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Effects of switching from a dipeptidyl peptidase-4 inhibitor to oral semaglutide on glucose metabolism in patients with type 2 diabetes: protocol for a multicentre, prospective, randomised, open-label, parallel-group comparison study (the SWITCH-SEMA 2 study)

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ABSTRACT

Introduction Incretin-based therapies exert antihyperglycaemic effects in patients with type 2 diabetes (T2D) in a blood glucose concentration-dependent fashion. The first-in-class oral glucagon-like peptide-1 receptor agonist semaglutide has potent effects on glycaemic and weight control, but little evidence has been published for the superiority of semaglutide for glycaemic control in patients after switching from a dipeptidyl peptidase-4 (DPP-4) inhibitor. Therefore, we aim to verify the efficacy of oral semaglutide in patients with T2D being treated with a DPP-4 inhibitor.

Methods and analysis This study is a multicentre, prospective, randomised, open-label, parallel-group trial. In total, 172 participants with T2D who have been treated with a DPP-4 inhibitor for more than 12 weeks and who have a glycated haemoglobin (HbA1c) level of 7.0%–9.9% will be randomised to continue using their existing DPP-4 inhibitor or switch to oral semaglutide for 24 weeks. Biochemical analyses and physical assessment will be performed, and adverse events will be recorded at baseline and at the end of the study. The primary endpoint will be the effect of oral semaglutide on the change in HbA1c. The secondary endpoints will be the mean changes in body weight, abdominal circumference, systolic and diastolic blood pressure (BP), pulse rate, the relationship between improvement of metabolic parameters including HbA1c and patient background characteristics, side effects and other laboratory parameters.

Ethics and dissemination This will be the first study to compare the effects of switching from a DPP-4 inhibitor to oral semaglutide on glycaemic control in patients with T2D. The results will be disseminated in peer-reviewed journals and at scientific conferences. Hokkaido University

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study is a multicentre, prospective, randomised, open-label, parallel-group trial.
⇒ The study will be conducted in a standard clinical practice setting, at eight medical centres, and will include broad eligibility criteria, reflecting the real-world situation.
⇒ The limitation of the study is the open-label aspect of the study design, which can create a bias toward observing a favourable result for oral semaglutide.

Certified Review Board (CRB no.1180001) has approved the protocol (no. 020–013).
Trial registration number UMIN000045270 in the University Hospital Medical Information Network; jRCT1011210032 in the Japan Registry of Clinical Trials.

INTRODUCTION

A goal in the treatment of patients with diabetes is to reduce mortality by preventing diabetic macrovascular and microvascular complications. Strict glycaemic control has been shown to reduce those complications[1]; however, intensive interventions can increase body weight as well as the risk of hypoglycaemia.[2 3] Therefore, comprehensive interventions targeting multiple risks, including obesity, lipid metabolism and blood pressure (BP) without causing hypoglycaemia, are required to achieve better outcomes.[4 5] As a consequence, treatment strategies that have

potent antihyperglycaemic effects without causing body weight gain and hypoglycaemia are sought after.

Incretin-based therapies have been shown to have ideal glucose-lowering effects in patients with type 2 diabetes (T2D) because their effects are blood glucose concentration dependent.[6] Currently, antihyperglycaemic treatment regimens including a dipeptidyl peptidase-4 (DPP-4) inhibitor are well recognised for patients with T2D all over the world.[7] DPP-4 inhibitors are one of the most frequently prescribed antihyperglycaemic drugs, especially in Japan, because of their safety and high efficacy in Asian populations.[8 9] Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have stronger antihyperglycaemic effects than conventional oral antihyperglycaemic agents,[10] and importantly, certain GLP-1RAs have been shown to have beneficial effects on cardiovascular outcomes in high-risk patients with T2D,[11–13] although that they require inconvenient parenteral administration.

Recently, oral semaglutide—the first-in-class oral GLP-1RA—has been approved with the report of its remarkable effects on hyperglycaemic and body weight, compared with either placebo, once-weekly semaglutide[14] or a DPP-4 inhibitor.[15] However, notably, these comparisons were performed during a phase III trial, and it is not known whether oral semaglutide administration is superior to that of a conventional DPP-4 inhibitor with respect to glycaemic control in daily clinical practice, and especially in patients that were previously treated using a DPP-4 inhibitor. Therefore, in this prospective, randomised, open-label, parallel-group trial, we will compare the effects of oral semaglutide administration to that of a DPP-4 inhibitor with respect to glycaemic control in Japanese patients with T2D.

METHODS
Study design
This is a multicentre, open-label prospective, randomised, parallel-group comparison study that will compare the glycaemic control of patients taking a DPP-4 inhibitor or the oral GLP-1RA semaglutide daily. Following enrolment and the provision of written informed consent, the participants will undergo serum and urine analyses and physical examination to obtain baseline data. At each study visit, clinic BP, pulse rate, body weight and abdominal circumference will be measured. After the initial assessment, all the participants will be randomly assigned to continue their DPP-4 inhibitor or to switch to oral semaglutide at a ratio of 1:1, according to their age, body mass index (BMI), HbA1c and institution. The randomisation and allocation of the participants will be performed using a web-based automated system that is independent of the participating sites (NorthNet; https://crmic.huhp.hokudai.ac.jp/page/?content=31), as described previously.[16] The glycaemic target is to be determined for each patient based on the recommendations of the Japan Diabetes Society.[17] Serum and urine metabolic
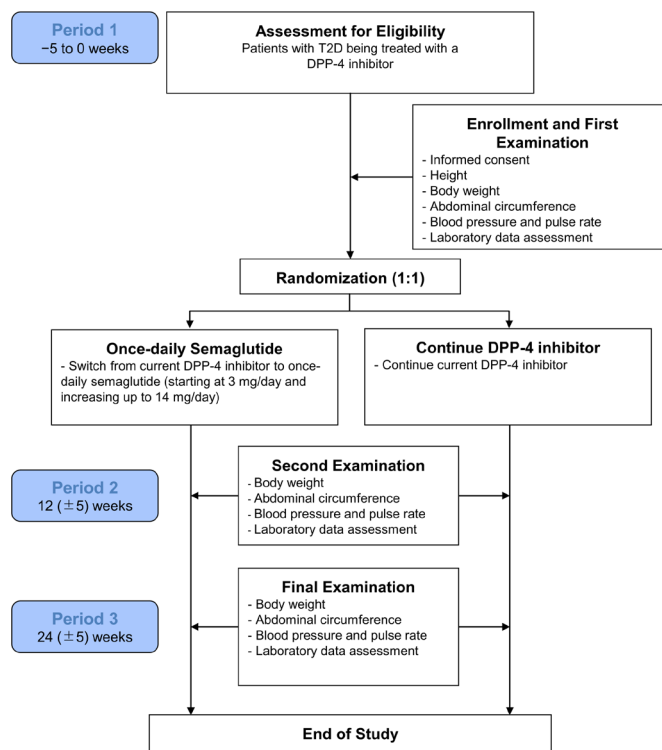

Figure 1 Patient recruitment scheme. Participants will be randomly assigned to either continue to use their existing DPP-4 inhibitor or to be switched to oral semaglutide (starting dose 3 mg/day). All the participants will undergo physical and biochemical examinations at baseline and at the end of the study. DPP-4, dipeptidyl peptidase-4 inhibitor; T2D, type 2 diabetes.

parameters, clinic BP, pulse rate, body weight and abdominal circumference will be measured at each study visit.

Oral semaglutide will be initiated at 3 mg once daily, which will be escalated to 7 mg after 4 weeks and then up to 14 mg if the glycaemic control is insufficient to reach the glycaemic target based on the recommendations of the Japan Diabetes Society and the participants agree. Participants will be instructed to take the oral semaglutide in the morning in a fasted state, with 120 mL of water, at least 30 min before breakfast and any other oral medication. They will also be encouraged to continue their diet and exercise therapy during the study. The treatments will be supervised through the appropriate medical care centre for 24 weeks, then the baseline serum and urine measurements and physical examination will be repeated (figure 1). The doses of antihyperglycaemic agents other than sulfonylureas, glinides and insulin, and concomitant treatments for metabolic disorders, will not be basically adjusted during the study period; however, if the glycaemic control does not reach the appropriate target and/or becomes worse despite suitable interventions in lifestyle behaviours, adjustment or addition of antihyperglycaemic agents will be considered. To avoid hypoglycaemia, the doses of sulfonylureas, glinides and insulin will be able to be adjusted, based on the recommendations of the Japan Diabetes Society.[17] Participant

Box 1   Inclusion criteria

Inclusion criteria
⇒ Japanese patients with type 2 diabetes.
⇒ Age 20–89 years.
⇒ Glycated haemoglobin 7.0%–9.9%.
⇒ Body mass index ≥18.5 kg/m^2.
⇒ Treatment with a dipeptidyl peptidase-4 inhibitor for at least 12 weeks before enrolment, without discontinuation for more than 1 week.

enrolment will take place between 9 July 2021 and 31 December 2023 at eight medical centres and clinics located in Hokkaido, Japan.

Sample selection

The inclusion criteria are as follows: Japanese patients with T2D who are aged 20–89 years, with HbA1c 7.0%–9.9% and BMI ≥18.5 kg/m^2, and who have been treated with a DPP-4 inhibitor for at least 12 weeks before enrolment, without being discontinued for more than 1 week (see box 1). The key exclusion criteria are as follows: (1) treatment with any GLP-1RA, (2) allergy to semaglutide, (3) unstable diabetic retinopathy, (4) current severe liver dysfunction or nephropathy, (5) severe infection, trauma and/or recent or planned surgery, (6) severe ketosis, (7) diabetic coma or precoma, (8) pregnancy, (9) poor compliance with medication, (10) inability to consume an appropriate diet and/or perform exercise and (11) incompatibility with the trial for other reasons, as determined by a physician (see box 2).

Physicians in the research team will obtain written informed consent from all the eligible participants. The written material, consisting of a participant information leaflet and consent documentation, has been approved by the research committee. There will be an opportunity for the participants to freely ask questions of members of the research team, and their consent will be able to be withheld at any time during the study period should they so wish. Patients will be withdrawn from the trial if any of the following criteria apply: (1) withdrawal of consent,

Box 2   Exclusion criteria

Exclusion criteria
⇒ Treatment with any lucagon-like peptide-1 receptor agonist within the 12 weeks prior to enrolment.
⇒ Allergy to semaglutide.
⇒ Unstable diabetic retinopathy.
⇒ Current severe liver dysfunction or nephropathy.
⇒ Severe infection, trauma and/or recent or planned surgery.
⇒ Severe ketosis.
⇒ Diabetic coma or precoma.
⇒ Pregnancy.
⇒ Low drug compliance rate.
⇒ Inability to consume an appropriate diet and/or perform exercise.
⇒ Incompatibility with the trial for other reasons, as determined by the physician.

(2) physician's decision, based on the patient's condition, (3) discontinuation of the study or (4) physician's decision, based on another reason.

Patient and public involvement statement

Participants were not directly involved in the design nor development of the study and will not be involved in the recruitment nor conduct of the trial. The results of their investigations will be provided to the participants after the study, during a medical consultation in their participating centre.

TRIAL ENDPOINT

Primary and secondary endpoints

The primary endpoint of the study is the change in HbA1c from baseline to week 24, which will be compared between the semaglutide group and control group. The secondary endpoints are as follows: the mean changes in: (1) body weight, (2) abdominal circumference, (3) systolic and diastolic BP, (4) pulse rate, (5) laboratory parameters reflecting glucose and lipid metabolism, and liver and renal function, (6) the relationship between improvement of metabolic parameters including HbA1c and patient background characteristics and (7) any side effects. Hypoglycaemia is defined as symptomatic hypoglycaemic events or blood glucose levels <70 mg/dL. We will prepare a time-course sheet for each study visit to minimise the risk of participants dropping out.

Sample size calculation

The sample size was calculated on the basis that oral semaglutide (3–14 mg/day) will improve HbA1c by at least a further 0.70% (SD 1.585%), compared with sitagliptin (100 mg/day), as shown in a phase III trial conducted in patients with T2D.[18] A power calculation determined that a sample size of 82 individuals per group would be required to achieve a power of at least 80% for the detection of superiority of oral semaglutide over DPP-4 inhibitor. P<0.05 will be considered to represent statistical significance, and all tests will be two sided. On the basis of an assumption that four participants (5%) will drop out from each group, the sample size has been set at 86 participants per group. To ensure that enough participants enrol to achieve the target sample size, we will conduct the study at eight medical centres in Hokkaido.

Data analysis

Analysis of the primary and secondary endpoint data will be principally performed using the full analysis set (FAS), which will comprise the participants who are enrolled in the study and assigned to treatment groups. Patients who do not meet the inclusion criteria, those with insufficient primary endpoint data or those appreciably deviated from the study protocol will be excluded from the FAS. Differences between the two groups will be analysed using the unpaired t-test or Mann-Whitney U test for continuous data, and Pearson's χ^2 test or Fisher's exact

test for categorical data. The factors associated with any improvements in HbA1c or other metabolic parameters will be identified using analysis of covariance and multivariate analysis. We will analyse the data using JMP Pro (SAS Institute, Cary, North Carolina, USA), BellCurve for Excel (Social Survey Research Information Co, Ltd, Japan) and GraphPad Prism (GraphPad Software, Inc, San Diego, California, USA).

ETHICS AND DISSEMINATION
Ethics approval
The trial was registered with the Japan Registry of Clinical Trials (jRCT1011210032) and the University Hospital Medical Information Network (UMIN) Centre (UMIN000045270) before enrolment commenced. The study protocol was approved by the Hokkaido University Certified Review Board (CRB no. 1180001; approval number 020–013), and the current version is 1.8 (approved on 14 April 2022). The study will be carried out in accordance with the principles of the Declaration of Helsinki and its amendments.

Data protection and management
Data management, including coding, security, storage and cleaning, will be performed by researchers throughout the trial. The study data will be archived at Hokkaido University for 5 years after study completion. The participants will also be able to obtain the final results of the study. The UMIN and jRCT databases will contain detailed information regarding the study. Study conduct will be evaluated by a monitor who will be independent of the investigators. Monitoring will be performed on the first and fifth participants at Hokkaido University Hospital and the first participant at each of the other study sites. In line with the provisions of the Clinical Trials Act in Japan, adverse events and other information, including modifications to the trial, will be disclosed publicly.

Availability of data and materials
The data analysed during this study will be available from the corresponding author of this article on reasonable request.

DISCUSSION
To our knowledge, this will be the first prospective clinical trial to be conducted in a real-world setting, comparing the efficacy of oral semaglutide after switching from DPP-4 inhibitors with respect to glycaemic control in Asian patients with T2D. Oral semaglutide has been shown to exert a potent antihyperglycaemic effect. A recent network meta-analysis that compared the relative efficacy of oral semaglutide and injectable GLP-1RAs revealed that 14 mg/day oral semaglutide was associated with a significantly larger reduction in HbA1c than most of the comparators, with the exception of weekly semaglutide.[19] Furthermore, a previous phase III trial showed that the

administration of oral semaglutide at 7 mg or 14 mg/day resulted in a larger reduction in HbA1c than sitagliptin at 100 mg/day.[15] Because it has been demonstrated that DPP-4 inhibitors have potent antihyperglycaemic effects in Asian populations,[9] however, it is important to confirm that similar differences exist in the Japanese population.

The management of obesity during the treatment of diabetes is important but presents a difficult challenge. A treatment strategy not causing body weight gain would be ideal. DPP-4 inhibitors have no effect on body weight, whereas other insulin secretagogues tend to cause body weight gain.[20] One of the advantages of using a GLP-1RA would be related with appetite. Notably, a phase III trial that assessed the dose–response and efficacy of oral semaglutide in Japanese patients showed that the weight loss induced by semaglutide was greater than that induced by liraglutide at 0.9 mg/day, although the incidence of gastrointestinal events was comparable between the groups.[21]

A switch from a DPP-4 inhibitor to oral semaglutide may represent a promising 'step-up' therapeutic strategy. However, most patients being treated in routine clinical practice who are receiving a DPP-4 inhibitor are also taking other oral antihyperglycaemic agents.[8] Because semaglutide must be taken at least 30 min before breakfast and any other oral medication, a switch to oral semaglutide forces patients to take their medication at two separate times, leading to poorer compliance and diminished efficacy of the therapy. Therefore, it is important to confirm the efficacy and safety of oral semaglutide in a study conducted in a real-world clinical practice setting.

In conclusion, the present study will be the first clinical trial to evaluate the efficacy of oral semaglutide for glycaemic control in patients with T2D who were previously being treated using a DPP-4 inhibitor in a real-world clinical practice setting. Therefore, the results should provide new insights into the efficacy of oral semaglutide in patients with T2D.

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enrolment. KYC will collect the data and contribute to statistical analysis. HM is the guarantor of this work and will take responsibility for the integrity of the data and the accuracy of the data analysis. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for the authorship of this article, take responsibility for the integrity of the work as a whole and have given their approval for this version of the manuscript to be published.

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