ORIGINAL ARTICLE

WILEY

# Dose-dependent reduction in body weight with LIK066 (licogliflozin) treatment in Japanese patients with obesity

Koutaro Yokote MD[1,2] 🔴 | Misako Sano MMSc[3] | Isao Tsumiyama MMath[4] | Deborah Keefe MD[5]

[1]Department of Endocrinology, Hematology and Gerontology, Chiba University Hospital, Chiba, Japan

[2]Department of Diabetes, Metabolism and Endocrinology, Chiba University Hospital, Chiba, Japan

[3]Cardio-Metabolic Clinical Development Department, Clinical Development & Analytics, Novartis Pharma K.K., Tokyo, Japan

[4]Integrated Biostatistics Japan Department, Clinical Development & Analytics, Novartis Pharma K.K., Tokyo, Japan

[5]Rheumatology, Clinical Development & Analytics, Novartis Pharmaceuticals Corporation, East Hanover, New, Jersey

**Correspondence**
Prof. Koutaro Yokote MD, Department of Endocrinology, Hematology and Gerontology, Chiba University Graduate School of Medicine, Chiba, Japan,
Email: kyokote@faculty.chiba-u.jp

## Abstract

**Aims:** LIK066 (licogliflozin) is a dual sodium glucose co-transporter 1/2 inhibitor with potential benefits in weight loss. This study evaluated the efficacy, tolerability and safety of licogliflozin in Japanese adults with obesity.

**Materials and methods:** This study was a randomized, double-blind, placebo-controlled, dose-finding study to evaluate the effect of licogliflozin (2.5, 10, 25 and 50 mg once daily) in 126 Japanese patients with obesity. The primary objective was to examine the dose–response relationship of licogliflozin treatment in body weight reduction relative to placebo at 12 weeks. The secondary objectives included assessment of responder rates, change in parameters related to complications, visceral and subcutaneous fat area, and safety during 12 weeks of treatment.

**Results:** The placebo-subtracted least square mean percentage change in body weight from baseline at week 12 was −1.99 (95% confidence interval −2.92, −0.21), −3.00 (−4.15, −1.70), −3.54 (−4.54, −2.26) and −3.91% (−5.01, −2.77) in licogliflozin 2.5, 10, 25 and 50 mg once-daily dose groups, respectively. The proportion of responders with ≥3% reduction in body weight in the licogliflozin 2.5, 10, 25 and 50 mg once-daily dose groups were 15.8%, 55.6%, 50.0% and 56.7%, respectively, versus placebo [7.1%; $P \leq 0.002$ for all except the 2.5 mg once-daily group ($P = 0.39$)]. Dose-dependent reductions were observed significantly in haemoglobin A1c, uric acid, fasting plasma glucose and potentially in the waist circumference, diastolic blood pressure and visceral fat area.

**Conclusion:** Dual inhibition of SGLT1/2 with licogliflozin treatment induced a dose-dependent reduction in body weight in Japanese patients with obesity. Treatment with licogliflozin was safe and well tolerated in this study. The study is registered with ClinicalTrials.gov (NCT03320941).

**KEYWORDS**
licogliflozin, LIK066, obesity, SGLT1 inhibition, weight control

## 1 | INTRODUCTION

Obesity affects over 650 million people worldwide and is a leading cause of cardiovascular mortality and morbidity.[1] Asians, including the Japanese, tend to have a disproportionate accumulation of visceral fat even at a low body mass index (BMI), thus rendering them at greater risk for obesity-related cardiometabolic diseases compared with people in Western countries.[2] For instance, in Japanese patients with obesity, visceral fat

---

accumulates at a lower BMI (25 kg/m$^2$) than the Western criterion (30 kg/m$^2$), increasing the risk of cardiovascular events associated with obesity.[3] Therefore, the Japan Society for the Study of Obesity (JASSO) defined BMI ≥25 kg/m$^2$ accompanied with health problems caused by or related to being obese as obesity, also referred to as obesity disease in Japan.[4]

Current management of obesity focuses on lifestyle management (low calorie intake and increased physical exercise), pharmacotherapy and bariatric surgery.[5] The use of pharmacotherapy in combination with lifestyle intervention is recommended for patients with obesity with BMI ≥35 kg/m$^2$ and at least one comorbidity, or patients with BMI ≥25 kg/m$^2$ and at least two comorbidities [JASSO defined 11 comorbidities for diagnosis, such as type 2 diabetes mellitus (T2DM), hypertension, dyslipidaemia, hyperuricaemia and gout], which are inadequately controlled with diet and exercise therapies.[4] However, pharmacological agents that are effective in weight management are limited, with only four new drugs approved by the FDA since 2012.[6] In Japan, the only anti-obesity drug available is mazindol (approved only for severely obese patients with BMI ≥35 kg/m$^2$).[7] In addition, prolonged use of some of the anti-obesity drugs is associated with central nervous system-related adverse events (AEs).[8] Therefore, there is a need to develop novel weight-loss drugs for the management of obesity, which are safe and efficacious.

Sodium glucose co-transporter-2 (SGLT2) inhibitors improve glycaemic control in an insulin-independent manner by decreasing glucose reabsorption in the renal proximal tubule, and increasing urinary glucose excretion. SGLT2 inhibitors have other beneficial effects such as reductions in body weight and serum uric acid, blood pressure (BP) lowering and attenuation of glomerular hyperfiltration, which are probably linked to glycosuria-accompanied natriuresis.[9,10]

LIK066 (licogliflozin) is an SGLT1/2 inhibitor.[11] In addition to inhibiting renal SGLT2, licogliflozin inhibits enteric SGLT1.[11] SGLT1 inhibition results in reduced intestinal glucose and galactose absorption leading to calorie wasting, and promotes weight loss through several potential endocrine-based mechanisms such as a reduction in postprandial insulin levels and appetite suppression because of the increased secretion of glucagon-like peptide-1 and peptide YY.[12-15] While inhibition of SGLT2 alone can reduce the body weight to a limited extent,[10] dual SGLT1/2 inhibition is expected to decrease the body weight greatly, particularly in obese patients. Because weight loss is reported to improve not only glucose metabolism but also BP, lipids and liver function, licogliflozin is expected to improve obesity-related complications through body weight reduction. Therefore, the purpose of this study is to evaluate the efficacy, tolerability and safety of licogliflozin in Japanese adults with obesity.

## 2 | METHODS

### 2.1 | Study design

This multicentre, Phase II, randomized, double-blind, parallel-group dose-finding study evaluated the effect of four doses of licogliflozin versus placebo on weight, tolerability and safety. The study consisted of three phases: (i) screening (2 weeks); (ii) single-blind placebo run-in (4 weeks); and (iii) randomized, double-blind treatment (12 weeks). Patient eligibility was assessed at the screening phase and eligible patients entered the single-blind placebo run-in period. Following the run-in phase, eligible patients were randomized in the ratio of 2:2:3:3:3 to receive either 2.5, 10, 25, 50 mg once-daily licogliflozin, or placebo. At randomization, patients were stratified according to their glycaemic status (dysglycaemic/T2DM) at screening. Dysglycaemia was defined as no previous clinical diagnosis of T2DM, fasting plasma glucose (FPG) ≥110 mg/dL and/or haemoglobin A1c (HbA1c) ≥5.6%, except for HbA1c ≥6.5% and FPG ≥126 mg/dL at screening. To ensure that treatment assignment was unbiased and concealed from subjects and investigator staff, a patient randomization list was produced by a vendor using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers were linked to the different treatment arms, which in turn were linked to medication numbers. A separate medication list was produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug.

The study was conducted according to the ethical principles laid down in the Declaration of Helsinki. The study protocol and all amendments were approved by the Independent Ethics Committee and Institutional Review Board for each centre. All patients provided written informed consent to participate in the study. This study is registered with ClinicalTrials.gov (NCT03320941).

### 2.2 | Study population

Male and female patients (aged 20–75 years) fulfilling all of the following criteria were eligible: (i) obesity and inadequately controlled body weight with diet and/or exercise for 3 months before screening (BMI ≥25 kg/m$^2$ combined with at least two obesity-related comorbidities or BMI ≥35 kg/m$^2$ with at least one obesity-related comorbidity); (ii) FPG ≥110 mg/dL and/or 5.6% ≤HbA1c ≤10.0%, or T2DM with HbA1c ≤10.0%; (iii) waist circumference at umbilical level, ≥85 cm for men and ≥90 cm for women; (iv) visceral fat area (VFA) ≥100 cm$^2$; (v) agreement to comply with the study-required lifestyle intervention and treatment during the full duration of the study. All subjects received diet and exercise advice in accordance with Japanese guidelines (JASSO 2016)[4] at the beginning of the study and compliance was reviewed and reinforced at every visit. Key exclusion criteria were use of pharmacologically active weight-loss medications, bariatric surgery, ketoacidosis, lactic acidosis or hyperosmolar coma, symptomatic genital infection or urinary tract infection in the 4 weeks before screening, gastrointestinal disorders associated with chronic diarrhoea and congestive heart failure [New York Heart Association (NYHA) class III or IV]. All exclusion criteria are listed in Table S1 (see Supporting Information).

### 2.3 | Study objectives

The primary objective of the study was to examine the dose–response relationship of licogliflozin (2.5, 10, 25 and 50 mg once daily) as

measured by percentage change in body weight from baseline relative to placebo after 12 weeks of treatment. The secondary objectives were to assess responder rates at week 12 (according to percentage change in body weight ≥3%, ≥5%, ≥10% from baseline), dose–response relationship for weight loss among subgroups (dysglycaemic and T2DM) at week 12, change from baseline at week 12 in waist circumference at umbilical level, HbA1c, FPG, systolic BP (SBP) and diastolic BP (DBP), fasting lipid profile and high-sensitivity C-reactive protein (hsCRP), uric acid, urine albumin, urine albumin to creatinine ratio, VFA and subcutaneous fat area (SFA) by computed tomography (CT) and safety during 12 weeks of treatment. Two independent radiologists centrally reviewed the CT-generated images of the abdomen at the level of the umbilicus to measure VFA and SF.[4,16] Safety included monitoring of AEs and laboratory parameters.

## 2.4 | Statistical analysis

The study planned to randomize approximately 130 patients in total, assuming 10% loss to follow-up. Dose–response was to be assessed by controlling the overall family-wise type I error at a one-sided significance level of 2.5%. To preserve the family-wise error rate at a one-sided significance level of 2.5%, the optimal contrasts derived from the model candidate set were individually compared with the critical value derived using a multiplicity adjustment accounting for all tests comparing licogliflozin doses to placebo. The rejection of the null hypothesis was achieved using the maximum test statistic from each estimated contrast test in the candidate set. Another consideration was to collect as much safety data of licogliflozin 25 mg once daily, 50 mg once daily and the placebo as possible, as to the best of our knowledge, this was the first study in Japanese patients with obesity.

The full analysis set (FAS) comprised all randomized patients except those randomized inadvertently who did not take any study drug. The safety analysis set (SAF) comprised all patients who received at least one dose of study medication. All analyses on primary and secondary variables were performed in the FAS, whereas all safety analyses were performed in the SAF. The subgroups of interest included baseline glycaemic status as dysglycaemic and T2DM. The primary endpoint was the percentage change in body weight (kg) from baseline at week 12 and was evaluated by the methodology using an optimally weighted contrast test.[17] The contrast test was based on adjusted means based on an ANCOVA model with treatment and strata as factors, and baseline body weight as a covariate. Baseline was defined as the last body weight value measured before or at the randomization visit. For the responder analysis, a logistic regression analysis was performed by including treatment and strata as factors, and baseline body weight as a covariate. For the dose–response relationship according to the baseline glycaemic status, the dose–response modelling for the primary variable was performed on percentage change of body weight from baseline at week 12 by the glycaemic status separately. For changes from baseline at week 12 in HbA1c, FPG, uric acid, urine albumin, urine albumin to creatinine ratio and $log_{10}$-transformed hsCRP, and percentage changes of lipid

parameters, fat area parameters, ANCOVA models were performed separately for each variable by including treatment and strata as factors, and baseline value as a covariate. Similar repeated measure ANCOVA models, including treatment, strata and treatment-by-visit interaction as factors, and baseline value as a covariate, were applied to changes of waist circumstances and BP from baseline.

## 3 | RESULTS

## 3.1 | Patients

In total, 168 patients were enrolled into the study, 126 (75%) of whom were randomized (19 each in licogliflozin 2.5 and 10 mg once daily; 28 in licogliflozin 25 mg once daily; 31 in licogliflozin 50 mg once daily; 29 in placebo groups) and received at least one dose of the study drug. In total, 125 patients completed the study and one patient belonging to the licogliflozin 50 mg once-daily treatment subgroup discontinued the study owing to the patient/guardian decision (Figure S1; see Supporting Information). Demographics and baseline characteristics of patients are presented in Table 1. The mean age and weight of all patients across the groups was 57.7 years (min-max: 33–75) and 83.7 kg (min-max: 58.1–145.6), respectively, whereas the mean BMI was 30.9 kg/m² (min-max: 25.2–48.4). Baseline characteristics of all patients were comparable across all treatment subgroups.

## 3.2 | Efficacy

### 3.2.1 | Primary endpoint

After 12 weeks of licogliflozin treatment, the placebo-subtracted percentage change in body weight from baseline was −1.99 (95% confidence interval −2.92, −0.21), −3.00 (−4.15, −1.70), −3.54 (−4.54, −2.26) and −3.91% (−5.01, −2.77) in the 2.5, 10, 25 and 50 mg once-daily dose groups, respectively. There was a dose-dependent reduction in body weight across all treatment groups (licogliflozin 2.5, 10, 25 and 50 mg once daily) as compared with placebo (Table 2, and Figure S2; see Supporting Information). The median (Q1, Q3) percentage change in body weight at week 12 from baseline was −1.46 (−2.23, −0.54), −3.13 (−5.16, −2.27), −2.92 (−4.00, −1.52), −3.67 (−5.65, −2.07) and −0.75% (−1.35, 1.46) in the licogliflozin 2.5, 10, 25 and 50 mg once-daily dose groups and the placebo, respectively.

All the models used in this study for testing a dose–response signal for percentage change in body weight from baseline at week 12 were statistically significant ($P < 0.001$), confirming the dose-dependent activity of licogliflozin over 12 weeks as compared with the placebo (Table S2; see Supporting Information). The least square mean percentage change in body weight from baseline in patients with BMI <30 kg/m² was −1.98, −3.57, −3.10, −3.88 and −0.38% in the licogliflozin 2.5, 10, 25 and 50 mg once-daily dose groups, and the placebo, respectively, whereas for patients with

**TABLE 1** Demographics and baseline characteristics

| Characteristics | Placebo N = 29 | Licogliflozin 2.5 mg qd N = 19 | Licogliflozin 10 mg qd N = 19 | Licogliflozin 25 mg qd N = 28 | Licogliflozin 50 mg qd N = 31 | Total N = 126 |
|---|---|---|---|---|---|---|
| Age (years), mean ± SD | 59.3 ± 9.8 | 57.2 ± 10.4 | 57.2 ± 7.5 | 56.8 ± 9.5 | 57.9 ± 11.4 | 57.7 ± 9.8 |
| Male, n (%) | 17 (58.6) | 15 (78.9) | 12 (63.2) | 17 (60.7) | 17 (54.8) | 78 (61.9) |
| Asian, n (%) | 29 (100) | 19 (100) | 19 (100) | 28 (100) | 31 (100) | 126 (100) |
| Weight (kg), mean ± SD | 85.9 ± 19.4 | 83.3 ± 15.4 | 83.8 ± 14.0 | 84.4 ± 14.1 | 81.0 ± 16.3 | 83.7 ± 16.0 |
| SBP (mmHg), mean ± SD | 129.9 ± 15.1 | 128.2 ± 14.1 | 136.5 ± 13.9 | 127.9 ± 12.1 | 130.7 ± 13.9 | 130.4 ± 13.9 |
| DBP (mmHg), mean ± SD | 83.3 ± 10.0 | 81.8 ± 10.7 | 86.4 ± 10.3 | 82.9 ± 8.4 | 82.8 ± 9.1 | 83.3 ± 9.5 |
| BMI (kg/m$^2$), mean ± SD | 32.3 ± 6.2 | 29.7 ± 3.7 | 30.7 ± 4.3 | 30.9 ± 4.2 | 30.5 ± 4.4 | 30.9 ± 4.8 |
| BMI (kg/m$^2$), n (%) | | | | | | |
| <30 | 14 (48.3) | 12 (63.2) | 11 (57.9) | 15 (53.6) | 18 (58.1) | 70 (55.6) |
| ≥30 | 15 (51.7) | 7 (36.8) | 8 (42.1) | 13 (46.4) | 13 (41.9) | 56 (44.4) |
| <35 | 21 (72.4) | 18 (94.7) | 16 (84.2) | 24 (85.7) | 28 (90.3) | 107 (84.9) |
| ≥35 | 8 (27.6) | 1 (5.3) | 3 (15.8) | 4 (14.3) | 3 (9.7) | 19 (15.1) |
| Waist circumference (cm), mean ± SD | 107.2 ± 14.4 | 101.5 ± 9.2 | 102.3 ± 9.3 | 103.7 ± 8.3 | 102.8 ± 10.7 | 103.7 ± 10.8 |
| Visceral fat area (cm$^2$), mean ± SD | 179.0 ± 55.7 | 186.1 ± 67.1 | 168.9 ± 36.4 | 178.5 ± 50.9 | 187.4 ± 75.2 | 180.5 ± 59.1 |
| Subcutaneous fat area (cm$^2$), mean ± SD | 294.2 ± 136.0 | 231.3 ± 71.7 | 244.4 ± 90.0 | 282.3 ± 103.2 | 261.4 ± 115.8 | 266.5 ± 109.5 |
| HbA1c (%), mean ± SD | 6.5 ± 0.6 | 6.9 ± 1.0 | 6.7 ± 0.8 | 6.6 ± 0.7 | 6.6 ± 0.8 | 6.6 ± 0.8 |
| Fasting plasma glucose (mmol/L), mean ± SD | 6.7 ± 1.1 | 7.4 ± 1.7 | 7.1 ± 1.3 | 7.0 ± 1.4 | 7.0 ± 1.3 | 7.0 ± 1.4 |
| Dysglycaemic, n (%) | 14 (48.3) | 8 (42.1) | 9 (47.4) | 13 (46.4) | 13 (41.9) | 57 (45.2) |
| Type 2 diabetes mellitus, n (%) | 15 (51.7) | 11 (57.9) | 10 (52.6) | 15 (53.6) | 18 (58.1) | 69 (54.8) |
| eGFR (mL/min), mean ± SD | 100.4 ± 17.5 | 104.0 ± 17.9 | 101.7 ± 20.6 | 103.2 ± 20.1 | 105.4 ± 22.0 | 103.0 ± 19.6 |

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; N, number of patients; qd, once daily; SBP, systolic blood pressure; SD, standard deviation.

**TABLE 2** Dose–response results of percentage change in body weight from baseline at week 12 (full analysis set)

| Treatment | Placebo-subtracted change[a] | | Dose response[a] | |
|---|---|---|---|---|
| | Model-based (95% CI) | ANCOVA (95% CI) | Model-based (95% CI) | ANCOVA (95% CI) |
| Placebo (n = 29) | | | 0.11 (−0.90, 0.97) | 0.09 (−0.79, 0.96) |
| Licogliflozin 2.5 mg qd (n = 19) | −1.99 (−2.92, −0.21) | −1.69 (−3.06, −0.31) | −1.86 (−2.59, −0.67) | −1.60 (−2.66, −0.54) |
| Licogliflozin 10 mg qd (n = 19) | −3.00 (−4.15, −1.70) | −3.50 (−4.89, −2.11) | −2.84 (−3.79, −2.16) | −3.42 (−4.49, −2.34) |
| Licogliflozin 25 mg qd (n = 28) | −3.54 (−4.54, −2.26) | −3.02 (−4.26, −1.79) | −3.41 (−3.96, −2.84) | −2.94 (−3.81, −2.06) |
| Licogliflozin 50 mg qd (n = 31) | −3.91 (−5.01, −2.77) | −4.09 (−5.32, −2.86) | −3.80 (−4.48, −3.17) | −4.00 (−4.85, −3.16) |

Abbreviations: CI, confidence interval; qd, once daily.
[a]Modelling is based on estimates from the ANCOVA model, adjusting for glycaemic factor and body weight at baseline.

BMI ≥30 kg/m$^2$, it was −0.97%, −3.18%, −2.73%, −4.22% and 0.56% in the licogliflozin 2.5, 10, 25 and 50 mg once-daily dose groups and the placebo, respectively.

### 3.2.2 | Secondary endpoints

*Responder rate*
The percentages of responders with ≥3% reduction in body weight from baseline at week 12 reached a plateau at 10 mg with 15.8%, 55.6%, 50.0% and 56.7% for the licogliflozin 2.5, 10, 25 and 50 mg once-daily dose groups, respectively, versus placebo (7.1%). A similar pattern was observed with responders with ≥5% reduction in body weight from baseline at week 12 where responder rates in the licogliflozin 2.5, 10, 25 and 50 mg once-daily dose groups were 5.3%, 27.8%, 17.9% and 26.7%, respectively, versus none in the placebo group (Table 3). A response of ≥10% change in body weight from baseline at week 12 was reported in only one patient from the licogliflozin 50 mg once-daily dose group.

**TABLE 3** Key secondary endpoints (full analysis set)

| Parameter | Placebo | Licogliflozin 2.5 mg qd | Licogliflozin 10 mg qd | Licogliflozin 25 mg qd | Licogliflozin 50 mg qd |
|---|---|---|---|---|---|
| Percentage decrease in body weight from baseline at week 12[a] | | | | | |
| ≥3% | | | | | |
| n/M (%) | 2/28 (7.1) | 3/19 (15.8) | 10/18 (55.6) | 14/28 (50.0) | 17/30 (56.7) |
| Odds ratio vs. placebo | | 2.30 | 15.8 | 12.7 | 16.8 |
| 95% CI | | (0.34, 15.35) | (2.84, 87.55) | (2.51, 64.32) | (3.36, 84.09) |
| 2-sided P-value | | 0.390 | 0.002 | 0.002 | <0.001 |
| ≥5% | | | | | |
| n/M (%) | 0/28 | 1/19 (5.3) | 5/18 (27.8) | 5/28 (17.9) | 8/30 (26.7) |
| Odds ratio vs. placebo | | NC | NC | NC | NC |
| 95% CI | | NC | NC | NC | NC |
| 2-sided P-value | | <0.001 | <0.001 | <0.001 | <0.001 |
| Waist circumference (cm) | | | | | |
| N | 28 | 19 | 18 | 28 | 30 |
| Adjusted mean change | −1.37 | −2.47 | −2.63 | −2.65 | −3.11 |
| Comparison of adjusted mean changes vs. placebo | | −1.10 | −1.26 | −1.28 | −1.74 |
| 95% CI | | (−3.10, 0.90) | (−3.26, 0.75) | (−3.07, 0.50) | (−3.50, 0.02) |
| 2-sided P-value | | 0.278 | 0.216 | 0.158 | 0.053 |
| HbA1c (%) in patients with T2DM | | | | | |
| N | 15 | 11 | 10 | 15 | 17 |
| Adjusted mean change | −0.09 | −0.40 | −0.49 | −0.50 | −0.62 |
| Comparison of adjusted mean changes vs. placebo | | −0.31 | −0.40 | −0.41 | −0.53 |
| 95% CI | | (−0.59, −0.03) | (−0.68, −0.12) | (−0.66, −0.16) | (−0.77, −0.28) |
| 2-sided P-value | | 0.029 | 0.006 | 0.002 | <0.001 |
| FPG (mmol/L) in patients with T2DM | | | | | |
| N | 15 | 11 | 10 | 15 | 17 |
| Adjusted mean change | −0.08 | −0.60 | −1.11 | −1.14 | −1.38 |
| Comparison of adjusted mean changes vs. placebo | | −0.53 | −1.03 | −1.06 | −1.3 |
| 95% CI | | (−1.18, 0.12) | (−1.69, −0.37) | (−1.65, −0.48) | (−1.87, −0.73) |
| 2-sided P-value | | 0.110 | 0.003 | <0.001 | <0.001 |
| SBP (mmHg) | | | | | |
| N | 28 | 19 | 18 | 28 | 30 |
| Adjusted mean change | −5.36 | −4.90 | −5.12 | −6.36 | −6.94 |
| Comparison of adjusted mean changes vs. placebo | | 0.46 | 0.24 | −1.00 | −1.58 |
| 95% CI | | (−4.90, 5.82) | (−5.24, 5.72) | (−5.82, 3.82) | (−6.31, 3.14) |
| 2-sided P-value | | 0.865 | 0.931 | 0.682 | 0.508 |
| DBP (mmHg) | | | | | |
| N | 28 | 19 | 18 | 28 | 30 |
| Adjusted mean change | −3.12 | −3.72 | −3.54 | −4.36 | −5.23 |
| Comparison of adjusted mean changes vs. placebo | | −0.59 | −0.42 | −1.23 | −2.11 |
| 95% CI | | (−4.58, 3.39) | (−4.46, 3.63) | (−4.81, 2.34) | (−5.62, 1.40) |
| 2-sided P-value | | 0.769 | 0.839 | 0.496 | 0.237 |
| Uric acid (μmol/L) | | | | | |
| N | 28 | 19 | 18 | 28 | 30 |
| Adjusted mean change | 12.4 | −52.6 | −55.2 | −58.4 | −62.0 |

(Continues)

**TABLE 3** (Continued)

| Parameter | Placebo | Licogliflozin 2.5 mg qd | Licogliflozin 10 mg qd | Licogliflozin 25 mg qd | Licogliflozin 50 mg qd |
|---|---|---|---|---|---|
| Comparison of adjusted mean changes vs. placebo | | −65.1 | −67.7 | −70.8 | −74.4 |
| 95% CI | | (−90.86, −39.25) | (−93.85, −41.54) | (−93.94, −47.74) | (−97.12, −51.70) |
| 2-sided P-value | | <0.001 | <0.001 | <0.001 | <0.001 |
| Visceral fat area (cm$^2$) | | | | | |
| N | 29 | 19 | 19 | 28 | 31 |
| Adjusted mean change | −3.95 | −4.14 | −5.83 | −9.18 | −11.35 |
| Comparison of adjusted mean changes | | −0.19 | −1.88 | −5.24 | −7.40 |
| 95% CI | | (−9.60, 9.22) | (−11.30, 7.53) | (−13.68, 3.20) | (−15.65, 0.84) |
| 2-sided P-value | | 0.968 | 0.693 | 0.222 | 0.078 |
| Subcutaneous fat area (cm$^2$) | | | | | |
| N | 27 | 19 | 18 | 28 | 31 |
| Adjusted mean change | −3.48 | −6.56 | −4.45 | −7.98 | −5.74 |
| Comparison of adjusted mean changes vs. placebo | | −3.09 | −0.98 | −4.51 | −2.27 |
| 95% CI | | (−8.70, 2.52) | (−6.64, 4.69) | (−9.48, 0.47) | (−7.15, 2.62) |
| 2-sided P-value | | 0.278 | 0.733 | 0.075 | 0.360 |

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; M, total number of patients in the treatment group with response variable defined; n, number of responders; N, number of patients with non-missing value at the corresponding time point of interest; NC, not calculated; qd, once daily; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.
[a]A response of ≥10% change in body weight from baseline at week 12 was reported in only one patient from the licogliflozin 50 mg qd dose group (data not shown).

## Dose–response relationship for weight loss in patients with dysglycaemia and with type 2 diabetes

The dose–response relationship in both subgroups (patients with dysglycaemia and with T2DM) was similar to that observed in the group overall (Figure S3; see Supporting Information).

## Waist circumference

The mean placebo-subtracted change from baseline in waist circumference at week 12 was −1.10, −1.26, −1.28 and −1.74 cm in the licogliflozin 2.5, 10, 25 and 50 mg once-daily dose groups, respectively (all P >0.05) (Table 3).

## Haemoglobin A1c

In patients with T2DM, the mean placebo-subtracted change from baseline in HbA1c at week 12 was dose-dependent at −0.31%, −0.40%, −0.41% and −0.53% in the licogliflozin 2.5, 10, 25 and 50 mg once-daily dose groups, respectively (all P <0.05) (Table 3).

HbA1c data in overall patients and the dysglycaemic population are presented in Table S3 (see Supporting Information).

## Fasting plasma glucose

Licogliflozin induced a dose-dependent reduction in FPG with an increase in dose over 12 weeks. In patients with T2DM, the mean placebo-subtracted change from baseline in FPG was −0.53, −1.03, −1.07 and −1.30 mmol/L in the licogliflozin 2.5, 10, 25 and 50 mg once-daily dose groups, respectively (all P <0.05 except for the licogliflozin 2.5 mg once-daily dose group) (Table 3).

FPG data in overall patients and the dysglycaemic population are presented in Table S3 (see Supporting Information).

## Systolic blood pressure and diastolic blood pressure

The mean placebo-subtracted change from baseline in SBP at week 12 was 0.46, 0.24, −1.0 and −1.58 mmHg in the licogliflozin 2.5, 10, 25 and 50 mg once-daily dose groups, respectively (all P >0.05).

The mean placebo-subtracted change from baseline in DBP at week 12 was −0.59, −0.42, −1.23 and −2.11 mmHg in the licogliflozin 2.5, 10, 25 and 50 mg once-daily dose groups, respectively (all P >0.05) (Table 3).

## Uric acid

Licogliflozin induced a dose-dependent reduction in uric acid with an increase in dose over 12 weeks. The mean placebo-subtracted change from baseline at week 12 in uric acid was −65.1, −67.7, −70.8 and −74.4 µmol/L in the licogliflozin 2.5, 10, 25 and 50 mg once-daily dose groups, respectively (all P <0.001) (Table 3).

## Visceral fat area and subcutaneous fat area

The mean placebo-subtracted percentage change in VFA from baseline at week 12 was −0.19%, −1.88%, −5.24% and −7.40% in the licogliflozin 2.5, 10, 25 and 50 mg once-daily dose groups, respectively (all P >0.05).

The mean placebo-subtracted percentage change in SFA from baseline at week 12 was −3.09%, −0.98%, −4.51% and −2.27% in the licogliflozin 2.5, 10, 25 and 50 mg once-daily dose groups, respectively (all P >0.05) (Table 3).

*Urine albumin and urine albumin to creatinine ratio*

The mean placebo-subtracted change from baseline in urine albumin at week 12 was −0.56, 1.29, −2.62 and −1.82 × 10$^4$ mmol/L in the licogliflozin 2.5, 10, 25 and 50 mg once-daily dose groups, respectively (all *P* >0.05).

The mean placebo-subtracted change from baseline in urine albumin to creatinine ratio at week 12 was 0.65, 0.66, −1.05 and −0.37 mg/mmol in the licogliflozin 2.5, 10, 25 and 50 mg once-daily dose groups, respectively (all *P* >0.05) (Table S3; see Supporting Information).

*Fasting lipid profile*

Licogliflozin did not show dose-dependent changes from baseline in triglycerides, total cholesterol, high-density lipoprotein and low-density lipoprotein with increase in dose over 12 weeks across all patients (all *P* >0.05) (Table S3; see Supporting Information).

*High-sensitivity C-reactive protein*

The mean placebo-subtracted percentage change in hsCRP from baseline at week 12 was 44.8%, 162.3%, 69.1% and 37.7% in the licogliflozin 2.5, 10, 25 and 50 mg once-daily dose groups, respectively (all *P* >0.05) (Table 3; see Supporting Information).

## 3.3 | Safety

Treatment-emergent AEs (TEAEs) were comparable between the licogliflozin dose groups (2.5, 10, 25 mg once daily) and the placebo group, with a higher incidence of AEs in the licogliflozin 50 mg once-daily dose group (n = 23; 74.2%) (Table S4; see Supporting Information). The most commonly reported TEAEs (>5%) with the licogliflozin 50 mg once-daily dose group were diarrhoea (n = 12; 38.7%) and nasopharyngitis (n = 4; 12.9%), which were followed by flatulence, hypoglycaemia and increased urine albumin/creatinine ratio (n = 2 each; 6.5% each).

The most commonly reported AE of special interest was diarrhoea of mild to moderate severity and it increased in a dose-dependent manner. Diarrhoea was not reported in the licogliflozin 2.5 and 10 mg once-daily dose groups. However, diarrhoea was reported during the early treatment period (0 to <2 weeks) in the licogliflozin 25 mg (n = 1; 3.6%) and 50 mg (n = 3; 9.7%) once-daily dose groups and during the 2- to <4-week treatment period with placebo (n = 1; 3.4%). The mean duration of diarrhoea was approximately 50 days in the licogliflozin 25 and 50 mg once-daily dose groups as well as in the placebo group. Two patients (6.5%) from the licogliflozin 50 mg once-daily dose group and one patient (3.4%) from the placebo group discontinued the study due to diarrhoea (Table S5; see Supporting Information). No major changes in liver enzymes were reported. No urinary tract infection was reported with any dose of licogliflozin. The incidence of hypoglycaemia was similar between the higher doses of licogliflozin (25 and 50 mg once daily) and the placebo group.

Of the total 31 patients in the licogliflozin 50 mg once-daily dose group, one non-fatal serious AE (acute cholecystitis) was reported.

The event was not related to the study treatment and no dose adjustment was made. The event was resolved after 7 days. No ketoacidosis or death was reported during the study (Table S5; see Supporting Information).

## 4 | DISCUSSION

The Japanese guidelines for the management of obesity recommend achieving ≥3% weight loss during 3–6 months.[4] The licogliflozin 10, 25 and 50 mg once-daily dose treatment for 12 weeks resulted in ≥3% weight loss from baseline compared with the placebo group, thus achieving the Japanese treatment goal for patients with obesity for 3 months.

A lifestyle-modification programme in 3480 Japanese patients with obesity (defined as BMI ≥25 kg/m$^2$ and one or more lifestyle-related diseases) reported that weight loss was clinically beneficial. In the study, weight loss of ≥3% for 1 year showed improvements in obesity-related complications such as HbA1c, FPG, SBP/DBP, lipid profile and uric acid, which provided a rationale for Japanese guidelines for the management of obesity to recommend a weight reduction of ≥3%.[4,18] However, lifestyle-modification demonstrated only 33.3% of patients reduced their weight by ≥3% from their initial weight.[18] It means approximately 67% of patients with obesity need additional intervention to reduce their weight by ≥3%.

In this study, treatment with licogliflozin was associated with a significant dose-dependent reduction in HbA1c and FPG in patients with T2DM.[11] Licogliflozin also induced a potentially dose-dependent reduction in waist circumference, DBP and VFA in patients overall; however, this effect was not statistically significant. All other parameters such as SBP, urine albumin, albumin to creatinine ratio, fasting lipid profile and inflammation biomarkers and SFA showed no consistent dose-dependent changes across all groups. These observations must be considered with caution given the relatively small sample size and will require validation in future larger clinical trials.

Hyperuricaemia is frequently observed in patients with obesity and T2DM, and elevated levels of serum uric acid have been associated with the development of nephropathy and increased risk of hypertension and cardiovascular disease in such patients. SGLT2 inhibitors have been suggested to have a class effect in reducing serum uric acid levels in patients with T2DM.[19] Licogliflozin induced a dose-dependent reduction in uric acid in patients overall and the mean placebo-subtracted change from baseline ranged between −65.1 and −74.4 μmol/L. This effect of licogliflozin on uric acid seems stronger than marketed SGLT2 inhibitors (−37.7 to −45.8 μmol/L), an effect probably due to dual inhibition of SGLT1/2.[19,20]

It has been reported that Asians have a higher prevalence of T2DM at relatively lower BMI thresholds, such as 23–25 kg/m$^2$, than white people do because of a propensity to develop visceral fat.[21,22] Excessive visceral fat accumulation is associated with several metabolic (including diabetogenic) and atherogenic effects increasing the risk of atherosclerotic cardiovascular diseases and its reduction is

associated with a decrease in the number of obesity-related cardio-vascular risk factors.[23-27] In the current study, licogliflozin showed dose-dependent reductions in VFA with greatest reductions observed with 50 mg once daily ($P$ = 0.078); however, the changes in VFA were not significant. Although there are no treatment goals for VFA reduction, VFA >100 cm$^2$ has been associated with an increased risk of obesity-related cardiovascular events.[23] The observed reductions in VFA (11.35%) with licogliflozin are close to those observed in previous studies with SGLT2 inhibitors and other interventions (6%–17%), and could be clinically significant, particularly in combination with other interventions such as calorie restriction.[26-28]

Treatment with licogliflozin was generally safe and well tolerated with no new safety signals. Diarrhoea is one of the known AEs of SGLT1 inhibition and was the most commonly observed AE in the present study, with a dose-dependent increase in its incidence. SGLT1 inhibition results in glucose/galactose malabsorption that may lead to elevated incidences of gastrointestinal side effects such as diarrhoea.[11]

There are some limitations in this study. Sample size was relatively small, and the short duration (12 weeks) provided limited information on long-term efficacy (weight loss) and/or safety risks associated with licogliflozin.

## 5 | CONCLUSIONS

Licogliflozin induced a dose-dependent reduction in body weight following administration of once-daily doses of 2.5, 10, 25 and 50 mg in Japanese patients with obesity. Administration of once-daily doses of licogliflozin (2.5, 10, 25 and 50 mg) over 12 weeks were safe and well tolerated in this study.

### CONFLICT OF INTEREST

M.S., I.T. and D.K. are employees of Novartis. K.Y. reports personal fees from Astellas Pharma, Kowa Pharmaceutical, MSD, Nippon Boehringer Ingelheim, Amgen Astellas BioPharma, Mitsubishi Tanabe Pharma, Eli Lilly Japan, Takeda Pharmaceutical, Sanofi, Ono Pharmaceutical, Novo Nordisk Pharma, Sumitomo Dainippon Pharma, Novartis Pharma, Janssen Pharmaceutical, Taisho Toyama Pharmaceutical, Daiichi Sankyo, Kowa, Shionogi, AstraZeneca, Kyowa Hakko Kirin, grants from Takeda Pharmaceutical, Ono, Daiichi Sankyo, Sumitomo Dainippon Pharma, MSD, Taisho Toyama Pharmaceutical, Teijin Pharma, Terumo, Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim, Mochida Pharmaceutical, Shionogi, Pfizer Japan, Novo Nordisk Pharma, Eli Lilly Japan, Kowa Pharmaceutical, Astellas Pharma belongs to

endowed chairs that receive the grants from MSD, outside the submitted work.

### AUTHOR CONTRIBUTIONS

All authors reviewed and approved the manuscript.

### DATA SHARING STATEMENT

Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations.

### ORCID

*Koutaro Yokote* https://orcid.org/0000-0003-3033-4813

### REFERENCES

1. Hall JE. do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity, kidney dysfunction and hypertension: mechanistic links. *Nat Rev Nephrol*. 2019;15:367-385.
2. Nishi N. Monitoring Obesity Trends in Health Japan 21. *J Nutr Sci Vitaminol (Tokyo)*. 2015;61(Suppl):S17-S19.
3. Examination Committee of Criteria for 'Obesity Disease' in Japan. Japan Society for the Study of Obesity. New criteria for 'obesity disease' in Japan. *Circ J*. 2002;66:987-992.
4. Japan Society for the Study of Obesity. *Guidelines for the management of obesity disease 2016*: Tokyo: Life Science Publishing Co., Ltd., 2016 http://www.jasso.or.jp/contents/magazine/journal.html.
5. Heymsfield SB, Wadden TA. Mechanisms, Pathophysiology, and Management of Obesity. *N Engl J Med*. 2017;376:1492.
6. Jackson VM, Breen DM, Fortin JP, et al. Latest approaches for the treatment of obesity. *Expert Opin Drug Discov*. 2015;10:825-839.
7. Lucchetta RC, Riveros BS, Pontarolo R, et al. Systematic review and meta-analysis of the efficacy and safety of amfepramone and mazindol as a monotherapy for the treatment of obese or overweight patients. *Clinics (Sao Paulo)*. 2017;72:317-324.
8. Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. *JAMA*. 2014;311:74-86.
9. Harada N, Inagaki N. Role of sodium-glucose transporters in glucose uptake of the intestine and kidney. *J Diabetes Investig*. 2012;3: 352-353.
10. Lee PC, Ganguly S, Goh SY. Weight loss associated with sodium-glucose cotransporter-2 inhibition: a review of evidence and underlying mechanisms. *Obes Rev*. 2018;19:1630-1641.
11. He YL, Haynes W, Meyers CD, et al. The effects of licogliflozin, a dual SGLT1/2 inhibitor, on body weight in obese patients with or without diabetes. *Diabetes Obes Metab*. 2019;21:1311-1321.
12. Ezcurra M, Reimann F, Gribble FM, Emery E. Molecular mechanisms of incretin hormone secretion. *Curr Opin Pharmacol*. 2013;13: 922-927.
13. Holzer P, Reichmann F, Farzi A. Neuropeptide Y, peptide YY and pancreatic polypeptide in the gut-brain axis. *Neuropeptides*. 2012;46: 261-274.
14. Turk E, Zabel B, Mundlos S, Dyer J, Wright EM. Glucose/galactose malabsorption caused by a defect in the Na+/glucose cotransporter. *Nature*. 1991;350:354-356.
15. Vilsboll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. *BMJ*. 2012; 344:d7771.

16. Ryo M, Kishida K, Nakamura T, Yoshizumi T, Funahashi T, Shimomura I. Clinical significance of visceral adiposity assessed by computed tomography: A Japanese perspective. *World J Radiol*. 2014; 6:409-416.

17. Pinheiro J, Bornkamp B, Glimm E, Bretz F. Model-based dose finding under model uncertainty using general parametric models. *Stat Med*. 2014;33:1646-1661.

18. Muramoto A, Matsushita M, Kato A, et al. Three percent weight reduction is the minimum requirement to improve health hazards in obese and overweight people in Japan. *Obes Res Clin Pract*. 2014;8: e466-e475.

19. Zhao Y, Xu L, Tian D, et al. Effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors on serum uric acid level: A meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. 2018;20:458-462.

20. Ouchi M, Oba K, Kaku K, et al. Uric acid lowering in relation to HbA1c reductions with the SGLT2 inhibitor tofogliflozin. *Diabetes Obes Metab*. 2018;20:1061-1065.

21. Hsu WC, Araneta MR, Kanaya AM, Chiang JL, Fujimoto W. BMI cut points to identify at-risk Asian Americans for type 2 diabetes screening. *Diabetes Care*. 2015;38:150-158.

22. Chan JC, Malik V, Jia W, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA*. 2009;301:2129-2140.

23. Hiuge-Shimizu A, Kishida K, Funahashi T, et al. Reduction of visceral fat correlates with the decrease in the number of obesity-related cardiovascular risk factors in Japanese with Abdominal Obesity (VACATION-J Study). *J Atheroscler Thromb*. 2012;19: 1006-1018.

24. Okauchi Y, Kishida K, Funahashi T, et al. 4-year follow-up of cardiovascular events and changes in visceral fat accumulation after health promotion program in the Amagasaki Visceral Fat Study. *Atherosclerosis*. 2010;212:698-700.

25. Ryo M, Kishida K, Nakamura T, Funahashi T, Shimomura I. Short-term intervention reduces bioelectrical impedance analysis-measured visceral fat in type 2 diabetes mellitus. *Diabetes Res Clin Pract*. 2014; 103:e27-e29.

26. Ito D, Shimizu S, Inoue K, et al. Comparison of Ipragliflozin and Pioglitazone Effects on Nonalcoholic Fatty Liver Disease in Patients With Type 2 Diabetes: A Randomized, 24-Week, Open-Label. *Active-Controlled Trial Diabetes Care*. 2017;40:1364-1372.

27. Tosaki T, Kamiya H, Himeno T, et al. Sodium-glucose Co-transporter 2 Inhibitors Reduce the Abdominal Visceral Fat Area and May Influence the Renal Function in Patients with Type 2 Diabetes. *Intern Med*. 2017;56:597-604.

28. Sasaki T, Sugawara M, Fukuda M. Sodium-glucose cotransporter 2 inhibitor-induced changes in body composition and simultaneous changes in metabolic profile: 52-week prospective LIGHT (Luseogliflozin: the Components of Weight Loss in Japanese Patients with Type 2 Diabetes Mellitus) Study. *J Diabetes Investig*. 2019;10:108-117.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.