Efficacy and safety of canagliflozin as add-on therapy to teneligliptin in Japanese patients with type 2 diabetes mellitus: Results of a 24-week, randomized, double-blind, placebo-controlled trial

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Aims: To investigate efficacy and safety of the sodium–glucose co-transporter 2 (SGLT2) inhibitor canagliflozin administered as add-on therapy to the dipeptidyl peptidase-4 (DPP-4) inhibitor teneligliptin in patients with type 2 diabetes mellitus (T2DM).

Materials and methods: We conducted a multicentre, randomized, double-blind, placebo-controlled, phase 3 clinical trial in Japanese patients with T2DM who had inadequate glycaemic control with teneligliptin. Patients were randomized to receive teneligliptin 20 mg plus either canagliflozin 100 mg (T + C, n = 70) or placebo (T + P, n = 68) once daily. The primary endpoint was the change in glycated haemoglobin (HbA1c) from baseline to week 24. Other endpoints included changes in fasting plasma glucose, body weight, proinsulin/C-peptide ratio, homeostatic model assessment 2-%B and adverse events. Patients also underwent mixed-meal tolerance tests.

Results: The difference between the T + C and T + P groups for HbA1c change from baseline to week 24 was −0.88% (least-squares mean, \(P < .001\)). Fasting plasma glucose, body weight and the proinsulin/C-peptide ratio were significantly lower in the T + C group than in the T + P group. Homeostatic model assessment 2-%B improved with T + C compared with T + P. The T + C group exhibited a decrease in the 2-hour postprandial plasma glucose and plasma glucose area under the curve (AUC0-2h) in a mixed-meal tolerance test. No significant between-group differences were observed for C-peptide AUC0-2h or glucagon AUC0-2h after meals. Incidences of adverse events were 60.0% and 47.1% in the T + C and T + P groups, respectively. No hypoglycaemia was observed.

Conclusions: Canagliflozin administered as add-on therapy to teneligliptin was effective and well tolerated in Japanese T2DM patients.

KEYWORDS
canagliflozin, co-transporter 2 inhibitors, dipeptidyl peptidase-4 inhibitors, sodium glucose type 2 diabetes mellitus, teneligliptin
1 | INTRODUCTION

Dipeptidyl peptidase-4 (DPP-4) inhibitors promote insulin secretion in a glucose-dependent manner by increasing active glucagon-like peptide-1 (GLP-1) levels and decreasing glucose levels without causing hypoglycaemia. In Japan, several DPP-4 inhibitors, including teneligliptin,1,2 are available and are used in a wide range of patients with type 2 diabetes mellitus (T2DM). Recently, it was reported that DPP-4 inhibitors are more potent in lowering glycated haemoglobin (HbA1c) levels in Asian populations with T2DM, including Japanese patients, compared with Western (Caucasian) populations.3,4 The difference in efficacy of DPP-4 inhibitors between these populations may be related to differences in the pathophysiology of T2DM. For example, Caucasian patients are more likely to develop insulin resistance associated with obesity which then leads to T2DM, whereas Japanese patients more often exhibit a decrease in insulin secretion capacity that leads to the development of T2DM.5-8 The safety of DPP-4 inhibitors, particularly the absence of hypoglycaemia, together with the difference in T2DM pathophysiology, possibly contributed to the rapid increase in prescriptions for DPP-4 inhibitors for T2DM in Japan since their launch in 2009.9-11

Sodium–glucose co-transporter 2 (SGLT2) inhibitors, novel antidiabetic agents, have a selective inhibitory effect on SGLT2, a protein expressed in the proximal renal tubules. They enhance urinary glucose excretion, which consequently reduces hyperglycaemia. The efficacy and safety of SGLT2 inhibitors, either as monotherapy or in combination with other drugs, in Japanese patients with T2DM has been reported in several studies.12-19 Because a large proportion of patients with T2DM in Japan are taking a DPP-4 inhibitor, SGLT2 inhibitors are often prescribed as add-on therapy to DPP-4 inhibitors in clinical practice.20 SGLT2 inhibitors block glucose reabsorption in the kidney, and their use in combination with a DPP-4 inhibitor brings together distinct mechanisms of action for reducing glucose levels.21 Thus, combination therapy with a DPP-4 inhibitor and SGLT2 inhibitor would be expected to achieve a potent plasma glucose-lowering effect.

Previous clinical trials investigating the use of SGLT2 inhibitors as add-on therapy to DPP-4 inhibitors in Japanese patients with T2DM and inadequate glycaemic control have been limited to open-label studies, for example, that by Inagaki et al.14 To date, there have been no randomized, controlled trials examining the efficacy of an SGLT2 inhibitor added on to a DPP-4 inhibitor in Asian patients. Therefore, to evaluate the efficacy and safety of SGLT2 inhibitors as add-on therapy to DPP-4 inhibitors, we conducted a randomized, double-blind, placebo-controlled clinical trial in which Japanese patients with T2DM and inadequate glycaemic control with teneligliptin monotherapy along with diet and exercise were randomized to either the SGLT2 inhibitor canagliflozin or placebo once daily as an add-on to teneligliptin.

2 | MATERIALS AND METHODS

2.1 | Ethical statement

The Institutional Review Boards at all participating institutions approved the study after reviewing its ethical, scientific, medical and pharmaceutical validity. The study was conducted in accordance with the ethical principles of the Helsinki Declaration, the Japanese “Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices,” Good Clinical Practice and the study protocol. The participating institutions are listed online (Appendix S1). The trial was registered at ClinicalTrials.gov (NCT02354235).

2.2 | Patients

Informed consent was obtained from all patients prior to enrolment in the trial. Japanese patients with T2DM, aged 20 to 75 years, who had undergone a diet and exercise regimen and had received teneligliptin 20 mg monotherapy once daily for at least 8 weeks prior to initiation of the run-in period were enrolled. Patients using antidiabetic drugs other than teneligliptin were also eligible, providing the other antidiabetic drug was withdrawn for an 8-week washout period; that is, they used only teneligliptin for at least 8 weeks before the run-in period (Figure S1, Supporting Information). Other inclusion criteria were HbA1c ≥ 7.0% and < 10.5% at initiation of the run-in period and by week 2 of the run-in period, with a difference of ≤0.5% in HbA1c between those time points, and fasting plasma glucose (FPG) of ≤270 mg/dL at initiation of the run-in period. Exclusion criteria and withdrawal criteria are given online (Tables S1 and S2, Appendix S1, respectively).

2.3 | Study design, treatments and blinding

The study design is shown in Figure S1, Appendix S1. The study was a multicentre, randomized, double-blind, placebo-controlled trial. During the 4-week run-in period, all patients were administered teneligliptin 20 mg orally and placebo once daily before breakfast. At the start of the treatment period, all patients continued to take teneligliptin 20 mg and were randomized 1:1 in a double-blind manner by a permuted block method to receive either placebo (T + P) or canagliflozin (T + C) 100 mg (the approved dose in Japan), administered orally once daily before breakfast. After the treatment period, patients were observed for an additional 2 weeks (post-treatment observation period), during which they continued to receive teneligliptin 20 mg orally once daily before breakfast.

At the end of the 4-week run-in period (hereafter referred to as baseline) and at the end of the treatment period, patients underwent a mixed-meal tolerance test after a ≥10-hour fast (water was permitted). After basal blood sampling, patients consumed (within 15 minutes) a standard test meal (energy content, 500 kcal; carbohydrate, 60%; lipid, 25%; protein, 15%). Blood samples were obtained at 0.5, 1 and 2 hours after beginning the meal.

2.4 | Efficacy outcomes

The primary endpoint was change in HbA1c from baseline to the end of the treatment period. Secondary endpoints included the following: change in HbA1c from baseline at each measurement time point; change in FPG from baseline to each measurement time point and to the end of the treatment period; the proportion of patients achieving HbA1c < 7.0%; the proportion of patients achieving HbA1c < 8.0%;...
the absolute and percentage changes in body weight; changes in fasting glucagon, proinsulin/C-peptide ratio, total adiponectin and high-molecular weight (HMW) adiponectin; change in homeostatic model assessment (HOMA) 2-%B; 2-hour postprandial plasma glucose; plasma glucose, C-peptide and glucagon areas under the curve from 0 to 2 hours (AUC0-2h) (preprandial to postprandial) and change in C-peptide AUC0-2h/plasma glucose AUC0-2h ratio.

2.5 | Safety

Safety endpoints were adverse events (AEs), hypoglycaemia, laboratory values (haematology, blood biochemistry and urinalysis), electrocardiogram and vital signs. AEs and drug-related AEs were classified according to MedDRA (J. version 18.1) System Organ Class and Preferred Term. For each event, the number of patients and the incidence were calculated. Hypoglycaemia was classified according to the criteria summarized in Appendix S1.

2.6 | Determination of sample size

For the change in HbA1c from baseline to the end of the treatment period, with the assumption that the mean difference to be detected in the T + C group compared with the T + P group was −0.50%, and considering that a decrease of >0.3% is a clinically significant change in HbA1c22 with the SD estimated to be 0.8% based on a previous study,13 55 patients per group were required (t test) to ensure a power of 90% with a 2-sided significance level of 0.05. Therefore, taking into consideration the safety evaluation and the number of withdrawals, the target sample size was determined to be 140 patients (70 patients per group).

2.7 | Statistical analysis

All statistical analyses were performed using Windows SAS (v.9.2 or later version). A 2-sided test was used, with the significance level set at α = .05. Data that were not measured or were immeasurable because of sample issues were handled as missing data. The missing value was imputed with the last available value, using the last observation carried forward (LOCF) approach.

Efficacy was analysed using the full analysis set. For measurements at the end of the treatment period, descriptive statistics, change from baseline to end of treatment period for each group, 95% confidence interval (CI) of the mean for each group, between-group difference (T + C − T + P group) and 95% CI of the difference were calculated. The impact of the baseline measurement on changes in each efficacy endpoint was determined by analysis of covariance using the baseline measurement as the covariate. For the primary endpoint, the least square mean (LS mean) and standard error (SE) of the LS mean were calculated for each group. The point estimate of the between-group difference in LS mean (T + C group − T + P group) as well as the SE, 95% CI and P value were also calculated.

For each secondary endpoint, the change (percent change) from each measurement time point to end of the treatment period (except for HbA1c and evaluation parameters of the mixed-meal tolerance test) was analysed in the same manner as the primary endpoint. The proportions of patients achieving HbA1c < 7.0% and HbA1c < 8.0% in each group at end of the treatment period were calculated, along with the between-group difference (T + C group − T + P group) and P value (Fisher’s exact test).

Safety analysis was performed on the safety analysis set, which included all randomized patients except those who did not receive any dose of canagliflozin or placebo in combination with teneligliptin during the treatment period or patients for whom no safety data were collected after randomization.

3 | RESULTS

3.1 | Patients

The dispositions of patients included in each analysis set are shown in Figure S2, Appendix S1. Of the 185 patients who provided informed consent, 177 patients enrolled in the study and received teneligliptin 20 mg and placebo once daily during the 4-week run-in period. A total of 47 patients discontinued prior to the treatment period. The remaining 138 patients were randomized to receive placebo (T + P group, n = 68) or canagliflozin 100 mg (T + C group, n = 70) for the treatment period. All patients were included in the full analysis set and the safety analysis set. Seven patients in the T + P group and 3 in the T + C group withdrew from the study during the treatment period; reasons for discontinuation were patient request (n = 3), determination of ineligibility by the investigator because of AEs (n = 3) and development of myocardial infarction, congestive cardiac failure, unstable angina or cerebrovascular disorders (n = 1). Sixty-one patients in the T + P group and 67 in the T + C group completed the treatment period.

Demographic and other baseline characteristics are shown in Table 1. Age, body mass index (BMI) and baseline HbA1c and FPG values were comparable between groups.

3.2 | Efficacy

Changes in HbA1c from baseline to week 24 and changes over time in both groups are shown in Table 2 and Figure 1, respectively. The LS mean ± SE change in HbA1c from baseline to week 24 (LOCF) was −0.10% ± 0.10% in the T + P group and −0.97% ± 0.10% in the T + C group, with a significant between-group difference of −0.88% (P < .001) (Table 2). HbA1c in the T + C group rapidly decreased from week 4 to week 12 and then remained low to week 24. By contrast, in the T + P group, HbA1c decreased only slightly to week 24 (Figure 1). In addition, the T + C group showed a significant decrease in HbA1c at each time point compared with the T + P group (P < .001 for all time points).

The proportion of patients achieving HbA1c < 7.0% at week 24 was 19.12% in the T + P group and 40.91% in the T + C group. The proportion of patients achieving HbA1c < 8.0% was 30.43% in the T + P group and 80.00% in the T + C group. There was a significant difference in these proportions between the T + C group and the T + P group for both HbA1c targets (P = .008 for HbA1c < 7.0% and P < .001 for HbA1c < 8.0%).
also showed larger decreases in plasma glucose AUC 0-2h/dL, with a difference of −9.2 mg/dL, significantly greater than that seen in the T + P group (9.2 mg/dL, with a difference of −5.6 mg/dL from baseline to week 24; this reduction was significantly greater in the T + C group compared with the T + P group (P < .001).

There was no significant difference in change from baseline in C-peptide or glucagon AUC0-2h at week 24 between the 2 groups. However, change in the C-peptide AUC0-2h/plasma glucose AUC0-2h ratio from baseline to week 24 was significantly greater in the T + C group compared with the T + P group (P < .001).

### 3.3 Safety

During the treatment and post-treatment observation periods, AEs occurred in 47.1% and 60.0% and drug-related AEs occurred in 11.8% and 10.0% of patients in the T + P and T + C groups, respectively. Serious AEs occurred in 2.9% and 1.4% of patients in the T + P and T + C groups, respectively. Serious drug-related AEs occurred in 1 patient in the T + P group. AEs leading to discontinuation occurred in 2 patients in each group, and drug-related AEs leading to discontinuation occurred in 1 patient in each group. There were no AEs leading to death. AEs are shown in Table 3.

No hypoglycaemia was observed in either group. A urinary tract infection-related AE and a fracture were reported in 1 patient in the T + P and 1 patient in the T + C group, respectively. Increased blood ketone bodies occurred in 2.9% of patients in both the T + P and T + C groups. All of these cases were mild in severity and no cases of ketoacidosis were observed. Cardiovascular-related AEs occurred in 2.9% and 1.4% of patients in the T + P and T + C groups, respectively. Skin disorder-related AEs occurred in 2.9% and 10.0% of patients in the T + P and T + C groups, respectively. One patient in the T + C group developed a rash of moderate severity and discontinued canagliflozin; all other events were mild in severity. AEs related to gastrointestinal disorders occurred in 1.5% and 14.3% of patients in the T + P and T + C groups, respectively. All these events were mild in severity. Two patients in the T + P group developed impaired hepatic function.

Genital infection, osmotic diuresis-related AEs, dehydration and pyelonephritis, which are associated with use of canagliflozin, were not observed in the T + C group. Furthermore, no intestinal obstruction or interstitial pneumonia, which are associated with use of teneligliptin, occurred in the T + C group. Transient increases in total ketone bodies were observed in both groups; however, no patients experienced ketone body increase-related symptoms leading to discontinuation. There were no noteworthy changes in other laboratory values, electrocardiogram findings or vital signs (data not shown).

### 4 Discussion

This randomized, placebo-controlled trial investigated the efficacy and safety of canagliflozin as add-on therapy in Japanese patients who had inadequate glycaemic control with teneligliptin monotherapy. Add-on canagliflozin to teneligliptin was associated with greater reductions in HbA1c, FPG and postprandial glucose
Some patients treated with a DPP-4 inhibitor require additional antidiabetic agents to achieve and maintain favourable glycaemic control. As we expected, canagliflozin added on to teneligliptin compared with placebo. These results were consistent with those of prior studies of SGLT2 inhibitors added on to a DPP-4 inhibitor.\textsuperscript{14,16}

### TABLE 2

Effects of canagliflozin vs placebo added to teneligliptin on primary and secondary endpoints at 24 weeks

|                         | T + P (n = 68) | T + C (n = 70) |
|-------------------------|---------------|---------------|
| **HbA1c (%)**           |               |               |
| Baseline                | Mean (SD)     | 7.87 (0.83)   | 8.18 (0.90)   |
| Change from baseline    | LS mean (SE)  | −0.10 (0.10)  | −0.97 (0.10)  |
| Difference vs placebo   | LS mean (95% CI) | −0.88 (−1.15, −0.60) | .001 |
| **FPG\textsuperscript{1} (mg/dL)** | n 67 | 69 |
| Baseline                | Mean (SD)     | 167.0 (33.6)  | 173.9 (30.6)  |
| Change from baseline    | LS mean (SE)  | 3.9 (3.5)     | −34.9 (3.4)   |
| Difference vs placebo   | LS mean (95% CI) | −38.8 (−48.5, −29.2) | .001 |
| **Body weight (kg)**    | n 67          | 69            |
| Baseline                | Mean (SD)     | 73.35 (12.98) | 71.68 (15.79) |
| Change from baseline    | LS mean (SE)  | −0.78 (0.23)  | −2.29 (0.22)  |
| Difference vs placebo   | LS mean (95% CI) | −1.51 (−2.15, −0.88) | .001 |
| **Percent change from baseline** | n 67 | 69 |
| Fasting proinsulin/C-peptide | Mean (SD) | 0.0166 (0.0080) | 0.0176 (0.0089) |
| Change from baseline    | LS mean (SE)  | 0.0002 (0.0005) | −0.0029 (0.0005) |
| Difference vs placebo   | LS mean (95% CI) | −0.0031 (−0.0045, −0.0016) | .001 |
| **HOMA2-%B**            | n 67          | 69            |
| Baseline                | Mean (SD)     | 38.42 (15.47) | 34.20 (14.77) |
| Change from baseline    | LS mean (SE)  | −2.04 (1.41)  | 10.83 (1.38)  |
| Difference vs placebo   | LS mean (95% CI) | 12.87 (8.95, 16.79) | .001 |
| **Fasting glucagon\textsuperscript{2} (pg/mL)** | n 67 | 69 |
| Baseline                | Mean (SD)     | 121.4 (19.4)  | 116.7 (21.3)  |
| Change from baseline    | LS mean (SE)  | 8.5 (2.1)     | 5.7 (2.1)     |
| Difference vs placebo   | LS mean (95% CI) | −2.7 (−8.6, 3.1) | .355 |
| **Fasting total adiponectin (\(\mu\)g/mL)** | n 61 | 66 |
| Baseline                | Mean (SD)     | 3.488 (1.686) | 3.594 (1.714) |
| Change from baseline    | LS mean (SE)  | −0.234 (0.107) | 0.150 (0.103) |
| Difference vs placebo   | LS mean (95% CI) | 0.384 (0.090, 0.677) | .011 |
| **Fasting HMW adiponectin (\(\mu\)g/mL)** | n 61 | 66 |
| Baseline                | Mean (SD)     | 1.1135 (0.8935) | 1.2381 (0.9480) |
| Change from baseline    | LS mean (SE)  | 0.0628 (0.0697) | 0.2612 (0.0670) |
| Difference vs placebo   | LS mean (95% CI) | 0.1984 (0.0068, 0.3899) | .043 |

LS mean by analysis of covariance (factor: treatment group; covariate: baseline value)

Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HMW, high-molecular weight; HOMA, homeostatic model assessment; LS mean, least squares mean; n, number of patients with values at baseline or week 24 (last observation carried forward); SD, standard deviation; SE, standard error; T + C, teneligliptin plus canagliflozin; T + P, teneligliptin plus placebo.

\textsuperscript{1} FPG conversion factor: 1 mg/dL = 0.0555 mmol/L.

\textsuperscript{2} Fasting glucagon conversion factor: 1 pg/mL = 1 ng/L.
improved glycaemic control and was associated with a reduction in body weight.

The HbA1c-lowering effect of DPP-4 inhibitors is influenced by BMI, with reduced efficacy in obese patients, because obesity decreases peripheral insulin sensitivity. Conversely, canagliflozin significantly lowers blood glucose and reduces body weight, regardless of BMI. It is possible that the greater efficacy of teneligliptin and canagliflozin in lowering HbA1c may be explained in part by the reduction in body weight associated with canagliflozin, which would facilitate the blood glucose-lowering effect of teneligliptin. In addition, canagliflozin has been reported to increase total GLP-1 levels. This suggests that the combination of teneligliptin and canagliflozin may boost active GLP-1 levels through the combined effect of canagliflozin on GLP-1 secretion and DPP-4 inhibition by teneligliptin.

Both total adiponectin and HMW adiponectin, which were measured as exploratory endpoints, significantly increased in the T + C group compared with the T + P group. This increase in adiponectin may be the result of reduction in body weight in the T + C group. C-peptide is secreted with insulin at a ratio of 1:1. C-peptide was selected as a marker of insulin secretion because canagliflozin might influence insulin clearance but does not affect the kinetics of C-peptide secretion. In the T + C group, the proinsulin/C-peptide ratio decreased significantly from baseline to week 24 compared with the T + P group. Decreases in the proinsulin/C-peptide ratio with canagliflozin as monotherapy or as combination therapy (including concomitant use with a DPP-4 inhibitor) were previously reported in studies conducted in Japanese patients with T2DM. Furthermore, we observed an improvement in HOMA2-%B in the T + C group, suggesting an improvement in pancreatic β-cell function, which confirms the findings of previous studies of canagliflozin monotherapy or in combination with a DPP-4 inhibitor.

In the mixed-meal tolerance test, a reduction in postprandial plasma glucose occurred in the T + C group. Although there was no difference in the C-peptide AUCO-2h between groups, the C-peptide AUCO-2h/plasma glucose AUCO-2h ratio was increased. These results suggest that canagliflozin may improve β-cell function in the setting of postprandial hyperglycaemia. Taken together, these findings suggest that canagliflozin, which has insulin-independent glucose-lowering activity, may reduce glucose toxicity and the burden on β-cells, leading to an improvement in β-cell function.
In the current study, no significant differences in fasting glucagon or postprandial glucagon levels were observed between the T + C and T + P groups. Regarding the time course of glucagon after a meal, a previous study reported increased glucagon secretion as an acute effect of canagliflozin (300 mg) compared with placebo. Dapagliflozin was shown previously to increase fasting and postprandial glucagon levels, while empagliflozin increased glucagon responses after meal ingestion, leading to an increase in endogenous glucose production. DPP-4 inhibitors have been shown to suppress glucagon responses, and teneligliptin was also reported to lower postprandial glucagon levels. Interestingly, a combination of saxagliptin and dapagliflozin prevented the dapagliflozin-mediated increase in postprandial glucagon levels. For these reasons, the lack of effect of canagliflozin on fasting and postprandial glucagon compared with placebo in this study may be attributable to the suppressive effect of teneligliptin or the use of a low dose of canagliflozin (100 mg).

With regard to safety, the incidence of AEs was higher in the T + C group than in the T + P group. Although the incidence of AEs related to gastrointestinal disorders and skin disorders was higher in the T + C group, only 1 gastrointestinal event and 3 skin disorders were considered to be drug-related in the T + C group. Examination of the details of AEs related to gastrointestinal or skin disorders revealed no specific individual AEs with a disproportionately high incidence. AEs commonly associated with SGLT2 inhibitors, such as genital infection or osmotic diuresis, were not observed in this study. Furthermore, no hypoglycaemia was observed in either group and there were no new safety signals that have not already been reported for canagliflozin or teneligliptin.

This study had some limitations. First, it was conducted in Japanese patients only. As there are differences in diet as well as T2DM pathophysiology between Japanese and Western populations, including insulin secretion capacity, the study findings may not be extrapolated to other ethnic groups without consideration of these points. In addition, because the present study had a 24-week treatment period, the long-term safety and efficacy of canagliflozin as an add-on therapy to teneligliptin is unknown and needs to be evaluated. Finally, the sample size of this study might be considered small, but the study was appropriately powered based on a sample size calculation, and was designed in accordance with local and international recommendations for clinical trials of antidiabetic drugs.

In conclusion, canagliflozin as add-on therapy to teneligliptin significantly improved HbA1c and postprandial plasma glucose in this randomized clinical trial in Japanese patients with T2DM, suggesting that the treatment led to an improvement in β-cell function and relief from burden on β-cells. We observed no deviations from the known safety profiles of both teneligliptin and canagliflozin in this combination treatment study. These results confirm the efficacy and tolerability of canagliflozin add-on therapy to teneligliptin in Japanese T2DM patients.

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**Conflict of interest**

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Author contributions

T. K., N. I. and K. K. were the medical advisors for this study and contributed to the study design. K. N., G. K. and N. M. contributed to the study design and performed data collection. N. N. was involved in data analysis. Y. W., H. I. and M.G. contributed to the writing of the manuscript. All authors contributed to interpretation of data and review of the manuscript, and approved this manuscript for submission.

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Additional Supporting Information may be found online in the supporting information tab for this article.

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