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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 multi-center, prospective, randomized, open-label, parallel-group comparison study (the SWITCH-SEMA 2 study)

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Keywords:	DIABETES & ENDOCRINOLOGY, CLINICAL PHARMACOLOGY, GENERAL MEDICINE (see Internal Medicine)

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Manuscripts

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15 4 **glucose metabolism in patients with type 2 diabetes: protocol for a multi-center,**
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18 5 **prospective, randomized, open-label, parallel-group comparison study (the**
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21 6 **SWITCH-SEMA 2 study)**
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46 32 **Word count:** 2,892

47
48 33 **Keywords:** dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 receptor agonist,

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51 34 type 2 diabetes mellitus

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6 **36 ABSTRACT**
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12 **38 Introduction** Incretin-based therapies exert anti-hyperglycemic effects in patients with
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15 **39** type 2 diabetes (T2D) in a blood glucose concentration-dependent fashion. The first-in-
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18 **40** class oral glucagon-like peptide-1 receptor agonist semaglutide has potent effects on
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21 **41** glycemic and weight control, but little evidence has been published for the superiority of
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24 **42** semaglutide for glycemic control in patients after switching from a dipeptidyl peptidase-
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27 **43** 4 (DPP-4) inhibitor. Therefore, we aim to verify the efficacy of oral semaglutide in
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30 **44** patients with T2D being treated with a DPP-4 inhibitor.
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33 **45 Methods and analysis** This study is a multi-center, prospective, randomized, open-label,
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36 **46** parallel-group trial. In total, 172 participants with T2D who have been treated with a DPP-
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39 **47** 4 inhibitor for more than 12 weeks and who have a glycated hemoglobin (HbA1c) level
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42 **48** of 7.0%–9.9% will be randomized to continue using their existing DPP-4 inhibitor or
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45 **49** switch to oral semaglutide for 24 weeks. Biochemical analyses and physical assessment
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48 **50** will be performed and adverse events will be recorded at baseline and at the end of the
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51 **51** study. The primary endpoint will be the effect of oral semaglutide on the change in HbA1c.
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54 **52** The secondary endpoints will be the mean changes in body mass, abdominal
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57 **53** circumference, systolic and diastolic blood pressure, pulse rate, factors associated with
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6 54 any improvements in HbA1c or secondary endpoints, side-effects, and other laboratory
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9 55 parameters.

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12 56 **Ethics and dissemination** This will be the first study to compare the effects of switching
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15 57 from a DPP-4 inhibitor to oral semaglutide on glycemic control in patients with T2D. The
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18 58 results will be disseminated in peer-reviewed journals and at scientific conferences.
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21 59 Hokkaido University Certified Review Board (CRB no.1180001) has approved the
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24 60 protocol (No.020-013).

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27 61 **Trial registration number**

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30 62 UMIN000045270 in the University Hospital Medical Information Network (UMIN);
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33 63 jRCT1011210032 in the Japan Registry of Clinical Trials (jRCT)

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66 **Strengths and limitations of this study**

67 - This randomized controlled study will be the first to directly compare the glycaemic
68 control of patients with type 2 diabetes who switch from a DPP-4 inhibitor to oral
69 semaglutide administration.

70 - The study is a multi-center, prospective, randomized, parallel-group trial. Participants
71 will not be blinded to their treatment.

72 - The study will be conducted in a standard clinical practice setting, at eight medical
73 centers, and will include broad eligibility criteria, reflecting the real-world situation.

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6 75 **INTRODUCTION**

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11 77 A goal in the treatment of patients with diabetes is to reduce mortality by
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14 78 preventing diabetic macro- and microvascular complications. Strict glycaemic control has
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17 79 been shown to reduce those complications ¹; however, intensive interventions can
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20 80 increase body mass as well as the risk of hypoglycaemia ^{2 3}. Therefore, comprehensive
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23 81 interventions targeting multiple risks, including obesity, lipid metabolism, and blood
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26 82 pressure without causing hypoglycaemia are required to achieve better outcomes ^{4 5}. As a
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29 83 consequence, treatment strategies that have potent anti-hyperglycaemic effects without
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32 84 causing body mass gain and hypoglycaemia are sought after.

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35 85 Incretin-based therapies have been shown to have ideal glucose-lowering effects
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38 86 in patients with type 2 diabetes (T2D) because their effects are blood glucose
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41 87 concentration-dependent ⁶. Currently, anti-hyperglycaemic treatment regimens including
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44 88 a dipeptidyl peptidase-4 (DPP-4) inhibitor are well recognized for patients with T2D all
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47 89 over the world ⁷. DPP-4 inhibitors are one of the most frequently prescribed anti-
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50 90 hyperglycaemic drugs, especially in Japan, because of their safety and high efficacy in
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53 91 Asian populations ^{8 9}. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have
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56 92 stronger anti-hyperglycaemic effects than conventional oral antihyperglycaemic agents ¹⁰,

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6 93 and importantly, certain GLP-1RAs have been shown to have beneficial effects on
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9 94 cardiovascular outcomes in high-risk patients with T2D ¹¹⁻¹³, albeit that they require
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12 95 inconvenient parenteral administration.
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15 96 Recently, oral semaglutide—the first-in-class oral GLP-1RA—has been
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18 97 approved with the report of its remarkable effects on hyperglycemia and body mass,
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21 98 compared with either placebo, once-weekly semaglutide ¹⁴, or a DPP-4 inhibitor ¹⁵.
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24 99 However, notably, these comparisons were performed during a phase III trial, and it is
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27 100 not known whether oral semaglutide administration is superior to that of a conventional
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30 101 DPP-4 inhibitor with respect to glycemic control in daily clinical practice, and especially
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33 102 in patients that were previously treated using a DPP-4 inhibitor. Therefore, in this
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36 103 prospective, randomized, open-label, parallel-group trial, we will compare the effects of
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39 104 oral semaglutide administration to that of a DPP-4 inhibitor with respect to glycemic
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42 105 control in Japanese patients with T2D.
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48 107 **METHODS**

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54 109 *Study design*

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57 110 This is a multi-center, open-label prospective, randomized, parallel-group
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6 111 comparison study that will compare the glyceemic control of patients taking a DPP-4
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9 112 inhibitor or the oral GLP-1RA semaglutide daily. Following enrollment and the provision
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12 113 of written informed consent, the participants will undergo serum and urine analyses and
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15 114 physical examination to obtain baseline data. At each study visit, clinic blood pressure
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18 115 (BP), pulse rate, body mass, and abdominal circumference will be measured. After the
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21 116 initial assessment, all the participants will be randomly assigned to continue their DPP-4
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24 117 inhibitor or to switch to oral semaglutide at a ratio of 1:1, according to their age, body
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27 118 mass index (BMI), HbA1c, and institution. The randomization and allocation of the
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30 119 participants will be performed using a web-based automated system that is independent
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33 120 of the participating sites (NorthNet; <https://crmic.huhp.hokudai.ac.jp/page/?content=31>),
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36 121 as described previously ¹⁶. The glyceemic target is to be determined for each patient based
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39 122 on the recommendations of the Japan Diabetes Society ¹⁷. Serum and urine metabolic
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42 123 parameters, clinic BP, pulse rate, body mass, and abdominal circumference will be
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45 124 measured at each study visit.

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48 125 Oral semaglutide will be initiated at 3 mg once daily, which will be escalated to
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51 126 7 mg after 4 weeks and then up to 14 mg if necessary. Participants will be instructed to
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54 127 take the oral semaglutide in the morning in a fasted state, with 120 mL of water, at least
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57 128 30 min before breakfast and any other oral medication. They will also be encouraged to

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6 129 continue their diet and exercise therapy during the study. The treatments will be
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9 130 supervised through the appropriate medical care center for 24 weeks, then the baseline
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12 131 serum and urine measurements and physical examination will be repeated (Figure 1). The
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15 132 doses of anti-hyperglycemic agents other than sulfonylureas, glinides, and insulin, and
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18 133 concomitant treatments for metabolic disorders, will not be adjusted during the study
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21 134 period. To avoid hypoglycemia, the doses of sulfonylureas, glinides, and insulin will be
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24 135 able to be adjusted, based on the recommendations of the Japan Diabetes Society ¹⁷.
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27 136 Participant enrollment will take place between 9th July 2021 and 31st December 2023 at
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30 137 eight medical centers and clinics located in Hokkaido, Japan.
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36 139 ***Sample selection***

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39 140 The inclusion criteria are as follows: Japanese patients with T2D who are aged
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42 141 20–89 years, with HbA1c 7.0%–9.9% and BMI ≥ 18.5 kg/m², and who have been treated
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45 142 with a DPP-4 inhibitor for at least 12 weeks before enrollment, without being
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48 143 discontinued for more than 1 week (see Box 1). The key exclusion criteria are as follows:
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51 144 1) treatment with any GLP-1RA, 2) allergy to semaglutide, 3) unstable diabetic
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54 145 retinopathy, 4) current severe liver dysfunction or nephropathy, 5) severe infection,
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57 146 trauma, and/or recent or planned surgery, 6) severe ketosis, 7) diabetic coma or pre-coma,
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6 147 8) pregnancy, 9) poor compliance with medication, 10) inability to consume an
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9 148 appropriate diet and/or perform exercise, and 11) incompatibility with the trial for other
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12 149 reasons, as determined by a physician (see Box 2).
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15 150 Physicians in the research team will obtain written informed consent from all the
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18 151 eligible participants. The written material, consisting of a participant information leaflet
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21 152 and consent documentation, has been approved by the Research Committee. There will
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24 153 be an opportunity for the participants to freely ask questions of members of the research
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27 154 team, and their consent will be able to be withheld at any time during the study period,
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30 155 should they so wish. Patients will be withdrawn from the trial if any of the following
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33 156 criteria apply: 1) withdrawal of consent, 2) physician's decision, based on the patient's
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36 157 condition, 3) discontinuation of the study, or 4) physician's decision, based on another
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39 158 reason.
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45 160 ***Patient and public involvement statement***
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48 161 Participants were not directly involved in the design nor development of the
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51 162 study, and will not be involved in the recruitment nor conduct of the trial. The results of
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54 163 their investigations will be provided to the participants after the study, during a medical
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57 164 consultation in their participating center.
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9 166 **TRIAL ENDPOINT**

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15 168 *Primary and secondary endpoints*

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18 169 The primary endpoint of the study is the change in HbA1c from baseline to week
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21 170 24, which will be compared between the semaglutide group and control group. The
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24 171 secondary endpoints are as follows: the mean changes in 1) body mass, 2) abdominal
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27 172 circumference, 3) systolic and diastolic BP, 4) pulse rate, 5) laboratory parameters
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30 173 reflecting glucose and lipid metabolism, and liver and renal function, 6) factors associated
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33 174 with any improvement of HbA1c or secondary endpoints, and 7) any side-effects. We
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36 175 will prepare a time-course sheet for each study visit to minimize the risk of participants
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39 176 dropping out.

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45 178 *Sample size calculation*

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48 179 The sample size was calculated on the basis that oral semaglutide (3–14 mg/day)
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51 180 will improve HbA1c by at least a further 0.70% (SD 1.585%), compared with sitagliptin
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54 181 (100 mg/day), as shown in a phase III trial conducted in patients with T2D¹⁸. A power
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57 182 calculation determined that a sample size of 82 individuals per group would be required

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6 183 to achieve a power of at least 80% for the detection of a difference between treatments.
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9 184 $P < 0.05$ will be considered to represent statistical significance and all tests will be two-
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12 185 sided. On the basis of an assumption that four participants (5%) will drop out from each
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15 186 group, the sample size has been set at 86 participants per group. To ensure that enough
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18 187 participants enroll to achieve the target sample size, we will conduct the study at eight
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21 188 medical centers in Hokkaido.
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27 190 ***Data analysis***
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30 191 Analysis of the primary and secondary endpoint data will be principally
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33 192 performed using the full analysis set (FAS), which will comprise the participants who are
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36 193 enrolled in the study and assigned to treatment groups. Patients who do not meet the
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39 194 inclusion criteria, those with insufficient primary endpoint data, or those appreciably
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42 195 deviated from the study protocol will be excluded from the FAS. Differences between the
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45 196 two groups will be analyzed using the unpaired t -test or Mann–Whitney U-test for
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48 197 continuous data, and Pearson’s chi-square test or Fisher’s exact test for categorical data.
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51 198 The factors associated with any improvements in HbA1c or other metabolic parameters
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54 199 will be identified using analysis of covariance and multivariate analysis. We will analyze
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57 200 the data using JMP Pro (SAS Institute, Cary, NC, USA), BellCurve for Excel (Social
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6 201 Survey Research Information Co., Ltd., JP), and GraphPad Prism (GraphPad Software,
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9 202 Inc. San Diego, CA, USA).

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15 204 **ETHICS AND DISSEMINATION**

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21 206 *Ethics approval*

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24 207 The trial was registered with the Japan Registry of Clinical Trials
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27 208 (jRCT1011210032) and the University Hospital Medical Information Network (UMIN)
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30 209 Center (UMIN000045270) before enrollment commenced. The study protocol was
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33 210 approved by the Hokkaido University Certified Review Board (CRB no. 1180001;
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36 211 approval number 020-013), and the current version is 1.5 (approved on August 3, 2021).

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39 212 The study will be carried out in accordance with the principles of the Declaration of
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42 213 Helsinki and its amendments.

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48 215 *Data protection and management*

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51 216 Data management, including coding, security, storage, and cleaning, will be
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54 217 performed by researchers throughout the trial. The study data will be archived at
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57 218 Hokkaido University for 5 years after study completion. The participants will also be able

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6 219 to obtain the final results of the study. The UMIN and jRCT databases will contain
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9 220 detailed information regarding the study. Study conduct will be evaluated by a monitor
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15 222 and fifth participants at Hokkaido University Hospital, and the first participant at each of
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18 223 the other study sites. In line with the provisions of the Clinical Trials Act in Japan, adverse
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21 224 events and other information, including modifications to the trial, will be disclosed
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24 225 publicly.
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30 227 *Availability of data and materials*

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33 228 The data analyzed during this study will be available from the corresponding
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36 229 author of this article upon reasonable request.
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42 231 **DISCUSSION**

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48 233 To our knowledge, this will be the first prospective clinical trial to be
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51 234 conducted in a real-world setting, comparing the efficacy of oral semaglutide after
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54 235 switching from DPP-4 inhibitors with respect to glycemic control in Asian patients with
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57 236 T2D. Oral semaglutide has been shown to exert a potent anti-hyperglycemic effect. A
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6 237 recent network meta-analysis that compared the relative efficacy of oral semaglutide
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9 238 and injectable GLP-1RAs revealed that 14 mg/day oral semaglutide was associated with
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12 239 a significantly larger reduction in HbA1c than most of the comparators, with the
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15 240 exception of weekly semaglutide¹⁹. Furthermore, a previous phase III trial showed that
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18 241 the administration of oral semaglutide at 7 mg or 14 mg/day resulted in a larger
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21 242 reduction in HbA1c than sitagliptin at 100 mg/day¹⁵. Because it has been demonstrated
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24 243 that DPP-4 inhibitors have potent anti-hyperglycemic effects in Asian populations⁹,
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27 244 however, it is important to confirm that similar differences exist in the Japanese
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30 245 population.

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33 246 The management of obesity during the treatment of diabetes is important but
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36 247 presents a difficult challenge. A treatment strategy not causing body mass gain would
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39 248 be ideal. DPP-4 inhibitors have no effect on body mass, whereas other insulin
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42 249 secretagogues tend to cause body mass gain²⁰. One of the advantages of using a GLP-
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45 250 1RA would be related with appetite. Notably, a phase III trial that assessed the dose-
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48 251 response and efficacy of oral semaglutide in Japanese patients showed that the weight
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51 252 loss induced by semaglutide was greater than that induced by liraglutide at 0.9 mg/day,
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54 253 although the incidence of gastrointestinal events was comparable between the groups²¹.

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6 254 A switch from a DPP-4 inhibitor to oral semaglutide may represent a promising
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9 255 “step-up” therapeutic strategy. However, most patients being treated in routine clinical
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12 256 practice who are receiving a DPP-4 inhibitor are also taking other oral anti-
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15 257 hyperglycemic agents⁸. Because semaglutide must be taken at least 30 min before
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18 258 breakfast and any other oral medication, a switch to oral semaglutide forces patients to
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21 259 take their medication at two separate times, leading to poorer compliance and
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24 260 diminished efficacy of the therapy. Therefore, it is important to confirm the efficacy and
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27 261 safety of oral semaglutide in a study conducted in a real-world clinical practice setting.
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30 262 In conclusion, the present study will be the first clinical trial to evaluate the
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33 263 efficacy of oral semaglutide for glycemic control in patients with T2D who were
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36 264 previously being treated using a DPP-4 inhibitor in a real-world clinical practice setting.
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39 265 Therefore, the results should provide new insights into the efficacy of oral semaglutide in
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42 266 patients with T2D.
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48 268 **LIST OF ABBREVIATIONS**

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6 270 BP, blood pressure; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; GLP-1RA,
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9 271 glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; T2D, type 2
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18 274 **DECLARATIONS**

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24 276 *Patient consent for publication*

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27 277 Not required.
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33 279 *Competing interests*

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36 280 A.N., T.A., and H.M. have received honoraria for lectures and received research
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39 281 funding from some organizations as described below. A.N. has obtained research
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41
42 282 support from Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim Co., Kissei
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15 309 ***Author contributions***

16
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18 310 H.M. designed the original study protocol. H.N. and KY.C. contributed to modification
19
20
21 311 of the study design. H.N. and H.M. drafted the manuscript, and all the other authors
22
23
24 312 contributed to its revision. All authors will contribute to participant enrollment. KY.C.
25
26
27 313 will collect the data and contribute to statistical analysis. H.M. is the guarantor of this
28
29
30 314 work and will take responsibility for the integrity of the data and the accuracy of the
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33 315 data analysis.

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39 317 (ICMJE) criteria for the authorship of this article, take responsibility for the integrity of
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41
42 318 the work as a whole, and have given their approval for this version of the manuscript to
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51 321 ***Data availability statement***

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54 322 The datasets generated and/or analyzed during the current study are available from the
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57 323 corresponding author on reasonable request.
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24 330 **REFERENCES**

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6 402 **Figure legends**
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12 404 Figure 1. Patient recruitment scheme

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15 405 Participants will be randomly assigned to either continue to use their existing DPP-4

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18 406 inhibitor or to be switched to oral semaglutide (starting dose 3 mg/day). All the

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21 407 participants will undergo physical and biochemical examinations at baseline and at the

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24 408 end of the study. DPP-4, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like

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27 409 peptidase-1; T2D, type 2 diabetes.
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412 Box 1. Inclusion criteria

413 Inclusion criteria

- 414 - Japanese patients with T2D
- 415 - Age 20–89 years
- 416 - HbA1c 7.0%–9.9%
- 417 - Body mass index ≥ 18.5 kg/m²
- 418 - Treatment with a DPP-4 inhibitor for at least 12 weeks before enrollment, without
419 discontinuation for more than 1 week

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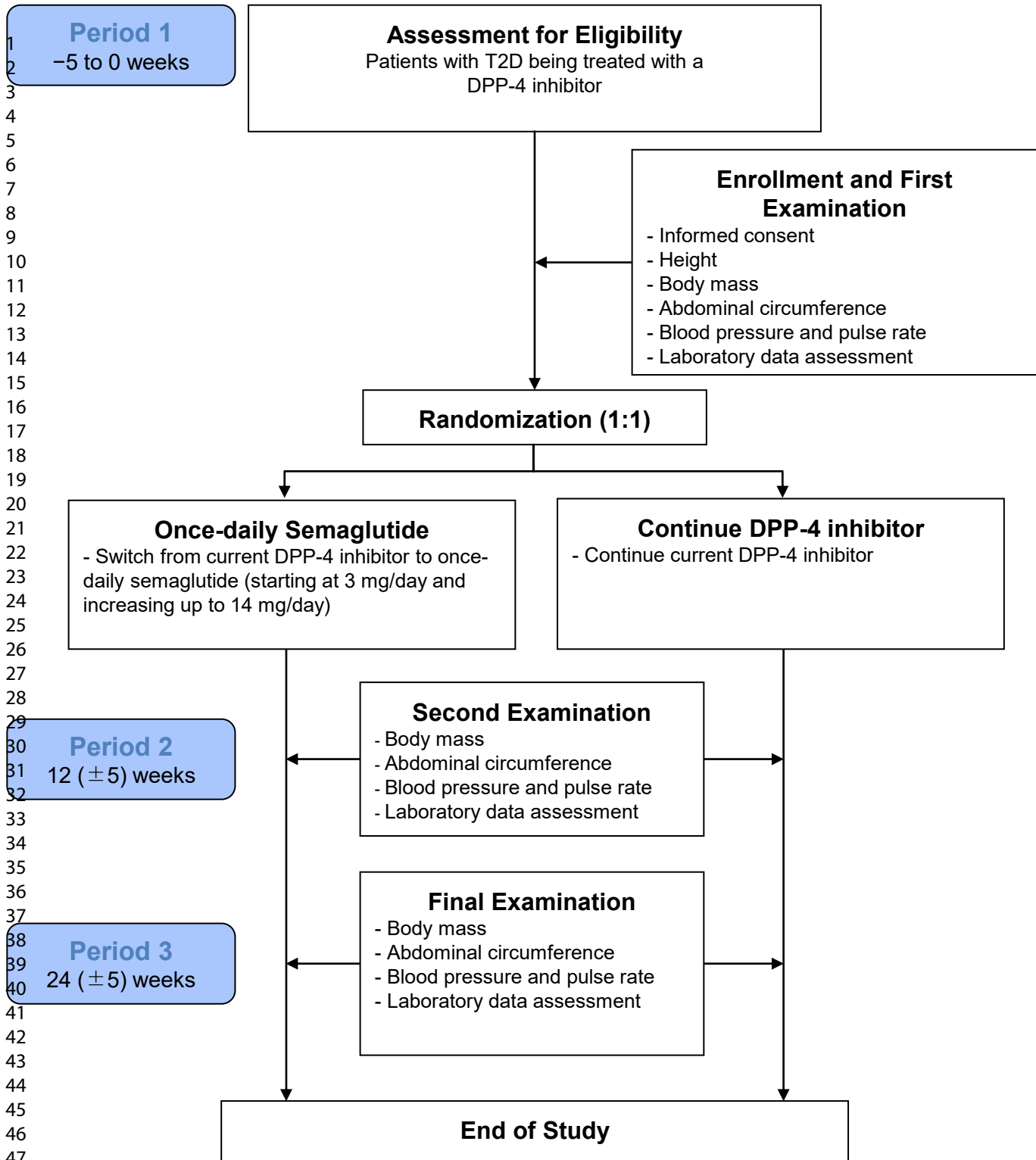
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422 Box 2. Exclusion criteria

423 Exclusion criteria

- 424 - Treatment with any GLP-1 receptor agonist within the 12 weeks prior to enrollment
- 425 - Allergy to semaglutide
- 426 - Unstable diabetic retinopathy
- 427 - Current severe liver dysfunction or nephropathy
- 428 - Severe infection, trauma, and/or recent or planned surgery
- 429 - Severe ketosis
- 430 - Diabetic coma or pre-coma
- 431 - Pregnancy
- 432 - Low drug compliance rate
- 433 - Inability to consume an appropriate diet and/or perform exercise
- 434 - Incompatibility with the trial for other reasons, as determined by the physician

435





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

1			
2	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
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6			Answer: pp.6-7
7			
8		6b	Explanation for choice of comparators
9			
10			Answer: pp.6-7
11			
12	Objectives	7	Specific objectives or hypotheses
13			
14			Answer: pp.6-7
15			
16	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)
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19			
20			Answer: pp.7-9
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24	Methods: Participants, interventions, and outcomes		
25			
26	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
27			
28			Answer: pp.7-8, UMIN and jRCT web site
29			
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32	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)
33			
34			Answer: pp.9-10
35			
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37	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
38			
39		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)
40			
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42		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
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47		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
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49			Answer: pp.7-10
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2 Outcomes 12 Primary, secondary, and other outcomes, including the specific
3 measurement variable (eg, systolic blood pressure), analysis metric
4 (eg, change from baseline, final value, time to event), method of
5 aggregation (eg, median, proportion), and time point for each
6 outcome. Explanation of the clinical relevance of chosen efficacy and
7 harm outcomes is strongly recommended
8

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10 **Answer:** p.11

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12 Participant 13 Time schedule of enrolment, interventions (including any run-ins and
13 timeline assessments, and visits for participants. A schematic
14 diagram is highly recommended (see Figure)
15

16 **Answer:** pp.7-9 and Figure 1.

17
18 Sample size 14 Estimated number of participants needed to achieve study objectives
19 and how it was determined, including clinical and statistical
20 assumptions supporting any sample size calculations
21

22 **Answer:** pp.11-12

23
24 Recruitment 15 Strategies for achieving adequate participant enrolment to reach
25 target sample size
26

27 **Answer:** pp.9,11-12
28

29 **Methods: Assignment of interventions (for controlled trials)**

30 Allocation:

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32
33 Sequence 16a Method of generating the allocation sequence (eg, computer-
34 generation generated random numbers), and list of any factors for stratification.
35 To reduce predictability of a random sequence, details of any planned
36 restriction (eg, blocking) should be provided in a separate document
37 that is unavailable to those who enrol participants or assign
38 interventions
39

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41 Allocation 16b Mechanism of implementing the allocation sequence (eg, central
42 concealment telephone; sequentially numbered, opaque, sealed envelopes),
43 mechanism describing any steps to conceal the sequence until interventions are
44 assigned
45

46
47 Implementation 16c Who will generate the allocation sequence, who will enrol participants,
48 and who will assign participants to interventions
49

50 **Answer:** pp.7-8

51
52 Blinding 17a Who will be blinded after assignment to interventions (eg, trial
53 (masking) participants, care providers, outcome assessors, data analysts), and
54 how
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- 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

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- 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

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2	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
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6			Answer: p.19
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8	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
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11			Answer: pp.13-14
12			
13	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
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16			Answer: p.10
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21		31b	Authorship eligibility guidelines and any intended use of professional writers
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24			Answer: pp.18-19
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27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
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30			Answer: Not applicable
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32	Appendices		
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34	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
35			
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37			Answer: pp.10 and 13
38			
39	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
40			
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43			Answer: Not applicable
44			

*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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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Secondary Subject Heading:	Diabetes and endocrinology, Medical management
Keywords:	DIABETES & ENDOCRINOLOGY, CLINICAL PHARMACOLOGY, GENERAL MEDICINE (see Internal Medicine)

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6 1 *Protocol*
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12 3 **Effects of switching from a dipeptidyl peptidase-4 inhibitor to oral semaglutide on**
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15 4 **glucose metabolism in patients with type 2 diabetes: protocol for a multi-center,**
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18 5 **prospective, randomized, open-label, parallel-group comparison study (the**
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21 6 **SWITCH-SEMA 2 study)**
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48 33 **Keywords:** dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 receptor agonist,

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51 34 type 2 diabetes mellitus

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6 **36 ABSTRACT**
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12 **38 Introduction** Incretin-based therapies exert anti-hyperglycemic effects in patients with
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15 **39** type 2 diabetes (T2D) in a blood glucose concentration-dependent fashion. The first-in-
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18 **40** class oral glucagon-like peptide-1 receptor agonist semaglutide has potent effects on
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21 **41** glycemic and weight control, but little evidence has been published for the superiority of
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24 **42** semaglutide for glycemic control in patients after switching from a dipeptidyl peptidase-
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27 **43** 4 (DPP-4) inhibitor. Therefore, we aim to verify the efficacy of oral semaglutide in
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30 **44** patients with T2D being treated with a DPP-4 inhibitor.
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33 **45 Methods and analysis** This study is a multi-center, prospective, randomized, open-label,
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36 **46** parallel-group trial. In total, 172 participants with T2D who have been treated with a DPP-
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39 **47** 4 inhibitor for more than 12 weeks and who have a glycated hemoglobin (HbA1c) level
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42 **48** of 7.0%–9.9% will be randomized to continue using their existing DPP-4 inhibitor or
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45 **49** switch to oral semaglutide for 24 weeks. Biochemical analyses and physical assessment
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48 **50** will be performed and adverse events will be recorded at baseline and at the end of the
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51 **51** study. The primary endpoint will be the effect of oral semaglutide on the change in HbA1c.
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54 **52** The secondary endpoints will be the mean changes in body weight, abdominal
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57 **53** circumference, systolic and diastolic blood pressure, pulse rate, the relationship between
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6 54 improvement of metabolic parameters including HbA1c and patient background
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9 55 characteristics, side-effects, and other laboratory parameters.
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12 56 **Ethics and dissemination** This will be the first study to compare the effects of switching
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15 57 from a DPP-4 inhibitor to oral semaglutide on glycemic control in patients with T2D. The
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18 58 results will be disseminated in peer-reviewed journals and at scientific conferences.
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21 59 Hokkaido University Certified Review Board (CRB no.1180001) has approved the
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24 60 protocol (No.020-013).
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27 61 **Trial registration number**

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30 62 UMIN000045270 in the University Hospital Medical Information Network (UMIN);
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33 63 jRCT1011210032 in the Japan Registry of Clinical Trials (jRCT)
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66 **Strengths and limitations of this study**

- 67 - The study is a multi-center, prospective, randomized, open-label, parallel-group trial.
- 68 - The study will be conducted in a standard clinical practice setting, at eight medical
- 69 centers, and will include broad eligibility criteria, reflecting the real-world situation.
- 70 - The limitation of the study is the open-label aspect of the study design, which can
- 71 create a bias toward observing a favorable result for oral semaglutide.

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6 73 **INTRODUCTION**
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12 A goal in the treatment of patients with diabetes is to reduce mortality by
13 preventing diabetic macro- and microvascular complications. Strict glycaemic control has
14 been shown to reduce those complications ¹; however, intensive interventions can
15 increase body weight as well as the risk of hypoglycaemia ^{2 3}. Therefore, comprehensive
16 interventions targeting multiple risks, including obesity, lipid metabolism, and blood
17 pressure without causing hypoglycaemia are required to achieve better outcomes ^{4 5}. As a
18 consequence, treatment strategies that have potent anti-hyperglycaemic effects without
19 causing body weight gain and hypoglycaemia are sought after.
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35 83 Incretin-based therapies have been shown to have ideal glucose-lowering effects
36 in patients with type 2 diabetes (T2D) because their effects are blood glucose
37 concentration-dependent ⁶. Currently, anti-hyperglycaemic treatment regimens including
38 a dipeptidyl peptidase-4 (DPP-4) inhibitor are well recognized for patients with T2D all
39 over the world ⁷. DPP-4 inhibitors are one of the most frequently prescribed anti-
40 hyperglycaemic drugs, especially in Japan, because of their safety and high efficacy in
41 Asian populations ^{8 9}. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have
42 stronger anti-hyperglycaemic effects than conventional oral antihyperglycaemic agents ¹⁰,
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6 91 and importantly, certain GLP-1RAs have been shown to have beneficial effects on
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9 92 cardiovascular outcomes in high-risk patients with T2D ¹¹⁻¹³, albeit that they require
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12 93 inconvenient parenteral administration.
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15 94 Recently, oral semaglutide—the first-in-class oral GLP-1RA—has been
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18 95 approved with the report of its remarkable effects on hyperglycemia and body weight,
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21 96 compared with either placebo, once-weekly semaglutide ¹⁴, or a DPP-4 inhibitor ¹⁵.
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24 97 However, notably, these comparisons were performed during a phase III trial, and it is
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27 98 not known whether oral semaglutide administration is superior to that of a conventional
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30 99 DPP-4 inhibitor with respect to glycemic control in daily clinical practice, and especially
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33 100 in patients that were previously treated using a DPP-4 inhibitor. Therefore, in this
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36 101 prospective, randomized, open-label, parallel-group trial, we will compare the effects of
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39 102 oral semaglutide administration to that of a DPP-4 inhibitor with respect to glycemic
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42 103 control in Japanese patients with T2D.
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48 105 **METHODS**

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54 107 *Study design*

57 108 This is a multi-center, open-label prospective, randomized, parallel-group
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6 109 comparison study that will compare the glyceemic control of patients taking a DPP-4
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9 110 inhibitor or the oral GLP-1RA semaglutide daily. Following enrollment and the provision
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12 111 of written informed consent, the participants will undergo serum and urine analyses and
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15 112 physical examination to obtain baseline data. At each study visit, clinic blood pressure
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18 113 (BP), pulse rate, body weight, and abdominal circumference will be measured. After the
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21 114 initial assessment, all the participants will be randomly assigned to continue their DPP-4
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24 115 inhibitor or to switch to oral semaglutide at a ratio of 1:1, according to their age, body
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27 116 mass index (BMI), HbA1c, and institution. The randomization and allocation of the
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30 117 participants will be performed using a web-based automated system that is independent
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33 118 of the participating sites (NorthNet; <https://crmic.huhp.hokudai.ac.jp/page/?content=31>),
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36 119 as described previously¹⁶. The glyceemic target is to be determined for each patient based
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39 120 on the recommendations of the Japan Diabetes Society¹⁷. Serum and urine metabolic
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42 121 parameters, clinic BP, pulse rate, body weight, and abdominal circumference will be
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45 122 measured at each study visit.

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48 123 Oral semaglutide will be initiated at 3 mg once daily, which will be escalated to
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51 124 7 mg after 4 weeks and then up to 14 mg if the glyceemic control is insufficient to reach
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54 125 the glyceemic target based on the recommendations of the Japan Diabetes Society and the
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57 126 participants agree. Participants will be instructed to take the oral semaglutide in the

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6 127 morning in a fasted state, with 120 mL of water, at least 30 min before breakfast and any
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9 128 other oral medication. They will also be encouraged to continue their diet and exercise
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12 129 therapy during the study. The treatments will be supervised through the appropriate
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15 130 medical care center for 24 weeks, then the baseline serum and urine measurements and
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18 131 physical examination will be repeated (Figure 1). The doses of anti-hyperglycemic agents
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21 132 other than sulfonylureas, glinides, and insulin, and concomitant treatments for metabolic
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24 133 disorders, will not be basically adjusted during the study period; however, if the glycemic
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27 134 control does not reach the appropriate target and/or becomes worse despite suitable
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30 135 interventions in lifestyle behaviors, adjustment or addition of anti-hyperglycemic agents
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33 136 will be considered. To avoid hypoglycemia, the doses of sulfonylureas, glinides, and
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36 137 insulin will be able to be adjusted, based on the recommendations of the Japan Diabetes
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39 138 Society ¹⁷. Participant enrollment will take place between 9th July 2021 and 31st
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42 139 December 2023 at eight medical centers and clinics located in Hokkaido, Japan.
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141 ***Sample selection***

51 142 The inclusion criteria are as follows: Japanese patients with T2D who are aged
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54 143 20–89 years, with HbA1c 7.0%–9.9% and BMI \geq 18.5 kg/m², and who have been treated
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57 144 with a DPP-4 inhibitor for at least 12 weeks before enrollment, without being
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6 145 discontinued for more than 1 week (see Box 1). The key exclusion criteria are as follows:
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9 146 1) treatment with any GLP-1RA, 2) allergy to semaglutide, 3) unstable diabetic
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12 147 retinopathy, 4) current severe liver dysfunction or nephropathy, 5) severe infection,
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15 148 trauma, and/or recent or planned surgery, 6) severe ketosis, 7) diabetic coma or pre-coma,
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18 149 8) pregnancy, 9) poor compliance with medication, 10) inability to consume an
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21 150 appropriate diet and/or perform exercise, and 11) incompatibility with the trial for other
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24 151 reasons, as determined by a physician (see Box 2).

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27 152 Physicians in the research team will obtain written informed consent from all the
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30 153 eligible participants. The written material, consisting of a participant information leaflet
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33 154 and consent documentation, has been approved by the Research Committee. There will
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36 155 be an opportunity for the participants to freely ask questions of members of the research
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39 156 team, and their consent will be able to be withheld at any time during the study period,
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42 157 should they so wish. Patients will be withdrawn from the trial if any of the following
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45 158 criteria apply: 1) withdrawal of consent, 2) physician's decision, based on the patient's
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48 159 condition, 3) discontinuation of the study, or 4) physician's decision, based on another
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51 160 reason.

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57 162 ***Patient and public involvement statement***

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6 163 Participants were not directly involved in the design nor development of the
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9 164 study, and will not be involved in the recruitment nor conduct of the trial. The results of
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12 165 their investigations will be provided to the participants after the study, during a medical
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15 166 consultation in their participating center.
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21 168 **TRIAL ENDPOINT**

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27 170 *Primary and secondary endpoints*

30 171 The primary endpoint of the study is the change in HbA1c from baseline to week
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33 172 24, which will be compared between the semaglutide group and control group. The
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36 173 secondary endpoints are as follows: the mean changes in 1) body weight, 2) abdominal
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39 174 circumference, 3) systolic and diastolic BP, 4) pulse rate, 5) laboratory parameters
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42 175 reflecting glucose and lipid metabolism, and liver and renal function, 6) the relationship
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45 176 between improvement of metabolic parameters including HbA1c and patient background
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48 177 characteristics, and 7) any side-effects. Hypoglycemia is defined as symptomatic
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51 178 hypoglycemic events or blood glucose levels <70 mg/dL. We will prepare a time-course
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54 179 sheet for each study visit to minimize the risk of participants dropping out.
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6 181 ***Sample size calculation***
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9 182 The sample size was calculated on the basis that oral semaglutide (3–14 mg/day)
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12 183 will improve HbA1c by at least a further 0.70% (SD 1.585%), compared with sitagliptin
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15 184 (100 mg/day), as shown in a phase III trial conducted in patients with T2D¹⁸. A power
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18 185 calculation determined that a sample size of 82 individuals per group would be required
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21 186 to achieve a power of at least 80% for the detection of superiority of oral semaglutide
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24 187 over DPP-4 inhibitor. $P < 0.05$ will be considered to represent statistical significance and
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27 188 all tests will be two-sided. On the basis of an assumption that four participants (5%) will
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30 189 drop out from each group, the sample size has been set at 86 participants per group. To
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33 190 ensure that enough participants enroll to achieve the target sample size, we will conduct
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36 191 the study at eight medical centers in Hokkaido.
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42 193 ***Data analysis***
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45 194 Analysis of the primary and secondary endpoint data will be principally
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48 195 performed using the full analysis set (FAS), which will comprise the participants who are
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51 196 enrolled in the study and assigned to treatment groups. Patients who do not meet the
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54 197 inclusion criteria, those with insufficient primary endpoint data, or those appreciably
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57 198 deviated from the study protocol will be excluded from the FAS. Differences between the
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6 199 two groups will be analyzed using the unpaired *t*-test or Mann–Whitney U-test for
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9 200 continuous data, and Pearson’s chi-square test or Fisher’s exact test for categorical data.
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12 201 The factors associated with any improvements in HbA1c or other metabolic parameters
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15 202 will be identified using analysis of covariance and multivariate analysis. We will analyze
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18 203 the data using JMP Pro (SAS Institute, Cary, NC, USA), BellCurve for Excel (Social
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21 204 Survey Research Information Co., Ltd., JP), and GraphPad Prism (GraphPad Software,
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24 205 Inc. San Diego, CA, USA).

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207 **ETHICS AND DISSEMINATION**

209 *Ethics approval*

210 The trial was registered with the Japan Registry of Clinical Trials
211 (jRCT1011210032) and the University Hospital Medical Information Network (UMIN)
212 Center (UMIN000045270) before enrollment commenced. The study protocol was
213 approved by the Hokkaido University Certified Review Board (CRB no. 1180001;
214 approval number 020-013), and the current version is 1.7 (approved on February 3, 2022).
215 The study will be carried out in accordance with the principles of the Declaration of
216 Helsinki and its amendments.

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9 218 ***Data protection and management***

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12 219 Data management, including coding, security, storage, and cleaning, will be
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15 220 performed by researchers throughout the trial. The study data will be archived at
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18 221 Hokkaido University for 5 years after study completion. The participants will also be able
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21 222 to obtain the final results of the study. The UMIN and jRCT databases will contain
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24 223 detailed information regarding the study. Study conduct will be evaluated by a monitor
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27 224 who will be independent of the investigators. Monitoring will be performed on the first
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30 225 and fifth participants at Hokkaido University Hospital, and the first participant at each of
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33 226 the other study sites. In line with the provisions of the Clinical Trials Act in Japan, adverse
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36 227 events and other information, including modifications to the trial, will be disclosed
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45 230 ***Availability of data and materials***

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48 231 The data analyzed during this study will be available from the corresponding
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51 232 author of this article upon reasonable request.

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57 234 **DISCUSSION**

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9 236 To our knowledge, this will be the first prospective clinical trial to be
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12 237 conducted in a real-world setting, comparing the efficacy of oral semaglutide after
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15 238 switching from DPP-4 inhibitors with respect to glycemic control in Asian patients with
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18 239 T2D. Oral semaglutide has been shown to exert a potent anti-hyperglycemic effect. A
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21 240 recent network meta-analysis that compared the relative efficacy of oral semaglutide
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24 241 and injectable GLP-1RAs revealed that 14 mg/day oral semaglutide was associated with
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27 242 a significantly larger reduction in HbA1c than most of the comparators, with the
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30 243 exception of weekly semaglutide¹⁹. Furthermore, a previous phase III trial showed that
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33 244 the administration of oral semaglutide at 7 mg or 14 mg/day resulted in a larger
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36 245 reduction in HbA1c than sitagliptin at 100 mg/day¹⁵. Because it has been demonstrated
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39 246 that DPP-4 inhibitors have potent anti-hyperglycemic effects in Asian populations⁹,
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42 247 however, it is important to confirm that similar differences exist in the Japanese
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45 248 population.

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48 249 The management of obesity during the treatment of diabetes is important but
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51 250 presents a difficult challenge. A treatment strategy not causing body weight gain would
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54 251 be ideal. DPP-4 inhibitors have no effect on body weight, whereas other insulin
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57 252 secretagogues tend to cause body weight gain²⁰. One of the advantages of using a GLP-

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6 253 1RA would be related with appetite. Notably, a phase III trial that assessed the dose-
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9 254 response and efficacy of oral semaglutide in Japanese patients showed that the weight
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12 255 loss induced by semaglutide was greater than that induced by liraglutide at 0.9 mg/day,
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15 256 although the incidence of gastrointestinal events was comparable between the groups ²¹.

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18 257 A switch from a DPP-4 inhibitor to oral semaglutide may represent a promising
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21 258 “step-up” therapeutic strategy. However, most patients being treated in routine clinical
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24 259 practice who are receiving a DPP-4 inhibitor are also taking other oral anti-
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27 260 hyperglycemic agents ⁸. Because semaglutide must be taken at least 30 min before
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30 261 breakfast and any other oral medication, a switch to oral semaglutide forces patients to
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33 262 take their medication at two separate times, leading to poorer compliance and
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36 263 diminished efficacy of the therapy. Therefore, it is important to confirm the efficacy and
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39 264 safety of oral semaglutide in a study conducted in a real-world clinical practice setting.

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42 265 In conclusion, the present study will be the first clinical trial to evaluate the
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45 266 efficacy of oral semaglutide for glycemic control in patients with T2D who were
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48 267 previously being treated using a DPP-4 inhibitor in a real-world clinical practice setting.
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51 268 Therefore, the results should provide new insights into the efficacy of oral semaglutide in
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54 269 patients with T2D.

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6 271 **LIST OF ABBREVIATIONS**
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12 273 BP, blood pressure; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; GLP-1RA,

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15 274 glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; T2D, type 2

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24 277 **DECLARATIONS**
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30 279 *Patient consent for publication*
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33 280 Not required.
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39 282 *Competing interests*
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41
42 283 A.N., T.A., and H.M. have received honoraria for lectures and received research

43
44
45 284 funding from some organizations as described below. A.N. has obtained research

46
47
48 285 support from Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim Co., Kissei

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50
51 286 Pharmaceutical Co., Ltd., and Taisho Pharmaceutical Co., Ltd. A.T. has received

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53
54 287 research grants from Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Mitsubishi

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57 288 Tanabe Pharma Co., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co. Ltd., Otsuka
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6 289 Pharmaceutical Co., Ltd. Pfizer Inc., Alexion Inc., Ono Pharmaceutical Co., Ltd., and
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9 290 Teijin Pharma Ltd.; speaking fees from Mitsubishi Tanabe Pharma Co., Chugai
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12 291 Pharmaceutical Co., Ltd., Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Pfizer
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15 292 Inc., AbbVie Inc., Eisai Co. Ltd., Daiichi Sankyo Co., Ltd., Bristol-Myers Squibb Co.,
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18 293 UCB Japan Co. Ltd., Eli Lilly Japan K.K., Novartis Pharma K.K., Eli Lilly Japan K.K.,
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21 294 Kyowa Kirin Co., Ltd., and Taiho Pharmaceutical Co., Ltd.; and fees for consultancies
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23
24 295 from AstraZeneca plc., Medical & Biological Laboratories Co., Ltd., Pfizer Inc.,
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26
27 296 AbbVie Inc., Ono Pharmaceutical Co. Ltd., Novartis Pharma K.K., and Nippon
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29
30 297 Boehringer Ingelheim Co., Ltd. H.M. has received honoraria for lectures from Astellas
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32
33 298 Pharma Inc., Sumitomo Dainippon Pharma Co., Ltd., Eli Lilly Japan K.K., Mitsubishi
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36 299 Tanabe Pharma Co., MSD K.K., Novo Nordisk Pharma Ltd., Kowa Pharmaceutical Co.,
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39 300 Ltd., Nippon Boehringer Ingelheim Co., Ono Pharmaceutical Co., Ltd., and Sanofi; and
40
41
42 301 has received research funding from Astellas Pharma Inc., Daiichi Sankyo Co.,
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44
45 302 Sumitomo Dainippon Pharma Co. Ltd., Eli Lilly Japan K.K., Mitsubishi Tanabe Pharma
46
47
48 303 Co., Novo Nordisk Pharma, Kowa Pharmaceutical Co., Ltd., Abbott Japan Co., Nippon
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51 304 Boehringer Ingelheim Co., Ono Pharmaceutical Co., Ltd., LifeScan Japan Inc., and
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53
54 305 Taisho Pharmaceutical Co., Ltd. H.N., S.F., J.T., S.N., H.Y., I.S., S.T., Y.K., S.A.,
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57 306 A.M., H.K., and KY. C., have no conflicts of interest to declare.
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9 308 ***Funding statement***

10
11
12 309 This research received no specific grant from any funding agency in the public,
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14
15 310 commercial or not-for-profit sectors.

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20
21 312 ***Author contributions***

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24 313 H.M. designed the original study protocol. H.N. and KY.C. contributed to modification
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26
27 314 of the study design. H.N. and H.M. drafted the manuscript, and all the other authors
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29
30 315 contributed to its revision. H.N., S.F., A.N., J.T., S.N., H.Y., I.S., S.T., Y.K., S.A.,
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32
33 316 A.M., H.K., KY.C., T.A., and H.M. will contribute to participant enrollment. KY.C.
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35
36 317 will collect the data and contribute to statistical analysis. H.M. is the guarantor of this
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39 318 work and will take responsibility for the integrity of the data and the accuracy of the
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42 319 data analysis.

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45 320 All named authors meet the International Committee of Medical Journal Editors
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48 321 (ICMJE) criteria for the authorship of this article, take responsibility for the integrity of
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51 322 the work as a whole, and have given their approval for this version of the manuscript to
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54 323 be published.

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6 325 ***Data availability statement***
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9 326 The datasets generated and/or analyzed during the current study are available from the
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12 327 corresponding author on reasonable request.
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18 329 ***Acknowledgements***
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22
23
24 331 of this manuscript. We also thank the participants in the study.
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6 406 **Figure legends**
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12 408 Figure 1. Patient recruitment scheme

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15 409 Participants will be randomly assigned to either continue to use their existing DPP-4

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18 410 inhibitor or to be switched to oral semaglutide (starting dose 3 mg/day). All the

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21 411 participants will undergo physical and biochemical examinations at baseline and at the

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24 412 end of the study. DPP-4, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like

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27 413 peptidase-1; T2D, type 2 diabetes.
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416 Box 1. Inclusion criteria

417 Inclusion criteria

- 418 - Japanese patients with T2D
- 419 - Age 20–89 years
- 420 - HbA1c 7.0%–9.9%
- 421 - Body mass index ≥ 18.5 kg/m²
- 422 - Treatment with a DPP-4 inhibitor for at least 12 weeks before enrollment, without
423 discontinuation for more than 1 week

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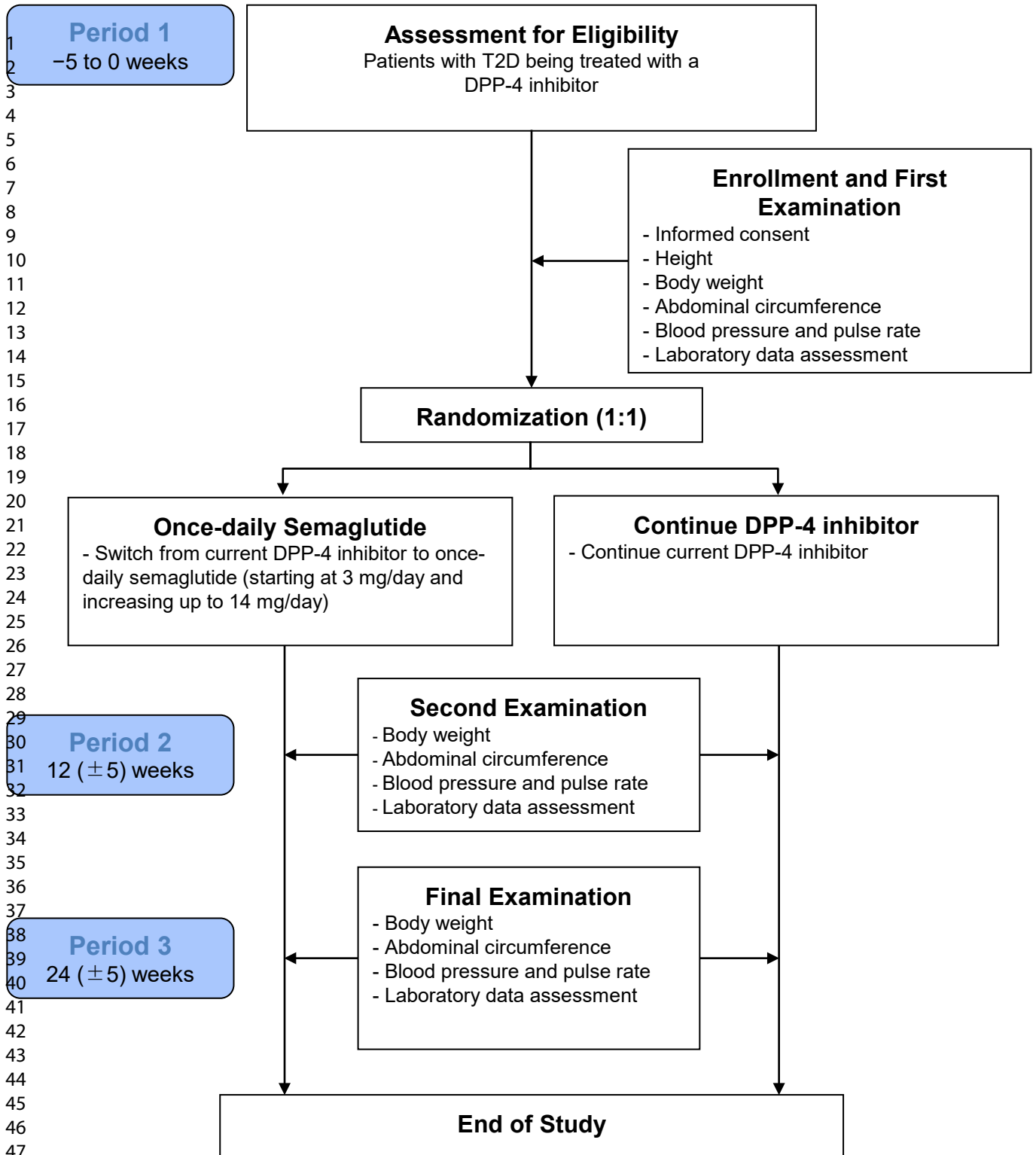
426 Box 2. Exclusion criteria

427 Exclusion criteria

- 428 - Treatment with any GLP-1 receptor agonist within the 12 weeks prior to enrollment
- 429 - Allergy to semaglutide
- 430 - Unstable diabetic retinopathy
- 431 - Current severe liver dysfunction or nephropathy
- 432 - Severe infection, trauma, and/or recent or planned surgery
- 433 - Severe ketosis
- 434 - Diabetic coma or pre-coma
- 435 - Pregnancy
- 436 - Low drug compliance rate
- 437 - Inability to consume an appropriate diet and/or perform exercise
- 438 - Incompatibility with the trial for other reasons, as determined by the physician

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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 <i>Answer: p.1</i>
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 <i>Answer: p.4</i>
Protocol version	3	Date and version identifier <i>Answer: p.13</i>
Funding	4	Sources and types of financial, material, and other support <i>Answer: p.18</i>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor <i>Answer: pp.18-19</i>
	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 <i>Answer: p.18</i>
	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) <i>Answer: Not applicable</i>

Introduction

1			
2	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
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6			Answer: pp.6-7
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8		6b	Explanation for choice of comparators
9			
10			Answer: pp.6-7
11			
12	Objectives	7	Specific objectives or hypotheses
13			
14			Answer: pp.6-7
15			
16	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)
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18			
19			Answer: pp.7-9
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24	Methods: Participants, interventions, and outcomes		
25			
26	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
27			
28			Answer: pp.7-8, UMIN and jRCT web site
29			
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32	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)
33			
34			Answer: pp.9-10
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37	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
38			
39		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)
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42		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
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47		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
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49			Answer: pp.7-10
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2 Outcomes 12 Primary, secondary, and other outcomes, including the specific
3 measurement variable (eg, systolic blood pressure), analysis metric
4 (eg, change from baseline, final value, time to event), method of
5 aggregation (eg, median, proportion), and time point for each
6 outcome. Explanation of the clinical relevance of chosen efficacy and
7 harm outcomes is strongly recommended
8

9
10 **Answer:** p.11

11
12 Participant 13 Time schedule of enrolment, interventions (including any run-ins and
13 timeline assessments, and visits for participants. A schematic
14 diagram is highly recommended (see Figure)
15

16 **Answer:** pp.7-9 and Figure 1.

17
18 Sample size 14 Estimated number of participants needed to achieve study objectives
19 and how it was determined, including clinical and statistical
20 assumptions supporting any sample size calculations
21

22 **Answer:** pp.11-12

23
24 Recruitment 15 Strategies for achieving adequate participant enrolment to reach
25 target sample size
26

27 **Answer:** pp.9,11-12
28

29 **Methods: Assignment of interventions (for controlled trials)**

30 Allocation:

31
32
33 Sequence 16a Method of generating the allocation sequence (eg, computer-
34 generation generated random numbers), and list of any factors for stratification.
35 To reduce predictability of a random sequence, details of any planned
36 restriction (eg, blocking) should be provided in a separate document
37 that is unavailable to those who enrol participants or assign
38 interventions
39

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41 Allocation 16b Mechanism of implementing the allocation sequence (eg, central
42 concealment telephone; sequentially numbered, opaque, sealed envelopes),
43 mechanism describing any steps to conceal the sequence until interventions are
44 assigned
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47 Implementation 16c Who will generate the allocation sequence, who will enrol participants,
48 and who will assign participants to interventions
49

50 **Answer:** pp.7-8

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52 Blinding 17a Who will be blinded after assignment to interventions (eg, trial
53 (masking) participants, care providers, outcome assessors, data analysts), and
54 how
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- 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

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- 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

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2	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
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6			Answer: p.19
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8	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
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11			Answer: pp.13-14
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13	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
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16			Answer: p.10
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21		31b	Authorship eligibility guidelines and any intended use of professional writers
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24			Answer: pp.18-19
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27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
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30			Answer: Not applicable
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32	Appendices		
33			
34	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
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37			Answer: pp.10 and 13
38			
39	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
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43			Answer: Not applicable
44			

*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.