**Original Article**

**Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus from India**

K. M. Prasanna Kumar, Viswanathan Mohan¹, Bipin Sethi², Pramod Gandhi³, Ganapathi Bantwal⁴, John Xie⁵, Gary Meininger⁶, Rong Qiu⁸

Bangalore Diabetes Hospital, ¹Department of Endocrinology, St. John’s Medical College and Hospital, Bengaluru, Karnataka, ¹Dr. Mohan’s Diabetes Specialties Centre and Madras Diabetes Research Foundation, Chennai, Tamil Nadu, ²CARE Hospitals, Hyderabad, Telangana, ³Gandhi Research Institute, Nagpur, Maharashtra, India, ⁴Janssen Research and Development, LLC, Raritan, NJ, USA

**ABSTRACT**

**Background:** This post hoc analysis evaluated the efficacy and safety of canagliflozin, a sodium glucose co-transporter 2 inhibitor, in patients with type 2 diabetes mellitus (T2DM) from India. **Methods:** Changes from baseline in HbA₁c, fasting plasma glucose (FPG), body weight, and blood pressure (BP) with canagliflozin 100 and 300 mg were evaluated in a subgroup of patients from India (n = 124) from 4 randomized, double-blind, placebo- and active-controlled, Phase 3 studies (N = 2313; Population 1). Safety was assessed based on adverse event (AE) reports in these patients and in a broader subgroup of patients from India (n = 1036) from 8 randomized, double-blind, placebo- and active-controlled, Phase 3 studies (N = 9439; Population 2). **Results:** Reductions in HbA₁c with canagliflozin 100 and 300 mg were −0.74% and −0.88%, respectively, in patients from India, and −0.81% and −1.00%, respectively, in the 4 pooled Phase 3 studies. In the Indian subgroup, both canagliflozin doses provided reductions in FPG, body weight, and BP that were consistent with findings in the overall population. The incidence of overall AEs in patients from India was generally similar with canagliflozin 100 and 300 mg and noncanagliflozin. The AE profile in patients from India was generally similar to the overall population, with higher rates of genital mycotic infections and osmotic diuresis–related and volume depletion–related AEs with canagliflozin versus noncanagliflozin. **Conclusion:** Canagliflozin provided glycemic control, body weight reduction, and was generally well tolerated in patients with T2DM from India.

**Key words:** Fasting blood glucose, HbA₁c, hyperglycemia, oral medications, type 2 diabetes

**INTRODUCTION**

The prevalence of type 2 diabetes mellitus (T2DM) is increasing globally, particularly in developing countries.¹,² In India, it is estimated that over 65 million people have T2DM, making it the country with the second highest number of cases, behind only China.³,⁴ It is projected that nearly 110 million people in India will have T2DM by 2035.² Thus, T2DM poses a significant economic and health care burden in India.

Many Indian patients have been shown to exhibit clinical and biochemical characteristics that predispose them to T2DM, including increased insulin resistance and abdominal obesity despite having lower body weight and body mass index (BMI).⁵,⁶,⁷ These characteristics are collectively referred to as the “Asian Indian Phenotype” and, along with lifestyle changes resulting from increased...
Canagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor developed for the treatment of adults with T2DM. Canagliflozin lowers plasma glucose via an insulin-independent mechanism by lowering the renal threshold for glucose and promoting urinary glucose excretion (~80–120 g/day), which leads to a mild osmotic diuresis and net caloric loss. Across Phase 3 studies, canagliflozin improved glycemic control and reduced body weight and blood pressure (BP) and was generally well tolerated in a broad range of patients with T2DM inadequately controlled by their current treatment regimen. In a preliminary post hoc analysis, canagliflozin was shown to reduce HbA1c, body weight, and BP in patients with T2DM from India using pooled data from 6 placebo-controlled studies, including the CANagliflozin cardioVascular Assessment Study (CANVAS) add-on to insulin and add-on to sulfonylurea substudies. An additional post hoc analysis was performed excluding the CANVAS substudies, which had a different design and patient population compared with the other studies, such as a shorter duration (18 weeks vs. 26 weeks) and a population of patients with T2DM who had a history or high risk of cardiovascular (CV) disease. This manuscript describes the efficacy findings from this analysis in subgroups of patients with T2DM from India based on pooled data from 4 placebo-controlled studies, as well as an assessment of the safety of canagliflozin based on pooled data from a broader population of patients with T2DM.

**Methods**

**Study design, patient populations, and treatments**

This post hoc analysis for efficacy was based on pooled data from patients with T2DM (N = 2313; Population 1) enrolled in four 52-week, double-blind, placebo- and active-controlled, Phase 3 studies, including canagliflozin as monotherapy, add-on to metformin, add-on to metformin plus sulfonylurea, and add-on to metformin plus pioglitazone. In each study, patients were randomized to receive canagliflozin 100 or 300 mg or placebo once daily. The add-on to metformin study included a sitagliptin treatment arm that was not included in this analysis. In the monotherapy, add-on to metformin, and add-on to metformin plus pioglitazone studies, patients in the placebo group were switched to sitagliptin 100 mg after 26 weeks. The safety and tolerability of canagliflozin 100 and 300 mg were assessed in Population 1 and in a broader population of patients with T2DM enrolled in 8 double-blind, placebo- and active-controlled, Phase 3 studies (N = 9439; Population 2). Population 2 included 26-week data from the studies described above, as well as the 52-week study of canagliflozin as add-on to metformin versus glimepiride, the 26-week study in older patients aged ≥55–≤80 years, the 26-week study in patients with moderate renal impairment (baseline estimated glomerular filtration rate ≥30–<50 mL/min/1.73 m²), and CANVAS. Safety analyses for CANVAS, an ongoing event-driven study, were performed using data up to a cut-off date of September 15, 2011.

At screening, eligible patients must have had inadequately controlled T2DM with diet and exercise (monotherapy study) or on the protocol-designated background antihyperglycemic agent (AHA) therapy. Key inclusion criteria for most studies included HbA1c ≥7.0% and ≤10.5% at screening and repeated fasting plasma glucose (FPG) <15.0 mmol/L during the pretreatment phase. The age range for most studies was ≥18–≤80 years; exceptions include the study in older patients aged ≥55–≤80 years; CANVAS, which enrolled patients aged ≥30 years (with CV history) or ≥50 years (with presence of CV risk factors) and had no upper age limit; and the study in patients with moderate renal impairment, which enrolled patients aged ≥25 years with no specified upper age limit. Common exclusion criteria included a history of diabetic ketoacidosis or type 1 diabetes; severe renal impairment; history of myocardial infarction, unstable angina, revascularization procedure, or a cerebrovascular accident within 3 months of screening; uncontrolled hypertension; and alanine aminotransferase level >2 times the upper limit of normal (ULN) or total bilirubin >1.5 times the ULN at screening. Details of the study design, including randomization, blinding, and glycemic rescue therapy, have previously been reported for the individual studies included in these pooled datasets.

All studies included in this analysis were conducted in accordance with ethical principles that comply with the Declaration of Helsinki and were consistent with Good Clinical Practices and applicable regulatory requirements. Study protocols and amendments were approved by the Institutional Review Boards and Independent Ethics Committees. All patients provided written informed consent prior to participation in the studies.

**Study endpoints and assessments**

This post hoc analysis evaluated changes from baseline in HbA1c, FPG, body weight, and systolic and diastolic
BP at week 52 in Population 1 (N = 2313) and in a
subgroup of patients from India (n = 124); safety and
tolerability were assessed in these patients based on
adverse event (AE) reports through week 52. Since therapy
with canagliflozin and sitagliptin were not concurrently
initiated in Population 1 (i.e., patients in the placebo
groups of the monotherapy, add-on to metformin, and
add-on to metformin plus pioglitazone studies switched
to sitagliptin 100 mg after 26 weeks), direct comparisons
for efficacy parameters at week 52 cannot be made as
the placebo/sitagliptin group served as a control group
for safety purposes only. Therefore, efficacy findings
are reported for canagliflozin 100 and 300 mg, while
safety findings are reported for canagliflozin 100 and
300 mg and placebo/sitagliptin. Safety and tolerability
were also assessed in Population 2 (N = 9439) and in
a subgroup of patients from India (n = 1038) through
the primary time point of studies (i.e., week 26 or 52,
or the cut-off date of September 15, 2011 for CANVAS).
Documented hypoglycemia episodes, including
biochemically documented episodes (≤3.9 mmol/L) and
severe episodes (i.e., requiring the assistance of another
individual or resulting in seizure or loss of consciousness),
were also evaluated separately in patients from India in
Population 2 in the pooled placebo-controlled studies by
baseline use of AHAs associated with hypoglycemia, and
in the individual add-on to metformin versus glimepiride
study.

Statistical analyses
Efficacy analyses were conducted using the modified
intent-to-treat population, which included all randomized
patients who received ≥1 dose of double-blind study drug.
The last observation carried forward approach was used
to impute missing data; for patients who received glycemic
rescue therapy, the last postbaseline value prior to initiation
of rescue was used for analysis. An analysis of covariance
model, with treatment and stratification factors as fixed effects
and the corresponding baseline value for each endpoint as
a covariate, was used to assess primary endpoints. The least
squares (LS) mean changes from baseline were estimated.
Safety analyses included all reported AEs, regardless of
rescue therapy, and included all randomized patients who
received ≥1 dose of double-blind study drug.

RESULTS

Patient disposition and baseline characteristics
Baseline demographic and disease characteristics were
generally similar across treatment groups within each
population [Tables 1 and 2]. Patients from India were
younger and tended to have a lower baseline body weight
and BMI compared with patients in the overall populations.
In Population 1, 23.9% of patients in the overall population
discontinued the study compared with 16.9% of patients
from India; rates of discontinuation with canagliflozin
100 and 300 mg and noncanagliflozin were 21.4%, 20.4%,
and 31.7%, respectively, in the overall population and
14.3%, 15.9%, and 22.6%, respectively, in patients from
India. In Population 2, rates of discontinuation were similar
in the overall population and Indian subgroup (15.3% and
14.2%, respectively).

Efficacy
Glycemic parameters
Efficacy parameters were assessed in a pooled population of
patients from 4 Phase 3 studies (N = 2313; Population 1) and
in a subgroup of patients from India (n = 124). Canagliflozin
100 and 300 mg provided clinically meaningful reductions
in HbA1c in the overall population and in the Indian
subgroup [Figure 1a]. In the overall population, LS mean
reductions in HbA1c with canagliflozin 100 and 300 mg
were −0.81% and −1.00%, respectively. In patients from
India, reductions in HbA1c with canagliflozin 100 and 300 mg
were −0.74% and −0.88%, respectively. Canagliflozin
100 and 300 mg also provided reductions in FPG in the
overall population and in the Indian subgroup [Figure 1b].
In the overall population, LS mean reductions in FPG
with canagliflozin 100 and 300 mg were −1.4 mmol/L
and −1.8 mmol/L, respectively. In patients from India,
reductions in FPG with canagliflozin 100 and 300 mg
were −1.0 mmol/L and −1.8 mmol/L, respectively.

Body weight and blood pressure
Both canagliflozin doses were associated with reductions
in body weight in the overall population and in the Indian
subgroup [Figure 1c]. In the overall population, LS mean
percent reductions in body weight with canagliflozin 100
and 300 mg were −2.9% and −3.6%, respectively. In patients
from India, mean percent reductions in body weight
with canagliflozin 100 and 300 mg were −2.5% and −3.2%,
respectively. Both canagliflozin doses also provided
reductions in BP in the overall population and in the Indian
subgroup [Figure 1d and e]. In the overall population, LS
mean reductions in systolic BP with canagliflozin 100 and
300 mg were −3.4 mmHg and −4.1 mmHg, respectively.
In patients from India, reductions with canagliflozin 100
and 300 mg were −3.4 mmHg and −4.4 mmHg, respectively.
Reductions in diastolic BP with canagliflozin 100 and
300 mg were −1.9 mmHg and −1.9 mmHg, respectively, in
the overall population, and −0.5 mmHg and −0.7 mmHg,
respectively, in the Indian subgroup.

Safety and tolerability
In Population 1, the overall incidence of AEs at week
52 was similar across treatment groups in the overall
population and in the Indian subgroup [Table 3]. In the overall population, the incidence of AEs leading to discontinuation with canagliflozin 100 and 300 mg and noncanagliflozin was 4.6\%, 4.0\%, and 3.7\%, respectively; the incidence of serious AEs was 4.9\%, 3.8\%, and 5.7\%, respectively. In the Indian subgroup, 1 patient in the noncanagliflozin group and no patients treated with canagliflozin experienced AEs that led to discontinuation; 4 patients in the canagliflozin 100 mg group and no patients in the canagliflozin 300 mg and noncanagliflozin groups reported serious AEs.

In Population 2, the overall incidence of AEs was higher with canagliflozin 300 mg compared with canagliflozin 100 mg and noncanagliflozin in both the overall population and in the Indian subgroup; the incidence of AEs was lower overall in patients from India [Table 4]. In the overall population, the incidence of AEs leading to discontinuation was 4.2\%, 5.6\%, and 3.7\% with canagliflozin 100 and 300 mg and noncanagliflozin, respectively; the incidence of serious AEs was 7.7\%, 8.1\%, and 8.3\%, respectively. In the Indian subgroup, the incidence of AEs leading to discontinuation was 1.8\%, 4.0\%, and 1.4\% with canagliflozin 100 and 300 mg and noncanagliflozin, respectively; the incidence of serious AEs was 7.0\%, 4.6\%, and 6.9\%, respectively.

In Populations 1 and 2, incidences of genital mycotic infections in men and women were higher with canagliflozin compared with noncanagliflozin in the overall populations.
and in the Indian subgroups; these AEs were mild to moderate in intensity, and few led to study discontinuation. In Population 2, the incidence of genital mycotic infections was lower across treatment groups in patients from India than in the overall population. Rates of urinary tract infections (UTIs) were generally similar across treatment groups in the overall population of Population 1; in patients from India in Population 1 (n = 124), UTI rates were lower with canagliflozin 300 mg (2.3%) versus canagliflozin 100 mg (14.3%) and noncanagliflozin (12.9%). In Population 2, UTI rates were higher with canagliflozin versus noncanagliflozin in both the overall population and in the Indian subgroup. The incidence of osmotic diuresis–related and volume depletion–related AEs was higher with canagliflozin versus noncanagliflozin in the overall population of Populations 1 and 2 and in the Indian subgroup of Population 2; in the Indian subgroup of Population 1, osmotic diuresis–related and volume depletion–related AEs were each reported by only 1 patient with canagliflozin 100 mg.
Among patients from India in the placebo-controlled studies of Population 2 not on a background AHA associated with hypoglycemia (n = 200), 4 patients experienced a documented hypoglycemia episode with canagliflozin 100 mg over 26 weeks; no documented hypoglycemia episodes were reported with canagliflozin 300 mg or placebo, and no severe episodes of hypoglycemia were reported in any treatment group [Supplemental Table 1]. Among those on a background AHA associated with hypoglycemia (n = 650), higher rates of documented hypoglycemia were seen with canagliflozin 100 and 300 mg versus placebo over 26 weeks (16.5%, 20.5%, and 11.8%, respectively); the incidence of severe hypoglycemia was 1.4%, 1.9%, and 0%, respectively. In patients from India in the study of canagliflozin as add-on to metformin (n = 109), the incidence of documented hypoglycemia was lower with canagliflozin 100 and 300 mg versus glimepiride over 52 weeks (5.9%, 2.9%, and 24.4%, respectively), despite HbA1c reductions of 0.71%, 0.65%, and 0.50%, respectively; the incidence of severe hypoglycemia was low and similar across treatment groups.

**DISCUSSION**

Findings from this post hoc analysis of pooled Phase 3 studies demonstrated that canagliflozin provided glycemic improvements and reductions in body weight and BP in patients with T2DM from India. In contrast to what was seen in the initial analysis that included the CANVAS substudies, canagliflozin provided dose-dependent reductions in HbA1c in patients from India, which is consistent with findings across Phase 3 studies of
canagliflozin. Similar to what has been reported in studies of canagliflozin in other Asian populations, canagliflozin was associated with reductions in body weight and BP provided by canagliflozin may be particularly beneficial in treating Asian patient populations that generally have a higher prevalence of insulin resistance and beta-cell dysfunction. As canagliflozin does not directly affect insulin secretion or insulin sensitivity, it is expected that canagliflozin would be similarly efficacious in Asian patients compared with a broader population of patients with T2DM, as demonstrated in this analysis. Incretin-based therapies, such as dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, may lose effectiveness over time as insulin resistance worsens and beta cells deteriorate. Canagliflozin provides reductions in HbA1c comparable to what has been reported with DPP-4 and GLP-1 agonists in Asian patients with T2DM and has been shown to improve model-based indices of insulin sensitivity and beta-cell function with sustained treatment.

Canagliflozin was generally well tolerated in patients with T2DM from India with a safety profile similar to that seen in previous Phase 3 studies and in the overall populations reported in the current manuscript. In the broader safety population (Population 2), the incidence of male and female genital mycotic infections was lower in patients from India compared with the overall population and other Phase 3 studies of canagliflozin. A similar pattern of genital mycotic infections has been reported in studies of canagliflozin in other Asian populations as well as in studies of other SGLT2 inhibitors in Asian patients. The incidence of osmotic diuresis–related and volume depletion–related AEs was also lower across treatment groups in patients from India than in the overall Population 2.

In Population 2, the incidence of documented hypoglycemia among patients from India on background AHAs associated with hypoglycemia was low across treatment groups. Among patients from India on a background AHA associated with hypoglycemia (i.e., insulin and/or sulfonylurea), the incidence of documented hypoglycemia was higher with both canagliflozin doses compared with placebo; the incidence of severe hypoglycemia episodes was low across groups. These findings are consistent with the overall population and other Phase 3 studies of canagliflozin, in which the incidence of hypoglycemia was low when canagliflozin was used in conjunction with background therapies that are not associated with hypoglycemia, and higher with background therapies associated with hypoglycemia.

Limitations of this study include the relatively small sample size of patients from India, the lack of a control group for week 52 efficacy data, and the post hoc analysis of data. Longer-term prospective studies would provide a better assessment of the durability of canagliflozin in patients with T2DM from India and would confirm that the efficacy and safety findings from studies of canagliflozin in broader patient populations also apply to these patients.

Conclusions

In summary, canagliflozin provided glycemic improvements and reductions in body weight and BP and was generally well-tolerated in patients with T2DM from India on a range of background therapies.

Acknowledgments

Canagliflozin has been developed by Janssen Research and Development, LLC, in collaboration with Mitsubishi Tanabe Pharma Corporation.

This study was previously presented, in part, in abstract form at the 10th International Diabetes Federation-Western Pacific Region Congress; 21–24 November 2014; Suntec, Singapore.

Financial support and sponsorship

This study was sponsored by Janssen Research and Development, LLC. Editorial support was provided by Kimberly Fuller, Ph.D., of MedErgy, and was funded by Janssen Global Services, LLC.

Conflicts of interest


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