated.

[b]Percentages may not total 100.0% because of rounding.

[c]Includes American Indian or Alaska Native, multiple, unknown, and other in the hot climate subset; and American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, not reported, unknown or others in the other climate subset.

TABLE 3 Baseline demographic and disease characteristics in the active-controlled study[a]

	Hot climate subset			Other climate subset		
	GLIM (n=102)	CANA 100 mg (n=103)	CANA 300 mg (n=102)	GLIM (n=380)	CANA 100 mg (n=380)	CANA 300 mg (n=383)
Sex, n (%)[b]						
Male	56 (54.9)	47 (45.6)	48 (47.1)	207 (54.5)	205 (53.9)	193 (50.4)
Female	46 (45.1)	56 (54.4)	54 (52.9)	173 (45.5)	175 (46.1)	190 (49.6)
Age (years)	52.7±8.2	52.1±8.5	52.3±9.6	57.3±9.0	57.5±9.4	56.7±8.8
Race, n (%)[b]						
White	3 (2.9)	5 (4.9)	5 (4.9)	319 (83.9)	318 (83.7)	328 (85.6)
Black/African American	1 (1.0)	0	0	21 (5.5)	20 (5.3)	18 (4.7)
Asian	58 (56.9)	63 (61.2)	59 (57.8)	35 (9.2)	36 (9.5)	34 (8.9)
Other[c]	40 (39.2)	35 (34.0)	38 (37.3)	5 (1.3)	6 (1.6)	3 (0.8)
HbA1c (%)	7.8±0.7	7.8±0.8	7.7±0.7	7.8±0.8	7.8±0.8	7.8±0.8
BMI (kg/m^2)	27.0±4.4	28.0±4.2	28.0±4.5	31.9±5.4	31.8±5.3	32.0±5.3
eGFR (mL/min/1.73 m^2)	91.2±18.1	91.4±18.4	94.3±19.4	89.0±17.3	89.2±19.5	90.6±19.3
Duration of T2DM (years)	6.3±5.3	5.5±4.7	5.4±4.9	6.7±4.9	6.7±5.6	7.1±5.6

GLIM, glimepiride; CANA, canagliflozin; BMI, body mass index; eGFR, estimated glomerular filtration rate; T2DM, type 2 diabetes mellitus; SD, standard deviation.

[a]Data are mean±SD unless otherwise indicated.

[b]Percentages may not total 100.0% because of rounding.

[c]Includes multiple and other in the hot climate subset; and American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple and others in the other climate subset.

pooled, placebo-controlled studies (Table 2) and the active-controlled study (Table 3). Most patients in the hot climate subset were in the Asian or other racial groups, as expected because of the countries included in this subset; the majority of patients in the other climate subset were White. Consistent with the higher proportion of Asian patients in the hot climate subsets of each population, baseline body mass index was lower among those living in hot climates vs other climates.

3.2 | Efficacy

3.2.1 | Glycaemic efficacy

Pooled, placebo-controlled studies

At week 26, placebo-subtracted LS mean reductions (95% CI) in HbA1c were −0.88% (−1.05 to −0.71) and −0.98% (−1.16 to −0.81) with canagliflozin 100 and 300 mg, respectively, in the hot climate subset and −0.67% (−0.77 to −0.57) and −0.89% (−0.99 to −0.79), respectively, in the other climate subset (Fig. 1A). Relative to placebo, dose-dependent reductions in FPG were seen with canagliflozin 100 and 300 mg in both subsets (Fig. 1B).

Active-controlled Study

Relative to glimepiride, canagliflozin 100 and 300 mg provided LS mean reductions (95% CI) in HbA1c of −0.21% (−0.47 to 0.04) and −0.31% (−0.57 to −0.06), respectively, in the hot climate subset and −0.06% (−0.18 to 0.05) and −0.15% (−0.26 to −0.03), respectively, in the other climate subset at week 104 (Fig. 2A). Dose-dependent reductions in FPG were seen with canagliflozin 100 and 300 mg compared with glimepiride in both subsets (Fig. 2B).

3.2.2 | Body weight and BP

Pooled, placebo-controlled studies

In the hot climate subset, canagliflozin 100 and 300 mg provided per cent reductions in body weight compared with placebo that were consistent with those seen in patients living in other climates over 26 weeks (Fig. 3). Because of the lower baseline body weight in the hot climate subset, absolute changes in body weight were smaller in the hot climate subset than in the other climate subset. Compared with placebo, canagliflozin 100 and 300 mg provided reductions in systolic BP (Fig. 4A) and diastolic BP in the hot climate and other climate subsets at week 26 (Fig. 4B).

Active-controlled study

Canagliflozin 100 and 300 mg were associated with reductions in body weight, whereas an increase in body weight was seen with glimepiride in the hot climate and other climate subsets at week 104 (Fig. 5). Numerically larger reductions in systolic BP were seen with canagliflozin 100 and 300 mg compared with glimepiride in patients living in hot climates at week 104; systolic BP reductions were also seen with both canagliflozin doses in the other climate subset compared with a small increase with glimepiride (Fig. 6A). Canagliflozin 100 and 300 mg provided numerical reductions in diastolic BP compared with glimepiride in the hot climate and other climate subsets at week 104 (Fig. 6B).

3.2.3 | Safety

Pooled, placebo-controlled studies

Canagliflozin 100 and 300 mg were generally well tolerated in the hot climate subset, with a safety profile similar to that seen in patients living in other climates (Table 4). The overall incidence of AEs was similar across groups, with low rates of AEs leading to discontinuation and serious AEs in both subsets.

The incidence of osmotic diuresis–related AEs was higher with canagliflozin 100 and 300 mg compared with placebo in both the hot climate subset (5.0%, 2.2%, and 0.6%, respectively) and the other climate subset (7.4%, 6.9%, and 0.8%, respectively); pollakiuria was the most commonly reported osmotic diuresis–related AE with canagliflozin in both subsets. The incidence of volume depletion–related AEs with canagliflozin 100 and 300 mg and placebo was 0.9%, 0.9% and 0%, respectively, in the hot climate subset, and 1.3%, 1.5% and 1.4%, respectively, in the other climate subset. Specific AEs related to volume depletion that were reported in the canagliflozin-treated patients in the hot climate subset included postural dizziness (n=2), orthostatic hypotension (n=1) and syncope (n=1). There were no AEs of dehydration reported in the hot climate subset, and one patient in the canagliflozin 300 mg group from the other climate subset reported dehydration. Of

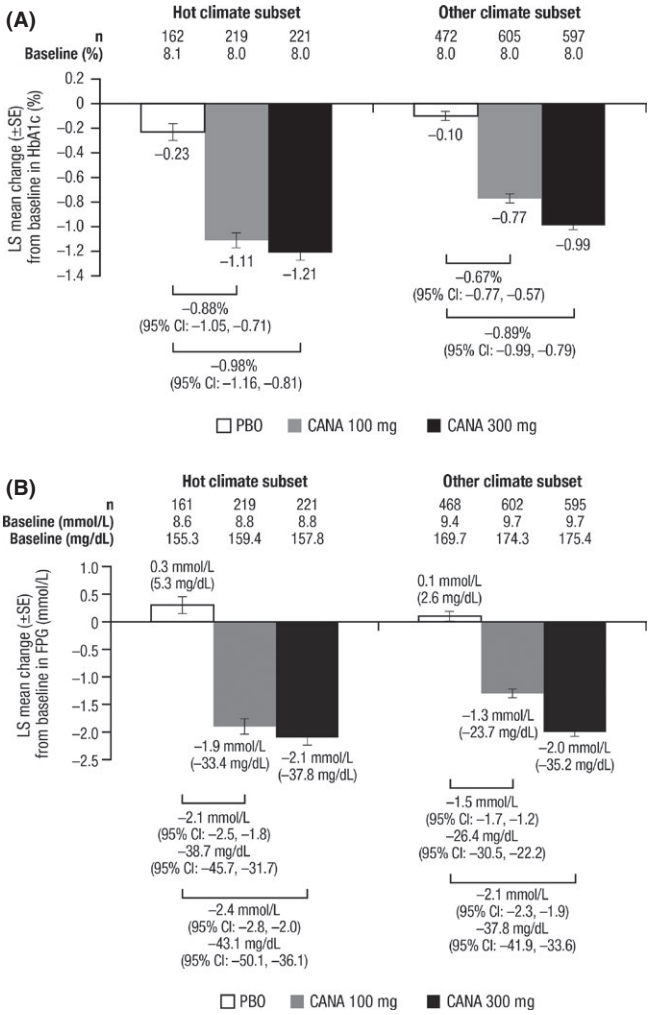

FIGURE 1 Glycaemic efficacy in the hot climate and other climate subsets of the pooled, placebo-controlled studies at week 26: change from baseline in (A) HbA1c and (B) FPG. LS, least squares; SE, standard error; CI, confidence interval; PBO, placebo; CANA, canagliflozin; FPG, fasting plasma glucose

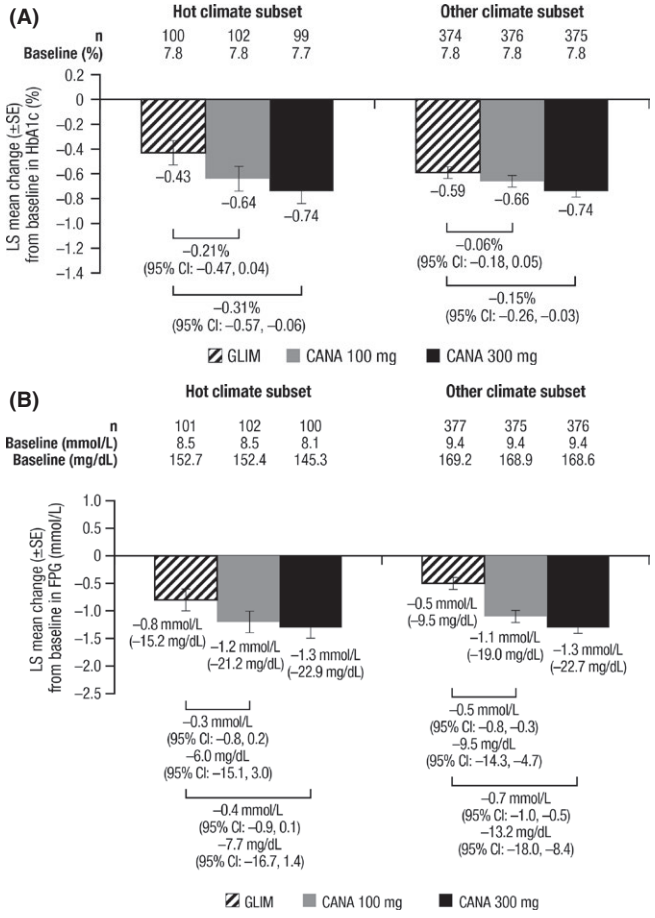

FIGURE 2 Glycaemic efficacy in the hot climate and other climate subsets of the active-controlled study at week 104: change from baseline in (A) HbA1c and (B) FPG. FPG, fasting plasma glucose; LS, least squares; SE, standard error; CI, confidence interval; GLIM, glimepiride; CANA, canagliflozin

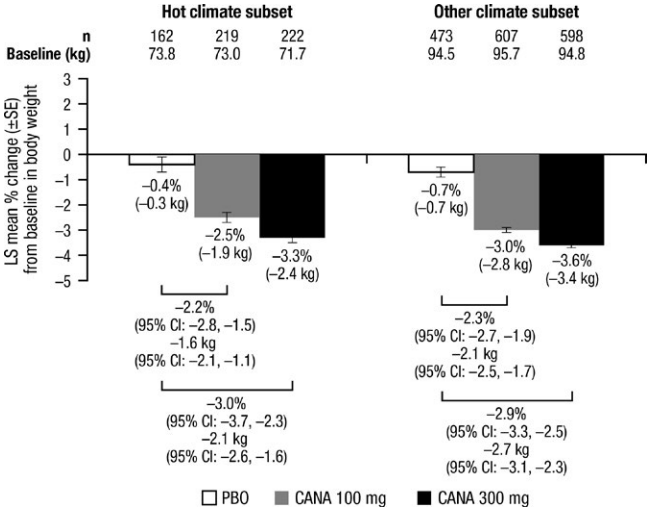

FIGURE 3 Per cent change from baseline in body weight in the hot climate and other climate subsets of the pooled, placebo-controlled studies at week 26. LS, least squares; SE, standard error; CI, confidence interval; PBO, placebo; CANA, canagliflozin

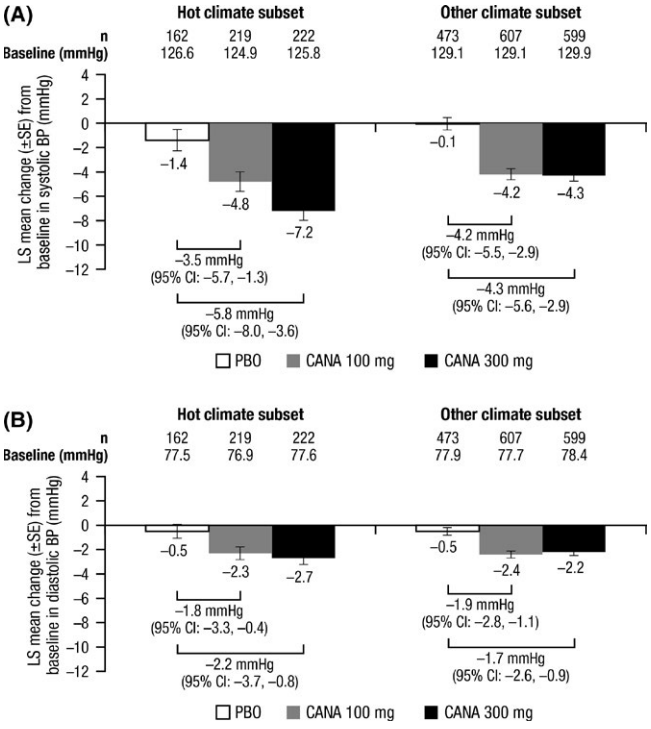

FIGURE 4 Change from baseline in (A) systolic BP and (B) diastolic BP in the hot climate and other climate subsets of the pooled, placebo-controlled studies at week 26. LS, least squares; SE, standard error; BP, blood pressure; CI, confidence interval; PBO, placebo; CANA, canagliflozin

note, 3.6% and 9.6% of patients in the hot climate and other climate subsets, respectively, were at high risk for volume depletion–related AEs at baseline [i.e. estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, on loop diuretic, and/or ≥75 years of age].

The incidence of male genital mycotic infections was higher with canagliflozin 100 and 300 mg compared with placebo in the hot climate subset (3.7%, 6.4% and 0%, respectively) and the other climate subset (4.3%, 3.1% and 0.8%, respectively). At baseline, 83% of men in the hot climate subset and 56% of men in the other climate subset were uncircumcised, and circumcision status was balanced across treatment groups; 94% of men in the hot climate subset and 95% of men in the other climate subset had no history of balanitis. The incidence of female genital mycotic infections was also higher with canagliflozin 100 and 300 mg compared with placebo in the hot climate subset (6.4%, 6.8% and 1.1%, respectively) and the other climate subset (12.3%, 13.8% and 4.1%, respectively). The incidence of UTIs with canagliflozin 100 and 300 mg and placebo was 9.5%, 7.1% and 7.4%, respectively, in the hot climate subset, and 4.6%, 3.3% and 2.9%, respectively, in the other climate subset.

Among patients who were not on background sulphonylurea, documented hypoglycaemia rates with canagliflozin 100 and 300 mg and placebo were 6.5%, 4.0% and 1.5%, respectively, in the hot climate subset, and 2.7%, 4.4% and 2.5%, respectively, in the other climate subset. Among patients on background sulphonylurea, documented hypoglycaemia rates were 39.1%, 18.5% and 19.2%, respectively, in the hot climate subset, and 25.4%, 32.6% and 14.6%, respectively,

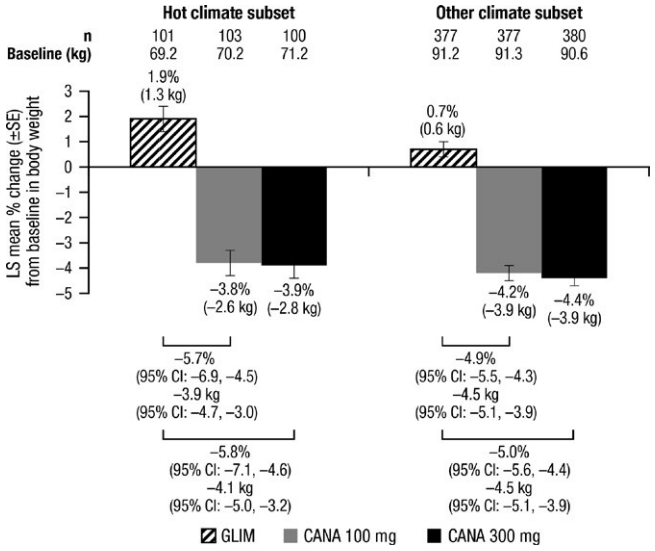

FIGURE 5 Per cent change from baseline in body weight in the hot climate and other climate subsets of the active-controlled study at week 104. LS, least squares; SE, standard error; CI, confidence interval; GLIM, glimepiride; CANA, canagliflozin

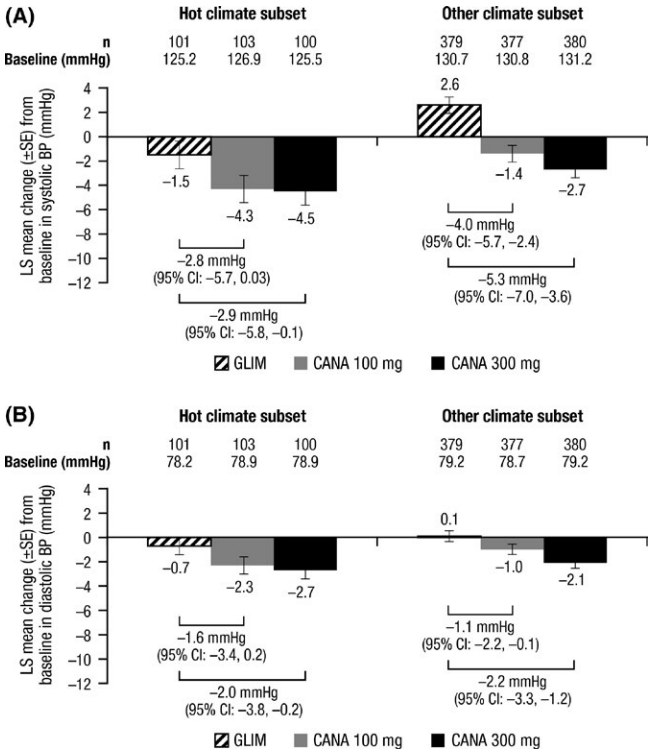

FIGURE 6 Change from baseline in (A) systolic BP and (B) diastolic BP in the hot climate and other climate subsets the active-controlled study at week 104. LS, least squares; SE, standard error; BP, blood pressure; CI, confidence interval; GLIM, glimepiride; CANA, canagliflozin

in the other climate subset. The incidence of severe hypoglycaemia episodes was low across groups and ≤1.0% with canagliflozin in both subsets.

Active-controlled study

Canagliflozin 100 and 300 mg were generally well tolerated compared with glimepiride in the hot climate subset, with a safety profile similar to that seen in patients from other climates (Table 5). The overall incidence of AEs was similar across groups in the hot climate subset; there was no notable trend in the incidences of AEs leading to discontinuation or serious AEs.

The incidence of osmotic diuresis–related AEs with canagliflozin 100 and 300 mg and glimepiride was 1.9%, 2.9% and 2.9%, respectively, in the hot climate subset, and 6.8%, 7.6% and 1.8%, respectively, in the other climate subset. The most common osmotic diuresis–related AE with canagliflozin in the hot climate subset was polyuria. The incidence of volume depletion–related AEs with canagliflozin 100 and 300 mg and glimepiride was 1.0%, 2.0% and 0%, respectively, in the hot climate subset, and 1.8%, 2.6% and 2.9%, respectively, in the other climate subset. Specific AEs related to volume depletion that were reported in canagliflozin-treated patients in the hot climate subset included postural dizziness (n=1), hypotension (n=1) and orthostatic hypotension (n=1). There were no AEs of dehydration reported in the hot climate subset; in the other climate subset, one patient in the canagliflozin 300 mg group and two patients in the glimepiride group reported AEs of dehydration. Among those in the hot climate and other climate subsets, 2.9% and 8.0% of patients were at high risk of volume depletion–related AEs at baseline.

The incidence of male genital mycotic infections was higher with canagliflozin 100 and 300 mg compared with glimepiride in both the hot climate subset (6.4%, 2.1% and 0%, respectively) and the other climate subset (10.2%, 10.9% and 2.4%, respectively). At baseline, 89% of men in the hot climate subset and 65% of men in the other climate subset were uncircumcised, and circumcision status was balanced across treatment groups; 98% of men in the hot climate subset and 94% of men in the other climate subset did not have a history of balanitis. The incidence of female genital mycotic infections was also higher with canagliflozin 100 and 300 mg compared with glimepiride in the hot climate subset (14.3%, 13.0% and 0%, respectively) and the other climate subset (13.7%, 16.3% and 3.5%, respectively). The incidence of UTIs with canagliflozin 100 and 300 mg and glimepiride was 22.3%, 16.7% and 15.7%, respectively, in the hot climate subset, and 7.4%, 6.5% and 4.5%, respectively, in the other climate subset.

The incidence of documented hypoglycaemia with canagliflozin 100 and 300 mg and glimepiride was 4.9%, 11.8% and 35.3%, respectively, in the hot climate subset and 7.4%, 7.3% and 42.4%, respectively, in the other climate subset. The incidence of severe hypoglycaemia episodes was low across groups and ≤1.0% with canagliflozin in both subsets.

4 | DISCUSSION

Canagliflozin 100 and 300 mg improved glycaemic control and lowered body weight and BP compared with placebo and glimepiride in patients with T2DM who live in hot climates, consistent with findings from patients who live in other climates. Canagliflozin 100 and

TABLE 4 Summary of overall safety and selected AEs in the pooled, PBO-controlled studies at week 26[a]

	Hot climate subset			Other climate subset		
Parameter, n (%)	PBO (n=163)	CANA 100 mg (n=222)	CANA 300 mg (n=226)	PBO (n=483)	CANA 100 mg (n=611)	CANA 300 mg (n=608)
Any AE	93 (57.1)	130 (58.6)	138 (61.1)	291 (60.2)	371 (60.7)	356 (58.6)
AEs leading to discontinuation	2 (1.2)	2 (0.9)	5 (2.2)	18 (3.7)	34 (5.6)	25 (4.1)
AEs related to study drug[b]	18 (11.0)	38 (17.1)	39 (17.3)	67 (13.9)	133 (21.8)	152 (25.0)
Serious AEs	1 (0.6)	5 (2.3)	7 (3.1)	21 (4.3)	23 (3.8)	14 (2.3)
Deaths	0	0	0	2 (0.4)	1 (0.2)	1 (0.2)
UTIs	12 (7.4)	21 (9.5)	16 (7.1)	14 (2.9)	28 (4.6)	20 (3.3)
Genital mycotic infections						
Male[c,d]	0	3 (3.7)	5 (6.4)	2 (0.8)	14 (4.3)	10 (3.1)
Female[e,f]	1 (1.1)	9 (6.4)	10 (6.8)	9 (4.1)	35 (12.3)	39 (13.8)
Osmotic diuresis–related AEs[g]	1 (0.6)	11 (5.0)	5 (2.2)	4 (0.8)	45 (7.4)	42 (6.9)
Dry mouth	0	3 (1.4)	0	0	3 (0.5)	2 (0.3)
Micturition urgency	0	0	0	0	2 (0.3)	3 (0.5)
Nocturia	0	0	0	1 (0.2)	3 (0.5)	1 (0.2)
Pollakiuria	1 (0.6)	6 (2.7)	5 (2.2)	3 (0.6)	29 (4.7)	21 (3.5)
Polydipsia	0	3 (1.4)	0	0	3 (0.5)	2 (0.3)
Polyuria	0	0	1 (0.4)	0	6 (1.0)	11 (1.8)
Thirst	0	0	0	1 (0.2)	11 (1.8)	16 (2.6)
Urine output increased	0	0	0	0	1 (0.2)	1 (0.2)
Volume depletion-related AEs	0	2 (0.9)	2 (0.9)	7 (1.4)	8 (1.3)	9 (1.5)
Dehydration	0	0	0	0	0	1 (0.2)
Dizziness postural	0	1 (0.5)	1 (0.4)	2 (0.4)	2 (0.3)	3 (0.5)
Hypotension	0	0	0	4 (0.8)	6 (1.0)	2 (0.3)
Orthostatic hypotension	0	0	1 (0.4)	1 (0.2)	0	3 (0.5)
Syncope	0	1 (0.5)	0	0	0	0
Hypoglycaemia episodes[h]						
Patients not on SU, n	137	199	199	353	477	479
Documented hypoglycaemia	2 (1.5)	13 (6.5)	8 (4.0)	9 (2.5)	13 (2.7)	21 (4.4)
Severe hypoglycaemia	0	1 (0.5)	0	0	0	1 (0.2)
Patients on SU, n	26	23	27	130	134	129
Documented hypoglycaemia	5 (19.2)	9 (39.1)	5 (18.5)	19 (14.6)	34 (25.4)	42 (32.6)
Severe hypoglycaemia	1 (3.8)	0	0	0	1 (0.7)	0

AE, adverse event; PBO, placebo; CANA, canagliflozin; UTI, urinary tract infection; SU, sulphonylurea.

[a]All AEs are reported for regardless of rescue medication; hypoglycaemia episodes are reported for prior to rescue medication.

[b]Possibly, probably or very likely related to study drug, as assessed by investigators.

[c]PBO, n=71; CANA 100 mg, n=81; CANA 300 mg, n=78 in the hot climate subset. PBO, n=263; CANA 100 mg, n=327; CANA 300 mg, n=326 in the other climate subset.

[d]Includes balanitis, balanitis candida and balanoposthitis in the hot climate subset; and balanitis, balanitis candida, balanoposthitis and genital infection fungal in the other climate subset.

[e]PBO, n=92; CANA 100 mg, n=141; CANA 300 mg, n=148 in the hot climate subset. PBO, n=220; CANA 100 mg, n=284; CANA 300 mg, n=282 in the other climate subset.

[f]Includes vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection and vulvovaginitis in the hot climate subset; and genital infection fungal, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection and vulvovaginitis in the other climate subset.

[g]Some patients experienced >1 specific AE in this category.

[h]Includes biochemically documented episodes [≤3.9 mmol/L (70 mg/dL)] with or without symptoms and severe episodes (i.e. requiring the assistance of another individual or resulting in seizure or loss of consciousness).

300 mg were also generally well tolerated in the hot climate subsets of the pooled, placebo-controlled studies and the active-controlled study, with a safety and tolerability profile that was generally consistent with that seen in patients living in other climates.

Because the mechanism of canagliflozin is associated with a potential for increased risk of AEs related to osmotic diuresis and volume depletion,[26] these AEs may be of concern for patients with T2DM in hot climates who are at increased risk of dehydration.[1]

TABLE 5 Summary of overall safety and selected AEs in the active-controlled study at week 104[a]

Parameter, n (%)	Hot climate subset			Other climate subset		
	GLIM (n=102)	CANA 100 mg (n=103)	CANA 300 mg (n=102)	GLIM (n=380)	CANA 100 mg (n=380)	CANA 300 mg (n=383)
Any AE	91 (89.2)	82 (79.6)	84 (82.4)	287 (75.5)	272 (71.6)	294 (76.8)
AEs leading to discontinuation	6 (5.9)	2 (1.9)	6 (5.9)	29 (7.6)	28 (7.4)	40 (10.4)
AEs related to study drug[b]	41 (40.2)	29 (28.2)	28 (27.5)	93 (24.5)	109 (28.7)	131 (34.2)
Serious AEs	9 (8.8)	5 (4.9)	12 (11.8)	60 (15.8)	42 (11.1)	35 (9.1)
Deaths	1 (1.0)	1 (1.0)	2 (2.0)	1 (0.3)	2 (0.5)	1 (0.3)
UTIs	16 (15.7)	23 (22.3)	17 (16.7)	17 (4.5)	28 (7.4)	25 (6.5)
Genital mycotic infections						
Male[c,d]	0	3 (6.4)	1 (2.1)	5 (2.4)	21 (10.2)	21 (10.9)
Female[e,f]	0	8 (14.3)	7 (13.0)	6 (3.5)	24 (13.7)	31 (16.3)
Osmotic diuresis–related AEs[g]	3 (2.9)	2 (1.9)	3 (2.9)	7 (1.8)	26 (6.8)	29 (7.6)
Dry mouth	0	1 (1.0)	0	2 (0.5)	3 (0.8)	2 (0.5)
Micturition urgency	0	0	0	0	1 (0.3)	1 (0.3)
Nocturia	1 (1.0)	0	0	3 (0.8)	1 (0.3)	3 (0.8)
Pollakiuria	1 (1.0)	0	1 (1.0)	1 (0.3)	13 (3.4)	11 (2.9)
Polydipsia	0	0	0	0	2 (0.5)	0
Polyuria	2 (2.0)	2 (1.9)	2 (2.0)	1 (0.3)	2 (0.5)	3 (0.8)
Thirst	0	0	0	0	8 (2.1)	14 (3.7)
Urine output increased	0	0	0	0	5 (1.3)	2 (0.5)
Volume depletion–related AEs[g]	0	1 (1.0)	2 (2.0)	11 (2.9)	7 (1.8)	10 (2.6)
Blood pressure decreased	0	0	0	0	2 (0.5)	1 (0.3)
Dehydration	0	0	0	2 (0.5)	0	1 (0.3)
Dizziness postural	0	0	1 (1.0)	5 (1.3)	3 (0.8)	2 (0.5)
Hypotension	0	1 (1.0)	0	2 (0.5)	1 (0.3)	2 (0.5)
Orthostatic hypotension	0	0	1 (1.0)	0	1 (0.3)	1 (0.3)
Presyncope	0	0	0	2 (0.5)	0	0
Syncope	0	0	0	2 (0.5)	0	4 (1.0)
Hypoglycaemia episodes[h]						
Documented hypoglycaemia	36 (35.3)	5 (4.9)	12 (11.8)	161 (42.4)	28 (7.4)	28 (7.3)
Severe hypoglycaemia	2 (2.0)	1 (1.0)	1 (1.0)	14 (3.7)	2 (0.5)	0

AE, adverse event; GLIM, glimepiride; CANA, canagliflozin; UTI, urinary tract infection.

[a]All AEs are reported for regardless of rescue medication; hypoglycaemia episodes are reported for prior to rescue medication.

[b]Possibly, probably or very likely related to study drug, as assessed by investigators.

[c]GLIM, n=56; CANA 100 mg, n=47; CANA 300 mg, n=48 in the hot climate subset. GLIM, n=207; CANA 100 mg, n=205; CANA 300 mg, n=193 in the other climate subset.

[d]Includes balanoposthitis and genital infection fungal in the hot climate subset; and balanitis, balanitis candida, balanoposthitis, genital candidiasis and genital infection fungal in the other climate subset.

[e]GLIM, n=46; CANA 100 mg, n=56; CANA 300 mg, n=54 in the hot climate subset. GLIM, n=173; CANA 100 mg, n=175; CANA 300 mg, n=190 in the other climate subset.

[f]Includes vaginal infection, vulvitis, vulvovaginal candidiasis and vulvovaginitis in the hot climate subset; and genital infection fungal, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection and vulvovaginitis in the other climate subset.

[g]Some patients experienced >1 specific AE in this category.

[h]Includes biochemically documented episodes (≤3.9 mmol/L [70 mg/dL]) with or without symptoms and severe episodes (i.e. requiring the assistance of another individual or resulting in seizure or loss of consciousness).

The incidence of osmotic diuresis–related AEs was higher with both canagliflozin doses vs placebo in both subsets of the pooled, placebo-controlled studies; in the active-controlled study, the incidence of osmotic diuresis–related AEs was similar across groups in the hot climate subset. The incidence of osmotic diuresis–related AEs associated with urination (e.g. pollakiuria, polyuria, nocturia, urine output increased) was lower in patients from hot climates vs those who were from other climates. There was no imbalance in the incidence of volume depletion–related AEs in either subset; specifically, no AEs of dehydration were reported with canagliflozin among

patients in both hot climate subsets. Of note, the observed incidence of volume depletion–related AEs was lower than the proportion of patients who were at higher risk of these AEs.

Consistent with previous results across studies[7–21] and in those living in other climates, canagliflozin was associated with higher incidences of male and female genital mycotic infections compared with placebo or glimepiride in the hot climate subset of each population; the overall incidence of genital mycotic infections was lower across groups in the hot climate subset compared with the other climate subset. There was no clear trend in UTI incidence with canagliflozin vs either placebo or glimepiride; however, UTI incidence was generally higher across groups in the hot climate subsets compared with the other climate subsets. Previous studies have suggested that there is seasonality for the incidence of UTIs, with more UTIs reported during warmer months.[27] It has been postulated that this trend may be related, in part, to dehydration, which can decrease the frequency of urination; swimming in natural bodies of water; warm weather creating a suitable environment for bacterial transfer to the urethra; or poor sanitation and contaminated drinking water.[27,28]

Patients with T2DM who live in warm climates have a high risk of hypoglycaemia, primarily because of the increased likelihood of dehydration.[29] The incidence of documented hypoglycaemia was higher with canagliflozin vs placebo and lower with canagliflozin vs glimepiride in the hot climate subsets, with no clear trend showing increased incidence compared with the other climate subset. Furthermore, the incidence of severe hypoglycaemia episodes was low across groups and ≤1.0% with canagliflozin in patients living in hot climates in both populations. Therefore, there does not appear to be an increased risk of hypoglycaemia with canagliflozin in patients who live in hot climates. This may have important implications for Muslim patients with T2DM who fast during the holy month of Ramadan, many of whom also live in warmer climates.[30] Changes in eating and drinking habits during this time may increase the risk of hypoglycaemia and dehydration; therefore, medications that can be used to control T2DM with a low risk of these AEs would be beneficial.[30] To date, there have been limited studies of SGLT2 inhibitors in patients with T2DM during Ramadan[31]; therefore, safety findings from the current analysis in patients from hot climates may help to inform clinician decisions related to T2DM management during Ramadan.

The efficacy of canagliflozin 100 and 300 mg in the hot climate subsets of each study was consistent with trends observed in the broader study populations, including improvements in glycaemic efficacy and reductions in body weight and systolic BP.[7–21] Compared with the other climate subsets, numerically larger reductions in HbA1c were seen with canagliflozin 100 and 300 mg relative to either placebo or glimepiride in the hot climate subsets; however, there is no clear explanation for this trend. Because of the lower baseline body weight of patients in the hot climate subsets, absolute changes in body weight were smaller in the hot climate subsets than in the other climate subsets.

This analysis was limited by its post hoc nature and the small number of patients living in hot climates in the studies, which may have led to some of the spurious results for safety data in the hot climate subsets (e.g. hypoglycaemia, UTIs). Furthermore, patient enrolment by country was not stratified to be balanced among countries in hot climates and differed in the two populations because individual studies were conducted at different study centres worldwide. In addition, while countries with study centres located between the Tropics of Cancer and Capricorn were selected to be representative of hot climates, local climates in cities where the studies were conducted could vary depending on geography and seasonality. Similarly, study centres in countries not classified as having a hot climate may still have seasonal variations in weather that could impact treatment.

In summary, canagliflozin provided glycaemic improvements, weight loss and BP reductions, and was generally well tolerated in patients with T2DM living in hot climates, with low incidences of volume depletion–related AEs and hypoglycaemia. Therefore, findings from this analysis support the use of canagliflozin for the treatment of patients with T2DM who live in hot climates.

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AUTHOR CONTRIBUTIONS

M.J., S.C., R.V., C.D. and M.H. contributed to the interpretation of the data, and drafted, reviewed and approved the manuscript. A.S. contributed to the analysis and interpretation of the data, and drafted, reviewed and approved the manuscript. W.C. and G.H. contributed to the design and conduct of the analysis; the acquisition, analysis and interpretation of the data; and drafted, reviewed and approved the manuscript.

DISCLOSURE

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