



# Efficacy and safety of co-administered cagrilintide and semaglutide versus semaglutide alone in adults with overweight or obesity with or without type 2 diabetes in Japan and Taiwan (REDEFINE 5): a multicentre, randomised, active-controlled, phase 3a trial

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## Summary

**Background** The combination of cagrilintide and semaglutide has been shown in global studies to induce reductions in bodyweight. We assessed the efficacy and safety of a fixed-dose combination of cagrilintide 2.4 mg and semaglutide 2.4 mg versus semaglutide 2.4 mg for weight management in an east Asian population.

**Methods** This double-blind, parallel-group, phase 3a trial (REDEFINE 5) was conducted across 21 sites (community, hospital) in Japan and one site in Taiwan. We included participants aged at least 18 years with a BMI of at least 27 kg/m<sup>2</sup> and at least two obesity-related complications, or with a BMI of at least 35 kg/m<sup>2</sup> and at least one obesity-related complication (per the Japan Society for the Study of Obesity guidelines), with or without type 2 diabetes. Participants were randomly assigned (1:1) to once-weekly subcutaneous injections of cagrilintide–semaglutide or semaglutide (both escalated to 2.4 mg), plus lifestyle intervention, for 68 weeks. Randomisation was done centrally using an interactive web response system and stratified according to planned CT scan, BMI of at least 35 kg/m<sup>2</sup>, and type 2 diabetes status. Participants, site staff, investigators, and study funder were all masked to active study treatments. The primary endpoint was relative change in bodyweight from baseline to week 68. Efficacy analyses were done in all participants who underwent randomisation, using the trial product estimand (ie, assuming the treatment was taken as intended, regardless of dose) as the primary estimand. Missing data at week 68 were imputed. Safety analyses were done in all participants who underwent randomisation and received at least one dose of trial product. This trial is registered with ClinicalTrials.gov (NCT05813925) and is complete.

**Findings** Between April 3, 2023, and Sept 15, 2023, we screened 355 individuals; 331 were randomly assigned to cagrilintide–semaglutide (n=164) or semaglutide (n=167). 226 (68%) participants were male and 105 (32%) were female; 80 (24%) had type 2 diabetes. 17 (10%) participants discontinued cagrilintide–semaglutide and ten (6%) discontinued semaglutide. The estimated mean change in bodyweight from baseline to week 68 was –18.4% (SE 0.7) in the cagrilintide–semaglutide group versus –11.9% (0.7) in the semaglutide group (estimated treatment difference [ETD] –6.5 percentage points [95% CI –8.4 to –4.6]; p<0.0001). Adverse events were reported by 143 (87%) of 164 participants in the cagrilintide–semaglutide group and 141 (84%) of 167 in the semaglutide group, the most common of which were gastrointestinal disorders (87 [53%] of 164 participants in the cagrilintide–semaglutide group vs 85 [51%] of 167 in the semaglutide group). One death was reported in the semaglutide 2.4 mg group, which was not judged to be treatment related by the investigator.

**Interpretation** These findings support the efficacy and safety of cagrilintide–semaglutide for weight management in individuals from east Asia with overweight or obesity, with or without type 2 diabetes.

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## Introduction

More than 2 billion adults are classified as having overweight or obesity, with a BMI of at least 25 kg/m<sup>2</sup> for overweight and at least 30 kg/m<sup>2</sup> for obesity, as defined by WHO.<sup>1</sup> Incidence rates continue to rise, including in the Asia–Pacific region.<sup>2,3</sup> Obesity-related

complications include type 2 diabetes, dyslipidaemia, hypertension, mental health conditions, and many others, which can negatively affect physical function, quality of life, and overall life expectancy.<sup>4–6</sup> East Asian populations, including people from Japan, have an increased risk of obesity-related complications, which

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For the Japanese translation of the abstract see Online for appendix 1

For the Mandarin translation of the abstract see Online for appendix 2

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## Research in context

### Evidence before this study

We searched PubMed from database inception to July 16, 2025, without language restrictions, using the search terms “glucagon-like peptide-1 receptor agonist”, “GLP-1RA”, “long-acting amylin analogue”, “obesity”, “overweight”, “BMI  $\geq 25$ ”, and “East Asia”. To date, no randomised clinical trials have investigated fixed-dose combination treatment with a GLP-1 receptor agonist and a long-acting amylin analogue for weight management in east Asian adults with overweight or obesity. The search results included previous studies that have examined GLP-1 receptor agonists, including semaglutide, and dual GLP-1–glucose-dependent insulintropic polypeptide receptor agonists, including tirzepatide, in individuals with overweight or obesity. In STEP 6, a mean bodyweight reduction of 13.5% was achieved following treatment for 68 weeks with semaglutide 2.4 mg in Japanese and Korean participants with overweight or obesity, with or without type 2 diabetes (assessed using the trial product estimand). In SURMOUNT-1, a mean bodyweight reduction of –22.7% was achieved following treatment for 72 weeks with tirzepatide 15 mg in Japanese participants with obesity disease and without diabetes (assessed using the trial product estimand). Previous clinical studies have examined treatment with a combination of GLP-1 receptor agonist and long-acting amylin for bodyweight reduction in global populations: REDEFINE 1 reported a mean change in bodyweight of –22.7% at week 68 in participants with overweight or obesity, without type 2 diabetes, following treatment with once-weekly subcutaneous cagrilintide–semaglutide (2.4 mg each; assessed using the trial product estimand). REDEFINE 2 reported a mean change in bodyweight of –15.7% at week 68 in participants with obesity and type 2 diabetes, following treatment with cagrilintide 2.4 mg–semaglutide 2.4 mg (assessed using the trial product estimand). In the global REDEFINE phase 3 clinical trials examining cagrilintide 2.4 mg–semaglutide 2.4 mg for weight management, the trial populations were predominantly White and recruited across 12–22 countries.

### Added value of this study

Combination treatment with medications for obesity with different and complementary modes of action in individuals with overweight or obesity might lead to superior weight loss compared with the constituent monotherapies. Given the differences in body composition and definitions of obesity used in Asian populations compared with non-Asian populations, this study was done to assess the efficacy and safety of a fixed dose combination of cagrilintide 2.4 mg–semaglutide 2.4 mg as an adjunct to lifestyle intervention for bodyweight reduction

in east Asian adults with obesity, with or without type 2 diabetes. Cagrilintide–semaglutide was compared with an active control, semaglutide 2.4 mg, to evaluate the combination treatment against a monotherapy approved and used in current practice for weight management. To our knowledge, this is the first trial to report significantly greater bodyweight reductions in participants receiving cagrilintide–semaglutide compared with semaglutide alone in east Asian adults with overweight or obesity with or without type 2 diabetes. A significantly greater proportion of participants receiving cagrilintide–semaglutide achieved bodyweight reduction of at least 20% compared with semaglutide. Participants in the cagrilintide–semaglutide group also achieved a significantly greater reduction in waist circumference compared with those in the semaglutide group. Among those with a visceral fat area of at least 100 cm<sup>2</sup> at baseline (and therefore defined as having visceral fat obesity by the Japan Society for the Study of Obesity [JASSO] guidelines), a higher proportion of participants receiving cagrilintide–semaglutide achieved visceral fat area less than 100 cm<sup>2</sup> compared with those receiving semaglutide. Concurrent with bodyweight reduction, improvements in cardiometabolic risk factors, such as high-sensitivity C-reactive protein, lipids, and blood pressure, were observed with cagrilintide–semaglutide compared with semaglutide. The safety data for cagrilintide–semaglutide and semaglutide were generally consistent with previous findings.

### Implications of all the available evidence

These results highlight the need to account for ethnicity in obesity treatment and might inform regional practice or global guideline updates to help achieve holistic weight management care across populations. Obesity is associated with a range of complications, and incidence rates continue to rise in the Asia-Pacific region. Our findings are clinically relevant as most participants receiving cagrilintide–semaglutide achieved categorical bodyweight reductions that met current JASSO recommendations for individuals with obesity disease and high-degree obesity disease. Furthermore, participants achieved a greater mean bodyweight reduction and waist circumference reduction compared with participants receiving semaglutide 2.4 mg. Adverse events were generally consistent with previous clinical studies evaluating cagrilintide–semaglutide and semaglutide. Collectively, these results support the safety and tolerability of cagrilintide–semaglutide in east Asian adults with overweight or obesity, with or without type 2 diabetes.

present at lower BMI thresholds than in non-Asian populations.<sup>7</sup> Owing to a combination of genetic, lifestyle, and environmental factors, east Asian populations are more susceptible to metabolic disease at a lower BMI compared with populations in other regions, often due to a higher proportion of visceral fat

at a lower level of obesity.<sup>8</sup> According to the treatment guidelines of the Japan Society for the Study of Obesity (JASSO), obesity is defined as a BMI of at least 25 kg/m<sup>2</sup>. The term obesity disease refers to cases in which obesity is accompanied by specific complications that weight reduction could alleviate or by a visceral fat

area (VFA) accumulation ( $\geq 100$  cm<sup>2</sup> as measured by CT, or waist circumference  $\geq 85$  cm in adult Japanese men and  $\geq 90$  cm in adult Japanese women). Pharmacological therapy should be considered if weight reduction goals are not achieved through diet, exercise, and behavioural changes.<sup>7</sup>

Pharmacotherapy, in combination with lifestyle intervention, can aid sustained bodyweight reduction and reduce the effect and risk of obesity-related complications.<sup>4–6</sup> GLP-1 receptor agonists have shown efficacy in reducing bodyweight and improving obesity-related risk factors in participants with overweight or obesity, with and without type 2 diabetes.<sup>9–11</sup> Semaglutide is a GLP-1 receptor agonist approved at the once-weekly subcutaneous dose of 2.4 mg for the treatment of obesity disease in Japan;<sup>12</sup> it led to a change in bodyweight of  $-13.5\%$  in east Asian adults with or without type 2 diabetes, compared with a change of  $-2.2\%$  in those receiving placebo (assessed using the trial product estimand).<sup>13</sup>

Cagrilintide is a long-acting analogue of human amylin, a hormone that regulates appetite, bodyweight, and glycaemia.<sup>14,15</sup> In a phase 2 clinical trial, treatment with cagrilintide 2.4 mg led to a change in bodyweight of  $-9.7\%$  by week 26.<sup>16</sup> Given that cagrilintide and semaglutide have complementary yet distinct mechanisms of action, further clinical trials were initiated to establish whether using both in combination results in superior bodyweight reduction and cardiometabolic health benefits compared with the use of either medication alone. In the global, phase 3 clinical trial REDEFINE 1, cagrilintide–semaglutide (2.4 mg each) resulted in a change in bodyweight of  $-22.7\%$  in adults with overweight or obesity compared with  $-16.1\%$  with semaglutide 2.4 mg,  $-11.8\%$  with cagrilintide 2.4 mg, and  $-2.3\%$  with placebo (assessed using the trial product estimand).<sup>15</sup> In REDEFINE 2, cagrilintide–semaglutide (2.4 mg each) resulted in a change in bodyweight of  $-15.7\%$  in adults with obesity and type 2 diabetes versus  $-3.1\%$  with placebo (assessed using the trial product estimand).<sup>14</sup> Here, we report the efficacy and safety of cagrilintide–semaglutide (2.4 mg each) versus semaglutide 2.4 mg for weight management in an east Asian population.

## Methods

### Study design and participants

REDEFINE 5 was a double-blind, active-controlled, two-arm, parallel-group, multicentre trial conducted across 21 sites (community, hospital) in Japan and one in Taiwan. Eligibility criteria for sites included possession of suitable equipment or access to a local facility able to perform protocol-required assessments. Each participating site secured approval from its respective Institutional Review Board before study initiation.

This trial is registered with ClinicalTrials.gov (NCT05813925) and is complete. It was conducted in

accordance with the protocol, applicable laws and regulations, and consensus ethical principles derived from international guidelines including the Declaration of Helsinki and applicable ICH Good Clinical Practice Guidelines. The protocol was updated based on changes in estimands and statistical considerations, and the addition of supportive endpoints. Further details on changes to the protocol are outlined in appendix 4 (p 2).

We included adults aged at least 18 years with a BMI of at least 27 kg/m<sup>2</sup> and at least two obesity-related complications, or a BMI of at least 35 kg/m<sup>2</sup> with at least one obesity-related complication, with or without type 2 diabetes. Obesity-related complications were defined according to the JASSO guidelines:<sup>17</sup> (1) impaired glucose tolerance (prediabetes), (2) dyslipidaemia, (3) hypertension, (4) hyperuricaemia or gout, (5) coronary artery disease, (6) cerebral infarction, (7) metabolic dysfunction-associated steatotic liver disease, (8) menstrual disorder or infertility, (9) obstructive sleep apnoea syndrome or obesity-hypoventilation syndrome, (10) locomotory disease, or (11) obesity-related kidney disease. Prediabetes was defined as HbA<sub>1c</sub> of at least 5.7% (39 mmol/mol) to less than 6.5% (48 mmol/mol). In each participant, at least one obesity-related complication was required to be hypertension, dyslipidaemia, or type 2 diabetes. At least 25% of participants enrolled were required to have a BMI of at least 35 kg/m<sup>2</sup> and at least one obesity-related complication, and no more than 25% were required to have type 2 diabetes at screening. Additional eligibility criteria for participants with type 2 diabetes are provided in appendix 3 (pp 4–5).

Key exclusion criteria were treatment with medication for obesity within 90 days before screening; a history of diabetes or HbA<sub>1c</sub> of at least 6.5% (48 mmol/mol) for those without type 2 diabetes; and renal impairment (estimated glomerular filtration rate  $< 30$  mL/min per 1.73 m<sup>2</sup>) for those with type 2 diabetes. Full eligibility criteria can be found in appendix 3 (p 4).

Race, ethnicity, and sex were self-reported by participants. All participants provided written informed consent. The trial protocol is available as appendix 4 and the statistical analysis plan as appendix 5.

### Randomisation and masking

Participants were randomly assigned (1:1) to receive either once-weekly subcutaneous cagrilintide–semaglutide or semaglutide for 68 weeks, as an adjunct to lifestyle intervention. Randomisation was conducted using an interactive web response system and stratified according to planned CT scan (prespecified for a subset of participants from Japan), BMI of at least 35 kg/m<sup>2</sup>, and type 2 diabetes status. Active treatments were visually identical and supplied in identical packaging to maintain masking of the participants, site staff, investigators, and the funder and sponsor of the trial (Novo Nordisk). Further information on randomisation and masking can be found in appendix 3 (p 5).

See Online for appendix 3

See Online for appendix 4 and 5

## Procedures

All participants received lifestyle intervention, in which they were encouraged to maintain a deficit of at least 500 kcal per day relative to their estimated total energy expenditure (calculated once at randomisation) and to engage in moderate-intensity physical activity for 150 min per week for the duration of the study. Cagrilintide–semaglutide was initiated at a dose of 0.25 mg of each drug and the dose escalated every 4 weeks until the maximum dose of 2.4 mg of each drug was reached at week 16. Semaglutide was initiated at 0.25 mg and the dose escalated every 4 weeks until the maximum dose of 2.4 mg was reached at week 16. This period of dose escalation was followed by a 52-week maintenance period and a 7-week off-treatment follow-up period. Both investigational products were administered as single subcutaneous injections using a dual-chamber, single-dose, single-use pen device, either by delegated site staff or through self-administration at home. Investigators had the discretion to postpone dose escalation or lower the dose if the current dose was associated with adverse effects or if a participant with a BMI within the lower normal range continued to lose weight and had a related health concern. Although the aim was to escalate to the maximum dose, participants were

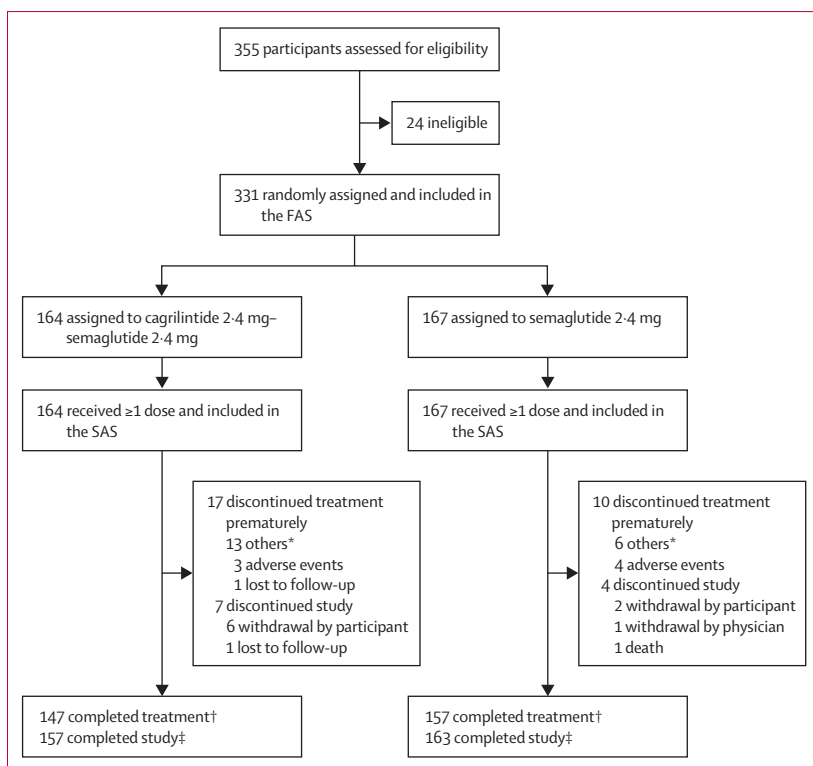
permitted to continue in the trial on a submaximal dose as established by clinical judgement. In a prespecified analysis, a Japanese subpopulation (prespecified to 50% of total participants from Japan with a maximum of 25% of participants with type 2 diabetes) underwent a CT scan before randomisation (at screening) and at the end of treatment (week 68) to assess VFA and subcutaneous fat area (SFA).

Adverse events selected for adjudication were assessed in an independent blinded manner by external medical experts using predefined event definitions and guidelines to align confirmation of event types globally. The investigator was responsible for detecting, documenting, recording, and following up on events that met the definition of an adverse event or serious adverse event; these were reported systematically. The severity of adverse events (mild, moderate, or severe) and likelihood of a relationship between the trial product and occurrence of adverse events (probable, possible, or unlikely) were assessed by the investigator. Further information on adverse event and serious adverse event definitions, and assessment of severity and causality, can be found in the protocol (appendix 4, pp 87–92).

## Outcomes

The primary endpoint was relative change (%) in bodyweight. Confirmatory (ie, included in the statistical testing hierarchy) secondary efficacy endpoints were the proportion of participants achieving at least 20% bodyweight reduction and change in waist circumference (cm) measured according to JASSO guidelines.<sup>7</sup> Relative change (%) in bodyweight was also compared between those with and without type 2 diabetes. All efficacy endpoints were measured from baseline to week 68 unless otherwise specified.

Supportive secondary efficacy endpoints were relative change in VFA (%); absolute change in VFA (cm<sup>2</sup>); and the proportion of participants achieving a VFA of less than 100 cm<sup>2</sup> (%; for those with VFA ≥100 cm<sup>2</sup> at baseline) in the Japanese subpopulation that underwent a CT scan before randomisation and at the end of treatment. Other supportive secondary efficacy endpoints included the proportion of participants achieving at least 10%, at least 15%, and at least 25% bodyweight reduction (%); relative change in bodyweight (%) from baseline to week 20; change in bodyweight (kg), BMI (kg/m<sup>2</sup>), HbA<sub>1c</sub> (percentage points; mmol/mol), fasting plasma glucose (mmol/L; mg/dL), systolic blood pressure (mm Hg), and diastolic blood pressure (mm Hg); ratio to baseline in fasting insulin; ratio to baseline in lipids; change in Impact of Weight on Quality of Life–Lite Clinical Trials Version (IWQOL-Lite-CT) Physical Function score (points) and Short Form 36-Item Health Survey (acute version, SF-36v2) Physical Functioning score (points); proportion of participants achieving at least a



**Figure 1: Trial profile**

FAS=full analysis set. SAS=safety analysis set. \*Other reasons for premature treatment discontinuation include “at the discretion of the investigator”, “withdrawal of consent”, and “other”. †Participants were considered to have completed treatment if they were on treatment at week 68. ‡Participants were considered to have completed the trial if they attended the end-of-trial visit at week 75, regardless of whether they completed treatment.

14·6-point increase in IWQOL-Lite-CT Physical Function score; proportion achieving at least a 3·7-point increase in SF-36v2 Physical Functioning score (meaningful within-participant changes); and number of treatment-emergent adverse events and serious adverse events up to week 75. Selection of safety focus areas was based on an assessment of clinical relevance.

Key exploratory endpoints included the proportion of participants achieving at least 5% bodyweight reduction and changes in SF-36v2 Acute Physical Component Summary and Mental Component Summary scores (points). Exploratory analyses were conducted to assess changes in Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) score and changes in the ratio of visceral to subcutaneous fat area (VFA:SFA).

### Statistical analysis

A sample size of 330 participants was required to provide greater than 99% power for showing superiority of cagrilintide–semaglutide over semaglutide for the primary endpoint, and at least 95% power for showing superiority for the two confirmatory secondary endpoints, tested according to a predefined hierarchy. The effective power (product of marginal powers) for achieving superiority in all three tests above was estimated to be greater than 90%. Efficacy outcomes were assessed in the full analysis set (all participants who underwent randomisation, in accordance with the intention-to-treat principle), and safety outcomes were assessed in the safety analysis set (all participants who underwent randomisation and received at least one dose of trial product).

There were two observation periods: on-treatment (time from first dose of trial product up to first treatment discontinuation [date when no trial product has been administered for 14 days] or to rescue intervention, whichever comes first; or 49 days [safety analyses] after last dose, excluding temporary interruptions) and in-trial (time from randomisation to last contact, irrespective of trial product discontinuation or other bodyweight-lowering intervention use). Two different estimands were used to evaluate the efficacy of cagrilintide–semaglutide: the trial product estimand was based on data from the on-treatment period and assessed the effects if either drug was taken as intended (regardless of dose), and the treatment policy estimand was based on data from the in-trial period and assessed the effects regardless of discontinuation of either drug or receipt of rescue intervention (consistent with the intention-to-treat principle). The trial product estimand was the primary estimand; all efficacy results are reported using this estimand unless otherwise stated. A brief description of all statistical analyses is available in appendix 3 (pp 8–9).

Results from statistical analyses were accompanied by two-sided 95% CIs and corresponding p values (superiority was  $p < 0.05$ ). Only the primary and

confirmatory secondary endpoints were controlled for multiplicity. Sensitivity analyses were conducted to assess the robustness of the superiority conclusions in case of violation of the missing at random assumption for the primary statistical analysis.

	Cagrilintide 2·4 mg– semaglutide 2·4 mg (n=164)	Semaglutide 2·4 mg (n=167)	Total (N=331)
Age, years	50·9 (11·3)	51·4 (10·5)	51·1 (10·9)
Sex			
Female	58 (35%)	47 (28%)	105 (32%)
Male	106 (65%)	120 (72%)	226 (68%)
Country of residence			
Japan	160 (98%)	161 (96%)	321 (97%)
Taiwan	4 (2%)	6 (4%)	10 (3%)
Race			
Asian	164 (100%)	167 (100%)	331 (100%)
Ethnic origin			
Hispanic or Latino	1 (1%)	0	1 (0·3%)
Not Hispanic or Latino	163 (99%)	167 (100%)	330 (>99%)
Type 2 diabetes at screening	38 (23%)	42 (25%)	80 (24%)
Bodyweight, kg	95·2 (20·2)	95·4 (16·1)	95·3 (18·2)
BMI, kg/m <sup>2</sup>	34·2 (5·6)	34·0 (4·8)	34·1 (5·2)
BMI category, kg/m <sup>2</sup>			
<30	48 (29%)	38 (23%)	86 (26%)
30–<35	52 (32%)	62 (37%)	114 (34%)
35–<40	40 (24%)	50 (30%)	90 (27%)
≥40	24 (15%)	17 (10%)	41 (12%)
Waist circumference, cm	111·0 (13·2)	110·8 (10·5)	110·9 (11·9)
HbA <sub>1c</sub> , %	6·2 (1·2)	6·3 (1·2)	6·3 (1·2)
HbA <sub>1c</sub> , mmol/mol	44·8 (12·7)	45·1 (13·6)	44·9 (13·1)
Fasting plasma glucose, mmol/L	6·5 (1·7)	6·6 (1·8)	6·5 (1·7)
Fasting serum insulin, pmol/L, geometric mean (CV)	93·7 (67·6)	99·2 (64·1)	96·4 (65·8)
Systolic blood pressure, mm Hg	129·0 (14·1)	127·8 (14·1)	128·4 (14·1)
Diastolic blood pressure, mm Hg	83·1 (10·1)	83·1 (10·3)	83·1 (10·2)
Lipids, mmol/L, geometric mean (CV)			
Total cholesterol	4·8 (17·9)	4·9 (17·3)	4·9 (17·6)
HDL cholesterol	1·3 (25·5)	1·2 (25·2)	1·2 (25·5)
LDL cholesterol	2·7 (31·8)	2·7 (31·7)	2·7 (31·7)
Non-HDL cholesterol	3·5 (23·2)	3·6 (23·7)	3·6 (23·5)
VLDL cholesterol	0·7 (45·4)	0·8 (52·0)	0·7 (49·3)
Free fatty acids	0·6 (36·8)	0·7 (31·5)	0·6 (34·3)
Triglycerides	1·6 (48·4)	1·7 (55·2)	1·6 (52·0)
High-sensitivity C-reactive protein, mg/L, geometric mean (CV)	1·3 (160·9)	1·5 (151·8)	1·4 (156·1)
Physical Functioning			
SF-36v2, score	51·9 (6·1)	51·0 (6·3)	51·5 (6·2)
IWQOL-Lite-CT, score	64·0 (20·3)	62·5 (20·3)	63·2 (20·3)
VFA, cm <sup>2</sup> *	162·3 (62·2)	183·8 (79·4)	173·1 (72·0)
VFA ≥100 cm <sup>2</sup> *	66 (83%)	72 (89%)	138 (86%)

Data are n (%) or mean (SD) unless otherwise stated. CV=coefficient of variation. IWQOL-Lite-CT=Impact of Weight on Quality of Life–Lite Clinical Trials Version. SF-36v2=Short Form 36-Item Health Survey (acute version). VFA=visceral fat area. \*CT scan subpopulation (cagrilintide–semaglutide, n=80; semaglutide, n=81).

**Table 1: Demographic and clinical characteristics of the participants at baseline (full analysis set)**

	Cagrilintide 2.4 mg- semaglutide 2.4 mg (n=164)	Semaglutide 2.4 mg (n=167)	Treatment difference or ratio (95% CI)*	p value
<b>Bodyweight-related endpoints</b>				
Change in bodyweight†	-18.4%	-11.9%	-6.5 (-8.4 to -4.6)	<0.0001
Participants achieving ≥5% bodyweight reduction‡	95%	79%	16.7 (9.4 to 24.0)	<0.0001
Participants achieving ≥10% bodyweight reduction§	82%	49%	33.4 (23.5 to 43.2)	<0.0001
Participants achieving ≥15% bodyweight reduction§	60%	30%	30.2 (19.7 to 40.6)	<0.0001
Participants achieving ≥20% bodyweight reduction¶	39%	19%	20.8 (11.1 to 30.6)	<0.0001
Participants achieving ≥25% bodyweight reduction§	22%	10%	12.8 (4.7 to 20.9)	0.0020
Change in bodyweight, kg§	-17.2	-11.0	-6.2 (-8.1 to -4.4)	<0.0001
Relative change in bodyweight at week 20§	-11.0%	-7.0%	-4.0 (-4.9 to -3.1)	<0.0001
Change in waist circumference, cm¶	-13.5	-9.7	-3.8 (-5.6 to -2.0)	<0.0001
Change in BMI, kg/m <sup>2</sup> §	-6.2	-4.0	-2.2 (-2.9 to -1.6)	<0.0001
Change in bodyweight in participants with type 2 diabetes	-14.6% (n=38)	-10.0% (n=42)	-4.6 (-8.3 to -0.9)	0.015
Change in bodyweight in participants without type 2 diabetes	-19.5% (n=126)	-12.5% (n=125)	-7.0 (-9.3 to -4.8)	<0.0001
<b>Cardiometabolic-related endpoints</b>				
Change in systolic blood pressure, mmHg§	-10.0	-5.2	-4.9 (-7.7 to -2.0)	0.0008
Change in diastolic blood pressure, mmHg§	-4.9	-1.2	-3.8 (-5.7 to -1.9)	0.0001
Change in HOMA-IR	-2.5	-1.9	-0.6 (-1.0 to -0.2)	0.0035
Ratio to baseline in lipids§				
Total cholesterol	0.93	0.91	ETR 1.02 (0.98 to 1.05)	0.33
HDL cholesterol	1.15	1.06	ETR 1.08 (1.05 to 1.12)	<0.0001
LDL cholesterol	0.91	0.92	ETR 0.99 (0.94 to 1.04)	0.70
VLDL cholesterol	0.63	0.73	ETR 0.86 (0.79 to 0.93)	0.0003
Non-HDL cholesterol	0.84	0.86	ETR 0.98 (0.94 to 1.03)	0.46
Triglycerides	0.62	0.72	ETR 0.86 (0.79 to 0.93)	0.0003
Free fatty acids	0.87	0.89	ETR 0.97 (0.90 to 1.05)	0.52
Ratio to baseline in high-sensitivity C-reactive protein§	0.46	0.67	ETR 0.69 (0.56 to 0.85)	0.0004
<b>Glucose metabolism-related endpoints</b>				
Change in HbA <sub>1c</sub> , %§	-1.1	-1.0	-0.1 (-0.2 to 0.0)	0.017
Change in HbA <sub>1c</sub> , mmol/mol§	-12.0	-10.9	-1.2 (-2.1 to -0.2)	0.017
Change in fasting plasma glucose, mmol/L§	-1.4	-1.4	-0.1 (-0.2 to 0.1)	0.43
Ratio to baseline in fasting serum insulin§	0.59	0.73	ETR 0.82 (0.72 to 0.92)	0.0014
<b>Clinical assessments</b>				
Change in IWQOL-Lite-CT Physical Function score§	14.9	13.5	1.4 (-2.0 to 4.8)	0.41
Change in SF-36v2 Physical Functioning score§	2.2	2.5	-0.3 (-1.2 to 0.6)	0.48
Participants achieving ≥14.6-point increase in IWQOL-Lite-CT Physical Function score§	50.3%	50.4%	-0.1 (-10.3 to 10.0)	0.98
Participants achieving ≥3.7-point increase in SF-36v2 Physical Functioning score§	35.5%	37.0%	-1.5 (-10.7 to 7.8)	0.76
<b>CT scan-related endpoints</b>				
Absolute change in VFA, cm <sup>2</sup> §	-79.9 (n=161)	-65.1 (n=161)	-14.8 (-30.5 to 1.0)	0.066
VFA percentage change§	-49.0% (n=161)	-40.4% (n=161)	-8.6 (-17.7 to 0.4)	0.060
Participants achieving a VFA of <100 cm <sup>2</sup> who had a VFA of ≥100 cm <sup>2</sup> at baseline§	61%	45%	15.7 (2.2 to 29.2)	0.023
Change in VFA:SFA ratio	-0.2	-0.1	0.0 (-0.1 to 0.0)	0.48

Data are estimated mean changes or estimated proportions that incorporate the assumptions of the trial product estimand (ie, based on data from the on-treatment period and assuming the drug was taken as intended [regardless of dose]), unless otherwise specified. ETD=estimated treatment difference. ETR=estimated treatment ratio. HOMA-IR=Homeostatic Model Assessment for Insulin Resistance. IWQOL-Lite-CT=Impact of Weight on Quality of Life-Lite Clinical Trials Version. SF-36v2=Short Form 36-Item Health Survey (acute version). SFA=subcutaneous fat area. VFA=visceral fat area. \*Treatment difference (95% CI) is ETD, unless otherwise specified, for cagrilintide-semaglutide versus semaglutide; ETR is cagrilintide-semaglutide:semaglutide. †Primary endpoint. ‡Exploratory endpoint. §Supportive secondary endpoint. ¶Confirmatory secondary endpoint; waist circumference measured according to JASSO guidelines. ||Exploratory post-hoc analysis.

**Table 2: Primary, selected secondary, and selected exploratory endpoints (trial product estimand)**

**Role of the funding source**

The study funder supplied the study drugs, and was responsible for the trial design, protocol, statistical analysis plan, and for performing the statistical analyses, but had no role in data collection. Medical writing support was paid for by the funder.

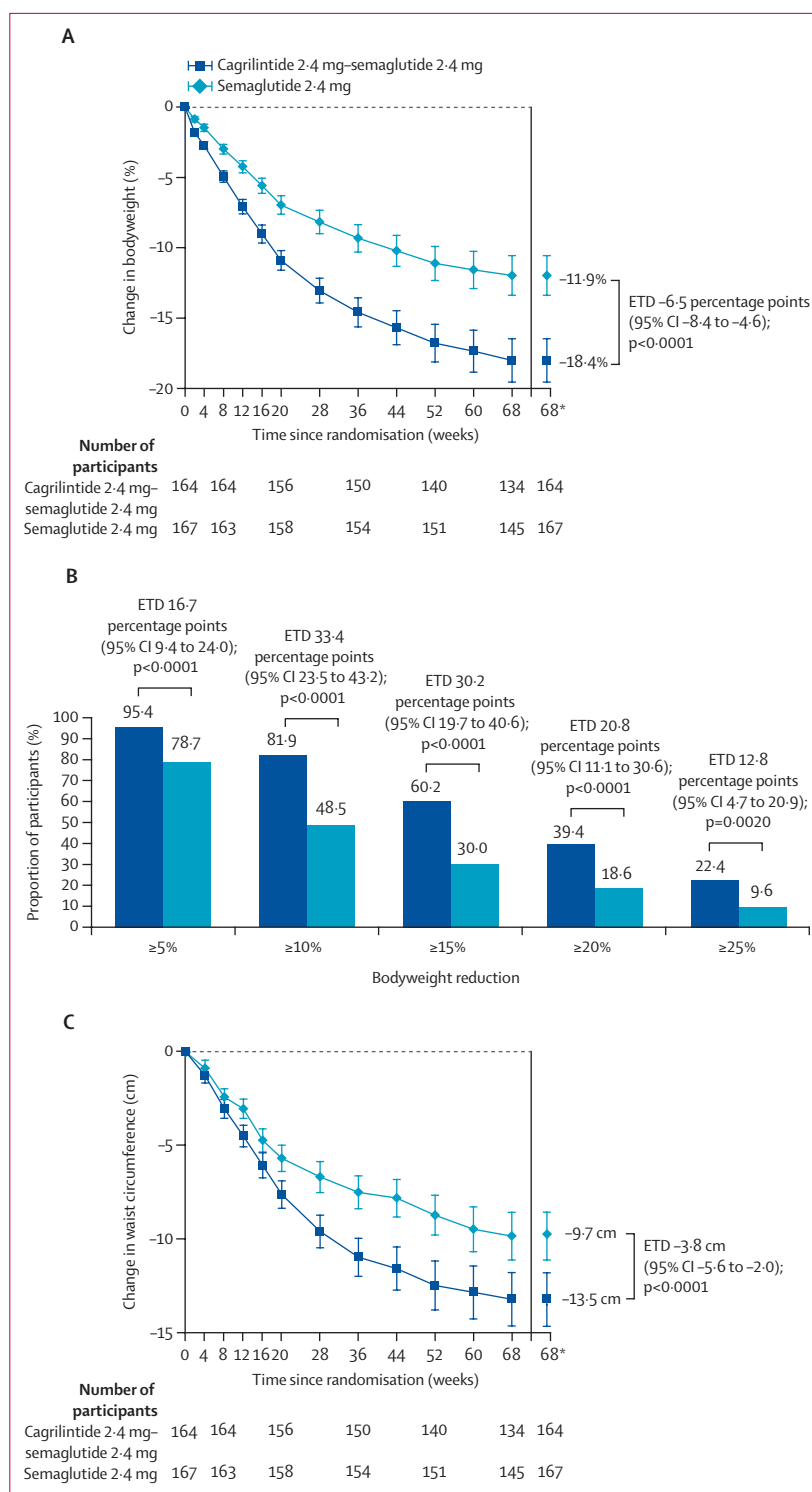
**Results**

Between April 3, 2023, and Sept 15, 2023, 355 individuals were screened for eligibility, 331 of whom were randomly assigned to once-weekly, subcutaneous cagrilintide–semaglutide (n=164) or semaglutide (n=167) (appendix 3 p 29) and included in the full analysis set. All participants who were randomly assigned to treatment received at least one dose of trial product and were included in the safety analysis. In total, 304 (92%) of 331 participants completed treatment (147 [90%] of 164 with cagrilintide–semaglutide, 157 [94%] of 167 with semaglutide; figure 1). A total of 27 (8%) participants permanently discontinued treatment: 17 (10%) discontinued cagrilintide–semaglutide and ten (6%) discontinued semaglutide. Reasons for discontinuation included adverse events (n=7), loss to follow-up (n=1), and other (n=19; included investigator discretion, withdrawal of consent, and other).

Baseline characteristics are presented in table 1 (appendix 3 p 13). 226 (68%) participants were male and 105 (32%) were female, with a mean age of 51.1 years (SD 10.9). All participants were Asian; 38 (23%) participants in the cagrilintide–semaglutide had type 2 diabetes at screening, with a mean duration of diabetes of 9.0 years (SD 7.1), and 42 (24%) had type 2 diabetes at screening in the semaglutide group, with a mean duration of 8.6 years (6.0). At baseline, mean bodyweight was 95.3 kg (18.2), mean BMI was 34.1 kg/m<sup>2</sup> (5.2), and mean HbA<sub>1c</sub> was 6.3% (1.2, 44.9 mmol/mol [13.1]; table 1). Most participants (272 [82%]) had two to four obesity-related complications at screening, with dyslipidaemia (286 [86%]) and hypertension (256 [77%]) being the most common; 127 (38%) had prediabetes at baseline (appendix 3 p 13).

At week 68, 119 (73%) of 164 participants received the maximum dose of cagrilintide–semaglutide and

150 (90%) of 167 received the maximum dose of semaglutide (appendix 3 p 14). 145 (88%) participants received the maximum dose of cagrilintide–semaglutide at any point after randomisation and 159 (95%) received the maximum dose of semaglutide.



**Figure 2: Change in bodyweight, bodyweight reductions at week 68, and change in waist circumference (trial product estimand)**

(A) Observed mean percentage changes (SE) in bodyweight from week 0 to week 68 during the on-treatment period, and estimated changes at week 68.

(B) Estimated proportions of participants who reached bodyweight reduction thresholds of 5–25% or more at week 68 and estimated differences. (C) Observed mean changes (SE) in waist circumference (cm) from week 0 to week 68 during the on-treatment period, and estimated changes at week 68. Numbers under the graphs indicate participants contributing to the mean. Waist circumference measurements were taken at the navel as per the Japan Society for the Study of Obesity Guidelines for the Management of Obesity Disease (2022).

ETD=estimated treatment difference. \*Estimated means incorporating the assumptions of the trial product estimand.

For the trial product estimand, participants receiving cagrilintide–semaglutide had a mean change in bodyweight of  $-18.4\%$  (SE 0.7) versus  $-11.9\%$  (0.7) for semaglutide; the estimated treatment difference (ETD) was  $-6.5$  percentage points (95% CI  $-8.4$  to  $-4.6$ ;  $p < 0.0001$ ; table 2; figure 2A). For the treatment policy estimand, participants receiving cagrilintide–semaglutide had a mean change in bodyweight of  $-16.9\%$  (0.7) versus  $-11.1\%$  (0.7) for semaglutide (ETD  $-5.8$  percentage points [ $-7.8$  to  $-3.8$ ];  $p < 0.0001$ ; appendix 3 pp 15, 31). In an analysis of those without type 2 diabetes, a mean change in bodyweight of  $-19.5\%$  (0.8) was achieved in the cagrilintide–semaglutide group and  $-12.5\%$  (0.8) in the semaglutide group (ETD  $-7.0$  percentage points [ $-9.3$  to  $-4.8$ ];  $p < 0.0001$ ). Among those with type 2 diabetes, a mean change in bodyweight of  $-14.6\%$  (1.3) was achieved in the cagrilintide–semaglutide group and  $-10.0\%$  (1.3) in the semaglutide group (ETD  $-4.6$  percentage points [ $-8.3$  to  $-0.9$ ];  $p = 0.015$ ).

The estimated proportion of participants achieving bodyweight reductions of at least 20% was 39% in the cagrilintide–semaglutide group and 19% in the semaglutide group (ETD 20.8 percentage points [11.1 to 30.6];  $p < 0.0001$ ; figure 2B). Participants receiving cagrilintide–semaglutide were also significantly more likely to achieve prespecified bodyweight reduction thresholds of at least 5%, at least 10%, at least 15%, and at least 25% compared with those receiving semaglutide ( $p \leq 0.0020$ ; figure 2B). Results for the treatment policy estimand were similar to those of the trial product estimand for these endpoints (appendix 3 p 15). Mean change in waist circumference for the cagrilintide–semaglutide group was  $-13.5$  cm (SE 0.7) versus  $-9.7$  cm (0.6) in the semaglutide group, corresponding to an ETD of  $-3.8$  cm ( $-5.6$  to  $-2.0$ ;  $p < 0.0001$ ; table 2, figure 2C). Results were similar for the treatment policy estimand (appendix 3 pp 15, 32). Mean change in BMI was greater for the cagrilintide–semaglutide group ( $-6.2$  kg/m<sup>2</sup> [SE 0.2]) compared with the semaglutide group ( $-4.0$  kg/m<sup>2</sup> [0.2]; table 2).

In the subpopulation of 80 participants in the cagrilintide–semaglutide group and 81 in the semaglutide group who underwent CT scans, no treatment difference was observed in absolute change in VFA between the two groups (ETD  $-14.8$  cm<sup>2</sup> [ $-30.5$  to 1.0];  $p = 0.066$ ; table 2; appendix 3 p 34). No treatment difference was observed in VFA percentage change between participants receiving cagrilintide–semaglutide and those receiving semaglutide (ETD  $-8.6$  percentage points [ $-17.7$  to 0.4];  $p = 0.060$ ; table 2; appendix 3 p 33). In participants with a VFA of at least 100 cm<sup>2</sup> at baseline (ie, with visceral fat obesity according to JASSO guidelines), 61% of participants receiving cagrilintide–semaglutide achieved a VFA of less than 100 cm<sup>2</sup> at week 68 compared with 45% receiving semaglutide (ETD 15.7 percentage points [2.2 to 29.2];  $p = 0.023$ ; table 2; appendix 3 p 35).

Results were similar for the treatment policy estimand (appendix 3 p 16). No difference was observed in the change in VFA:SFA ratio between participants in the cagrilintide–semaglutide group and those in the semaglutide group (ETD 0.0 [ $-0.1$  to 0.0];  $p = 0.48$ ; table 2; appendix 3 p 34).

Participants in the full analysis set who received cagrilintide–semaglutide achieved a significantly greater mean percentage reduction in HbA<sub>1c</sub> ( $-12.0$  mmol/mol [0.3]) compared with those receiving semaglutide ( $-10.9$  [0.3]) by week 68, corresponding to an ETD of  $-1.2$  mmol/mol ( $-2.1$  to  $-0.2$ ;  $p = 0.017$ ; table 2; appendix 3 p 36). We observed this superiority of cagrilintide–semaglutide over semaglutide treatment using the trial product estimand only (appendix 3 pp 15–16). The absolute reduction in fasting plasma glucose was similar in participants in the cagrilintide–semaglutide group and the semaglutide group (ETD  $-0.1$  mmol/L [ $-0.2$  to 0.1];  $p = 0.43$ ; table 2; appendix 3 p 36). Results for absolute reduction in fasting plasma glucose were similar for the treatment policy estimand (appendix 3 p 16). The ratio to baseline in fasting serum insulin was 0.59 for the cagrilintide–semaglutide group and 0.73 for the semaglutide group, corresponding to an estimated treatment ratio of 0.82 (0.72 to 0.92;  $p = 0.0014$ ; table 2); results were similar for the treatment policy estimand (appendix 3 p 16).

Improvements were also observed with cagrilintide–semaglutide compared with semaglutide for other secondary endpoints. In terms of fasting lipid profiles (ratio to baseline), participants receiving cagrilintide–semaglutide had significantly reduced VLDL cholesterol and triglycerides compared with those in the semaglutide group, and HDL cholesterol increased significantly more in the cagrilintide–semaglutide group compared with the semaglutide group (table 2). Reduction in systolic blood pressure was significantly greater in participants receiving cagrilintide–semaglutide compared with semaglutide (ETD  $-4.9$  mm Hg [ $-7.7$  to  $-2.0$ ];  $p = 0.0008$ ; table 2; appendix 3 p 37). Similarly, the reduction in diastolic blood pressure was significantly greater in participants receiving cagrilintide–semaglutide compared with semaglutide (ETD  $-3.8$  mm Hg [ $-5.7$  to  $-1.9$ ];  $p = 0.0001$ ; table 2; appendix 3 p 37). Reduction in HOMA-IR score was significantly greater with cagrilintide–semaglutide compared with semaglutide (ETD  $-0.6$  [ $-1.0$  to  $-0.2$ ];  $p = 0.0035$ ; table 2). Cagrilintide–semaglutide reduced high-sensitivity C-reactive protein (ratio to baseline) compared with semaglutide (estimated treatment ratio 0.69 [0.56 to 0.85];  $p = 0.0004$ ; table 2). For all cardiometabolic endpoints evaluated, similar results were observed using the treatment policy estimand (appendix 3 p 15).

For cagrilintide–semaglutide versus semaglutide, similar improvements in IWQOL-Lite-CT Physical Function score and SF-36v2 Physical Functioning score were observed for all participants, and no treatment differences were observed among those with clinically relevant changes (appendix 3 pp 16, 38–39).

143 (87%) of 164 participants in the cagrilintide–semaglutide group reported any adverse event from baseline to week 75 versus 141 (84%) of 167 in the semaglutide group (table 3). Adverse events occurring in at least 5% of participants are described by system organ class and preferred term in appendix 3 (p 17). A summary of all adverse events is provided in appendix 3 (p 18). The most common adverse events by system organ class were gastrointestinal-related disorders in 87 (53%) participants in the cagrilintide–semaglutide group versus 85 (51%) in the semaglutide group, infections and infestations (74 [45%] vs 84 [50%]), and general disorders and administration-site conditions (30 [18%] vs 19 [11%]).

Gastrointestinal adverse events occurred at similar rates in the two groups (appendix 3 p 17). These were all non-serious and mild-to-moderate in severity (appendix 3 p 40). Rates of vomiting were low and similar in both groups (appendix 3 p 17). Injection-site reactions (table 3) were more frequent in the cagrilintide–semaglutide group than the semaglutide group.

Rates of treatment discontinuation due to adverse events were generally low in both the cagrilintide–semaglutide group (three [2%] participants) and the semaglutide group (four [2%]; table 3). Serious adverse events were reported in six (4%) participants receiving cagrilintide–semaglutide and 11 (7%) receiving semaglutide (table 3; appendix 3 p 28), the most common being neoplasms (n=3) and musculoskeletal and connective tissue disorders (n=3) in

the cagrilintide–semaglutide group, and neoplasms (n=3) and infections and infestations (n=3) in the semaglutide group (appendix 3 p 28).

The sensitivity analyses to assess the robustness of the superiority conclusions using both the trial product estimand and the treatment policy estimand did not indicate strong violations of the missing at random assumption (appendix 3 p 41).

## Discussion

In east Asian adults with overweight or obesity, with or without type 2 diabetes, and obesity-related complications as defined by JASSO, both the cagrilintide–semaglutide combination and semaglutide alone were associated with reductions in bodyweight. Cagrilintide–semaglutide was superior to semaglutide in reducing mean bodyweight (–18.4% compared with –11.9%). A greater proportion of participants achieved bodyweight reductions of at least 5% and at least 10% with cagrilintide–semaglutide compared with semaglutide; these bodyweight percentage reductions are recommended by JASSO to improve obesity-related complications (including but not restricted to impaired glucose tolerance, hypertension, and coronary artery disease) that contribute to morbidity in individuals with obesity.<sup>7</sup> Most participants (82%) had two to four of the 11 obesity-related complications described in the JASSO guidelines that can be prevented or alleviated by bodyweight reduction.<sup>7</sup>

	Cagrilintide 2.4 mg– semaglutide 2.4 mg (n=164)			Semaglutide 2.4 mg (n=167)			Relative risk (95% CI)*	Absolute risk difference (95% CI)†
	Participants	Events	Events per 100 patient-years	Participants	Events	Events per 100 patient-years		
Any adverse event	143 (87%)	634	272.5	141 (84%)	646	270.7	1.03 (0.95 to 1.13)	0.027 (–0.048 to 0.103)
Serious adverse events	6 (4%)	9	3.9	11 (7%)	14	5.9	0.58 (0.23 to 1.44)	0.029 (–0.076 to 0.018)
Adverse events leading to permanent trial product discontinuation‡	3 (2%)	4	1.8	4 (2%)	4	1.7	0.79 (0.22 to 2.91)	0.006 (–0.037 to 0.025)
Gastrointestinal adverse events leading to discontinuation‡	1 (1%)	2	0.9	2 (1%)	2	0.9	0.61 (0.11 to 3.41)	0.006 (–0.026 to 0.015)
Fatal events§	0	..	..	1 (0.6%)	1	0.4	0.34 (0.09 to 1.27)	0.006 (–0.018 to 0.006)
Selected safety focus areas								
Gastrointestinal- related disorders‡	87 (53%)	202	90.3	85 (51%)	184	80.1	1.04 (0.11 to 0.85)	0.021 (–0.086 to 0.129)
Injection-site reactions‡	15 (9%)	27	12.1	4 (2%)	5	2.2	3.51 (1.31 to 9.41)	0.067 (0.017 to 0.117)
Allergic reactions‡	13 (8%)	15	6.7	9 (5%)	10	4.4	1.45 (0.66 to 3.19)	0.025 (–0.029 to 0.079)
Neoplasms	11 (7%)	13	5.6	9 (5%)	10	4.2	1.23 (0.54 to 2.80)	0.013 (–0.038 to 0.065)
Gallbladder-related disorders‡	6 (4%)	7	3.1	4 (2%)	4	1.7	1.47 (0.47 to 4.57)	0.013 (–0.024 to 0.050)
Malignant neoplasms¶	2 (1%)	2	0.9	2 (1%)	2	0.8	1.02 (0.21 to 4.90)	0.000 (–0.023 to 0.024)

Adverse events were assessed from baseline to week 75. Data are n (%) from the safety analysis set from the in-trial period unless otherwise stated. EAC=event adjudication committee. \*Cagrilintide–semaglutide:semaglutide. †Cagrilintide–semaglutide versus semaglutide. ‡Data for the on-treatment period. §One death was reported in the semaglutide 2.4 mg group; the EAC-established cause of death was malignancy. ¶Malignant neoplasms recorded here are those that were confirmed by the EAC.

Table 3: Adverse events (safety analysis set)

As cardiovascular risk factors and mortality increase in east Asian participants with a BMI of at least 27 kg/m<sup>2</sup>, this was considered a relevant threshold to use for investigating pharmacotherapeutic weight management.<sup>18–21</sup> More than 25% of participants had a BMI of at least 35 kg/m<sup>2</sup> and at least one obesity-related complication. This trial showed a greater proportion of participants achieving higher categories of bodyweight reduction ( $\geq 15\%$ ,  $\geq 20\%$ , and  $\geq 25\%$ ) with cagrilintide–semaglutide compared with semaglutide alone. Nearly 40% of participants receiving cagrilintide–semaglutide achieved at least 20% bodyweight reduction, with 60% achieving at least 15% reduction.

Although cagrilintide–semaglutide produced greater bodyweight reduction than semaglutide alone, changes in fasting plasma glucose were similar between treatments. This result likely reflects the distinct but complementary mechanisms of semaglutide and cagrilintide. Semaglutide lowers glucose through enhanced insulin secretion, suppressed glucagon release, delayed gastric emptying, and appetite suppression,<sup>22</sup> whereas cagrilintide enhances satiety and reduces postprandial glucagon secretion but has a less direct effect on insulin release than semaglutide.<sup>23,24</sup> Although cagrilintide–semaglutide led to a significantly greater percentage reduction in HbA<sub>1c</sub> compared with semaglutide, REDEFINE 5 was not a study in type 2 diabetes; the effect of cagrilintide–semaglutide compared with semaglutide alone on glycaemic control in type 2 diabetes will be fully elucidated in a separate study (NCT06403761).

In REDEFINE 5, nearly a quarter of participants had type 2 diabetes at screening. Although the subgroup analyses were not powered to detect statistically significant treatment-by-diabetes-status interactions, mean bodyweight reductions were numerically lower in participants with type 2 diabetes compared with those without. Substantial bodyweight reduction is more challenging in individuals with diabetes than in those without, due to several factors, including the use of diabetes medications that can lead to weight gain.<sup>25</sup> Mean bodyweight reductions among those with type 2 diabetes receiving cagrilintide–semaglutide appeared consistent with those observed in REDEFINE 2, which enrolled only individuals with overweight or obesity and type 2 diabetes.<sup>14</sup> These findings support the efficacy of cagrilintide–semaglutide across the glycaemic spectrum, although further exploration in east Asian populations with a higher proportion of individuals with type 2 diabetes is warranted.

Compared with results from the global REDEFINE 1 trial,<sup>15</sup> mean bodyweight reduction achieved with cagrilintide–semaglutide was lower for this trial. This might be partly due to the trial population in REDEFINE 5 being mostly male and nearly a quarter having type 2 diabetes; these factors, in addition to Asian ethnicity, have been shown to affect weight change associated with weight loss treatments.<sup>25–28</sup> However, this trial shows the efficacy of cagrilintide–semaglutide in a population with

an overall lower mean bodyweight and BMI compared with the global population included in REDEFINE 1. Our results are applicable to local practice as lower cutoffs are used for obesity disease diagnosis and weight management in east Asian countries (including Japan) than the rest of the world.<sup>7</sup> In the SURMOUNT-J trial evaluating once-weekly tirzepatide (a dual GLP-1–glucose-dependent insulinotropic polypeptide receptor agonist) in Japanese participants with obesity disease and without type 2 diabetes, a mean change in bodyweight of  $-17.8\%$  was achieved in the tirzepatide 10 mg group and  $-22.7\%$  in the tirzepatide 15 mg group, compared with a mean change of  $-1.7\%$  in those receiving placebo at week 72 (assessed using the trial product estimand).<sup>29</sup> Differences in mean bodyweight reduction between REDEFINE 5 and SURMOUNT-J might be partly explained by differences in demographics and baseline characteristics, including but not restricted to the proportion of male participants or participants with type 2 diabetes. Individuals with type 2 diabetes and overweight or obesity generally show lower bodyweight reductions compared with participants without type 2 diabetes.<sup>25</sup> In REDEFINE 5, participants with type 2 diabetes had a mean change in bodyweight of  $-14.6\%$  and those without type 2 diabetes had a mean change of  $-19.5\%$  with cagrilintide–semaglutide; in SURMOUNT-J, participants did not have type 2 diabetes and had a mean change in bodyweight of  $-22.7\%$  with tirzepatide 15 mg.<sup>29</sup> A previous study showed that female participants receiving semaglutide had greater bodyweight reductions than male participants.<sup>28</sup> In SURMOUNT-J, 41% of participants were female, compared with 32% in REDEFINE 5.<sup>29</sup> Comparing the two trials is, however, subject to limitations in interpretation arising from differences in selection criteria, protocols, and endpoint analyses, which limit the reliability of indirect comparisons.

In the STEP 6 trial evaluating once-weekly semaglutide in east Asian participants with overweight or obesity with or without type 2 diabetes, the mean change in bodyweight was greater ( $-13.5\%$ ) than that seen in the semaglutide 2.4 mg group of this current trial ( $-11.9\%$ ).<sup>13</sup> The greater proportion of female participants in STEP 6 receiving semaglutide 2.4 mg (43% compared with 28%) might partly explain this result.

Compared with non-Asian populations with the same BMI, east Asian populations are at greater risk of developing visceral obesity, which can contribute to the development of obesity-related complications.<sup>30–33</sup> Given that achievement of a VFA of less than 100 cm<sup>2</sup> and reductions in waist circumference are associated with lowering the risk of obesity-related metabolic disease in east Asian individuals,<sup>32,33</sup> these results, alongside beneficial changes in blood pressure, high-sensitivity C-reactive protein, and lipid profiles compared with semaglutide alone, indicate that cagrilintide–semaglutide might further improve cardiometabolic health in east Asian individuals living with obesity.

In this study, most participants were from Japan (97%). The WHO Expert Consultation has previously highlighted the heterogeneity in BMI thresholds for cardiometabolic risk across east Asian countries.<sup>34</sup> Although the consultation recommended that WHO BMI cutoff thresholds continue to be used for international classification, individual countries should be aware that risk of obesity-related complications and BMI are on a continuum, and BMI thresholds are utilised for convenience in public health and clinical settings. To reflect the predominantly Japanese participant population, the JASSO guidelines were used to define obesity-related complications.<sup>7</sup> Given that cardiovascular risk factors and mortality increase in east Asian individuals with a BMI of at least 27 kg/m<sup>2</sup>, this threshold was used to select participants with obesity to investigate pharmacotherapeutic weight management in the current study.<sup>18,20</sup> Due to heterogeneity in BMI thresholds for cardiometabolic risk, further studies are warranted in other east Asian countries.

Study participants showed high treatment adherence and trial completion rates. Nearly three-quarters of participants stayed on the target dose of cagrilintide–semaglutide (2.4 mg each) in this trial (during which investigators were permitted to follow protocol-specified dose-adjustment flexibility rules and maintain submaximal doses, according to their clinical judgement, to balance efficacy and adverse events). The proportion of participants reaching the target dose at the end of treatment was 90% with semaglutide alone compared with 73% with cagrilintide–semaglutide. This finding might be due to participants having a higher tolerance to semaglutide alone than to cagrilintide–semaglutide or a greater proportion of participants reaching lower BMI categories with cagrilintide–semaglutide than with semaglutide treatment. The proportion of participants treated with cagrilintide–semaglutide reaching the target dose at the end of treatment was greater in REDEFINE 5 than in the global REDEFINE 1 study (73% vs 57%).<sup>15</sup> This might be due to differences in demographics and baseline characteristics. Overall, the tolerability of cagrilintide–semaglutide was similar to that of semaglutide alone and more favourable in the current trial than in REDEFINE 1 and 2, particularly in relation to gastrointestinal adverse events.<sup>14,15</sup>

Strengths of this trial include its inclusion criteria for obesity-related complications based on the JASSO guidelines, the flexible dosing regimen, the active comparator (semaglutide monotherapy), and the high proportion of participants who completed the trial. A prespecified subpopulation underwent CT scans to assess the effect of treatment with cagrilintide–semaglutide versus semaglutide alone on abdominal obesity. These assessments provided further measurements in conjunction with waist circumference, which is more commonly used in clinical practice to assess abdominal obesity and visceral fat amount.

Limitations include the predominantly male population and relatively small sample size, particularly for those with overweight or obesity and with type 2 diabetes. The predominance of men in this study population might be due to a greater proportion of east Asian men having obesity compared with east Asian women, as has been observed in similar studies.<sup>13,29,35</sup> Similarly, CT scans, which provided valuable insight into body composition by evaluating changes in VFA, were conducted on only 161 participants. Future trials could utilise other methods such as MRI to provide further insights into body composition changes. There is also the possibility that trial participants might represent a subgroup with a greater determination to lose weight than the general population in east Asia. It is also worth noting that the population with a BMI of 25–27 kg/m<sup>2</sup> and obesity disease as defined by JASSO guidelines was not captured in this trial. Future trials evaluating obesity treatments in east Asian populations could capture this lower-risk population for greater representation of individuals with obesity disease per JASSO guidelines. This study did not have a cagrilintide monotherapy treatment group and was not placebo controlled. The comparator (semaglutide) is also manufactured by the funder of the study.

Cagrilintide and semaglutide have complementary effects on appetite regulation and weight by exerting distinct and overlapping effects on neuronal populations in the brain.<sup>23,36</sup> Use of these two products in combination results in greater bodyweight reduction but also reduced hunger, better satiety control, and improved quality of life metrics than using either product alone.<sup>16,23,37</sup> Studies of amylin biology indicate that amylin might inhibit bone resorption and stimulate bone formation via calcitonin receptor pathways.<sup>38–41</sup> The role of cagrilintide in bone metabolism during weight loss is currently being investigated (NCT07010432).

In conclusion, a once-weekly, fixed-dose combination of cagrilintide 2.4 mg and semaglutide 2.4 mg versus semaglutide 2.4 mg alone in east Asian adults with overweight or obesity with or without type 2 diabetes, for 68 weeks, led to a mean change in bodyweight of –18.4%, greater than the mean change in bodyweight with semaglutide 2.4 mg monotherapy (11.9%). The safety and tolerability data for cagrilintide–semaglutide in this population were consistent with previous observations in non-Asian populations. These results highlight the need to account for ethnicity when treating individuals with overweight or obesity, and might be used to help inform regional practice or global guideline updates and achieve holistic weight management care across populations.

#### Contributors

N-PB, CAH, AKo, and TT designed the trial and did the data analysis. AKo conducted the statistical analyses. All authors interpreted the data and were involved in the conduct of the trial. TY, K-CH, AKI, SL, YO, and YI contributed to data collection. TY and YI directly accessed and verified the underlying data reported in the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors contributed to the data

interpretation and manuscript writing (assisted by a medical writer paid for by the funder), approved the final version of the manuscript, and vouch for data accuracy and fidelity to the protocol.

#### Declaration of interests

AKI received honoraria for lectures from Novo Nordisk. AKO, CAH, N-PB, and TT are employees of Novo Nordisk. SL received research grants from Merck Sharp & Dohme, Novo Nordisk, and LG Chem; and honoraria as a consultant or speaker for AstraZeneca, Boehringer Ingelheim, Abbott, LG Chem, Daewoong Pharmaceutical, Chong Kun Dang Pharmaceutical, and Novo Nordisk. TY received research grants from Novo Nordisk, Mitsubishi Tanabe Pharma, Takeda Pharmaceutical, Ono Pharmaceutical, Sumitomo Pharma, Nipro, MED MIRAI, Boehringer Ingelheim Japan, Kowa Pharmaceuticals, Nitto Boseki, Asahi Mutual Life Insurance, and Sanwa Kagaku Kenkyusho; and received honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbott Japan, Daiichi Sankyo, Sanofi, Viatrix, Medtronic Japan, Astellas Pharma, AstraZeneca, Terumo, Taisho Pharmaceutical, Amgen, ARKRAY Marketing, Bayer Yakuhin, Lindsay Advice, Kyowa Kirin, Sanwa Kagaku Kenkyusho, GSK, Ono Pharmaceutical, Merck Sharp & Dohme (Merck), Sumitomo Pharma, Teijin, Boehringer Ingelheim Japan, Novo Nordisk, Eli Lilly, Kowa Pharmaceuticals, Nipro, Mitsubishi Tanabe Pharma, Amgen, Dexcom Japan, Nitto Boseki, and ViewSend ICT. YI received honoraria for lectures from Novo Nordisk, Eli Lilly Japan, Sumitomo Pharma, and Kowa Pharmaceuticals; and received research grants from Novo Nordisk and Sanofi. YO received honoraria for lectures from: Novo Nordisk, Eli Lilly Japan, Sumitomo Pharma, AstraZeneca, and Mitsubishi Tanabe Pharma. K-CH declares no competing interests.

#### Data sharing

Data will be shared with bona fide researchers who submit a research proposal approved by the independent review board. Individual participant data will be shared in data sets in a deidentified and anonymised format. Data will be made available after research completion and approval of the product and product use in the EU and the USA. Information about data access request proposals can be found at <https://www.novonordisk-trials.com/>.

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