



Efficacy and safety of once-weekly semaglutide 2.4 mg in Chinese adults with overweight or obesity (STEP 12): a randomised, double-blind, placebo-controlled, multicentre, phase 3b trial

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Summary

Background Semaglutide 2.4 mg is a GLP-1 receptor agonist that reduces bodyweight, and provides other cardiometabolic benefits, among people with a BMI at least 30 kg/m² or at least 27 kg/m² and with weight-related comorbidities. This trial aimed to evaluate the efficacy, tolerability, and safety of semaglutide 2.4 mg in adults from mainland China and Taiwan with overweight or obesity according to locally defined, BMI thresholds.

Methods This completed randomised, double-blind, placebo-controlled, multicentre, two-armed, parallel-group, phase 3b trial (STEP 12) was conducted at 19 sites across mainland China and Taiwan. Adults with a BMI of 24–<28 kg/m² and at least one weight-related comorbidity, or a BMI of 28–<30 kg/m², with or without type 2 diabetes, were randomly assigned (2:1) to once-weekly subcutaneous semaglutide 2.4 mg or placebo, plus lifestyle intervention, for 44 weeks. Randomisation was performed by the study sponsor using the Randomisation Trial Supplies Management System. Coprimary endpoints were percentage change in bodyweight and the proportion of participants achieving at least 5% bodyweight reduction. Safety was analysed descriptively in all participants who received the trial intervention. Missing data at week 44 were imputed with washout multiple imputation. This study is registered with ClinicalTrials.gov, NCT06041217, and is completed.

Findings Between Sept 15, 2023, and May 7, 2025, of 254 screened participants, 161 (66.5%) of 242 participants were randomly assigned to semaglutide 2.4 mg and 81 (33.5%) to placebo; 121 (50.0%) participants were female, and 47 (19.4%) participants had type 2 diabetes. Bodyweight reduction was greater with semaglutide versus placebo (–12.1% [SE 0.6] vs –2.2% [0.8]; estimated treatment difference –9.9 percentage points [95% CI –11.8 to –8.0]; $p < 0.0001$), with a greater proportion of participants achieving at least 5% bodyweight reduction (80.5% vs 24.4%; odds ratio [OR] 14.8 [95% CI 7.4 to 29.6]; $p < 0.0001$). Adverse events were reported in 141 (87.6%) of 161 participants in the semaglutide 2.4 mg group and 61 (75.3%) of 81 participants in the placebo group, with gastrointestinal disorders being the most common.

Interpretation Semaglutide 2.4 mg provided a superior reduction in bodyweight versus placebo in Chinese adults with overweight or obesity. The safety profile was consistent with the known profile of semaglutide.

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Introduction

Overweight and obesity, globally defined by WHO as a BMI between 25 kg/m² and less than 30 kg/m² for overweight and at least 30 kg/m² for obesity,¹ poses a major global public health challenge. Asian people are at an increased risk of obesity-related comorbidities and metabolic disorders at a lower BMI compared with White populations.² WHO recommends lower BMI thresholds for overweight (≥ 23 kg/m²) and obesity (≥ 25 kg/m²) in Asian populations,³ whereas the Working Group on Obesity in China (WGOC) defines overweight as a BMI between 24 kg/m² and less than 28 kg/m² and obesity as a BMI of at least 28 kg/m²,⁴ and the Ministry of Health and Welfare in Taiwan defines overweight as a BMI

between 24 kg/m² and less than 27 kg/m² and obesity as a BMI of at least 27 kg/m².⁵ Consequently, the prevalence of overweight and obesity in mainland China are underestimated when based on the global WHO definitions. In 2019, estimated prevalences of overweight and obesity in mainland China using the locally-defined WGOC threshold were 34–35% for overweight and 14–16% for obesity,^{6,7} compared with 31.9% and 6.2% when global WHO thresholds were used.⁶ Furthermore, projections suggest that the prevalence of overweight and obesity will rapidly increase by 2050.⁸

Pharmacotherapy, as an adjunct to lifestyle intervention, is recommended by Chinese guidelines in individuals with obesity or with overweight and

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For the Mandarin translation of the abstract see [Online](#) for appendix 1

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Research in context

Evidence before this study

We searched PubMed on Dec 12, 2025, using the search terms “semaglutide” AND (“China” OR “Chinese” OR “Taiwan” or “Taiwanese”) AND (“Obesity” OR “Obese” OR “Overweight”) from database inception to Dec 12, 2025. We searched for clinical trials and randomised clinical trials with no language restrictions, and found 11 relevant publications. After excluding one article describing the study design, three studies of interventions other than semaglutide, three studies without a focus on patients from mainland China and/or Taiwan, and one study in women with polycystic ovary syndrome, there were three relevant articles. Two of these articles described results from the STEP 7 trial, which was a randomised phase 3a, double-blind, multicentre, controlled trial that recruited participants from mainland China, Hong Kong, Brazil, and South Korea with overweight or obesity, defined as having a BMI of at least 30 kg/m², or at least 27 kg/m² with one or more weight-related comorbidities. The remaining article described a real-world study performed at a single centre in China exploring the use of GLP-1 receptor agonists in patients with type 2 diabetes and overweight or obesity, defined as having a BMI of at least 24 kg/m², in line with a locally defined, lower, China-specific BMI threshold. In the STEP 7 overall population, significant reductions in bodyweight and cardiometabolic parameters with semaglutide 2.4 mg (249 patients) versus placebo (126 patients) were demonstrated, and a prespecified analysis of participants from mainland China and Hong Kong demonstrated a significant bodyweight loss with semaglutide 2.4 mg (195 patients) versus placebo (105 patients). There were no randomised controlled trials assessing the efficacy or safety of semaglutide based on China-specific thresholds; however, the single-centre real-world study found that long-acting GLP-1 receptor agonists, including semaglutide 0.5–1.0 mg, significantly improved BMI among patients with type 2 diabetes and overweight or obesity, defined according to Chinese thresholds.

Added value of this study

The STEP 12 trial is, to our knowledge, the first randomised, double-blind, placebo-controlled, multicentre, two-armed, parallel-group, phase 3b trial investigating the efficacy and safety of semaglutide 2.4 mg among people from mainland China and Taiwan, with overweight or obesity according to locally defined Chinese BMI thresholds between 24 kg/m² and less than 28 kg/m² for overweight and at least 28 kg/m² for obesity. These BMI thresholds are lower than global thresholds defined by WHO, and there is potential for individuals with lower BMI to have different responses to weight management treatment. In this study, we found that participants treated with semaglutide 2.4 mg achieved significantly greater bodyweight reductions and that a greater proportion of participants achieved at least 5% bodyweight reduction compared with placebo-treated participants. The safety and tolerability of semaglutide 2.4 mg was also consistent with that observed in global populations with overweight and obesity.

Implications of all the available evidence

The complications of overweight and obesity affect Chinese individuals at a lower BMI than the general, global population. Overweight and obesity represent a substantial health burden in mainland China and Taiwan, and incidence is high and rising. This is, to our knowledge, the first randomised, placebo-controlled trial to demonstrate superior bodyweight reductions and cardiometabolic benefits with semaglutide 2.4 mg in adults with overweight or obesity as defined by local Chinese thresholds, with or without type 2 diabetes, from mainland China and Taiwan. Furthermore, adverse events were generally consistent with previous clinical studies of semaglutide 2.4 mg in this population. These findings support the use of semaglutide 2.4 mg for weight management among individuals in mainland China or Taiwan living with overweight or obesity, consistent with their regional guidelines.

weight-related comorbidities.⁹ Semaglutide, a GLP-1 receptor agonist, has demonstrated multiple health benefits in addition to weight loss, such as improvements in cardiovascular risk factors, glycaemia, and quality of life, and reductions in components of metabolic dysfunction-associated steatohepatitis across several studies within the phase 3 Semaglutide Treatment Effect in People with Obesity (STEP) programme in individuals with overweight or obesity.^{10–12} In the STEP 7 clinical trial among adults predominantly from mainland China, with or without type 2 diabetes, once-weekly subcutaneous semaglutide 2.4 mg demonstrated mean weight reductions of 12.1% from baseline to week 44.¹³ Consistent with the global STEP studies, STEP 7 included participants with a BMI of at least 30 kg/m², or at least 27 kg/m² with one or more weight-related comorbidity, but did not include participants from mainland China with lower BMIs

reflective of the lower WHO or WGOC regional thresholds.

Based on the STEP programme and other results, semaglutide 2.4 mg has been approved in many countries globally with varying indications, including chronic weight management, reduction of the risk of major adverse cardiovascular events, treatment of heart failure with preserved ejection fraction in people with overweight or obesity, and treatment of metabolic dysfunction-associated steatohepatitis in adults with moderate-to-advanced liver fibrosis varying by country. In mainland China and Taiwan, indications for semaglutide 2.4 mg include weight management in adults with a BMI of at least 30 kg/m² or at least 27 kg/m² with at least one weight-related comorbidity and the reduction of risk of major adverse cardiovascular events in individuals with a BMI of at least 27 kg/m² and established cardiovascular disease.^{14,15} In Taiwan,¹⁵

semaglutide 2.4 mg is also indicated for weight management for individuals aged at least 12 years with overweight or obesity, and for treatment of heart failure with preserved ejection fraction in adults with a BMI of at least 30 kg/m². These indications are reflective of the BMI inclusion criteria in the relevant global STEP trials, but exclude a proportion of participants with overweight or obesity according to the relevant local thresholds for mainland China and Taiwan.

To our knowledge, to date, no phase 3 studies have evaluated semaglutide 2.4 mg in adults from mainland China and Taiwan in accordance with regional thresholds for overweight and obesity. The STEP 12 trial aimed to evaluate the efficacy and safety of semaglutide 2.4 mg in adults from mainland China and Taiwan with overweight (BMI ≥24–<28 kg/m²) and at least one weight-related comorbidity or obesity (BMI ≥28–<30 kg/m²), with or without type 2 diabetes, in accordance with locally defined WGO definitions.

Methods

Study design and participants

STEP 12 was a randomised, double-blind, placebo-controlled, multicentre, two-armed, parallel-group, phase 3b trial that was conducted at 14 sites across mainland China and five sites across Taiwan. Sites were included based on findings from site selection visit assessments, which took site recruitment and retention goals, staff resources, facilities and equipment, data collection, and critical study processes into consideration. The trial compared once-weekly subcutaneous semaglutide 2.4 mg or placebo, both as adjunct to a reduced calorie diet and increased physical activity for 44 weeks, followed by 5 weeks of follow-up without treatment (appendix 2 p 31). The list of investigators is included in appendix 2 (pp 3–8).

Eligible participants were aged 18 years or older, with a BMI between 24 kg/m² and less than 28 kg/m², with at least one weight-related comorbidity (ie, type 2 diabetes, hypertension, dyslipidaemia, obstructive sleep apnoea, or cardiovascular disease) or BMI between 28 kg/m² and less than 30 kg/m², with or without weight-related comorbidities, and a history of at least one self-reported unsuccessful dietary effort to lose bodyweight. Participants with type 2 diabetes (defined as having a HbA_{1c} ≤10.0% [≤86 mmol/mol]) had to be diagnosed for 180 days or more before the day of screening and have received either lifestyle intervention or stable treatment (for ≥60 days before screening) with up to three marketed oral antidiabetic drugs (metformin, α-glucosidase inhibitors, sulfonylureas, glinides, SGLT2 inhibitors, or glitazone, as a single agent or in combination) according to the local label. Recruitment was monitored to ensure that a maximum of 20% of participants had type 2 diabetes.

Key exclusion criteria were a self-reported change in bodyweight of more than 5 kg or treatment with any medication for the indication of obesity within the past

90 days before screening. Additional exclusion criteria for participants without type 2 diabetes were a history of diabetes (or HbA_{1c} ≥6.5%, 48 mmol/mol) at screening, treatment with glucose-lowering agents within 90 days before screening, or an estimated glomerular filtration rate (eGFR) of less than 15 mL/min per 1.73 m².¹⁶ Participants with type 2 diabetes at screening were excluded if they were on treatment with any medication for the indication of diabetes other than stated in the inclusion criteria within the past 60 days before the day of screening or had an eGFR of less than 30 mL/min per 1.73 m².¹⁶ Full eligibility criteria are available in appendix 2 (pp 9–13). All participants provided informed consent before being randomly assigned. Data on sex were self-reported with the options of male or female. Data on race and ethnicity were self-reported.

The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines. The trial protocol and amendments were approved by the relevant institutional review board or independent ethics committee at each trial site (appendix 2 pp 14–15). The trial has been reported in accordance with CONSORT 2025 guidelines, and the trial protocol and the statistical analysis plan can be found in appendix 2 (p 47). There were amendments to the protocol after the trial commenced, including two important amendments to add change in waist-to-height ratio as a supportive secondary endpoint, and to update the primary imputation approach for the primary estimand. This study is registered with ClinicalTrials.gov, NCT06041217, and is completed.

Randomisation and masking

Participants were randomly assigned 2:1 to semaglutide 2.4 mg or placebo using the Randomisation Trial Supplies Management System (4G Clinical, Prancer 2.6.2, Wellesley, MA, USA) in a double-blind manner, and assigned the participants to the trial groups. Investigators enrolled the participants. All groups received visually identical injections to maintain masking of participants and site staff. Randomisation was stratified by type 2 diabetes diagnosis.

Procedures

Participants received once-weekly subcutaneous semaglutide 2.4 mg or placebo for 44 weeks as an adjunct to a reduced calorie diet and increased physical activity (approximately –500 kcal per day deficit and 150 min per week physical activity) followed by 5 weeks of follow-up without treatment. Participants who received semaglutide followed a fixed-dose escalation regimen, initiating at 0.25 mg, with dose increases every 4 weeks (to doses of 0.5 mg per week, 1.0 mg per week, 1.7 mg per week, and 2.4 mg per week) aiming at reaching the maintenance dose of 2.4 mg at week 16. Participants who did not tolerate the target dose were permitted to remain

See Online for appendix 2

on a lower dose if the investigator considered it safe, and the participant would otherwise discontinue; however, it was recommended to make at least one attempt to re-escalate to the target dose. The maintenance period lasted 28 weeks. Participants were offered dietary and physical activity counselling by a dietician or a similarly qualified health-care professional via visits or telephone. A subpopulation of 80 participants from Taiwan underwent dual-energy x-ray absorptiometry scans at randomisation and at end-of-treatment to evaluate body composition changes. Visits were scheduled every 4 weeks, and details of the assessment schedule are provided in appendix 2 (p 20).

Outcomes

All efficacy endpoints compared the effect of semaglutide 2.4 mg versus placebo from baseline to week 44. The co-primary endpoints were relative change in bodyweight (%) and proportion of participants achieving bodyweight reduction of 5% or more. The confirmatory secondary endpoints were the proportion of participants with a bodyweight reduction of 10% or more and change in waist circumference (cm). Supportive secondary endpoints were changes in bodyweight (kg), BMI (kg/m^2), waist-to-height ratio, systolic and diastolic blood pressure (mm Hg), HbA_{1c} (percentage-points, mmol/mol), fasting plasma glucose (mg/dL, mmol/L), ratio to baseline of lipids, and high-sensitivity C-reactive protein.

Exploratory endpoints in the dual-energy x-ray absorptiometry subpopulation were changes from baseline in total fat mass and lean soft tissue relative to total body mass, and visceral fat mass relative to abdominal total fat mass. Changes from baseline in total fat mass, lean soft tissue, and visceral fat mass (percentage-points, kg) were assessed post-hoc.

Safety assessments included the number of treatment-emergent adverse events and serious adverse events from baseline to week 49 and change in pulse rate (beats per min) from baseline to week 44. For participants with type 2 diabetes, endpoints also included the number of clinically significant hypoglycaemic episodes (level 2; $<3.0 \text{ mmol/L}$ [$<54 \text{ mg/dL}$]), confirmed by blood glucose meter. A full list of objectives and endpoints is included in appendix 2 (pp 16–18).

Statistical analysis

A sample size of 162 randomly assigned participants was predicted to provide an effective power of 92%, for all endpoints in the prespecified statistical hierarchy; however, a sample size of 242 participants was selected for the safety evaluation and regulatory purposes (appendix 2 p 19). Assumptions for the power calculations were based on efficacy findings from the STEP 6 trial,¹² which was performed in Japanese and South Korean participants with a BMI of at least $27.0 \text{ kg}/\text{m}^2$ with two or more weight-related comorbidities or a BMI of at least $35.0 \text{ kg}/\text{m}^2$ with one or more weight-related comorbidity,

taking into account a lower estimated treatment effect in this study owing to potential dose reduction when reaching a BMI in the normal range. Additionally, based on the STEP 1 trial,¹⁰ it was assumed that 20% of participants would discontinue study product permanently before week 44, and that approximately 60% would be retrievable at week 44. The effective power was calculated under the assumption of independence of endpoints by multiplying the respective marginal powers successively, which is a conservative approach. The power calculations for continuous endpoints were based on a t-test on the mean difference assuming equal variances, whereas those for the categorical endpoints were based on the Pearson χ^2 test for two independent proportions.

Efficacy endpoints were analysed using the full analysis set, which included all randomly assigned participants according to the intention-to-treat principle. Safety endpoints were analysed using the safety analysis set, which included all participants exposed to at least one dose of the trial product.

Two observation periods were defined. The in-trial period included the uninterrupted period from the date of randomisation to the end of trial visit, withdrawal of consent, or last contact with site, regardless of initiation of other therapies for obesity. The on-treatment period was the time from the date of first trial product administration to the date of last trial product administration, plus 14 days, excluding potential off-treatment time intervals, which were triggered if a participant missed at least two consecutive doses regardless of dose reduction, or by initiation of other obesity therapies. A longer ascertainment period of 35 days was used for the on-treatment period to evaluate adverse events and hypoglycaemic episodes.

Two estimands were employed to assess treatment efficacy and accounted differently for intercurrent events. The treatment policy estimand (primary, traditional intention-to-treat analysis) assessed treatment effect among all randomly assigned participants, regardless of trial product discontinuation, dose reduction, or initiation of other therapies for obesity. The trial product estimand (secondary) assumed that all participants were treated as intended and considered all data until first discontinuation of the trial product or initiation of other obesity therapies.

For the treatment policy estimand, continuous endpoints were analysed using an analysis of covariance model (linear regression), and categorical (responder) endpoints were analysed using a logistic regression model. Both models included randomised treatment and type 2 diabetes status at screening as factors and the baseline value of the endpoint as a covariate. Missing data at week 44 were imputed with washout multiple imputation based on available data from participants in each treatment group. For primary and confirmatory secondary endpoints, multiple sensitivity analyses were performed to assess the impact of missing data, including

the jump to reference multiple imputation approach, tipping-point multiple imputation analysis, analysis of covariance for unequal variances, and non-retrieved participants as non-responders (appendix 2 pp 21–25).

For the trial product estimand, continuous endpoints were analysed using a mixed model for repeated measures, with randomised treatment and type 2 diabetes status at screening as factors and the baseline value of the endpoint as a covariate, all nested within visits. Categorical (responder) endpoints were analysed using logistic regression, and the missing values at week 44 were imputed as predicted values from a mixed model for repeated measures.

Results from statistical analyses are shown with two-sided 95% CIs and corresponding p values. Confirmatory efficacy endpoints were tested for the superiority of semaglutide 2.4 mg versus placebo by use of a fixed sequence statistical strategy and were based only on analyses addressing the primary estimand (treatment policy estimand). This strategy tested the endpoints using a predefined hierarchical order, all at the significance level of 5%, moving to test the next endpoint only after a significant superiority result (ie, $p < 0.05$) was reached for the previous endpoint.

Safety endpoints were summarised by descriptive statistics. All adverse events were coded using the most recent version of the Medical Dictionary for Regulatory Activities (version 28.0). Details of the analysis and imputation methods are provided in appendix 2 (pp 21–25). Statistical analyses were performed using SAS (version 9.4).

Role of the funding source

The funder of the study was responsible for the study design, preparing the trial protocol and statistical analysis plan, and performing the statistical analyses. The investigators were responsible for trial-related medical decisions and data collection. This article was drafted under the guidance of the authors, with medical writing and editorial support paid for by the sponsor. Authors interpreted the data, agreed to the submission, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Results

Between Sept 15, 2023, and May 7, 2025, of 254 screened participants, 242 (95.3%) were randomly assigned to receive semaglutide 2.4 mg (161 [66.5%] of 242 participants) or placebo (81 [33.5%]; figure 1). Most participants completed the treatment (semaglutide 2.4 mg: 155 [96.3%] of 161 participants; placebo: 77 [95.1%] of 81 participants) and completed the trial (161 [100%] vs 79 [97.5%]; figure 1). Among the 155 participants who completed treatment in the semaglutide 2.4 mg group, 141 (91.0%) participants received the highest 2.4 mg dose, seven (4.5%) received

1.7 to less than 2.4 mg, and seven (4.5%) received less than 1.7 mg at the last treatment visit.

Overall, 50.0% (121 of 242 participants) of the trial population was female and 19.4% (47 participants) had type 2 diabetes. The mean age was 41 years (SD 11), bodyweight 78.0 kg (SD 9.9), BMI 27.9 kg/m² (SD 1.6), waist circumference 95.1 cm (SD 6.9), and HbA_{1c} 6.0% (SD 0.7; equivalent to 41.7 [SD 8.1] mmol/mol). No missing value of age, bodyweight, BMI, waist circumference or HbA_{1c} was observed at baseline. Although

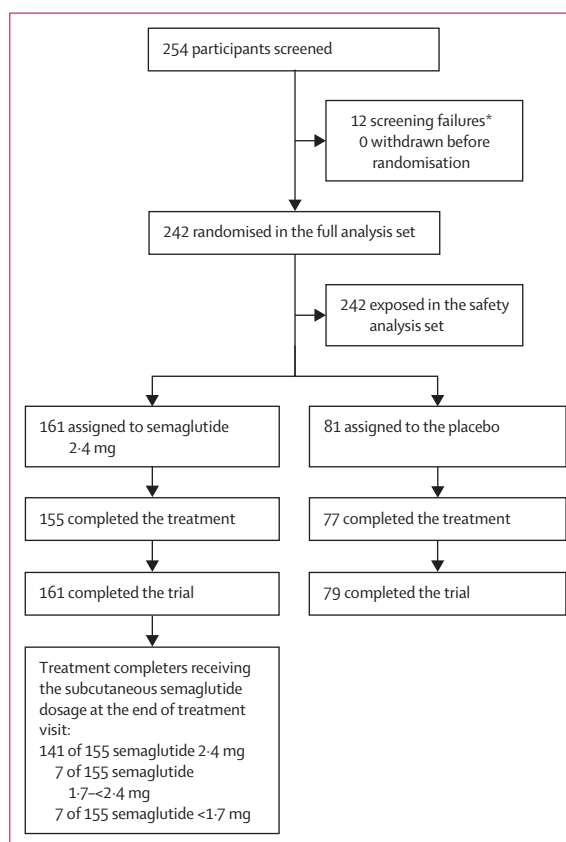


Figure 1: Trial profile

242 participants were included in the full analysis set and 242 participants were included in the safety analysis set (161 participants in the semaglutide 2.4 mg group and 81 participants in placebo group). *Of the 12 individuals who were excluded at screening, ten (83.3%) were excluded because of violation of the following exclusion criteria: HbA_{1c} at least 6.5% (48 mmol/mol) as measured by the central laboratory at screening (six [50%] of 12 participants); any disorder, unwillingness or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion might jeopardise the participant's safety or compliance with the protocol (three [25%] participants); and being a female who was pregnant or breastfeeding, intended to become pregnant, or was of childbearing potential and not using highly effective contraceptive methods before randomisation (one [8.3%] participant). Two individuals were excluded at screening because of violation of the following inclusion criteria: HbA_{1c} equal to or less than 10% (86 mmol/mol) as measured by the central laboratory at screening (two [16.7%] participants). †No participants discontinued semaglutide 2.4 mg owing to protocol violation, lack of efficacy, at the discretion of the investigator, safety concern as judged by the investigator, withdrawal of consent, or loss to follow-up. ‡No participants discontinued placebo owing to protocol violation, pregnancy, lack of efficacy, at the discretion of the investigator, or loss to follow-up.

baseline characteristics were generally balanced across groups (table 1), there was a slight imbalance in geometric mean high-sensitivity C-reactive protein concentrations, which were lower in the semaglutide 2.4 mg group (1.22 mg/L [coefficient of variation 130.2]) compared with

the placebo group (1.61 mg/L [160.6]). Among the female participants, 17 (21.5%) of 79 participants in the semaglutide 2.4 mg group and ten (23.8%) of 42 participants in the placebo group were reported to be post-menopausal by the investigator. The most commonly reported weight-related comorbidities among participants at screening were dyslipidaemia (153 [63.2%] of 242 participants), hypertension (88 [36.4%] participants), metabolic dysfunction-associated steatotic liver disease (73 [30.2%] participants), hyperuricaemia or gout (54 [22.3%] participants), and cardiovascular disease (29 [12.0%] participants). Similar proportions of participants in each treatment group (31 [19.3%] of 161 participants vs 16 [19.8%] of 81 participants) had type 2 diabetes at screening. Among participants with type 2 diabetes, mean diabetes duration was 4.5 years (SD 3.7), and mean HbA_{1c} was 7.0% (SD 1.0), and in the semaglutide 2.4 mg and placebo groups, 11 (35.5%) of 31 participants and five (31.3%) of 16 participants with type 2 diabetes at screening reported eye disorders at baseline (table 1).

From baseline to week 44, the percentage change in mean bodyweight with semaglutide 2.4 mg was -12.1% (SE 0.6) versus -2.2% (0.8) with placebo (estimated treatment difference [ETD] -9.9 percentage points, 95% CI -11.8 to -8.0; $p < 0.0001$) using the treatment policy estimand (figure 2A, table 2). The corresponding change in bodyweight for the trial product estimand was -12.7% (SE 0.6) with semaglutide 2.4 mg and -2.4% (0.8) with placebo (ETD -10.3 percentage points, 95% CI -12.3 to -8.3; $p < 0.0001$; figure 2B). Among participants with type 2 diabetes at screening, the estimated mean change in bodyweight from baseline to week 44 was -8.0% (SE 1.3) for the semaglutide 2.4 mg group and -0.6% (1.8) for the placebo group, with an ETD of -7.4 percentage points (95% CI -11.6 to -3.1; p interaction: 0.20 (appendix 2 p 33)). For participants without type 2 diabetes at baseline, the estimated mean change from baseline to week 44 was -13.1% (SE 0.6) for the semaglutide 2.4 mg group and -2.6% (0.9) for the placebo group, with an ETD of -10.5 percentage points (95% CI -12.6 to -8.4; p interaction: 0.20 (appendix 2 p 33)). The difference between semaglutide 2.4 mg and placebo in mean change from baseline was not significant between participants with and without type 2 diabetes at baseline (p interaction: 0.20). The estimated mean bodyweight change for semaglutide 2.4 mg versus placebo was greater for females (-14.7% [SE 0.8] vs -1.7% [1.1]) compared with males (-9.5% [0.8] vs -2.7% [1.1]), with an ETD of -13.0 percentage points (95% CI -15.6 to -10.4) for females and an ETD of -6.7 percentage points (-9.4 to -4.1) for males, resulting in a significant treatment-by-subgroup interaction ($p = 0.0010$); however, there was no statistically significant difference in mean bodyweight change for participants from mainland China compared with Taiwan, or among participants with BMI lower than 28 kg/m² compared with at least 28 kg/m² or

	Semaglutide 2.4 mg (n=161)	Placebo (n=81)	Total (N=242)
Age, years	42 (10)	41 (12)	41 (11)
Sex			
Male	82 (50.9%)	39 (48.1%)	121 (50.0%)
Female	79 (49.1%)	42 (51.9%)	121 (50.0%)
Region			
Mainland China	109 (67.7%)	53 (65.4%)	162 (66.9%)
Taiwan	52 (32.3%)	28 (34.6%)	80 (33.1%)
Race			
Asian	161 (100%)	81 (100%)	242 (100%)
Bodyweight, kg	77.9 (9.1)	78.2 (11.3)	78.0 (9.9)
BMI, kg/m ²			
Mean	27.8 (1.6)	28.0 (1.5)	27.9 (1.6)
24–<28	82 (50.9%)	34 (42.0%)	116 (47.9%)
28–<30	75 (46.6%)	46 (56.8%)	121 (50.0%)
30–<35	4 (2.5%)	1 (1.2%)	5 (2.1%)
≥35	0	0	0
Waist circumference, cm	95.0 (6.7)	95.2 (7.2)	95.1 (6.9)
Waist-to-height ratio	0.57 (0.03)	0.57 (0.04)	0.57 (0.04)
HbA _{1c} , %	5.9 (0.7)	6.0 (0.8)	6.0 (0.7)
HbA _{1c} , mmol/mol	41.4 (7.5)	42.1 (9.3)	41.7 (8.1)
FPG, mmol/L	5.7 (1.3)	5.6 (1.5)	5.7 (1.3)
FPG, mg/dL	102.7 (22.9)	101.6 (26.5)	102.3 (24.1)
Blood pressure, mm Hg			
Systolic	123 (13)	126 (14)	124 (13)
Diastolic	81 (10)	83 (9)	82 (9)
Lipids, geometric mean (coefficient of variation), mmol/L			
Total cholesterol	4.9 (21.7)	4.8 (19.2)	4.9 (20.9)
Low-density lipoprotein cholesterol	2.8 (35.6)	2.7 (33.8)	2.7 (35.0)
High-density lipoprotein cholesterol	1.2 (24.3)	1.2 (20.5)	1.2 (23.1)
Very-low-density lipoprotein cholesterol	0.8 (55.8)	0.7 (56.7)	0.7 (56.2)
Free fatty acids	0.5 (49.8)	0.4 (50.5)	0.5 (49.9)
Triglycerides	1.7 (59.1)	1.6 (62.4)	1.7 (60.2)
eGFR, geometric mean (coefficient of variation), mL/min per 1.73 m ²	105.7 (13.2)	105.3 (14.2)	105.6 (13.5)
hsCRP, geometric mean (coefficient of variation), mg/L	1.22 (130.2)	1.61 (160.6)	1.34 (141.5)
Weight-related comorbidities at screening in ≥5% of participants of either group			
Cardiovascular disease	23 (14.3%)	6 (7.4%)	29 (12.0%)
Dyslipidaemia	105 (65.2%)	48 (59.3%)	153 (63.2%)
Gastro-oesophageal reflux disease	10 (6.2%)	4 (4.9%)	14 (5.8%)
Hyperuricaemia or gout	34 (21.1%)	20 (24.7%)	54 (22.3%)
Hypertension	59 (36.6%)	29 (35.8%)	88 (36.4%)
MASLD	49 (30.4%)	24 (29.6%)	73 (30.2%)
Obstructive sleep apnoea syndrome	9 (5.6%)	3 (3.7%)	12 (5.0%)
Polycystic ovarian syndrome	3/79 (3.8%)	3/42 (7.1%)	6/121 (5.0%)
Type 2 diabetes*	31 (19.3%)	16 (19.8%)	47 (19.4%)

(Table 1 continues on next page)

less than 27 kg/m² compared with at least 27 kg/m² (appendix 2 p 33).

Overall, 80.5% of participants who received semaglutide 2.4 mg achieved a weight loss of at least 5% (co-primary endpoint) compared with 24.4% with placebo. The odds were significantly in favour of semaglutide 2.4 mg using the treatment policy estimand (odds ratio [OR] 14.8, 95% CI 7.4 to 29.6; $p < 0.0001$; figure 3, table 2). The proportion of participants achieving at least 10% reduction in baseline bodyweight (confirmatory secondary endpoint) at week 44 was 60.4% with semaglutide 2.4 mg and 11.5% with placebo (OR 13.0, 5.9 to 28.4; $p < 0.0001$; figure 3, table 2). Results for the trial product estimand were similar (figure 3, appendix 2 pp 26–28). Significantly greater reductions in mean waist circumference (confirmatory secondary endpoint) were observed from baseline to week 44 with semaglutide 2.4 mg (−9.0 cm [SE 0.5]) versus placebo (−2.4 cm [0.6]; ETD −6.6, 95% CI −8.1 to −5.0; $p < 0.0001$; appendix 2 p 34). Mean change from baseline to week 44 for absolute bodyweight was −9.2 kg (0.4) for semaglutide 2.4 mg versus −1.6 kg (0.6) for placebo (ETD −7.6 kg, 95% CI −9.0 to −6.1; $p < 0.0001$), BMI was −3.4 kg/m² (0.2) for semaglutide 2.4 mg versus −0.6 kg/m² (0.2) for placebo (ETD −2.8, −3.3 to −2.2; $p < 0.0001$; appendix 2 p 35), and waist-to-height ratio was −0.05 (0.00) for semaglutide 2.4 mg versus −0.01 (0.00) for placebo (ETD −0.04, −0.05 to −0.03; $p < 0.0001$; appendix 2 p 36).

Based on the treatment policy estimand, the mean change from baseline in systolic blood pressure was −7.7 mm Hg (0.8) for semaglutide 2.4 mg versus −3.0 mm Hg (1.2) for placebo (ETD −4.8 mm Hg, 95% CI −7.6 to −1.9; $p = 0.0012$; table 2; appendix 2 p 37). The mean change from baseline in diastolic blood pressure was −4.0 mm Hg (0.6) for semaglutide 2.4 mg versus −1.9 mm Hg (0.9) for placebo (ETD −2.0 mm Hg, −4.1 to 0.0; $p = 0.053$; table 2; appendix 2 p 37). For high-sensitivity C-reactive protein, the ratio to baseline was 0.66 (1.1) for semaglutide 2.4 mg versus 0.72 (1.1) for placebo (estimated treatment ratio 0.9, 95% CI 0.7 to 1.2; $p = 0.51$; table 2; appendix 2 p 38). HbA_{1c} was −0.4 percentage points (SE 0.0) for semaglutide 2.4 mg versus 0.1 percentage points (0.0) for placebo (ETD −0.5 percentage points, −0.6 to −0.4; $p < 0.0001$), and was greater among individuals with type 2 diabetes at screening (table 2; appendix 2 p 39). The mean change in fasting plasma glucose overall was −0.7 mmol/L (SE 0.1) versus 0.0 mmol/L (0.1; ETD −0.7 mmol/L, −0.9 to −0.5; $p < 0.0001$; table 2), and was greater among individuals with type 2 diabetes at screening (table 2; appendix 2 p 40). Significant improvements in mean lipid concentrations were also seen with semaglutide 2.4 mg versus placebo in total cholesterol ($p = 0.0007$), very-low-density lipoprotein cholesterol ($p < 0.0001$), and triglycerides ($p = 0.0001$; table 2). No statistically significant differences were observed

	Semaglutide 2.4 mg (n=161)	Placebo (n=81)	Total (N=242)
(Continued from previous page)			
Number of weight-related comorbidities at screening†			
0	18 (11.2%)	11 (13.6%)	29 (12.0%)
1	45 (28.0%)	20 (24.7%)	65 (26.9%)
2	41 (25.5%)	28 (34.6%)	69 (28.5%)
3	31 (19.3%)	12 (14.8%)	43 (17.8%)
4	14 (8.7%)	8 (9.9%)	22 (9.1%)
≥5	12 (7.5%)	2 (2.5%)	14 (5.8%)
Glycaemic status at baseline (participants without type 2 diabetes at screening)			
n (%)	130 (80.7%)	65 (80.2%)	195 (80.6%)
Normoglycaemia‡	74 (46.0%)	35 (43.2%)	109 (45.0%)
Prediabetes‡	55 (34.2%)	29 (35.8%)	84 (34.7%)
Diagnosed with type 2 diabetes	1 (1%)	1 (1.2%)	2 (1%)
Type 2 diabetes subpopulation			
n (%)	31 (19.3%)	16 (19.8%)	47 (19.4%)
Duration of diabetes, years	4.6 (4.3)	4.2 (2.3)	4.5 (3.7)
HbA _{1c} , %	6.9 (0.9)	7.1 (1.3)	7.0 (1.0)
HbA _{1c} , mmol/mol	52.4 (9.6)	54.3 (14.4)	53.1 (11.3)
FPG, mmol/L	7.5 (1.8)	7.3 (2.6)	7.4 (2.1)
FPG, mg/dL	134.3 (33.1)	132.4 (46.1)	133.6 (37.5)
Glucose-lowering drug class			
Biguanides	17 (10.6%)	12 (14.8%)	29 (12.0%)
SGLT2 inhibitors	8 (5.0%)	2 (2.5%)	10 (4.1%)
Alpha glucosidase inhibitors	1 (1%)	1 (1.2%)	2 (1%)
Thiazolidinediones	0	1 (1.2%)	1 (<1%)
Combinations of oral blood glucose-lowering drugs	1 (1%)	0	1 (<1%)

Data are n (%), mean (SD), or n/N (%), unless otherwise stated. The last available and eligible observation at or before the randomisation visit was used except for age, in which date of informed consent was used. eGFR was calculated by the central laboratory based on the creatinine value using the Chronic Kidney Disease Epidemiology Collaboration equation. Diabetes duration was only applicable for participants with diabetes at screening. eGFR=estimated glomerular filtration rate. FPG=fasting plasma glucose. hsCRP=high-sensitivity C-reactive protein. MASLD=metabolic dysfunction-associated steatotic liver disease. *Recruitment of participants with type 2 diabetes was capped at 20%. †Presence of specific weight-related comorbidities was collected systematically at screening by the investigator as part of the medical history and were: dyslipidaemia, hypertension, cardiovascular disease, obstructive sleep apnoea syndrome, knee osteoarthritis, asthma, chronic obstructive pulmonary disease, gastro-oesophageal reflux disease, musculoskeletal pain, osteoarthritis of the hip, hyperuricaemia or gout, polycystic ovarian syndrome (female participants only), infertility, urinary incontinence, MASLD, kidney disease, psoriasis, and type 2 diabetes. Participants with missing assessments for comorbidities were included in the category '0' given that the participants did not have comorbidity. ‡Glycaemic status was evaluated by the investigators based on medical history and glycaemic control at baseline.

Table 1: Baseline characteristics in the full analysis set

between semaglutide 2.4 mg and placebo in low-density lipoprotein cholesterol, free fatty acids, and high-density lipoprotein cholesterol (appendix 2 p 41).

All 80 participants from Taiwan (52 receiving semaglutide 2.4 mg and 28 receiving placebo) contributed to the body composition analyses, evaluated by dual-energy x-ray absorptiometry scans, at week 44. From baseline to week 44, the change (SE) from baseline in total fat mass was −27.4% (2.5) for semaglutide 2.4 mg and −6.8% (3.0) for placebo (ETD −20.6 percentage points, 95% CI −28.5 to −12.7; $p < 0.0001$), using the treatment policy estimand (appendix 2 p 42). The absolute change from baseline in total fat mass was −7.3 kg (0.7) for

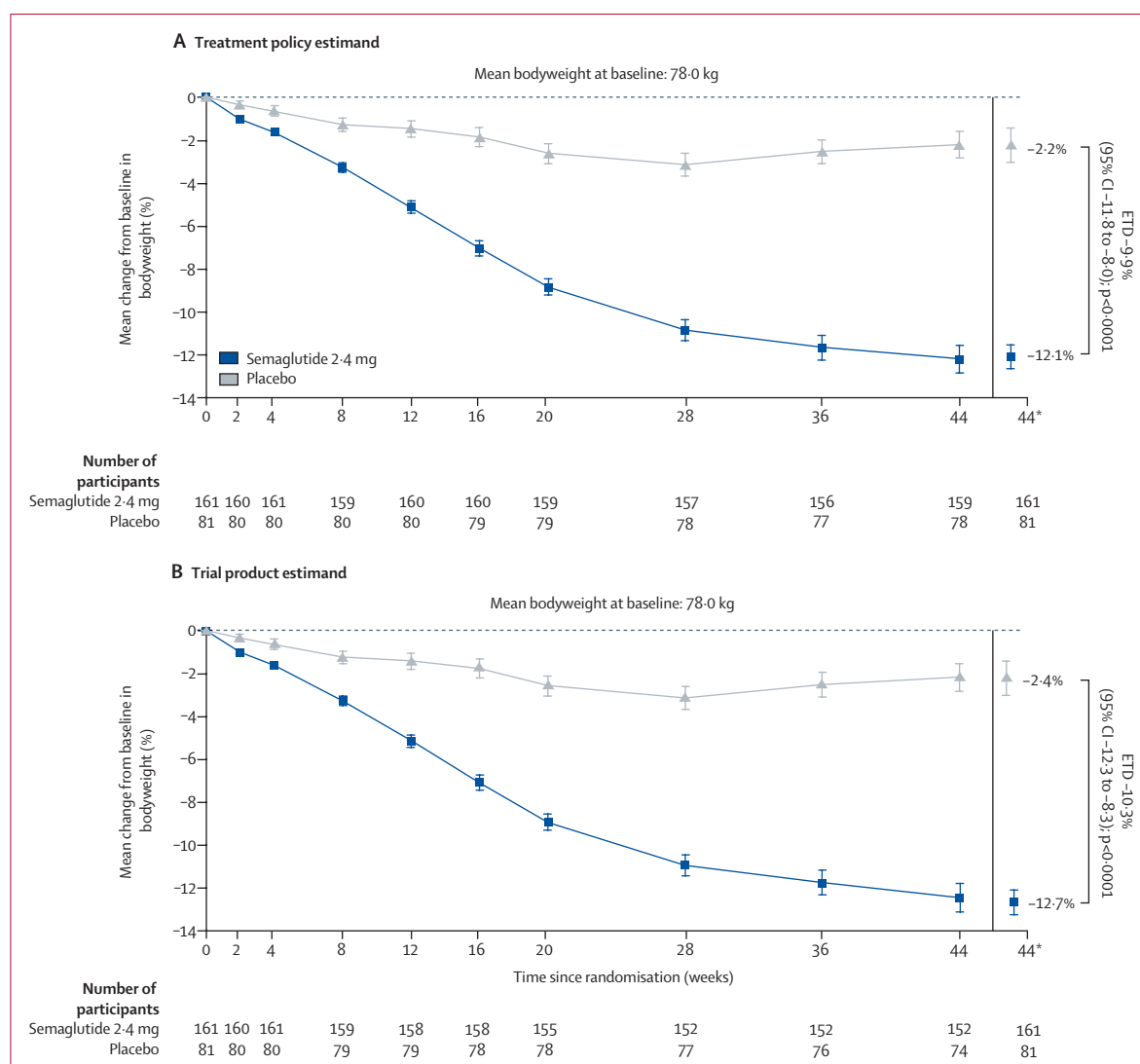


Figure 2: Change in bodyweight from baseline to week 44 for semaglutide 2.4 mg and placebo, given once a week

(A) Observed data from the in-trial observation period. (B) Observed data for the on-treatment observation period. Data are from the full analysis set. Error bars are plus or minus standard error of the mean. Numbers shown at each timepoint under the graphs are participants contributing to the mean. ETD=estimated treatment difference. *Estimated mean change from baseline at week 44.

semaglutide 2.4 mg and -1.8 kg (0.8) for placebo (ETD -5.5 kg, -7.6 to -3.4; $p < 0.0001$; appendix 2 p 42). The change from baseline in lean soft tissue was -5.9% (0.6) for semaglutide 2.4 mg versus -1.3% (0.8) for placebo (ETD -4.5 percentage points, -6.5 to -2.5; $p < 0.0001$; table 2), and the absolute change from baseline in lean soft tissue was -2.4 kg (0.3) for semaglutide 2.4 mg and -0.5 kg (0.3) for placebo (ETD -2.0 kg, -2.9 to -1.1; $p < 0.0001$). The change from baseline in visceral fat mass was -36.1% (4.1) for semaglutide 2.4 mg versus -8.3% (5.3) for placebo (ETD -27.8 percentage points, 95% CI -41.1 to -14.5; $p < 0.0001$). The absolute change from baseline in visceral fat mass was -0.4 kg (0.0) for semaglutide 2.4 mg and -0.1 kg (0.1) for placebo (ETD -0.3 kg, -0.4 to -0.2; $p < 0.0001$; appendix 2 p 42). The

ETD for change in lean soft tissue relative to total body mass with semaglutide 2.4 mg versus placebo was 4.1 percentage points (95% CI 2.1 to 6.0; $p < 0.0001$, appendix 2 p 43). In participants who received semaglutide 2.4 mg, the proportion of weight loss due to fat mass loss was 74.9% and due to lean soft tissue loss was 25.1%. In participants who received placebo, the proportion of weight loss due to fat mass loss was 79.6% and due to lean soft tissue mass was 20.4% (appendix 2 p 44).

Adverse events were reported by 141 (87.6%) of 161 participants receiving semaglutide 2.4 mg and 61 (75.3%) of 81 participants receiving placebo (table 3). Most events were mild to moderate in severity and were resolved without permanent discontinuation of treatment. Serious adverse events were reported by 12

	Semaglutide 2.4 mg (n=161)	Placebo (n=81)	Treatment comparison (95% CI) versus placebo	p value
Primary endpoints				
Bodyweight, %†	-12.1 (0.6)	-2.2 (0.8)	-9.9 (-11.8 to -8.0)‡	<0.0001
Proportion of participants with ≥5% bodyweight loss§	128/159 (80.5%)	19/78 (24.4%)	14.8 (7.4 to 29.6)¶	<0.0001
Confirmatory secondary endpoints				
Proportion of participants with ≥10% bodyweight loss§	96/159 (60.4%)	9/78 (11.5%)	13.0 (5.9 to 28.4)¶	<0.0001
Waist circumference, cm†	-9.0 (0.5)	-2.4 (0.6)	-6.6 (-8.1 to -5.0)‡	<0.0001
Supportive secondary endpoints†				
Absolute bodyweight, kg	-9.2 (0.4)	-1.6 (0.6)	-7.6 (-9.0 to -6.1)‡	<0.0001
BMI, kg/m²	-3.4 (0.2)	-0.6 (0.2)	-2.8 (-3.3 to -2.2)‡	<0.0001
Waist-to-height ratio	-0.05 (0.00)	-0.01 (0.00)	-0.04 (-0.05 to -0.03)‡	<0.0001
Blood pressure (mm Hg)				
Systolic	-7.7 (0.8)	-3.0 (1.2)	-4.8 (-7.6 to -1.9)‡	0.0012
Diastolic	-4.0 (0.6)	-1.9 (0.9)	-2.0 (-4.1 to 0.0)‡	0.053
Lipids, ratio to baseline				
Total cholesterol	0.9 (1.0)	1.0 (1.0)	0.9 (0.9 to 1.0)	0.0007
High-density lipoprotein cholesterol	1.0 (1.0)	1.1 (1.0)	1.0 (1.0 to 1.0)	0.39
Low-density lipoprotein cholesterol	1.0 (1.0)	1.0 (1.0)	1.0 (0.9 to 1.0)	0.12
Very-low-density lipoprotein cholesterol	0.7 (1.0)	0.9 (1.0)	0.8 (0.7 to 0.9)	<0.0001
Free fatty acids	0.9 (1.0)	1.0 (1.1)	0.9 (0.8 to 1.0)	0.14
Triglycerides	0.7 (1.0)	0.9 (1.0)	0.8 (0.7 to 0.9)	0.0001
hsCRP, ratio to baseline	0.66 (1.1)	0.72 (1.1)	0.9 (0.7 to 1.2)	0.51
HbA _{1c} , percentage-points	-0.4 (0.0)	0.1 (0.0)	-0.5 (-0.6 to -0.4)‡	<0.0001
Fasting plasma glucose, mmol/L	-0.7 (0.1)	0.0 (0.1)	-0.7 (-0.9 to -0.5)‡	<0.0001
Post-hoc exploratory endpoint				
Change from baseline in body composition in participants from Taiwan†				
Number of participants	52	28	..	..
Total fat mass, %	-27.4 (2.5)	-6.8 (3.0)	-20.6 (-28.5 to -12.7)‡	<0.0001
Lean soft tissue, %	-5.9 (0.6)	-1.3 (0.8)	-4.5 (-6.5 to -2.5)‡	<0.0001
Visceral fat mass, %	-36.1 (4.1)	-8.3 (5.3)	-27.8 (-41.1 to -14.5)‡	<0.0001

Data are n (%) or mean (SE), unless stated otherwise. All participants in the full-analysis set are included in the treatment comparisons. hsCRP=high-sensitivity C-reactive protein. *The treatment policy estimand assesses treatment effect among all randomly assigned participants, regardless of trial product discontinuation, dose reduction, or initiation of other therapies for obesity. †Week 44 responses were analysed using an analysis of covariance model with randomised treatment and type 2 diabetes status at screening as factors and baseline values as the covariate. ‡Estimated treatment difference (95% CI). §Week 44 responses were analysed using a binary logistic regression model with randomised treatment and type 2 diabetes status at screening as factors and baseline bodyweight as the covariate. Missing observations were multiple (×1000) imputed using without imputation. ¶Odds ratio (95% CI). ||Estimated treatment ratio (95% CI); the ratio to baseline and the corresponding baseline value were log-transformed before the analysis.

Table 2: Co-primary, confirmatory secondary, selected supportive secondary, and post-hoc exploratory study endpoints from baseline to week 44 (treatment policy estimand*)

(7.5%) of 161 participants with semaglutide 2.4 mg and by three (3.7%) of 81 participants with placebo, without any clustering on preferred term level (table 3). Adverse events leading to permanent treatment discontinuation were reported in two (1.2%) of 161 participants with semaglutide 2.4 mg due to open globe injury of the eye (one [0.6%] participant) and gastrointestinal disorders (abdominal distension: one [0.6%] participant). Abdominal discomfort led to permanent discontinuation in one of 81 participants (1.2%) in the placebo group (appendix 2 pp 29–30).

The most frequently reported adverse events were gastrointestinal disorders, occurring in 90 (55.9%) of 161 participants in the semaglutide 2.4 mg group versus 19 (23.5%) of 81 participants in the placebo group

(appendix 2 p 45). The most frequent gastrointestinal disorders occurring in the semaglutide 2.4 mg group were diarrhoea and nausea. Most gastrointestinal disorders events occurred during the dose escalation phase and were mild or moderate in severity, with their outcome reported as recovered or resolved (appendix 2 pp 29–30, 45–46).

Psychiatric disorders were reported in seven (4.3%) of 161 participants receiving semaglutide 2.4 mg versus three (3.7%) of 81 participants receiving placebo. Gallbladder disorders were reported in three (1.9%; four events) participants who received semaglutide 2.4 mg, two events of which were possibly related to the trial product. Of the four events, three were classified as mild and one as severe. Pancreatitis was not observed in

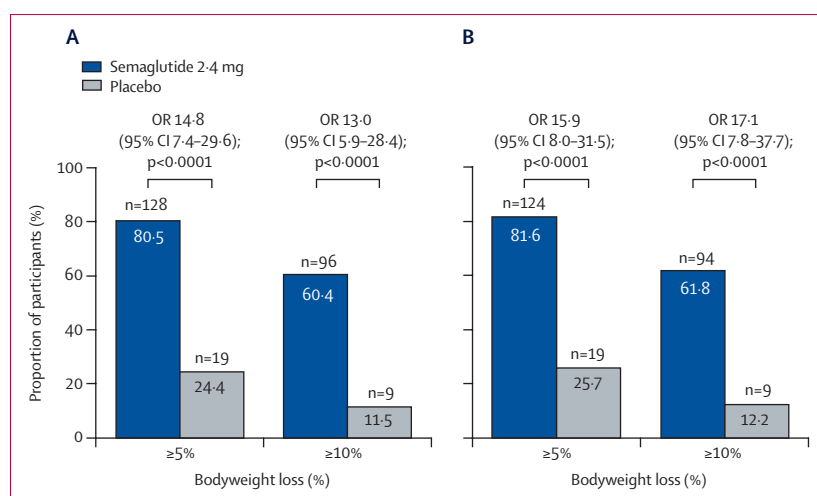


Figure 3: Proportion of participants achieving bodyweight loss of at least 5%, and at least 10%, with semaglutide 2.4 mg and placebo, given once a week

(A) In-trial observation period. (B) On-treatment observation period. Data are for the full analysis set. A timepoint is considered on-treatment if any dose of trial product has been administered within the previous 14 days. ORs for A and B are for the treatment policy estimand and trial product estimand, respectively. OR=odds ratio.

any trial participant. Among participants with type 2 diabetes at screening, five (16.1%) of 31 participants who received semaglutide 2.4 mg experienced eye disorders by week 44 (diabetic retinopathy: four [12.9%] of 31 participants; arteriosclerotic retinopathy: one [3.2%]). One participant who received semaglutide 2.4 mg experienced a level 2 hypoglycaemic episode with a blood glucose value of less than 3.0 mmol/L (54 mg/dL). No retinal disorders or level 2 hypoglycaemic episodes were recorded among participants in the placebo group. No participant in either group experienced a level 3 hypoglycaemic episode (table 3). There was an increase in pulse rate with semaglutide 2.4 mg treatment compared with placebo during the 44 weeks (ETD 3.9 beats per min, 95% CI 1.3 to 6.5; $p=0.0037$).

Discussion

This, to our knowledge, was the first phase 3 trial conducted in mainland China and Taiwan that investigated the efficacy and safety of semaglutide 2.4 mg in a trial population reflecting locally defined Chinese BMI thresholds for overweight and obesity. After 44 weeks, once-weekly subcutaneous semaglutide 2.4 mg was superior to placebo in reducing bodyweight, increasing the likelihood of achieving at least 5% and at least 10% bodyweight reductions, and reducing waist circumference. Safety and tolerability were consistent with the known profile of semaglutide.

The estimated mean bodyweight reduction of 12.1% observed from baseline to week 44 with semaglutide 2.4 mg is similar to that observed in the STEP 6 (13.2%) and STEP 7 (12.1%) trials in Asian populations.^{12,13} The bodyweight reduction was slightly lower than the reduction observed in the global STEP 1 trial, which was

of longer duration and did not include participants with type 2 diabetes (14.9% at week 68),¹⁰ but higher than in the STEP 2 trial, which only included participants with type 2 diabetes (9.6% at week 68).¹¹ The comparatively slightly lower bodyweight reduction observed in the STEP 12 trial compared with the STEP 1 trial might be attributable to a variety of factors, including a higher proportion of male participants (50.0% vs 25.9%), the inclusion of participants with type 2 diabetes (19.4% vs 0%), and the shorter trial duration of 44 versus 68 weeks in the STEP 12 trial.¹⁰

Participants who received semaglutide 2.4 mg were more likely to achieve at least 5% weight loss compared with those who received the placebo. Achievement of this threshold is associated with benefits in relation to weight-related comorbidities.¹⁷ Improvements were also observed in anthropometric measures of obesity (ie, waist circumference, BMI, and waist-to-height ratio), glycaemic parameters (HbA_{1c} and fasting plasma glucose), several cardiovascular risk factors (systolic blood pressure, total cholesterol, very-low-density lipoprotein cholesterol, and triglycerides), aligning with previous findings from STEP clinical trials.^{10-13,18}

Semaglutide 2.4 mg reduced high-sensitivity C-reactive protein concentrations by 34% versus 28% with placebo (estimated treatment ratio 0.9); however, in contrast with other STEP trials,^{11,12,18-22} this difference was not statistically significant. Potential contributory factors to these findings include the small sample size, which could have provided insufficient statistical power for this supportive secondary endpoint, a generally lower baseline high-sensitivity C-reactive protein with semaglutide 2.4 mg compared with most other STEP trials, and a slightly higher baseline high-sensitivity C-reactive protein in the placebo group compared with the semaglutide group.

The prevalences of dyslipidaemia, metabolic dysfunction-associated steatotic liver disease, and hyperuricaemia or gout at baseline were substantially higher in this trial compared with the previous STEP global phase 3 trials that did not include participants with type 2 diabetes.^{10,18,20,22} These differences could be reflective of the population from mainland China and Taiwan, the inclusion of participants with type 2 diabetes, or both; these conditions were also more prevalent among participants in the STEP 7 trial,¹³ whereas dyslipidaemia and non-alcoholic fatty liver disease were elevated among participants with type 2 diabetes in the STEP 2 trial.¹¹

In the dual-energy x-ray absorptiometry subpopulation, there were significant reductions in fat mass, visceral fat mass, and lean soft tissue among participants treated with semaglutide 2.4 mg compared with placebo; however, reductions in lean soft tissue were proportionally smaller than reductions in fat mass, demonstrating that semaglutide 2.4 mg improved body composition. These observations are consistent with findings from the STEP 1 trial in which greater reductions in fat mass compared with lean soft tissue were observed with semaglutide.¹⁰

The maintenance of lean soft tissue is vital as muscle mass loss is associated with increased risks of disability, frailty, and mortality;²³ however, muscle strength was not explicitly measured in this study and dual-energy x-ray absorptiometry is not a precise measurement of muscle mass or muscle quality.²⁴ Weight loss in participants receiving semaglutide is consistent with findings from dietary intervention studies, in which approximately 20–30% of the total reduction in bodyweight is attributed

to lean tissue, including muscle tissue.²⁵ It is well established that Asian people are predisposed to accumulate abdominal fat, even at lower BMIs.²⁶ The combination of reductions in visceral fat and improvements in cardiometabolic parameters indicates that weight management with semaglutide provides a beneficial effect in Asian adults with overweight or obesity with baseline BMI substantially lower than those previously studied.

	Semaglutide 2.4 mg (n=161)			Placebo (n=81)			Relative risk (95% CI)	Risk difference (95% CI)
	n (%)	Events	Events per 100 participant years	n (%)	Events	Events per 100 participant years		
Adverse events	141 (87.6%)	614	422.7	61 (75.3%)	183	253.6	1.16 (1.03 to 1.36)	0.123 (0.022 to 0.235)
Mild	132 (82.0%)	526	362.1	55 (67.9%)	148	205.1	1.21 (1.04 to 1.45)	0.141 (0.028 to 0.260)
Moderate	42 (26.1%)	81	55.8	14 (17.3%)	32	44.3	1.51 (0.90 to 2.62)	0.088 (–0.027 to 0.187)
Severe	6 (3.7%)	7	4.8	3 (3.7%)	3	4.2	1.01 (0.28 to 3.62)	0.000 (–0.069 to 0.048)
Serious adverse events	12 (7.5%)	14	9.6	3 (3.7%)	3	4.2	2.01 (0.63 to 6.55)	0.037 (–0.036 to 0.094)
Adverse events leading to discontinuation	2 (1.2%)	2	1.4	1 (1.2%)	1	1.4	1.01 (0.13 to 7.66)	0.000 (–0.055 to 0.033)
Gastrointestinal disorders leading to trial product discontinuation	1 (1%)	1	0.7	1 (1.2%)	1	1.4	0.50 (0.05 to 4.81)	–0.006 (–0.061 to 0.024)
Fatal adverse events	0	..	..	0	..	..	..	..
Adverse events reported in at least 10% of participants (in either group)								
Diarrhoea	30 (18.6%)	43	29.6	6 (7.4%)	6	8.3	..	..
Nausea	29 (18.0%)	37	25.5	2 (2.5%)	2	2.8	..	..
Constipation	22 (13.7%)	25	17.2	3 (3.7%)	3	4.2	..	..
Vomiting	16 (9.9%)	24	16.5	0	..	..	..	..
Upper respiratory tract infection	28 (17.4%)	34	23.4	12 (14.8%)	17	23.6	..	..
Decreased appetite	31 (19.3%)	34	23.4	2 (2.5%)	2	2.8	..	..
Adverse events of special interest								
Gastrointestinal adverse events*	90 (55.9%)	204	140.4	19 (23.5%)	23	31.9	2.38 (1.61 to 3.67)	0.324 (0.196 to 0.433)
Eye disorders in type 2 diabetes participants†‡	5/31 (16.1%)	5	17.1	0	..	..	..	0.161 (–0.052 to 0.326)
Cardiovascular disorders†	19 (11.8%)	22	15.1	12 (14.8%)	19	26.3	0.68 (0.37 to 1.29)	–0.055 (–0.160 to 0.034)
Hypoglycaemia in type 2 diabetes participants†§	3/31 (9.7%)	4	14.5	1/16 (6.3%)	1	6.8	1.55 (0.24 to 10.66)	0.034 (–0.195 to 0.195)
Allergic reactions*	14 (8.7%)	17	11.7	4 (4.9%)	5	6.9	1.76 (0.64 to 5.00)	0.038 (–0.041 to 0.099)
Hepatic events*	13 (8.1%)	15	10.3	4 (4.9%)	5	6.9	1.64 (0.59 to 4.68)	0.031 (–0.047 to 0.092)
Neoplasms†	12 (7.5%)	18	11.8	7 (8.6%)	9	11.9	0.86 (0.37 to 2.07)	–0.012 (–0.099 to 0.056)
Psychiatric disorders*	7 (4.3%)	8	5.5	3 (3.7%)	3	4.2	1.17 (0.34 to 4.11)	0.006 (–0.063 to 0.056)
Rare events*	4 (2.5%)	5	3.4	2 (2.5%)	2	2.8	1.01 (0.22 to 4.66)	0.000 (–0.063 to 0.042)
COVID-19*	3 (1.9%)	3	2.1	1 (1.2%)	2	2.8	1.51 (0.22 to 10.51)	0.006 (–0.049 to 0.042)
Dysaesthesia*	3 (1.9%)	3	2.1	0	..	..	..	0.019 (–0.028 to 0.053)
Gallbladder related disorders*	3 (1.9%)	4	2.8	0	..	..	..	0.019 (–0.028 to 0.053)
Acute renal failure*	1 (1%)	1	0.7	0	..	..	..	0.006 (–0.039 to 0.034)
Injection site reaction*	1 (1%)	1	0.7	0	..	..	..	0.006 (–0.039 to 0.034)
Malignant neoplasm*	1 (1%)	1	0.7	0	..	..	..	0.006 (–0.039 to 0.034)

Data are for participants in the safety analysis set (all randomly assigned participants exposed to at least one dose of randomised intervention) experiencing at least one event. Level 1 hypoglycaemia (alert value) was defined as a plasma glucose lower than 3.9 mmol/L (70 mg/dL) and at least 3.0 mmol/L (54 mg/dL), and level 2 (clinically significant hypoglycaemia) as lower than 3.0 mmol/L (54 mg/dL). Level 3 (severe hypoglycaemia) had no specific glucose threshold and was described as hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery. Data are for on-treatment adverse events. On-treatment adverse events have an onset date during on-treatment period. A timepoint was considered as on-treatment if any dose of trial product had been administered within the previous 35 days. Medical Dictionary for Regulatory Activities (version 28.0) searches were used to identify the preferred terms relevant for each of the safety focus areas. *On-treatment. †In-trial. ‡Of the five individuals who reported eye disorders at week 44, three individuals did not have eye disorders at baseline but reported diabetic retinopathy at week 44; one individual reported cataracts at baseline and reported arteriosclerotic retinopathy at week 44; and one individual reported diabetic retinopathy at baseline, which progressed by week 44. §In the semaglutide 2.4 mg group, there were four events in three participants; one level 2 event, two level 1 events, and one event with the level missing. In the placebo group, there was one event with the level missing in one participant.

Table 3: Adverse events

The safety and tolerability of semaglutide was consistent with findings of other trials in the STEP programme, and with the GLP-1 receptor agonist class in general.^{10–13,18,22} Gastrointestinal events were more frequent in the semaglutide group than in the placebo group, and there were few adverse events that led to permanent discontinuation (1.2% in both groups). Among participants with type 2 diabetes, three participants developed diabetic retinopathy during the trial, one participant experienced worsening of diabetic retinopathy, and one participant developed arteriosclerotic retinopathy. Owing to the small number of participants with type 2 diabetes in this study (47 participants), these data should be interpreted with caution and with consideration of the totality of evidence across the semaglutide development programme. Notably, an independent systematic review and meta-analysis found no association between semaglutide treatment and ocular adverse events based on data from 78 trials across multiple indications.²⁷ Additionally, a separate study (FOCUS, NCT03811561) investigating whether there is a causal association between semaglutide treatment, and development or worsening of diabetic retinopathy in individuals with type 2 diabetes is underway.

Key strengths of this trial are that it was the first, to our knowledge, to assess the efficacy and safety of semaglutide 2.4 mg using locally defined China-specific BMI thresholds, and that high rates of treatment completion (232 [95.9%] of 242 participants) and trial completion (240 [99.2%] participants) were achieved. The trial was designed based on the local cutoff for defining obesity in mainland China (WGOC threshold 28 kg/m²); however, we acknowledge that the different locally recommended cutoff for Taiwan (27 kg/m²) introduces a limitation in this regard as participants from Taiwan with a BMI between 27 kg/m² and less than 28 kg/m² had to have at least one weight-related comorbidity to be eligible, whereas participants with a BMI at least 28 kg/m² were not required to have a weight-related comorbidity. Although this trial was limited by the short treatment duration of 44 weeks, in line with regulatory requirements, the effectiveness and safety profiles of semaglutide 2.4 mg were generally consistent with results observed at week 68 in the wider STEP trial programme; however, because a weight loss plateau was not reached, the maximum treatment effect could not be assessed. The small body composition subpopulation (assessed by dual-energy x-ray absorptiometry) and no assessment of physical function or muscle strength were also limitations.

In conclusion, the STEP 12 trial in adults from mainland China and Taiwan with overweight or obesity, defined according to locally defined, China-specific BMI thresholds, demonstrated that treatment with semaglutide 2.4 mg resulted in statistically significant placebo-adjusted improvements in bodyweight, body composition, and other cardiometabolic risk factors, and

a safety profile consistent with the known profile of semaglutide. These findings suggest that semaglutide 2.4 mg could be used for the management of overweight and obesity in this population.

Contributors

BL, CL, KJK, and XB designed the trial and did the data analysis. LG, K-CH, YL, GY, and RFK contributed to the data collection. XB and RFK directly accessed and verified the underlying data reported in the manuscript. All authors interpreted the data and were involved in the conduct of the trial. 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. The investigators were responsible for trial-related medical decisions and data collection. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

BL was an employee of Novo Nordisk China at the time the study was performed, and is currently an employee of Eisai China. CL is an employee and shareholder of Novo Nordisk A/S. KJK is an employee and shareholder of Novo Nordisk A/S. LG reports grants or contracts from Abbott, AstraZeneca, Bayer, Dreisamtech, Eli Lilly, Hansoh, Hengrui, Hua Medicine, Huadong Medicine, Innovent, Meitekanger Tech, Novo Nordisk, Salubris, Sanofi, Synapsor, and Zense; participation on a data safety monitoring board or advisory board for Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Dreisamtech, Dongbao, Eli Lilly, Gan & Lee, Hansoh, Hengrui, Huadong Medicine, Hua Medicine, Innovent, Janssen, Novartis, Novo Nordisk, Merck, Pfizer, Sanofi, Synapsor, Takeda, Zense, and 3sbio; is Chairman of the Chinese Diabetes Society, Director of the Endocrinology Society, Beijing Medical Doctor Association, Former Chairman of the Beijing Diabetes Society, and Vice Director of the Diabetes Committee of Chinese Research Hospital Association. RFK is a consultant or advisory board member for AbbVie, Antag, AstraZeneca, Boehringer Ingelheim, Curax, Eli Lilly, Novo Nordisk, Structure, Viking, and Weight Watchers. XB is an employee of Novo Nordisk China and shareholder of Novo Nordisk A/S. All other authors declare no competing interests.

Data sharing

An authorised researcher can request access to the clinical study data by submitting a research proposal for review and approval by Novo Nordisk and an internal independent review panel. Requests are usually considered after the research is finished and the main results have been published. If the research supports a regulatory application, requests will be considered after the product and its intended use are approved in both the EU and the USA. Participants' clinical data will be anonymised, following an approved internal process, before data are shared to external third parties. For details on how to request access to clinical data, visit novonordisk-trials.com.

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