ORIGINAL ARTICLE

Survodutide Once Weekly for the Treatment of Adults with Obesity

C.W. le Roux,[1,2] S. Wharton,[3,4] E. Startseva,[5] I.M. Kloer,[5] S.A. Hussain,[5] A. Unseld,[6] B. Bozkurt,[7] J.D. Ard,[8,9] H.E. Bays,[10] P. Bogdański,[11] E.I. Ekinci,[12-15] A.M. Jastreboff,[16-18] L. Ji,[19,20] W. Ogawa,[21,22] S.D. Pedersen,[23,24] K.H. Pietiläinen,[25,26] N. Sattar,[27] J. Seufert,[28] K. Stenlöf,[29,30] A.P. van Beek,[31] R. Vangoitsenhoven,[32,33] M. Brueckmann,[5,34] R. Younes,[5] and L.M. Kaplan,[35,36] for the SYNCHRONIZE-1 Investigators*

ABSTRACT

BACKGROUND

Although medications with glucagon-like peptide-1 (GLP-1) receptor agonist activity have transformed the management of obesity and shown substantial cardiometabolic benefits, unmet needs remain. Survodutide, an investigational glucagon receptor–GLP-1 receptor dual agonist, led to substantial weight reduction in a phase 2 trial involving adults with obesity without diabetes.

METHODS

In this phase 3, double-blind trial, we randomly assigned adults with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or higher, or 27 or higher with at least one obesity-related complication (excluding diabetes), in a 1:1:1 ratio to receive once-weekly survodutide administered subcutaneously at a dose adjusted up to 3.6 mg or 6.0 mg or placebo, in addition to counseling for lifestyle modification. The two primary end points were the percent change in body weight and a reduction in body weight of at least 5% from baseline to week 76. The primary efficacy analysis was conducted according to the treatment-regimen estimand, which incorporates the effects of any early discontinuation of survodutide or placebo, the use of protocol-prohibited obesity medications, and a prolonged dose-escalation period.

RESULTS

Among 725 participants (241 in the 3.6-mg survodutide group, 242 in the 6.0-mg survodutide group, and 242 in the placebo group), the mean age was 47.1 years; 294 participants (40.6%) were men. At baseline, the mean BMI was 37.9, and the mean body weight was 108.8 kg. At week 76, the mean change in body weight from baseline according to the treatment-regimen estimand was –12.2% (95% confidence interval [CI], –13.6 to –10.8) in the 3.6-mg group, –13.0% (95% CI, –14.4 to –11.6) in the 6.0-mg group, and –5.4% (95% CI, –6.9 to –4.0) in the placebo group; 72.6%, 71.9% and 46.3% of the participants, respectively, had weight reduction of at least 5% ($P<0.001$ for all comparisons with placebo). The most common adverse events were gastrointestinal symptoms (typically mild to moderate), which occurred in 80.9% of the participants in the 3.6-mg group, in 89.7% of those in the 6.0-mg group, and in 47.9% of those in the placebo group. No deaths were reported.

CONCLUSIONS

Survodutide led to significantly greater reductions in body weight than placebo in adults with obesity without diabetes. (Funded by Boehringer Ingelheim; SYNCHRONIZE-1 ClinicalTrials.gov number, NCT06066515.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Carel W. le Roux can be contacted at carel.leroux@ucd.ie or at the Diabetes Complications Research Centre, Conway Institute, University College Dublin School of Medicine, Belfield, Dublin 4, D04 V1W8, Ireland.

*A complete list of the SYNCHRONIZE-1 investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on June 7, 2026, at NEJM.org.

DOI: 10.1056/NEJMoa2600751

Obesity is a chronic neurometabolic disease characterized by excess overall or ectopic adipose tissue; it can lead to serious health complications, reduced quality of life, and an increased risk of death.[1,2] Obesity affects approximately 1 billion adults worldwide,[3] a fact that highlights a pressing need for more effective therapies.[4-7]

Clinical guidelines worldwide emphasize long-term treatments such as obesity medications,[4-9] with the aim to avoid inadequate disease control or progression.[10] Medications with glucagon-like peptide-1 (GLP-1) receptor agonist activity — particularly the GLP-1 receptor agonist semaglutide[11,12] and the GLP-1 receptor–glucose-dependent insulinotropic polypeptide receptor dual agonist tirzepatide[13] — are associated with substantial health gains. However, heterogeneity in responses with current medications suggests that compounds with complementary mechanisms that may expand treatment options for managing the disease, addressing metabolic dysfunction beyond weight loss, and ameliorating complications would be useful.

Oxyntomodulin, an endogenous incretin-related peptide hormone, stimulates the glucagon receptor and the GLP-1 receptor; agonism of both is hypothesized to confer additional benefits owing to the physiological effects of glucagon, a peptide hormone that reduces appetite and induces lipolysis, in addition to its glycemic effects.[14] In animal models and exploratory studies involving humans, exogenous oxyntomodulin was associated with reduced food intake, increased energy expenditure, and a reduction in body weight.[15] Synthetic unimolecular peptide dual agonists of the glucagon and GLP-1 receptors with enhanced receptor activation capacity and extended half-lives have been developed, including survodutide[16] and mazdutide[17] (which was approved in 2025 in China[18]).

In a phase 2 dose-finding trial involving persons with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 27 or more who did not have diabetes, survodutide led to substantial weight reduction over a period of 46 weeks.[19] Given the results of early-phase clinical trials,[19-21] an international phase 3 program (SYNCHRONIZE) is evaluating survodutide for the treatment of obesity. Here, we report the results of SYNCHRONIZE-1, a phase 3 clinical trial that evaluated the efficacy and safety of survodutide, in addition to a reduced-calorie diet and increased physical activity, for the treatment of obesity in adults without diabetes.

METHODS

TRIAL DESIGN

We conducted this 76-week, phase 3, double-blind, randomized, placebo-controlled trial at 116 clinical sites across 14 countries.[22] The institutional review board or independent ethics committee at each site approved the trial protocol (available with the full text of this article at NEJM.org). The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice. All the participants provided written informed consent before trial entry. Boehringer Ingelheim sponsored and designed the trial. An executive committee of independent experts and sponsor-employed scientists and physicians with relevant clinical and methodologic expertise oversaw the trial. Independent committees regularly reviewed safety data and prospectively adjudicated major adverse cardiovascular events (MACE; including heart failure), death from noncardiovascular causes, acute pancreatitis, and thyroid and pancreatic cancers. The trial design has been published previously.[23] The authors wrote the first draft of the manuscript with assistance from a sponsor-funded medical writer. All the authors had access to the data, and they vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PARTICIPANTS

Eligible persons were at least 18 years of age, with a BMI of 30 or higher — or 27 or higher with at least one obesity-related complication (hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease, or metabolic dysfunction–associated steatohepatitis [MASH]) — and at least one previous participant-reported unsuccessful dietary effort to lose weight. Among the exclusion criteria were a change in body weight of more than 5% or treatment with an obesity medication within the previous 3 months, previous or planned bariatric surgery, a glycated hemoglobin level of 6.5% or higher (≥48 mmol per mole), a history of type 1 or type 2 diabetes, treat-

ment with a glucose-lowering drug within the previous 3 months, obesity resulting from a formally diagnosed endocrinologic or genetic cause, the presence of uncontrolled hypertension (defined as a systolic blood pressure of ≥160 mm Hg or a diastolic blood pressure of ≥100 mm Hg at screening) or a mood disorder that was not well controlled (e.g., unstable depression), the occurrence of a cardiovascular event within the previous 3 months, or a history of pancreatitis, medullary thyroid carcinoma, or multiple endocrine neoplasia type 2. A complete list of eligibility criteria and exclusion criteria is provided in the Supplementary Appendix, available at NEJM.org.

RANDOMIZATION AND TREATMENT

Participants were randomly assigned in a 1:1:1 ratio to receive survodutide at a dose adjusted up to 3.6 mg, survodutide at a dose adjusted up to 6.0 mg, or placebo, administered subcutaneously once weekly (Fig. S1 in the Supplementary Appendix). All persons involved in the conduct of the trial were unaware of the trial-group assignments. Survodutide doses were adjusted up to 3.6 mg or 6.0 mg according to a dose-escalation scheme that allowed flexibility to mitigate gastrointestinal side effects (see the Supplementary Appendix). Dose flexibility was initially limited to weeks 16 to 32 after randomization, and participants were to discontinue survodutide or placebo if three or more doses were missed, whether for gastrointestinal side effects or other reasons. A subsequent protocol amendment in February 2025 allowed participants to restart survodutide or placebo, but at that point, most participants were more than three quarters of the way through the treatment period.

Assessment of the participants occurred on site or remotely every 2 to 4 weeks until week 24 and every 6 weeks thereafter until week 76 (the end of the treatment period). During on-site visits, dietitians or similarly qualified trial personnel provided counseling on nutrition and physical activity. Participants were encouraged to follow a reduced-calorie diet (with a deficit of approximately 500 kcal per day relative to the estimated total daily energy expenditure) and engage in at least 150 minutes per week of moderate-intensity exercise. A subgroup of participants underwent analysis of body composition with the use of magnetic resonance imaging (MRI) (see the Supplementary Appendix).

END POINTS

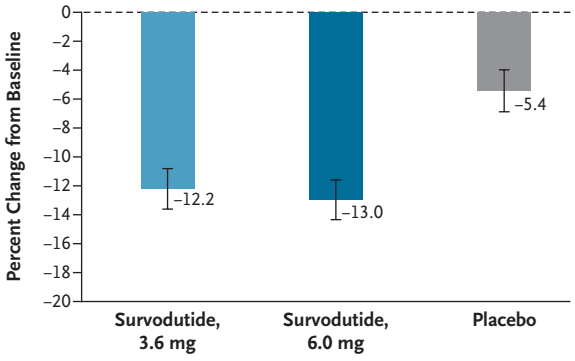
The two primary end points were the percent change in body weight and a reduction in body weight of at least 5% from baseline to week 76, in accordance with Food and Drug Administration (FDA) and European Medicines Agency guidance for the development of obesity medications.[23-25] Key secondary end points were reductions in body weight of at least 10%, at least 15%, and at least 20% from baseline to week 76; the absolute change in body weight from baseline to week 76; and the change in waist circumference, systolic blood pressure, and scores on the Eating Behavior Patient-Reported Outcome (EB PRO) measure from baseline to week 76.[26] EB PRO is a concise health survey for clinical assessment of eating behaviors in persons with obesity; it comprises 12 items across two domains (Desire to Eat and Capacity to Resist), which contribute to a Total Eating Behavior score. Scores in each domain range from 0 to 24, and total scores range from 0 to 48, with higher scores indicating greater disturbances in eating behavior; clinically meaningful thresholds are a 4-point change in individual domain scores and an 8-point change in the Total Eating Behavior score.[26]

Additional secondary and further end points are summarized in the Supplementary Appendix. Safety assessments included reported adverse events, physical examinations, vital-sign monitoring, laboratory tests, and 12-lead electrocardiography.

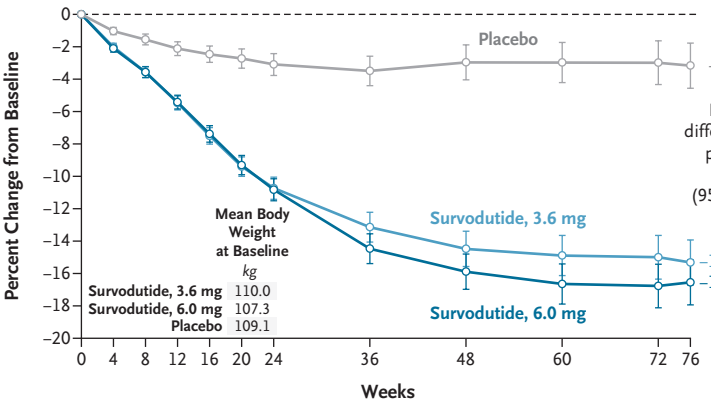
STATISTICAL ANALYSIS

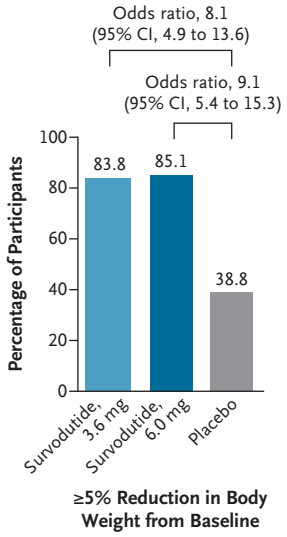
We calculated that a sample of 600 participants (200 per trial group) would provide the trial with more than 90% power to show the superiority of survodutide (at both 3.6-mg and 6.0-mg doses) over placebo for both primary end points, each at a two-sided significance level of 0.025. For the percent change in body weight from baseline to week 76, the sample-size calculation was performed with the assumption of an effect of 14% weight reduction in each survodutide group and 3% in the placebo group, with standard deviations of 10% for survodutide and 6% for placebo and with permanent discontinuation of survodutide or placebo in 20% of the participants. For a reduction in body weight of at least 5%, the assumption was that 60% of the participants in each survodutide group and 30% of those in the placebo group would reach the target. The sample size of

A Overall Change in Body Weight (treatment-regimen estimand)



B Change in Body Weight by Week and Percentage of Participants with ≥5% Weight Reduction at Week 76 (efficacy estimand)





No. of Participants											
Survodutide, 3.6 mg	236	234	231	224	213	200	191	177	168	155	141	141
Survodutide, 6.0 mg	239	236	233	224	215	201	195	174	164	158	145	147
Placebo	240	238	233	229	221	207	202	183	162	148	139	140

C Participants Who Met Weight-Reduction Targets (treatment-regimen estimand)

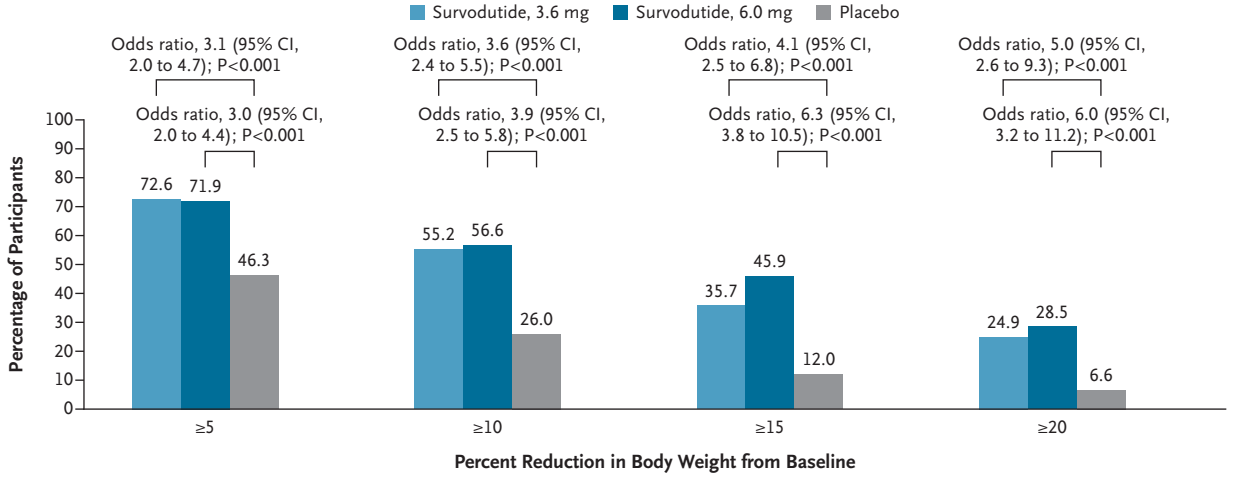


Figure 1 (facing page). Effects of Survodutide on Body Weight.

Panel A shows the percent change in body weight from baseline to week 76, derived from an analysis-of-covariance model, for the treatment-regimen estimand, which incorporates the effects of any early discontinuation of survodutide or placebo, the use of protocol-prohibited obesity medications, and a prolonged dose-escalation period. Panel B shows the percent change in body weight according to the number of weeks since randomization, derived from an analysis with a mixed model for repeated measures, and the percentage of participants who had weight reduction of at least 5% from baseline to week 76, both for the efficacy estimand, which represents the hypothetical treatment effect if all the participants had adhered to the assigned trial regimen and had not received prohibited therapy for obesity and which incorporates the effects of any prolonged dose-escalation phase. I bars in Panels A and B indicate 95% confidence intervals. The widths of the confidence intervals in Panel B have not been adjusted for multiplicity and should not be used for hypothesis testing. Panel C shows the percentages of participants who had weight reduction of at least 5%, at least 10%, at least 15%, or at least 20% from baseline to week 76 for the treatment-regimen estimand.

600 was defined primarily in order to collect sufficient safety data across the SYNCHRONIZE trial program to meet regulatory requirements (>4500 patients treated for >1 year).[19,24]

All efficacy and safety analyses were performed in the modified intention-to-treat population, which included all the participants who had undergone randomization and received at least one dose of survodutide or placebo. Two estimands that accounted for intercurrent events differently were used to assess treatment efficacy. The primary efficacy analysis was conducted according to the treatment-regimen estimand,[27] which incorporates the effects of any early discontinuation of survodutide or placebo, the use of protocol-prohibited obesity medications, and a prolonged dose-escalation period. Efficacy analyses were also conducted according to the efficacy estimand (hypothetical estimand), which represents the hypothetical treatment effect if all the participants had adhered to the assigned trial regimen and had not received prohibited therapy for obesity; it includes the effects of any prolonged dose-escalation phase.

Details on the estimands, the handling of missing values, and statistical analysis methods are provided in the Supplementary Appendix. The statistical analysis plan is available with the protocol. A multiple testing procedure for the primary end points and all key secondary end points was implemented with the use of a graphical approach that controls the family-wise error rate at an overall two-sided significance level of 5%. The widths of the confidence intervals for additional secondary end points and efficacy-estimand analyses were not adjusted for multiplicity and should not be used for hypothesis testing. Adverse events were reported descriptively, without hypothesis testing, and were coded with the use of the *Medical Dictionary for Regulatory Activities*, version 28.1.

RESULTS

PARTICIPANTS

The trial was conducted from November 2023 through February 2026. A total of 726 participants underwent randomization, and 725 received at least one dose of survodutide or placebo and were included in the modified intention-to-treat population: 241 in the 3.6-mg survodutide group, 242 in the 6.0-mg survodutide group, and 242 in the placebo group. One participant underwent randomization without meeting eligibility criteria, did not receive survodutide or placebo, and was omitted from analyses.

The characteristics of the participants at baseline across trial groups are summarized in Table S1. The mean age was 47.1 years; 40.6% of the participants were men, and 67.6% were White. Asian participants made up 22.3% of the trial population, and 7.2% of the participants were Black. The mean BMI was 37.9, the mean body weight was 108.8 kg, and the mean waist circumference was 115.0 cm; 94.9% of the participants had a BMI of 30 or higher. Most participants (69.7%) had at least one obesity-related complication, most commonly hypertension (in 40.1% of the participants), dyslipidemia (in 33.9%), and obstructive sleep apnea (in 18.3%). The representativeness of the participants is described in Table S2.

Overall, 91.3% of the participants completed the trial (90.9% of those in the 3.6-mg group, 95.5% of those in the 6.0-mg group, and 87.6% of those in the placebo group); 63.4% were still receiving survodutide or placebo at 76 weeks (64.7%, 65.7%, and 59.9%, respectively) (Fig. S2 and Table S3). In the survodutide groups, the last dose (at the end of the planned treatment period

or before discontinuation) was most commonly the assigned dose: 182 participants (75.5%) in the 3.6-mg group received 3.6 mg of survodutide as the last dose, and 151 participants (62.4%) in the 6.0-mg group received 6.0 mg as the last dose (Table S4). Although other obesity medications were prohibited, 2.5% of the participants in the 3.6-mg group, 3.7% in the 6.0-mg group, and 16.5% in the placebo group reported taking another medication with GLP-1 receptor agonist activity while still in the trial, most commonly after discontinuing survodutide or placebo (Table S5).

CHANGE IN BODY WEIGHT

For the treatment-regimen estimand, the mean change in body weight at week 76 was –12.2% (95% confidence interval [CI], –13.6 to –10.8) in the 3.6-mg group, –13.0% (95% CI, –14.4 to –11.6) in the 6.0-mg group, and –5.4% (95% CI, –6.9 to –4.0) in the placebo group (Fig. 1A, Table 1, and Fig. S3). The difference from placebo was –6.8 percentage points (95% CI, –8.8 to –4.8) in the 3.6-mg group and –7.5 percentage points (95% CI, –9.6 to –5.5) in the 6.0-mg group (P<0.001 for both comparisons). The mean absolute change in body weight was –13.1 kg (95% CI, –14.7 to –11.6) in the 3.6-mg group, –14.1 kg (95% CI, –15.6 to –12.6) in the 6.0-mg group, and –5.9 kg (95% CI, –7.5 to –4.4) in the placebo group (Table 1).

Full results for the efficacy estimand are provided in Figure 1B and Table S6; in brief, the mean change in body weight at week 76 was –15.3% with 3.6 mg of survodutide, –16.6% with 6.0 mg of survodutide, and –3.2% with placebo. The sensitivity analysis for the efficacy estimand (a complete-case analysis) is presented in Table S7.

For the treatment-regimen estimand, 72.6% of the participants in the 3.6-mg group and 71.9% of those in the 6.0-mg group had a body-weight reduction of at least 5% at 76 weeks, as compared with 46.3% of the participants in the placebo group (odds ratio for the 3.6-mg dose vs. placebo, 3.1 [95% CI, 2.0 to 4.7]; odds ratio for the 6.0-mg dose vs. placebo, 3.0 [95% CI, 2.0 to 4.4]; P<0.001 for both comparisons) (Fig. 1C). Table 1 shows the percentages of participants who had a body-weight reduction of at least 10%, at least 15%, or at least 20% at 76 weeks. Respective percentages for the efficacy estimand are shown in Figure 1B and Figure S4. Table S8 shows risk differences for the unconditional treatment-regimen estimand.

CARDIOVASCULAR, HEPATIC, AND METABOLIC RISK FACTORS AND OTHER OUTCOMES

In a prespecified analysis of the subgroup of participants who underwent MRI and had data available at baseline and week 76 (a total of 25 participants in each trial group), survodutide at a dose of 6.0 mg was associated with reductions of 27.8% in total body fat, 34.0% in visceral fat, 63.1% in liver fat, and 9.8% in lean body volume, as compared with reductions of 9.5% in total body fat, 11.8% in visceral fat, 24.5% in liver fat, and 2.9% in lean body volume with placebo (Table 2). Reductions in waist circumference, glycated hemoglobin and fasting plasma glucose levels, and cardiometabolic risk factors, as well as improvements in EB PRO scores, were noted in the overall trial population (Tables 1 and 2, Table S9, and Figs. S5 and S6).

SAFETY

Gastrointestinal adverse events — primarily nausea, vomiting, diarrhea, and constipation — occurred more often with survodutide than with placebo during the treatment period (Table 3 and Tables S10 and S11). These events occurred mainly during the dose-escalation period (Fig. S7), were mostly mild to moderate in severity, and led to discontinuation of the trial regimen in 17.8% of the participants in the 3.6-mg group, in 20.2% of those in the 6.0-mg group, and in 2.9% of those in the placebo group. Various strategies were used to mitigate gastrointestinal side effects, including a flexible dose-escalation scheme and treatment of gastrointestinal symptoms. Serious adverse events occurred in 8.3% of the participants in the 3.6-mg group, in 8.3% of those in the 6.0-mg group, and in 6.2% of those in the placebo group.

No severe hypoglycemia was reported; hyperglycemia was less common in the survodutide groups than in the placebo group. Cholecystitis and cholelithiasis were reported more commonly with survodutide, as was hypotension, including syncopal events (mostly mild to moderate and not serious in nature) and dysesthesia (all nonserious, mostly mild-to-moderate events). One participant receiving survodutide at a dose of 3.6 mg reported a suicide attempt in the context of psychosocial stressors (issues with family and partner and academic difficulties). Depression was reported less commonly in the survodutide groups than in the placebo group.

Table 1. Primary and Key Secondary End Points for the Treatment-Regimen Estimand.*

End Point	Survodutide, 3.6 mg (N=241)	Survodutide, 6.0 mg (N=242)	Placebo (N=242)
Primary end points			
Mean change in body weight (95% CI) — %	–12.2 (–13.6 to –10.8)	–13.0 (–14.4 to –11.6)	–5.4 (–6.9 to –4.0)
Difference vs. placebo (95% CI) — percentage points	–6.8 (–8.8 to –4.8)†	–7.5 (–9.6 to –5.5)†	
Weight reduction of ≥5% — % of participants	72.6	71.9	46.3
Odds ratio, survodutide vs. placebo (95% CI)	3.1 (2.0 to 4.7)†	3.0 (2.0 to 4.4)†	—
Key secondary end points			
Weight reduction of ≥10% — % of participants	55.2	56.6	26.0
Odds ratio, survodutide vs. placebo (95% CI)	3.6 (2.4 to 5.5)†	3.9 (2.5 to 5.8)†	—
Weight reduction of ≥15% — % of participants	35.7	45.9	12.0
Odds ratio, survodutide vs. placebo (95% CI)	4.1 (2.5 to 6.8)†	6.3 (3.8 to 10.5)†	—
Weight reduction of ≥20% — % of participants	24.9	28.5	6.6
Odds ratio, survodutide vs. placebo (95% CI)	5.0 (2.6 to 9.3)†	6.0 (3.2 to 11.2)†	—
Mean change in body weight — kg	–13.1	–14.1	–5.9
Difference vs. placebo (95% CI)	–7.2 (–9.4 to –5.0)†	–8.1 (–10.3 to –5.9)†	—
Mean change in waist circumference — cm	–10.5	–11.5	–5.4
Difference vs. placebo (95% CI)	–5.2 (–7.1 to –3.2)†	–6.1 (–8.0 to –4.1)†	—
Mean change in systolic blood pressure — mm Hg	–6.7	–5.4	–5.9
Difference vs. placebo (95% CI)	–0.7 (–3.0 to 1.6)‡	0.6 (–1.7 to 2.9)‡	—
Mean change in EB PRO total score — points§	–7.8	–8.1	–7.3
Difference vs. placebo (95% CI)	–0.5 (–2.2 to 1.3)	–0.9 (–2.6 to 0.9)	—
Mean change in EB PRO Capacity to Resist domain score — points§	–4.2	–4.3	–3.8
Difference vs. placebo (95% CI)	–0.4 (–1.3 to 0.6)	–0.5 (–1.4 to 0.5)	—

* All changes are from baseline to week 76, and all data are shown as estimated mean changes, differences from placebo, or estimated percentages of participants, unless otherwise specified. P values are reported only until the last comparison with placebo was significant.
† P<0.001 for the comparison with placebo.
‡ The difference from placebo was not significant.
§ The Eating Behavior Patient-Reported Outcome measure (EB PRO) is a survey for clinical assessment of eating behaviors in persons with obesity. Scores on each domain range from 0 to 24, and total scores range from 0 to 48, with higher scores indicating greater disturbances in eating behavior. Clinically meaningful thresholds are a 4-point change in individual domain scores and an 8-point change in the total score.

One adjudicated MACE occurred in the placebo group (ischemic stroke), and none occurred in the survodutide groups. No adjudication-confirmed cases of myocardial infarction, death from cardiovascular causes, heart failure, ischemia-related revascularization, pancreatic cancer, thyroid cancer, or acute pancreatitis occurred. Asymptomatic pancreatic hyperenzymemia occurred more commonly in the survodutide groups than in the placebo group (in 2.5% of the participants in the 3.6-mg group, in 1.7% of those in the 6.0-mg group, and in 1.2% of those in the placebo group); Table S12 shows the mean relative changes in levels of pancreatic enzymes and calcitonin from baseline to week 76. At week 76, heart rate had increased by 3.2 to 3.5 beats per minute from baseline in the survodutide groups and decreased by 0.4 beats per minute in the placebo group (Fig. S8); no new-onset increase of more than 500 msec or change from baseline of more than 60 msec in the QT interval corrected by Fridericia's formula (QTcF) occurred in the survodutide groups.

DISCUSSION

In this international, phase 3 trial, the glucagon receptor–GLP-1 receptor dual agonist survodutide was associated with significantly greater reductions in body weight than placebo over a period

of 76 weeks in adults with obesity without diabetes. Body-weight reductions were accompanied by reductions in cardiometabolic risk factors and improvements in body composition and in markers of liver health.

The development of glucagon receptor–GLP-1 receptor dual agonists to enhance the relative potency of the agonists at these receptors has been challenging, particularly with respect to net effects on glucose homeostasis. In this trial, treatment with survodutide did not increase glycated hemoglobin levels in participants without diabetes mellitus; a previous phase 2 trial involving persons with obesity and type 2 diabetes showed that survodutide significantly reduced glycated hemoglobin levels.[20]

Weight loss–dependent and –independent effects of obesity medications may both be involved in ameliorating obesity-related complications,[28] which we hypothesize may indicate that the mechanism by which weight loss is achieved may be as important as the magnitude of weight

Table 2. Additional Secondary End Points and Further End Points.*

End Point	Survodutide, 3.6 mg (N=241)	Survodutide, 6.0 mg (N=242)	Placebo (N=242)
Secondary end points for the treatment-regimen estimand			
Mean change in BMI (95% CI)	−4.6 (−5.2 to −4.1)	−5.0 (−5.6 to −4.5)	−2.1 (−2.7 to −1.5)
Mean change in diastolic blood pressure (95% CI) — mm Hg	−4.1 (−5.1 to −3.0)	−3.6 (−4.6 to −2.6)	−3.4 (−4.5 to −2.3)
Mean change in glycated hemoglobin level (95% CI) — percentage points	−0.2 (−0.2 to −0.1)	−0.2 (−0.2 to −0.1)	0.0 (−0.1 to 0.1)
Mean change in fasting plasma glucose level (95% CI) — mg/dl	−7.4 (−8.9 to −6.0)	−6.0 (−7.3 to −4.7)	−1.2 (−2.8 to 0.4)
Mean change in fasting plasma insulin level (95% CI) — %†	−28.4 (−34.3 to −22.1)	−29.2 (−34.6 to −23.3)	−8.6 (−16.4 to −0.04)
Mean changes in lipid levels (95% CI) — %†			
Total cholesterol	−7.6 (−9.7 to −5.5)	−8.4 (−10.3 to −6.5)	−4.5 (−6.8 to −2.2)
HDL cholesterol	1.4 (−0.7 to 3.6)	3.1 (1.0 to 5.2)	0.2 (−2.0 to 2.5)
LDL cholesterol	−8.8 (−11.7 to −5.8)	−9.0 (−11.8 to −6.2)	−5.7 (−9.0 to −2.4)
VLDL cholesterol	−24.6 (−28.9 to −19.9)	−30.1 (−33.9 to −26.0)	−10.6 (−16.0 to −4.8)
Triglycerides	−22.7 (−26.9 to −18.2)	−27.7 (−31.4 to −23.8)	−8.8 (−14.0 to −3.3)
Free fatty acids	−12.2 (−18.1 to −5.9)	−13.1 (−18.5 to −7.4)	−9.5 (−16.0 to −2.6)
Mean changes in liver markers (95% CI) — %†			
Alanine aminotransferase	−16.3 (−21.3 to −11.1)	−13.0 (−17.9 to −7.8)	−14.5 (−20.0 to −8.8)
Aspartate aminotransferase	−7.1 (−11.0 to −3.1)	−5.9 (−9.7 to −2.0)	−6.2 (−10.5 to −1.8)
Further end points‡			
Mean change in Fibrosis-4 index score (95% CI)§	0.10 (0.05 to 0.14)	0.05 (0.01 to 0.10)	0.05 (0.01 to 0.09)
Mean change in uric acid level (95% CI) — μmol/liter	−53.0 (−61.6 to −44.5)	−73.8 (−82.2 to −65.3)	−8.6 (−17.2 to −0.03)
Secondary end points for the substudy of body composition¶			
Mean change in total fat volume (95% CI)			
Absolute change — liters	−9.7 (−12.2 to −7.2)	−10.9 (−13.5 to −8.4)	−4.1 (−6.6 to −1.6)
Relative change — %	−22.9 (−28.7 to −17.0)	−27.8 (−33.8 to −21.9)	−9.5 (−15.3 to −3.6)
Mean change in lean body volume (95% CI)			
Absolute change — liters	−1.9 (−2.5 to −1.4)	−2.7 (−3.2 to −2.1)	−0.8 (−1.4 to −0.3)
Relative change — %	−7.2 (−9.3 to −5.2)	−9.8 (−11.8 to −7.7)	−2.9 (−5.0 to −0.9)
Lean loss ratio — %‖	11.1	10.8	12.8
Mean change in visceral fat volume (95% CI)			
Absolute change — liters	−1.6 (−2.1 to −1.2)	−1.9 (−2.5 to −1.4)	−0.7 (−1.2 to −0.2)
Relative change — %	−29.8 (−38.4 to −21.1)	−34.0 (−43.0 to −25.0)	−11.8 (−20.5 to −3.0)

Table 2. (Continued.)

End Point	Survodutide, 3.6 mg (N = 241)	Survodutide, 6.0 mg (N = 242)	Placebo (N = 242)
Mean change in subcutaneous fat volume (95% CI)			
Absolute change — liters	–7.2 (–9.1 to –5.4)	–8.0 (–9.8 to –6.1)	–3.2 (–5.0 to –1.3)
Relative change — %	–23.0 (–28.9 to –17.2)	–28.1 (–34.0 to –22.3)	–9.8 (–15.6 to –4.0)
Mean relative change in liver-fat content (95% CI) — %	–46.0 (–66.5 to –25.5)	–63.1 (–83.6 to –42.6)	–24.5 (–44.8 to –4.2)

* All changes shown are from baseline to week 76, and data are shown as estimated mean changes unless otherwise specified. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing. All the end points shown were defined as additional secondary end points, except for the change in the Fibrosis-4 index score and the change in the uric acid level, which were defined as further end points. To convert the values for glycated hemoglobin to millimoles per mole, multiply by 10.93 and then subtract 23.50. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for uric acid to milligrams per deciliter, divide by 59.48. BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters), HDL high-density lipoprotein, LDL low-density lipoprotein, and VLDL very low-density lipoprotein.

† Mean changes were analyzed with the use of log transformation.

‡ Further end points were analyzed with a mixed model for repeated measures.

§ The Fibrosis-4 index score is calculated as follows: (age × AST)/(platelets × $\sqrt{\text{ALT}}$), where age is expressed in years, ALT denotes the alanine aminotransferase level expressed in units per liter, AST denotes the aspartate aminotransferase level expressed in units per liter, and platelets is the number of platelets per liter divided by 10^9.

¶ Data shown are from a prespecified analysis of body composition among the subgroup of participants who underwent magnetic resonance imaging (25 participants in each trial group). The participants included in the analysis were taking survodutide or placebo as assigned at week 76, had had no previous interruptions of the trial regimen, and had data available at baseline and at week 76 for the respective end point. An analysis of covariance was used to test changes.

‖ The lean loss ratio is calculated as the slope of the regression line for the analysis of the correlation between the change in lean body mass and the change in total tissue mass (both measured with magnetic resonance imaging).

loss for some outcomes. Given the hepatic lipolytic effect of glucagon,[14] agonism of its receptor with survodutide may be relevant for persons with coexisting MASH (approximately one third of those with obesity[29]), as suggested by the improvements in hepatic markers in this trial and the reduction in MASH severity in a previous phase 2 trial.[30] Most studies of exercise and pharmacotherapies have not shown preferential targeting of visceral fat.[31] We speculate that the magnitude of reduction in visceral and liver fat in the subgroup of participants who underwent MRI in this trial may indicate beneficial effects of survodutide on body composition beyond weight loss — the 6.0-mg dose of survodutide appeared to be associated with greater reduction in liver fat than the 3.6-mg dose, although weight reduction was similar with the two doses. The magnitude of weight reduction itself, however, may additionally ameliorate obesity-related complications that are more dependent on weight loss.

The safety profile of survodutide in this trial appeared to be consistent with those of other obesity medications with GLP-1 receptor agonist activity, with gastrointestinal side effects in particular, which most commonly occurred soon after treatment initiation and were often mitigated with strategies such as slow, flexible dose escalation and treatment of symptoms.[32,33] Although flexibility to adjust dose was limited initially, greater flexibility was implemented with a protocol amendment late in the present trial; whether earlier implementation might have reduced gastrointestinal events and increased adherence to the trial regimen is unknown. Reported cardiovascular safety findings showed no adjudicated MACE with survodutide and only a modest increase in heart rate consistent with the known effects of this drug class, without associated clinically relevant QTcF prolongation. The ongoing SYNCHRONIZE-CVOT event-driven trial (ClinicalTrials.gov number, NCT06077864) aims to further characterize cardiovascular outcomes with survodutide.[34]

The present trial has several strengths and limitations. It included participants from several regions of the world, with approximately 32% of the participants identifying as non-White (although only 7% of the participants were Black and 22% were Asian, with some imbalance among the trial groups). In addition, 40.6% of the participants were men,[35] and men generally have less weight reduction than women with GLP-1 receptor agonists.[36]

Table 3. Adverse Events (Modified Intention-to-Treat Population).*

Event	Survodutide, 3.6 mg (N=241)	Survodutide, 6.0 mg (N=242)	Placebo (N=242)
	number of participants (percent)		
Any adverse event	232 (96.3)	236 (97.5)	208 (86.0)
Any serious adverse event	20 (8.3)	20 (8.3)	15 (6.2)
Any fatal adverse event	0	0	0
Adverse event leading to trial discontinuation	6 (2.5)	4 (1.7)	2 (0.8)
Adverse event leading to discontinuation of survodutide or placebo	57 (23.7)	60 (24.8)	13 (5.4)
Gastrointestinal adverse event	43 (17.8)	49 (20.2)	7 (2.9)
Adverse events occurring in ≥10% of the participants in any trial group†			
Nausea	147 (61.0)	157 (64.9)	42 (17.4)
Vomiting	98 (40.7)	108 (44.6)	15 (6.2)
Diarrhea	77 (32.0)	96 (39.7)	45 (18.6)
Constipation	75 (31.1)	79 (32.6)	30 (12.4)
Fatigue	45 (18.7)	36 (14.9)	21 (8.7)
Upper respiratory tract infection	40 (16.6)	31 (12.8)	29 (12.0)
Nasopharyngitis	31 (12.9)	27 (11.2)	33 (13.6)
Eructation	30 (12.4)	18 (7.4)	3 (1.2)
Dyspepsia	29 (12.0)	28 (11.6)	10 (4.1)
Decreased appetite	28 (11.6)	43 (17.8)	19 (7.9)
Gastroesophageal reflux disease	28 (11.6)	35 (14.5)	9 (3.7)
Headache	25 (10.4)	32 (13.2)	20 (8.3)
Dizziness	13 (5.4)	32 (13.2)	17 (7.0)
Events related to specific safety topics of interest			
Gastrointestinal disorder‡	195 (80.9)	217 (89.7)	116 (47.9)
Liver-related event§	13 (5.4)	10 (4.1)	14 (5.8)
Cholelithiasis†	3 (1.2)	5 (2.1)	1 (0.4)
Cholecystitis†	2 (0.8)	1 (0.4)	0
Hypersensitivity, including injection-site reactions§	19 (7.9)	18 (7.4)	18 (7.4)
Acute kidney injury†	1 (0.4)¶	1 (0.4)¶	0
Hypotension, including syncopal events§	5 (2.1)	18 (7.4)	4 (1.7)
Syncope†	5 (2.1)	4 (1.7)	2 (0.8)
Hypoglycemia§	3 (1.2)	2 (0.8)	1 (0.4)
Hyperglycemia§	2 (0.8)	4 (1.7)	14 (5.8)
Suicidal ideation or behavior§	1 (0.4)	0	0
Major depressive disorder§	8 (3.3)	6 (2.5)	12 (5.0)
Dysesthesia§	9 (3.7)	6 (2.5)	2 (0.8)
Adjudication-confirmed events‖			
5P-MACE**	0	0	1 (0.4)
Asymptomatic pancreatic hyperenzymemia	6 (2.5)	4 (1.7)	3 (1.2)

* Shown are numbers of adverse events that occurred during the treatment period (those events with onset on or after the date of the first dose of survodutide or placebo and up to 28 days after the last dose, which corresponds to the residual effect period for survodutide) in the modified intention-to-treat population, which included all the participants who had undergone randomization and received at least one dose of survodutide or placebo.

† Adverse events were coded according to the preferred terms in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 28.1.

‡ Events were tabulated on the basis of the system organ class in accordance with MedDRA, version 28.1.

§ Events were tabulated on the basis of grouped terms, which include nonserious events within the grouped terms.

¶ Acute kidney injury was stage 1 according to the Kidney Disease: Improving Global Outcomes classification system.

‖ No adjudication-confirmed cases of pancreatic cancer, medullary thyroid cancer, or acute pancreatitis were reported.

** A 5-point major adverse cardiac event (5P-MACE) was defined as nonfatal stroke, nonfatal myocardial infarction, death from cardiovascular causes, ischemia-related coronary revascularization, or hospitalization for heart failure.

Limitations include the lack of an active comparator, discontinuation of the trial regimen by a substantial percentage of the participants (which most likely drove the difference in results for the treatment-regimen estimand and the efficacy estimand), and the exclusion of persons with uncontrolled hypertension, recent cardiovascular events, or mood disorders that were not well controlled (e.g., unstable depression). Furthermore, weight reduction in the placebo group (mean, 5.4%) was much greater than the 2 to 3% anticipated on the basis of results from other trials,[11,13] a finding that possibly reflects participant access to obesity medications that were approved by the FDA or another applicable regulatory body or that were compounded.

In this trial, once-weekly survodutide led to significantly greater reductions in body weight than placebo in adults with obesity.

Supported by Boehringer Ingelheim.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the participants, site staff, and the members of the Boehringer Ingelheim trial team who were involved in the conduct of this trial; Ahmad Alhussein, Pharm.D., for critical review of an earlier version of the manuscript; and Giles Brooke, Ph.D. (of Envision Ignite, an Envision Medical Communications agency, a part of Envision Pharma Group), for medical writing and editorial assistance with an earlier version of the manuscript.

AUTHOR INFORMATION

Carel W. le Roux, M.B., Ch.B., Ph.D.,[1,2] Sean Wharton, M.D., Pharm.D.,[3,4] Elena Startseva, M.D.,[5] Isabel M. Kloer, M.D.,[5] Samina Ajaz Hussain, M.D.,[5] Anna Unseld, M.Sc.,[6] Biykem Bozkurt, M.D., Ph.D.,[7] Jamy D. Ard, M.D.,[8,9] Harold E. Bays, M.D.,[10] Pawel Bogdański, M.D., Ph.D.,[11] Elif I. Ekinci, M.B., B.S., Ph.D.,[12-15] Ania M. Jastreboff, M.D., Ph.D.,[16-18] Linong Ji, M.D.,[19,20] Wataru Ogawa, M.D., Ph.D.,[21,22] Sue D. Pedersen, M.D.,[23,24] Kirsi H. Pietiläinen, M.D., Ph.D.,[25,26] Naveed Sattar, M.B., Ch.B., Ph.D.,[27] Jochen Seufert, M.D., Ph.D.,[28] Kaj Stenlöf, M.D., Ph.D.,[29,30] André P. van Beek, M.D., Ph.D.,[31] Roman Vangoitsenhoven, M.D., Ph.D.,[32,33] Martina Brueckmann, M.D., Ph.D.,[5,34] Ramy Younes, M.D., Ph.D.,[5] and Lee M. Kaplan, M.D., Ph.D.[35,36]

[1] University College Dublin School of Medicine, Dublin; [2] Ulster University, Coleraine, United Kingdom; [3] McMaster University, Hamilton, ON, Canada; [4] University of Toronto, Toronto; [5] Boehringer Ingelheim International, Ingelheim am Rhein, Germany; [6] Boehringer Ingelheim Pharma, Biberach, Germany; [7] Winters Center for Heart Failure Research, Cardiovascular Research Institute, Baylor College of Medicine, Houston; [8] Department of Epidemiology and Prevention, Wake Forest School of Medicine, Winston-Salem, NC; [9] Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC; [10] Monroe Biomedical Research, Louisville Metabolic and Atherosclerosis Research Center, Louisville, KY; [11] Department of Obesity Treatment, Metabolic Disorders, and Clinical Dietetics, Poznan University of Medical Sciences, Poznan, Poland; [12] Australian Centre for Accelerating Diabetes Innovation (ACADI), University of Melbourne, Parkville, VIC, Australia; [13] Department of Medicine, Melbourne Medical School, University of Melbourne, Melbourne, VIC, Australia; [14] Centre for Research and Education in Diabetes and Obesity, Austin Health, Heidelberg, VIC, Australia; [15] Department of Endocrinology, Austin Health, Heidelberg, VIC, Australia; [16] Section of Endocrinology, Department of Internal Medicine, Yale School of Medicine, New Haven, CT; [17] Section of Endocrinology, Department of Pediatrics, Yale School of Medicine, New Haven, CT; [18] Yale Obesity Research Center (Y-Weight), Yale School of Medicine, New Haven, CT; [19] Department of Endocrinology and Metabolism, Peking University People's Hospital, Beijing; [20] Peking University Diabetes Center, Beijing; [21] Division of Diabetes and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan; [22] Section of Metabolic Disease, Division of Translational Research, Kobe University Graduate School of Medicine, Kobe, Japan; [23] C-ENDO Diabetes and Endocrinology Clinic, Calgary, AB, Canada; [24] University of Calgary, Calgary, AB, Canada; [25] Obesity Research Unit, Research Program for Clinical and Molecular Metabolism, Faculty of Medicine, University of Helsinki, Helsinki; [26] Healthy Weight Hub, Abdominal Center, Helsinki University Hospital, Helsinki; [27] School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, United Kingdom; [28] Division of Endocrinology and Diabetology, Department of Medicine II, Medical Center–University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg im Breisgau, Germany; [29] Center for Sleep and Wake Disorders, Institute of Medicine, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden; [30] Department of Internal Medicine, Carlanderska Hospital, Gothenburg, Sweden; [31] Department of Endocrinology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; [32] Clinical and Experimental Endocrinology, Department of Chronic Diseases and Metabolism, KU Leuven, Leuven, Belgium; [33] Department of Endocrinology, University Hospitals Leuven, Leuven, Belgium; [34] First Department of Medicine, Faculty of Medicine Mannheim, University of Heidelberg, Mannheim, Germany; [35] Obesity and Metabolism Institute, Boston; [36] Geisel School of Medicine at Dartmouth, Hanover, NH.

REFERENCES

1. Bray GA, Kim KK, Wilding JPH. Obesity: a chronic relapsing progressive disease process: a position statement of the World Obesity Federation. Obes Rev 2017;18:715-23.

2. Purnell JQ, le Roux CW. Hypothalamic control of body fat mass by food intake: the key to understanding why obesity should be treated as a disease. Diabetes Obes Metab 2024;26:Suppl 2:3-12.

3. GBD 2021 Adult BMI Collaborators. Global, regional, and national prevalence of adult overweight and obesity, 1990-2021, with forecasts to 2050: a forecasting study for the Global Burden of Disease Study 2021. Lancet 2025;405:813-38.

4. Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. Endocr Pract 2016;22:Suppl 3:1-203.

5. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

and the Obesity Society. J Am Coll Cardiol 2014;63:2985-3023.
6. McGowan B, Ciudin A, Baker JL, et al. Framework for the pharmacological treatment of obesity and its complications from the European Association for the Study of Obesity (EASO). Nat Med 2025; 31:3229-32.
7. American Diabetes Association Professional Practice Committee for Obesity. Pharmacologic treatment of obesity in adults: standards of care in overweight and obesity. BMJ Open Diabetes Res Care 2026;13:Suppl 1:e005729.
8. Ogawa W, Hirota Y, Miyazaki S, et al. Definition, criteria, and core concepts of guidelines for the management of obesity disease in Japan. Endocr J 2024;71:223-31.
9. Alexander L, Purnell JQ, Burridge K, et al. Joint TOS/OMA/OAC expert guidance statement on the pharmacological management of United States adults with overweight or obesity using the GRADE approach. Obesity (Silver Spring) 2026;34: 851-70.
10. Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of hormonal adaptations to weight loss. N Engl J Med 2011;365:1597-604.
11. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med 2021;384:989-1002.
12. Wharton S, Lingvay I, Bogdanski P, et al. Oral semaglutide at a dose of 25 mg in adults with overweight or obesity. N Engl J Med 2025;393:1077-87.
13. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med 2022; 387:205-16.
14. Müller TD, Finan B, Clemmensen C, DiMarchi RD, Tschöp MH. The new biology and pharmacology of glucagon. Physiol Rev 2017;97:721-66.
15. Kueh MTW, Chong MC, Miras AD, le Roux CW. Oxyntomodulin physiology and its therapeutic development in obesity and associated complications. J Physiol 2025;603:7683-93.
16. Zimmermann T, Thomas L, Baader-Pagler T, et al. BI 456906: discovery and preclinical pharmacology of a novel GCGR/GLP-1R dual agonist with robust anti-obesity efficacy. Mol Metab 2022;66: 101633.
17. Ji L, Jiang H, Bi Y, et al. Once-weekly mazdutide in Chinese adults with obesity or overweight. N Engl J Med 2025;392: 2215-25.
18. Shirley M. Mazdutide: first approval. Drugs 2025;85:1621-7.
19. le Roux CW, Steen O, Lucas KJ, Startseva E, Unseld A, Hennige AM. Glucagon and GLP-1 receptor dual agonist survodutide for obesity: a randomised, double-blind, placebo-controlled, dose-finding phase 2 trial. Lancet Diabetes Endocrinol 2024;12:162-73.
20. Blüher M, Rosenstock J, Hoefler J, Manuel R, Hennige AM. Dose-response effects on HbA_{1c} and bodyweight reduction of survodutide, a dual glucagon/GLP-1 receptor agonist, compared with placebo and open-label semaglutide in people with type 2 diabetes: a randomised clinical trial. Diabetologia 2024;67:470-82.
21. Jungnik A, Arrubla Martinez J, Plum-Mörschel L, et al. Phase I studies of the safety, tolerability, pharmacokinetics and pharmacodynamics of the dual glucagon receptor/glucagon-like peptide-1 receptor agonist BI 456906. Diabetes Obes Metab 2023;25:1011-23.
22. Wharton S, le Roux CW, Kosiborod MN, et al. Survodutide for treatment of obesity: rationale and design of two randomized phase 3 clinical trials (SYNCHRONIZE-1 and -2). Obesity (Silver Spring) 2025;33: 67-77.
23. Draft guidance for industry on developing products for weight management: availability. Fed Regist 2007;72(31):7441-2.
24. FDA Center for Drug Evaluation and Research. Obesity and overweight: developing drugs and biological products for weight reduction. Guidance document. January 2025 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/obesity-and-overweight-developing-drugs-and-biological-products-weight-reduction).
25. European Medicines Agency. Guideline on clinical evaluation of medicinal products used in weight management. January 1, 2017 (https://www.ema.europa.eu/en/clinical-evaluation-medicinal-products-used-weight-control-scientific-guideline).
26. Bushnell DM, Fung S, Brod M, et al. Development and validation of an eating behavior patient-reported outcome measure in people living with obesity or overweight. Obesity (Silver Spring) 2025;33: 1249-62.
27. European Medicines Agency. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. February 2020 (https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-and-sensitivity-analysis-clinical-trials-guideline-statistical-principles-clinical-trials-step-5_en.pdf).
28. Sattar N, Lee MMY. Estimating direct tissue effects versus weight loss effects of incretin-based drugs for obesity on various chronic conditions. Lancet Diabetes Endocrinol 2025;13:347-54.
29. Quek J, Chan KE, Wong ZY, et al. Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2023;8: 20-30.
30. Sanyal AJ, Bedossa P, Fraessdorf M, et al. A phase 2 randomized trial of survodutide in MASH and fibrosis. N Engl J Med 2024;391:311-9.
31. Rao S, Pandey A, Garg S, et al. Effect of exercise and pharmacological interventions on visceral adiposity: a systematic review and meta-analysis of long-term randomized controlled trials. Mayo Clin Proc 2019;94:211-24.
32. Wharton S, Davies M, Dicker D, et al. Managing the gastrointestinal side effects of GLP-1 receptor agonists in obesity: recommendations for clinical practice. Postgrad Med 2022;134:14-9.
33. Alhazmi A, le Roux CW. Do no harm: managing nausea and vomiting in GLP-1 based obesity therapies. Front Endocrinol (Lausanne) 2026;17:1788698.
34. Kosiborod MN, Platz E, Wharton S, et al. Survodutide for the treatment of obesity: rationale and design of the SYNCHRONIZE cardiovascular outcomes trial. JACC Heart Fail 2024;12:2101-9.
35. Moiz A, Filion KB, Toutounchi H, et al. Efficacy and safety of glucagon-like peptide-1 receptor agonists for weight loss among adults without diabetes: a systematic review of randomized controlled trials. Ann Intern Med 2025;178:199-217.
36. Alexander GC, Xiao X, Dilek S, et al. Heterogeneity of treatment effects of glucagon-like peptide-1 receptor agonists for weight loss in adults: a systematic review and meta-analysis. JAMA Intern Med 2026; 186:567-77.