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Complete List of Authors:	Nomoto, Hiroshi; Hokkaido University, Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine and Graduate School of Medicine Furusawa, Sho; Hokkaido University, Department of Rheumatology, Endocrinology, and Nephrology Nakamura, Akinobu; Hokkaido University, Department of Rheumatology, Endocrinology, and Nephrology Takeuchi, Jun; Sapporo Diabetes and Thyroid Clinic Nagai, So; Sapporo Medical Center NTT EC Yokoyama, H.; Jiyugaoka Med Clin, Sakuma, Ichiro; Caress Sapporo Hokko Memorial Clinic Taneda, Shinji; Manda Memorial Hospital Kurihara, Yoshio; Kurihara Clinic Aoki, Shin; Aoki Clinic Miya, Aika; Hokkaido University, Department of Rheumatology, Endocrinology, and Nephrology Kameda, Hiraku; Hokkaido University Graduate School of Medicine Department of Rheumatology Endocrinology and Nephrology Cho, Kyu Yong; Hokkaido University, Department of Rheumatology, Endocrinology, and Nephrology, Faculty of Medicine and Graduate School of Medicine Atsumi, Tatsuya; Hokkaido University, Department of Rheumatology, Endocrinology, and Nephrology, Faculty of Medicine and Graduate School of Medicine, Miyoshi, Hideaki; Hokkaido University, Department of Rheumatology, Endocrinology, and Nephrology; Hokkaido University
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Protocol

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

Hiroshi Nomoto[1], Sho Furusawa[1], Akinobu Nakamura[1], Jun Takeuchi[2], So Nagai[3], Hiroki Yokoyama[4], Ichiro Sakuma[5], Shinji Taneda[6], Yoshio Kurihara[7], Shin Aoki[8], Aika Miya[1], Hiraku Kameda[1], Kyu Yong Cho[1,9], Tatsuya Atsumi[1], and Hideaki Miyoshi[1,10]

[1] Department of Rheumatology, Endocrinology, and Nephrology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

[2] Sapporo Diabetes and Thyroid Clinic, Sapporo, Japan

[3] Division of Diabetes and Endocrinology, Department of Medicine, Sapporo Medical Center, NTT East Corporation, Sapporo, Japan

[4] Department of Internal Medicine, Jiyugaoka Medical Clinic, Obihiro, Japan

[5] Caress Sapporo Hokko Memorial Clinic, Sapporo, Japan

[6] Diabetes Center, Manda Memorial Hospital, Sapporo, Japan

[7] Kurihara Clinic, Sapporo, Japan

[8] Aoki Clinic, Sapporo, Japan

[9] Clinical Research and Medical Innovation Center, Hokkaido University Hospital, Sapporo, Japan

[10] Division of Diabetes and Obesity, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

Corresponding author: Hideaki Miyoshi, MD, PhD

Division of Diabetes and Obesity, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, N15 W7, Kita-ku, Sapporo 060-8638, Japan.

Tel: +81-11-706-8192; Fax: +81-11-706-8194; E-mail: hmiyoshi@med.hokudai.ac.jp

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ABSTRACT

Introduction Incretin-based therapies exert anti-hyperglycemic 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 glycemic and weight control, but little evidence has been published for the superiority of semaglutide for glycemic 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 multi-center, prospective, randomized, 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 hemoglobin (HbA1c) level of 7.0%–9.9% will be randomized 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 mass, abdominal circumference, systolic and diastolic blood pressure, pulse rate, factors associated with

any improvements in HbA1c or secondary endpoints, 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 glycemic control in patients with T2D. The results will be disseminated in peer-reviewed journals and at scientific conferences. Hokkaido University Certified Review Board (CRB no.1180001) has approved the protocol (No.020-013).

Trial registration number

UMIN000045270 in the University Hospital Medical Information Network (UMIN); jRCT1011210032 in the Japan Registry of Clinical Trials (jRCT)

Strengths and limitations of this study

- This randomized controlled study will be the first to directly compare the glycemic control of patients with type 2 diabetes who switch from a DPP-4 inhibitor to oral semaglutide administration.
- The study is a multi-center, prospective, randomized, parallel-group trial. Participants will not be blinded to their treatment.
- The study will be conducted in a standard clinical practice setting, at eight medical centers, and will include broad eligibility criteria, reflecting the real-world situation.

INTRODUCTION

A goal in the treatment of patients with diabetes is to reduce mortality by preventing diabetic macro- and microvascular complications. Strict glycemic control has been shown to reduce those complications [1]; however, intensive interventions can increase body mass as well as the risk of hypoglycemia [2 3]. Therefore, comprehensive interventions targeting multiple risks, including obesity, lipid metabolism, and blood pressure without causing hypoglycemia are required to achieve better outcomes [4 5]. As a consequence, treatment strategies that have potent anti-hyperglycemic effects without causing body mass gain and hypoglycemia 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, anti-hyperglycemic treatment regimens including a dipeptidyl peptidase-4 (DPP-4) inhibitor are well recognized for patients with T2D all over the world [7]. DPP-4 inhibitors are one of the most frequently prescribed anti-hyperglycemic 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 anti-hyperglycemic effects than conventional oral antihyperglycemic 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], albeit 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 hyperglycemia and body mass, 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 glycemic control in daily clinical practice, and especially in patients that were previously treated using a DPP-4 inhibitor. Therefore, in this prospective, randomized, open-label, parallel-group trial, we will compare the effects of oral semaglutide administration to that of a DPP-4 inhibitor with respect to glycemic control in Japanese patients with T2D.

METHODS

Study design

This is a multi-center, open-label prospective, randomized, parallel-group

comparison study that will compare the glycemic control of patients taking a DPP-4 inhibitor or the oral GLP-1RA semaglutide daily. Following enrollment 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 blood pressure (BP), pulse rate, body mass, 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 randomization 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 glycemic target is to be determined for each patient based on the recommendations of the Japan Diabetes Society [17]. Serum and urine metabolic parameters, clinic BP, pulse rate, body mass, 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 necessary. 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 center for 24 weeks, then the baseline serum and urine measurements and physical examination will be repeated (Figure 1). The doses of anti-hyperglycemic agents other than sulfonylureas, glinides, and insulin, and concomitant treatments for metabolic disorders, will not be adjusted during the study period. To avoid hypoglycemia, the doses of sulfonylureas, glinides, and insulin will be able to be adjusted, based on the recommendations of the Japan Diabetes Society [17]. Participant enrollment will take place between 9th July 2021 and 31st December 2023 at eight medical centers 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 enrollment, 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 pre-coma,

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, 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 center.

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 mass, 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) factors associated with any improvement of HbA1c or secondary endpoints, and 7) any side-effects. We will prepare a time-course sheet for each study visit to minimize 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 a difference between treatments. $P < 0.05$ 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 enroll to achieve the target sample size, we will conduct the study at eight medical centers 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 analyzed using the unpaired *t*-test or Mann–Whitney U-test for continuous data, and Pearson's chi-square 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 analyze the data using JMP Pro (SAS Institute, Cary, NC, USA), BellCurve for Excel (Social

Survey Research Information Co., Ltd., JP), and GraphPad Prism (GraphPad Software, Inc. San Diego, CA, 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) Center (UMIN000045270) before enrollment 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 1.5 (approved on August 3, 2021). 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 analyzed during this study will be available from the corresponding author of this article upon 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 glycemic control in Asian patients with T2D. Oral semaglutide has been shown to exert a potent anti-hyperglycemic 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 anti-hyperglycemic 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 mass gain would be ideal. DPP-4 inhibitors have no effect on body mass, whereas other insulin secretagogues tend to cause body mass 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 anti-hyperglycemic 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 glycemic 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.

LIST OF ABBREVIATIONS

BP, blood pressure; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; T2D, type 2 diabetes.

DECLARATIONS

Patient consent for publication

Not required.

Competing interests

A.N., T.A., and H.M. have received honoraria for lectures and received research funding from some organizations as described below. A.N. has obtained research support from Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim Co., Kissei Pharmaceutical Co., Ltd., and Taisho Pharmaceutical Co., Ltd. A.T. has received research grants from Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co. Ltd., Otsuka Pharmaceutical Co., Ltd. Pfizer Inc., Alexion Inc., Ono Pharmaceutical Co., Ltd., and Teijin Pharma Ltd.; speaking fees from Mitsubishi Tanabe Pharma Co., Chugai

Pharmaceutical Co., Ltd., Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Pfizer Inc., AbbVie Inc., Eisai Co. Ltd., Daiichi Sankyo Co., Ltd., Bristol-Myers Squibb Co., UCB Japan Co. Ltd., Eli Lilly Japan K.K., Novartis Pharma K.K., Eli Lilly Japan K.K., Kyowa Kirin Co., Ltd., and Taiho Pharmaceutical Co., Ltd.; and fees for consultancies from AstraZeneca plc., Medical & Biological Laboratories Co., Ltd., Pfizer Inc., AbbVie Inc., Ono Pharmaceutical Co. Ltd., Novartis Pharma K.K., and Nippon Boehringer Ingelheim Co., Ltd. H.M. has received honoraria for lectures from Astellas Pharma Inc., Sumitomo Dainippon Pharma Co., Ltd., Eli Lilly Japan K.K., Mitsubishi Tanabe Pharma Co., MSD K.K., Novo Nordisk Pharma Ltd., Kowa Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ono Pharmaceutical Co., Ltd., and Sanofi; and has received research funding from Astellas Pharma Inc., Daiichi Sankyo Co., Sumitomo Dainippon Pharma Co. Ltd., Eli Lilly Japan K.K., Mitsubishi Tanabe Pharma Co., Novo Nordisk Pharma, Kowa Pharmaceutical Co., Ltd., Abbott Japan Co., Nippon Boehringer Ingelheim Co., Ono Pharmaceutical Co., Ltd., LifeScan Japan Inc., and Taisho Pharmaceutical Co., Ltd.. H.N., S.F., J.T., S.N., H.Y., I.S., S.T., Y.K., S.A., A.M., H.K., and KY. C., have no conflicts of interest to declare.

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Author contributions

H.M. designed the original study protocol. H.N. and KY.C. contributed to modification of the study design. H.N. and H.M. drafted the manuscript, and all the other authors contributed to its revision. All authors will contribute to participant enrollment. KY.C. will collect the data and contribute to statistical analysis. H.M. 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.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figure legends

Figure 1. Patient recruitment scheme

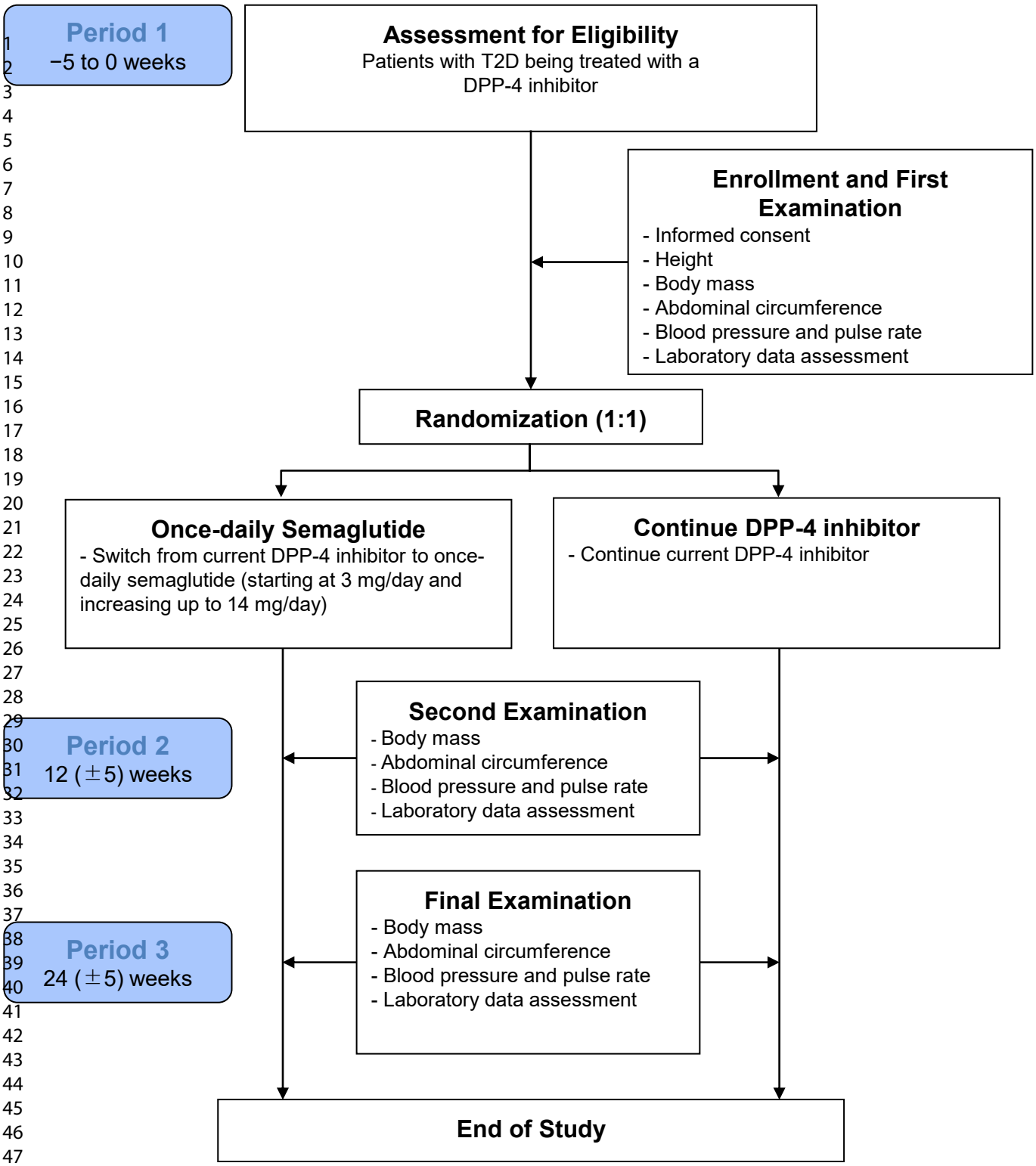
Participants will be randomly assigned to either continue to use their existing DPP-4 inhibitor or to be switched to oral semaglutide (starting dose 3 mg/day). All the participants will undergo physical and biochemical examinations at baseline and at the end of the study. DPP-4, dipeptidyl peptidase-4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

Box 1. Inclusion criteria

Inclusion criteria
- Japanese patients with T2D
- Age 20–89 years
- HbA1c 7.0%–9.9%
- Body mass index ≥ 18.5 kg/m^2
- Treatment with a DPP-4 inhibitor for at least 12 weeks before enrollment, without discontinuation for more than 1 week

Box 2. Exclusion criteria

Exclusion criteria
- Treatment with any GLP-1 receptor agonist within the 12 weeks prior to enrollment
- 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 pre-coma
- 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


Period 1
−5 to 0 weeks
Assessment for Eligibility
Patients with T2D being treated with a DPP-4 inhibitor
Enrollment and First Examination
- Informed consent
- Height
- Body mass
- Abdominal circumference
- Blood pressure and pulse rate
- Laboratory data assessment
Randomization (1:1)
Once-daily Semaglutide
- Switch from current DPP-4 inhibitor to once-daily semaglutide (starting at 3 mg/day and increasing up to 14 mg/day)
Continue DPP-4 inhibitor
- Continue current DPP-4 inhibitor
Period 2
12 (±5) weeks
Second Examination
- Body mass
- Abdominal circumference
- Blood pressure and pulse rate
- Laboratory data assessment
Period 3
24 (±5) weeks
Final Examination
- Body mass
- Abdominal circumference
- Blood pressure and pulse rate
- Laboratory data assessment
End of Study

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym Answer: p.1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set Answer: p.4
Protocol version	3	Date and version identifier Answer: p.13
Funding	4	Sources and types of financial, material, and other support Answer: p.18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor Answer: pp.18-19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities Answer: p.18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) Answer: Not applicable
Introduction		

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention Answer: pp.6-7
	6b	Explanation for choice of comparators Answer: pp.6-7
Objectives	7	Specific objectives or hypotheses Answer: pp.6-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) Answer: pp.7-9
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained Answer: pp.7-8, UMIN and jRCT web site
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) Answer: pp.9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Answer: pp.7-10

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended Answer: p.11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) Answer: pp.7-9 and Figure 1.
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations Answer: pp.11-12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size Answer: pp.9,11-12
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions Answer: pp.7-8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial Answer: Not applicable
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol Answer: pp.7-9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols Answer: p.11
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol Answer: pp.12-13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol Answer: pp.12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) Answer: Not applicable
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) Answer: pp.10, 12-13
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

		Answer: pp.13-14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial Answer: Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Answer: p.12-13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor Answer: Not applicable
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval Answer: pp.4 and 13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) Answer: pp.12-13
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Answer: p.10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable Answer: Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial Answer: pp.13-14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site Answer: pp.17-18

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators Answer: p.19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation Answer: pp.13-14
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions Answer: p.10
	31b	Authorship eligibility guidelines and any intended use of professional writers Answer: pp.18-19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code Answer: Not applicable
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates Answer: pp.10 and 13
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable Answer: Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

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

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Complete List of Authors:	Nomoto, Hiroshi; Hokkaido University, Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine and Graduate School of Medicine Furusawa, Sho; Hokkaido University, Department of Rheumatology, Endocrinology, and Nephrology Nakamura, Akinobu; Hokkaido University, Department of Rheumatology, Endocrinology, and Nephrology Takeuchi, Jun; Sapporo Diabetes and Thyroid Clinic Nagai, So; Sapporo Medical Center NTT EC Yokoyama, H.; Jiyugaoka Med Clin, Sakuma, Ichiro; Caress Sapporo Hokko Memorial Clinic Taneda, Shinji; Manda Memorial Hospital Kurihara, Yoshio; Kurihara Clinic Aoki, Shin; Aoki Clinic Miya, Aika; Hokkaido University, Department of Rheumatology, Endocrinology, and Nephrology Kameda, Hiraku; Hokkaido University Graduate School of Medicine Department of Rheumatology Endocrinology and Nephrology Cho, Kyu Yong; Hokkaido University, Department of Rheumatology, Endocrinology, and Nephrology, Faculty of Medicine and Graduate School of Medicine Atsumi, Tatsuya; Hokkaido University, Department of Rheumatology, Endocrinology, and Nephrology, Faculty of Medicine and Graduate School of Medicine, Miyoshi, Hideaki; Hokkaido University, Department of Rheumatology, Endocrinology, and Nephrology; Hokkaido University
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Protocol

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

Hiroshi Nomoto[1], Sho Furusawa[1], Akinobu Nakamura[1], Jun Takeuchi[2], So Nagai[3], Hiroki Yokoyama[4], Ichiro Sakuma[5], Shinji Taneda[6], Yoshio Kurihara[7], Shin Aoki[8], Aika Miya[1], Hiraku Kameda[1], Kyu Yong Cho[1,9], Tatsuya Atsumi[1], and Hideaki Miyoshi[1,10]

[1] Department of Rheumatology, Endocrinology, and Nephrology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

[2] Sapporo Diabetes and Thyroid Clinic, Sapporo, Japan

[3] Division of Diabetes and Endocrinology, Department of Medicine, Sapporo Medical Center, NTT East Corporation, Sapporo, Japan

[4] Department of Internal Medicine, Jiyugaoka Medical Clinic, Obihiro, Japan

[5] Caress Sapporo Hokko Memorial Clinic, Sapporo, Japan

[6] Diabetes Center, Manda Memorial Hospital, Sapporo, Japan

[7] Kurihara Clinic, Sapporo, Japan

[8] Aoki Clinic, Sapporo, Japan

[9] Clinical Research and Medical Innovation Center, Hokkaido University Hospital, Sapporo, Japan

[10] Division of Diabetes and Obesity, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

Corresponding author: Hideaki Miyoshi, MD, PhD

Division of Diabetes and Obesity, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, N15 W7, Kita-ku, Sapporo 060-8638, Japan.

Tel: +81-11-706-8192; Fax: +81-11-706-8194; E-mail: hmiyoshi@med.hokudai.ac.jp

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ABSTRACT

Introduction Incretin-based therapies exert anti-hyperglycemic 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 glycemic and weight control, but little evidence has been published for the superiority of semaglutide for glycemic 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 multi-center, prospective, randomized, 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 hemoglobin (HbA1c) level of 7.0%–9.9% will be randomized 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, 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 glycemic control in patients with T2D. The results will be disseminated in peer-reviewed journals and at scientific conferences. Hokkaido University Certified Review Board (CRB no.1180001) has approved the protocol (No.020-013).

Trial registration number

UMIN000045270 in the University Hospital Medical Information Network (UMIN); jRCT1011210032 in the Japan Registry of Clinical Trials (jRCT)

Strengths and limitations of this study

- The study is a multi-center, prospective, randomized, open-label, parallel-group trial.
- The study will be conducted in a standard clinical practice setting, at eight medical centers, 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 favorable result for oral semaglutide.

INTRODUCTION

A goal in the treatment of patients with diabetes is to reduce mortality by preventing diabetic macro- and microvascular complications. Strict glycemic control has been shown to reduce those complications [1]; however, intensive interventions can increase body weight as well as the risk of hypoglycemia [2 3]. Therefore, comprehensive interventions targeting multiple risks, including obesity, lipid metabolism, and blood pressure without causing hypoglycemia are required to achieve better outcomes [4 5]. As a consequence, treatment strategies that have potent anti-hyperglycemic effects without causing body weight gain and hypoglycemia 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, anti-hyperglycemic treatment regimens including a dipeptidyl peptidase-4 (DPP-4) inhibitor are well recognized for patients with T2D all over the world [7]. DPP-4 inhibitors are one of the most frequently prescribed anti-hyperglycemic 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 anti-hyperglycemic effects than conventional oral antihyperglycemic 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], albeit 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 hyperglycemia 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 glycemic control in daily clinical practice, and especially in patients that were previously treated using a DPP-4 inhibitor. Therefore, in this prospective, randomized, open-label, parallel-group trial, we will compare the effects of oral semaglutide administration to that of a DPP-4 inhibitor with respect to glycemic control in Japanese patients with T2D.

METHODS

Study design

This is a multi-center, open-label prospective, randomized, parallel-group

comparison study that will compare the glycemic control of patients taking a DPP-4 inhibitor or the oral GLP-1RA semaglutide daily. Following enrollment 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 blood pressure (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 randomization 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 glycemic target is to be determined for each patient based on the recommendations of the Japan Diabetes Society [17]. Serum and urine metabolic 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 glycemic control is insufficient to reach the glycemic 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 center for 24 weeks, then the baseline serum and urine measurements and physical examination will be repeated (Figure 1). The doses of anti-hyperglycemic 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 glycemic control does not reach the appropriate target and/or becomes worse despite suitable interventions in lifestyle behaviors, adjustment or addition of anti-hyperglycemic agents will be considered. To avoid hypoglycemia, the doses of sulfonylureas, glinides, and insulin will be able to be adjusted, based on the recommendations of the Japan Diabetes Society [17]. Participant enrollment will take place between 9th July 2021 and 31st December 2023 at eight medical centers 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 enrollment, 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 pre-coma, 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, 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 center.

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. Hypoglycemia is defined as symptomatic hypoglycemic events or blood glucose levels <70 mg/dL. We will prepare a time-course sheet for each study visit to minimize 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 enroll to achieve the target sample size, we will conduct the study at eight medical centers 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 analyzed using the unpaired *t*-test or Mann–Whitney U-test for continuous data, and Pearson's chi-square 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 analyze the data using JMP Pro (SAS Institute, Cary, NC, USA), BellCurve for Excel (Social Survey Research Information Co., Ltd., JP), and GraphPad Prism (GraphPad Software, Inc. San Diego, CA, 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) Center (UMIN000045270) before enrollment 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 1.7 (approved on February 3, 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 analyzed during this study will be available from the corresponding author of this article upon 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 glycemic control in Asian patients with T2D. Oral semaglutide has been shown to exert a potent anti-hyperglycemic 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 anti-hyperglycemic 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 anti-hyperglycemic 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 glycemic 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.

LIST OF ABBREVIATIONS

BP, blood pressure; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; T2D, type 2 diabetes.

DECLARATIONS

Patient consent for publication

Not required.

Competing interests

A.N., T.A., and H.M. have received honoraria for lectures and received research funding from some organizations as described below. A.N. has obtained research support from Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim Co., Kissei Pharmaceutical Co., Ltd., and Taisho Pharmaceutical Co., Ltd. A.T. has received research grants from Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co. Ltd., Otsuka

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Author contributions

H.M. designed the original study protocol. H.N. and KY.C. contributed to modification of the study design. H.N. and H.M. drafted the manuscript, and all the other authors contributed to its revision. H.N., S.F., A.N., J.T., S.N., H.Y., I.S., S.T., Y.K., S.A., A.M., H.K., KY.C., T.A., and H.M. will contribute to participant enrollment. KY.C. will collect the data and contribute to statistical analysis. H.M. 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.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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406 **Figure legends**

407

408 Figure 1. Patient recruitment scheme

409 Participants will be randomly assigned to either continue to use their existing DPP-4

410 inhibitor or to be switched to oral semaglutide (starting dose 3 mg/day). All the

411 participants will undergo physical and biochemical examinations at baseline and at the

412 end of the study. DPP-4, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like

413 peptidase-1; T2D, type 2 diabetes.

414

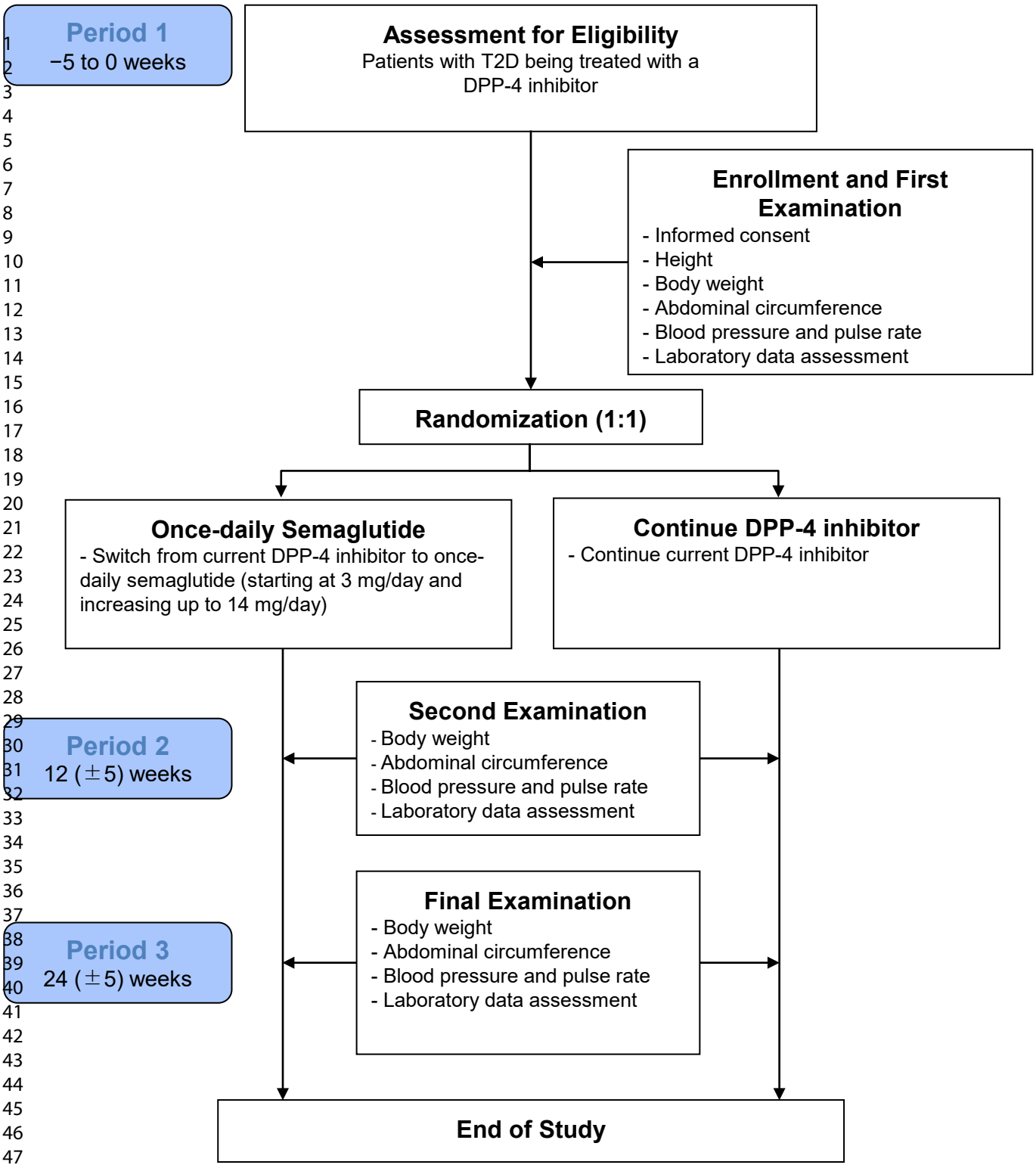
415

Box 1. Inclusion criteria

Inclusion criteria
- Japanese patients with T2D
- Age 20–89 years
- HbA1c 7.0%–9.9%
- Body mass index ≥ 18.5 kg/m^2
- Treatment with a DPP-4 inhibitor for at least 12 weeks before enrollment, without discontinuation for more than 1 week

Box 2. Exclusion criteria

Exclusion criteria
- Treatment with any GLP-1 receptor agonist within the 12 weeks prior to enrollment
- 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 pre-coma
- 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


Period 1
−5 to 0 weeks
Assessment for Eligibility
Patients with T2D being treated with a DPP-4 inhibitor
Enrollment and First Examination
- Informed consent
- Height
- Body weight
- Abdominal circumference
- Blood pressure and pulse rate
- Laboratory data assessment
Randomization (1:1)
Once-daily Semaglutide
- Switch from current DPP-4 inhibitor to once-daily semaglutide (starting at 3 mg/day and increasing up to 14 mg/day)
Continue DPP-4 inhibitor
- Continue current DPP-4 inhibitor
Period 2
12 (±5) weeks
Second Examination
- Body weight
- Abdominal circumference
- Blood pressure and pulse rate
- Laboratory data assessment
Period 3
24 (±5) weeks
Final Examination
- Body weight
- Abdominal circumference
- Blood pressure and pulse rate
- Laboratory data assessment
End of Study

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym Answer: p.1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set Answer: p.4
Protocol version	3	Date and version identifier Answer: p.13
Funding	4	Sources and types of financial, material, and other support Answer: p.18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor Answer: pp.18-19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities Answer: p.18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) Answer: Not applicable
Introduction		

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention Answer: pp.6-7
	6b	Explanation for choice of comparators Answer: pp.6-7
Objectives	7	Specific objectives or hypotheses Answer: pp.6-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) Answer: pp.7-9
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained Answer: pp.7-8, UMIN and jRCT web site
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) Answer: pp.9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Answer: pp.7-10

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended Answer: p.11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) Answer: pp.7-9 and Figure 1.
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations Answer: pp.11-12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size Answer: pp.9,11-12
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions Answer: pp.7-8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial Answer: Not applicable
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol Answer: pp.7-9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols Answer: p.11
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol Answer: pp.12-13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol Answer: pp.12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) Answer: Not applicable
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) Answer: pp.10, 12-13
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

		Answer: pp.13-14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial Answer: Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Answer: p.12-13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor Answer: Not applicable
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval Answer: pp.4 and 13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) Answer: pp.12-13
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Answer: p.10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable Answer: Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial Answer: pp.13-14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site Answer: pp.17-18

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators Answer: p.19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation Answer: pp.13-14
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions Answer: p.10
	31b	Authorship eligibility guidelines and any intended use of professional writers Answer: pp.18-19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code Answer: Not applicable
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates Answer: pp.10 and 13
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable Answer: Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.