



# Glucagon and GLP-1 receptor dual agonist survodutide for obesity: a randomised, double-blind, placebo-controlled, dose-finding phase 2 trial

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## Summary

**Background** Obesity is a widespread and chronic condition that requires long-term management; research into additional targets to improve treatment outcomes remains a priority. This study aimed to investigate the safety, tolerability, and efficacy of glucagon receptor–GLP-1 receptor dual agonist survodutide (BI 456906) in obesity management.

**Methods** In this randomised, double-blind, placebo-controlled, dose-finding phase 2 trial conducted in 43 centres in 12 countries, we enrolled participants (aged 18–75 years, BMI  $\geq 27$  kg/m<sup>2</sup>, without diabetes) and randomly assigned them by interactive response technology (1:1:1:1; stratified by sex) to subcutaneous survodutide (0.6, 2.4, 3.6, or 4.8 mg) or placebo once-weekly for 46 weeks (20 weeks dose escalation; 26 weeks dose maintenance). The primary endpoint was the percentage change in bodyweight from baseline to week 46. Primary analysis included the modified intention-to-treat population (defined as all randomly assigned patients who received at least one dose of trial medication and who had analysable data for at least one efficacy endpoint) and was based on the dose assigned at randomisation (planned treatment), including all data censored for COVID-19-related discontinuations; the sensitivity analysis was based on the actual dose received during maintenance phase (actual treatment) and included on-treatment data. Safety analysis included all participants who received at least one dose of study drug. The trial is registered with ClinicalTrials.gov (NCT04667377) and EudraCT (2020–002479–37).

**Findings** Between March 30, 2021, and Nov 11, 2021, we enrolled 387 participants; 386 (100%) participants were treated (0.6 mg, n=77; 2.4 mg, n=78; 3.6 mg, n=77; 4.8 mg, n=77; placebo n=77) and 233 (60.4%) of 386 completed the 46-week treatment period (187 [61%] of 309 receiving survodutide; 46 [60%] of 77 receiving placebo). When analysed according to planned treatment, mean (95% CI) changes in bodyweight from baseline to week 46 were –6.2% (–8.3 to –4.1; 0.6 mg); –12.5% (–14.5 to –10.5; 2.4 mg); –13.2% (–15.3 to –11.2; 3.6 mg); –14.9% (–16.9 to –13.0; 4.8 mg); –2.8% (–4.9 to –0.7; placebo). Adverse events occurred in 281 (91%) of 309 survodutide recipients and 58 (75%) of 77 placebo recipients; these were primarily gastrointestinal in 232 (75%) of 309 survodutide recipients and 32 (42%) of 77 placebo recipients.

**Interpretation** All tested survodutide doses were tolerated, and dose-dependently reduced bodyweight.

**Funding** Boehringer Ingelheim.

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## Introduction

Obesity is a chronic, relapsing, and progressive disease that requires long-term management.<sup>1,2</sup> Currently, lifestyle modifications remain the most common treatment modality.<sup>2</sup> However, if obesity is not managed effectively by lifestyle modifications alone then treatment with pharmacotherapy is recommended in individuals with a BMI of 27 kg/m<sup>2</sup> or greater in the presence of one or more concurrent conditions.<sup>2</sup> Bariatric surgery is an option for individuals with a BMI of 35 kg/m<sup>2</sup> or greater, or a BMI of 30 kg/m<sup>2</sup> or greater and type 2 diabetes.<sup>2,3</sup>

Currently, there are five pharmacological agents approved by the US Food and Drug Administration for the treatment of obesity, two of which are GLP-1 receptor agonists (semaglutide and liraglutide).<sup>2</sup> GLP-1 receptor agonists in

the efferent and satiety pathways in the brain alters energy homeostasis in favour of bodyweight loss, by reducing food intake and delaying gastric emptying, and improves glucose tolerance by stimulating insulin secretion.<sup>4,5</sup>

In phase 3 randomised controlled trials examining obesity, liraglutide 3.0 mg and semaglutide 2.4 mg showed sustained, clinically relevant reductions in bodyweight of up to 8.0% (*vs* 2.6% with placebo) following 56 weeks of treatment with liraglutide 3.0 mg and 14.9% (*vs* 2.4% with placebo) following 68 weeks of treatment with semaglutide 2.4 mg.<sup>6,7</sup> However, long-term treatment options are still required, with weight regain following treatment discontinuation remaining a key challenge with current therapies.<sup>8</sup> Therefore, research into additional targets for the treatment of obesity remains a priority.<sup>9</sup>

Lancet Diabetes Endocrinol

2024; 12: 162–73

Published Online

February 5, 2024

[https://doi.org/10.1016/S2213-8587\(23\)00356-X](https://doi.org/10.1016/S2213-8587(23)00356-X)

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## Research in context

### Evidence before this study

GLP-1 receptor agonists, such as liraglutide and semaglutide, have been approved for the treatment of obesity, promoting weight loss by altering energy homeostasis. Survodutide (BI 456906) is a glucagon receptor–GLP-1 receptor dual agonist currently being investigated as a treatment for obesity and non-alcoholic steatohepatitis.

We searched PubMed on July 4, 2023, for publications from the past 5 years, using the terms “obesity”, “glucagon-like peptide-1 receptor agonist”, “GLP-1 receptor agonist”, “glucagon receptor”, “bodyweight”, “body weight”, and “randomised clinical trial”.

Phase 3 trials of semaglutide 2.4 mg in participants with obesity without diabetes have reported bodyweight reductions from baseline of up to 14.9% (vs 2.4% with placebo) after 68 weeks. A number of agents with dual and triple mechanisms of action are now under investigation, as these have potential for enhanced therapeutic efficacy in the treatment of obesity.

### Added value of this study

In adults with BMI of 27 kg/m<sup>2</sup> or greater without diabetes, survodutide once weekly produced significant decreases in bodyweight versus placebo from baseline to week 46. Mean reductions in bodyweight were approximately 5 times greater

for participants receiving survodutide 4.8 mg versus placebo when analysed by planned treatment, and almost 7 times greater when analysed according to actual treatment. Furthermore, over half of the participants receiving survodutide 4.8 mg reached bodyweight reductions of 15% or more. The tolerability profile of survodutide was in line with what would be expected based on its mechanism of action, with participants most frequently reporting gastrointestinal adverse events.

### Implications of all the available evidence

Preclinical data and data from earlier phase trials have demonstrated clinically meaningful reductions in bodyweight. In this phase 2 clinical study, survodutide significantly reduced bodyweight relative to placebo. These results show the potential of survodutide to induce greater bodyweight loss than the approved GLP-1 receptor mono-agonist semaglutide. Survodutide appears to be a promising new anti-obesity treatment, and warrants further investigation in phase 3 trials. Survodutide could offer the potential for greater therapeutic efficacy compared with GLP-1 receptor agonism alone, and warrants further investigation in phase 3 trials.

Pharmacological agents targeting multiple pathological pathways that alter energy homeostasis might improve bodyweight loss efficacy versus currently approved GLP-1 receptor mono-agonists.<sup>9</sup> In a phase 3 trial in adults with obesity (n=2539), the glucose-dependent insulinotropic polypeptide–GLP-1 receptor dual agonist tirzepatide significantly reduced bodyweight relative to placebo (p<0.001). Following 72 weeks of once-weekly treatment, the mean percentage change from baseline in bodyweight ranged from –15.0% to –20.9% with tirzepatide (5–15 mg) versus –3.1% with placebo.<sup>10</sup>

Survodutide (BI 456906) is a glucagon receptor–GLP-1 receptor dual agonist derived from glucagon, with a C18 fatty diacid incorporated to enable once-weekly dosing.<sup>11</sup> Preclinical studies of survodutide showed that treatment reduced bodyweight in murine models to a greater extent than maximally effective semaglutide via simultaneous engagement of the glucagon receptor and GLP-1 receptor.<sup>11</sup> The improved efficacy of survodutide compared with semaglutide was partly attributed to increased energy expenditure, resulting from glucagon receptor agonism in the liver and adipose tissue to stimulate gluconeogenesis, glycogenolysis, and lipolysis,<sup>11–14</sup> in addition to reductions in gastric emptying and energy intake.<sup>11</sup> In a 16 week phase 2 study in adults with type 2 diabetes (n=413), treatment with survodutide at doses of up to 1.8 mg twice per week escalated over 5–9 weeks, produced greater mean (95% CI) bodyweight reductions than semaglutide 1.0 mg once weekly (survodutide, –8.7% [–10.1 to –7.3]; semaglutide,

–5.3% [–6.6 to –4.1]).<sup>15</sup> In a phase 1b study in adults with a BMI of 27–40 kg/m<sup>2</sup> (n=125), survodutide treatment escalated over 6 (Part A; n=80) or 16 (Part B; n=45) weeks resulted in mean bodyweight reductions of up to –6.7% at week 6 (survodutide 0.45 mg once daily; vs –0.9% with placebo) and –14.1% at week 16 (survodutide 2.4 mg once per week; vs –0.3% with placebo). These results highlight the potential of survodutide to induce greater bodyweight loss than approved GLP-1 receptor mono-agonists.<sup>16</sup>

Here, we report the results of a phase 2, randomised, dose-finding, double-blind, placebo-controlled, parallel-group trial of survodutide in adults with a BMI of 27 kg/m<sup>2</sup> or greater, which aimed to characterise the dose–response relationship of survodutide in obesity management to facilitate selection of the optimal dose for future phase 3 trials.

## Methods

### Study design and participants

We performed a multicentre, randomised, double-blind, parallel-group, and placebo-controlled phase 2 trials involving 43 sites in 12 countries (USA, Australia, Belgium, Canada, China, Germany, South Korea, Netherlands, New Zealand, Poland, Sweden, and UK). Clinical sites where the study was conducted comprised research units, dedicated weight management clinics, independent research units and university hospitals. The trial protocol was approved by the relevant Independent Ethics Committees or Institutional Review Boards for the

See Online for appendix

participating centres (appendix p 6). The trial was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice, applicable regulatory requirements, and standard operating procedures of the trial sponsor.

Participants were adults (aged  $\geq 18$  to  $< 75$  years) with a BMI of 27 kg/m<sup>2</sup> or greater, a stable bodyweight of 70 kg or greater (females) or 80 kg or greater (males), and with HbA<sub>1c</sub> less than 6.5% (without diabetes) at screening. Patients must have undergone at least one previous unsuccessful nonsurgical weight-loss attempt. A complete list of the inclusion and exclusion criteria is provided in the appendix (p 3). All participants provided written informed consent prior to participation in the trial.

### Randomisation and masking

After the assessment of all inclusion and exclusion criteria, eligible participants were randomly assigned by interactive response technology 1:1:1:1 (using a block size of 10) to receive survodutide (0.6, 2.4, 3.6, or 4.8 mg) or placebo; randomisation was stratified by sex. Randomisation lists were generated using a validated system involving a pseudorandom number generator. Access to the randomisation codes were kept restricted until final analysis. The trial was double blind; participants, investigators, central reviewers, and everyone involved in the trial conduct or analysis were blinded to the randomised treatment assignments until after database lock. Primary outcome assessors were blinded with respect to the study treatment. Participants in all dose groups received treatment (surdutide or placebo) in pre-filled syringes in a blinded manner with the solution looking similar for the active drug and the placebo.

### Procedures

Eligible participants were randomly assigned to receive subcutaneous survodutide (0.6, 2.4, 3.6, or 4.8 mg) or placebo once weekly for 46 weeks. Participants assigned to receive survodutide followed one of four dose-escalation schemes (appendix p 4). The treatment period comprised a 20-week rapid dose-escalation phase, with doses escalated every 2–4 weeks (fixed dosing, weeks 1 to 10; flexible dosing, weeks 11 to 20) followed by a 26-week dose-maintenance phase. For the first 10 weeks of dose escalation, all participants received treatment according to the dosing scheme assigned to them at randomisation, with no dose adjustments permitted (appendix p 4); between weeks 11 and 20, adjustments to the dosing scheme were allowed, in a blinded manner, based on the tolerance of gastrointestinal adverse events. Dosing was not flexible during the dose-maintenance phase (from week 21 until end of study), with all participants receiving one of the four planned survodutide doses (0.6, 2.4, 3.6, or 4.8 mg) or placebo. Participants who did not tolerate treatment due to gastrointestinal adverse events during

the dose-escalation phase did not continue titration to the next step, but had the option to receive a lower available survodutide dose and continue with the new scheme for the dose-maintenance phase. Participants who still did not tolerate treatment due to gastrointestinal adverse events, including at the lowest tested dose (0.6 mg), were discontinued from treatment.

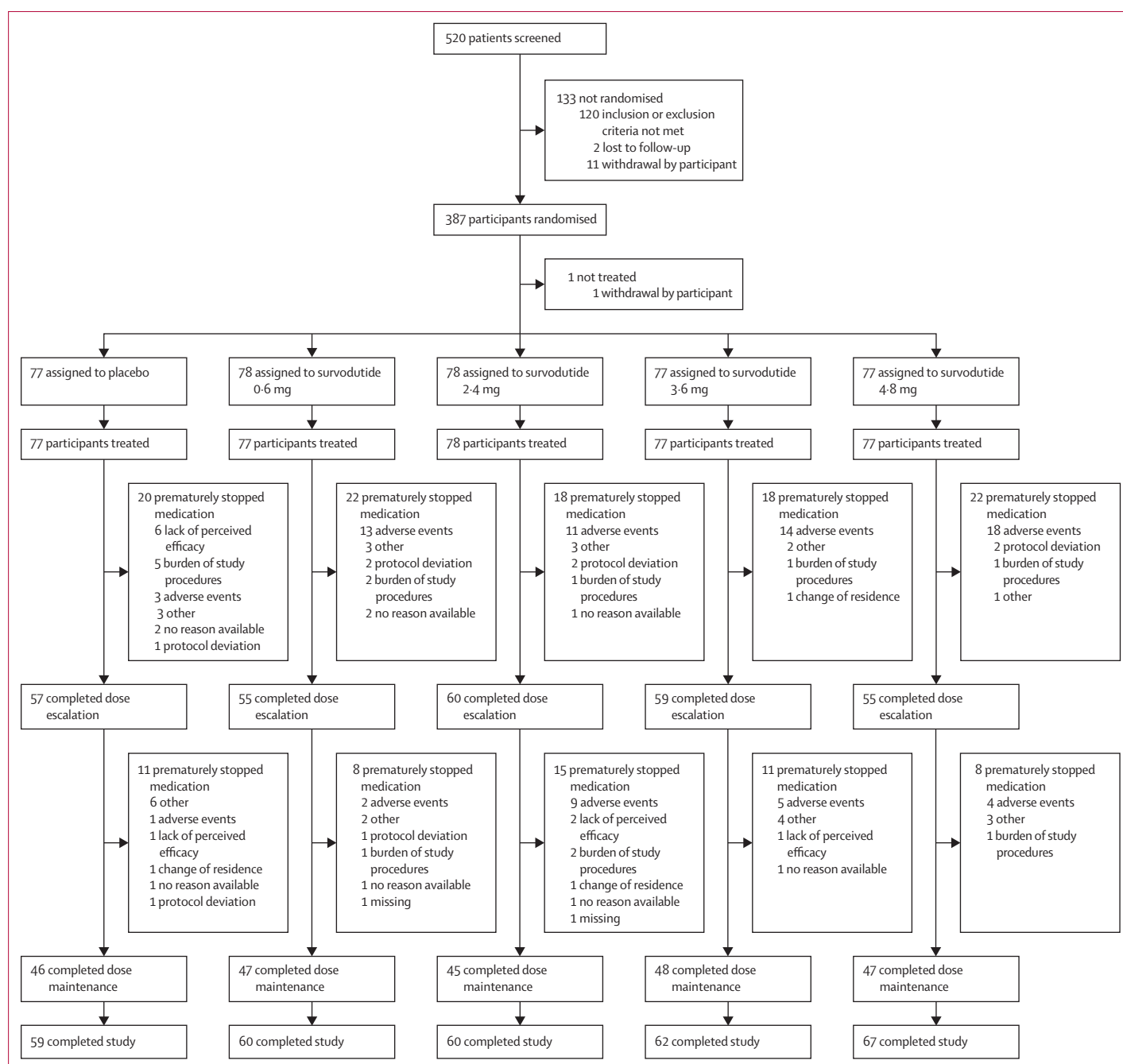
In addition to their assigned treatment or placebo, all participants received dietary and physical activity counselling (approximately 500 kcal/day energy deficit and 150–300 min per week of moderate-intensity aerobic and strength exercises) every 4 weeks between weeks 1 and 40, and at the end-of-treatment visit, by a dietician and site staff member, respectively. All participants who completed the treatment period had an end-of-treatment visit at week 46, followed by a 3-week follow-up period that ended in an end-of-study visit. If treatment was discontinued early, the end-of-treatment visit was conducted 7 days after administration of the last dose of survodutide or placebo. All efforts were made to conduct the week 46 visit for all participants, including those who discontinued treatment prematurely.

### Outcomes

The primary endpoint was the percentage change in bodyweight from baseline to week 46, assessed to characterise the dose–response relationship for survodutide. Secondary endpoints were the achievement of bodyweight reductions of 5% or greater, 10% or greater, and 15% or greater at week 46, and absolute changes in bodyweight, waist circumference, systolic blood pressure, and diastolic blood pressure from baseline to week 46. Bodyweight, waist circumference, and blood pressure were assessed at screening, baseline, and every visit (once every 2 weeks) to week 18; bodyweight and blood pressure were then assessed at weeks 20, 24, 28, 32, 36, 40, 46, and end-of-treatment, and waist circumference at weeks 24, 32, 40, 46, and end-of-treatment. Safety was assessed by the occurrence of adverse events and vital signs; adverse events were assessed from the signing of informed consent until the end of the study. Safety parameters were assessed at every visit (once every 2 weeks to week 20 then every 4 weeks to end-of-treatment), with a physical examination every other visit (every 4 weeks). Assessments of further exploratory endpoints are detailed in the appendix (p 2; effect on survodutide on levels of plasma triglyceride, cholesterol levels, HbA<sub>1c</sub>, glucagon, alanine aminotransferase concentrations, and change from baseline in BMI).

### Statistical analyses

Sample size calculation was performed using simulations in R software.<sup>17</sup> Based on an assumed placebo effect size of zero and a maximum effect size in the highest dose group of –10.0% (SD 7.0%<sup>18</sup>), a sample size of 70 participants per trial group gave 80% or greater probability of success



**Figure 1: Trial profile**

Completed study refers to patients who prematurely discontinued treatment but completed the week 46 visit.

for all assumed dose–response models. The maximum effect size of  $-10.0\%$  was not based on previous data but was considered a reasonable assumption at the time of trial design. An overall significance level of  $2.5\%$  (one-sided) for the contrast test of the null hypothesis of a flat dose–response was assumed.

The primary analysis of the primary endpoint was performed using the modified intention-to-treat population and based on the maintenance dose assigned to

participants at randomisation (planned treatment). The modified intention-to-treat population was defined as all randomly assigned participants who received at least one dose of trial treatment and who had analysable data (observed baseline and post-baseline value) for at least one efficacy endpoint. The primary analysis included all data (on-treatment and off-treatment) censored for COVID-19–related treatment discontinuations. Sensitivity analysis of the primary endpoint performed using the

	Survodutide dose group				Placebo (n=77)	Total (N=384)
	0.6 mg (n=77)	2.4 mg (n=78)	3.6 mg (n=76)	4.8 mg (n=76)		
Sex						
Female	51 (66%)	54 (69%)	51 (67%)	53 (70%)	53 (69%)	262 (68%)
Male	26 (34%)	24 (31%)	25 (33%)	23 (30%)	24 (31%)	122 (32%)
Age, years	48.6 (12.6)	49.0 (13.1)	50.3 (11.8)	47.6 (13.5)	50.0 (13.5)	49.1 (12.9)
Race						
White	59 (77%)	60 (77%)	63 (83%)	59 (78%)	60 (78%)	301 (78%)
Asian	8 (10%)	9 (12%)	9 (12%)	7 (9%)	7 (9%)	40 (10%)
Black or African American	10 (13%)	8 (10%)	3 (4%)	8 (11%)	8 (10%)	37 (10%)
Multiple	0	1 (1%)	1 (1%)	0	1 (1%)	3 (1%)
Native Hawaiian or Pacific Islander	0	0	0	1 (1%)	1 (1%)	2 (1%)
American Indian or Alaska Native	0	0	0	1 (1%)	0	1 (<1%)
BMI, kg/m <sup>2</sup>	37.8 (6.3)	37.6 (7.3)	37.0 (5.7)	37.6 (6.0)	35.8 (5.0)	37.1 (6.1)
Weight, kg	107.0 (18.7)	106.6 (23.0)	104.7 (19.6)	105.9 (17.4)	104.3 (23.0)	105.7 (20.4)
Waist circumference, cm	115.3 (13.4)	115.3 (17.0)	112.8 (13.9)	112.8 (13.0)	110.4 (14.6)	113.4 (14.5)
Systolic blood pressure, mm Hg	125.0 (13.4)	125.4 (13.3)	127.4 (13.2)	122.6 (12.3)	127.5 (14.2)	125.6 (13.4)
Diastolic blood pressure, mm Hg	80.5 (7.5)	80.7 (7.4)	81.8 (8.1)	80.8 (7.6)	82.4 (8.6)	81.3 (7.8)
Pulse rate, beats per minute	70.8 (9.4)	71.4 (10.1)	71.2 (9.6)	70.9 (9.0)	70.7 (9.4)	71.0 (9.5)

Modified intention-to-treat population. Data are mean (SD) or n (%).

**Table 1: Baseline characteristics**

modified intention-to-treat population was based on the actual dose per protocol that participants received during the dose-maintenance phase (actual treatment) and included on-treatment data only (collected from the date of administration of the first dose of survodutide or placebo until 28 days after the administration of the last dose of survodutide or placebo). A reduced dose could have been received by participants who did not tolerate treatment due to gastrointestinal adverse events during the dose-escalation phase. Furthermore, if the participant was known to have discontinued treatment during the dose-escalation phase, actual treatment was defined as the next planned maintenance dose up from the last dose taken before discontinuation. Analysis of continuous secondary endpoints was performed on the modified intention-to-treat population including on-treatment data.

For analysis of the primary endpoint, a mixed model for repeated measures was used to generate estimates of mean percentage changes from baseline in bodyweight at week 46 for each dose group. The mixed model for repeated measures analysis included a fixed effect for baseline bodyweight as a continuous covariate. Analysis of the dose–response relationship was performed using multiple comparison procedure and modelling (MCP-Mod) techniques. Adverse events were analysed in the treated set, comprising all randomly assigned participants who received at least one dose of trial treatment, and based on planned treatment; key safety analyses (eg, treatment discontinuations) were also performed based on actual treatment. Absolute change in bodyweight and waist circumference were analysed using a mixed model for repeated measures. The percentage of patients with

5% or greater or 10% or greater body weight loss from baseline to 16 weeks was analysed using logistic regression and descriptive statistics. Details on statistical analysis methods are provided in the appendix (p 2). A Data Monitoring Committee assessed the progress of the clinical trial, including an unblinded safety review at specified intervals, and a recommendation to the sponsor whether to continue, stop, or modify the trial.

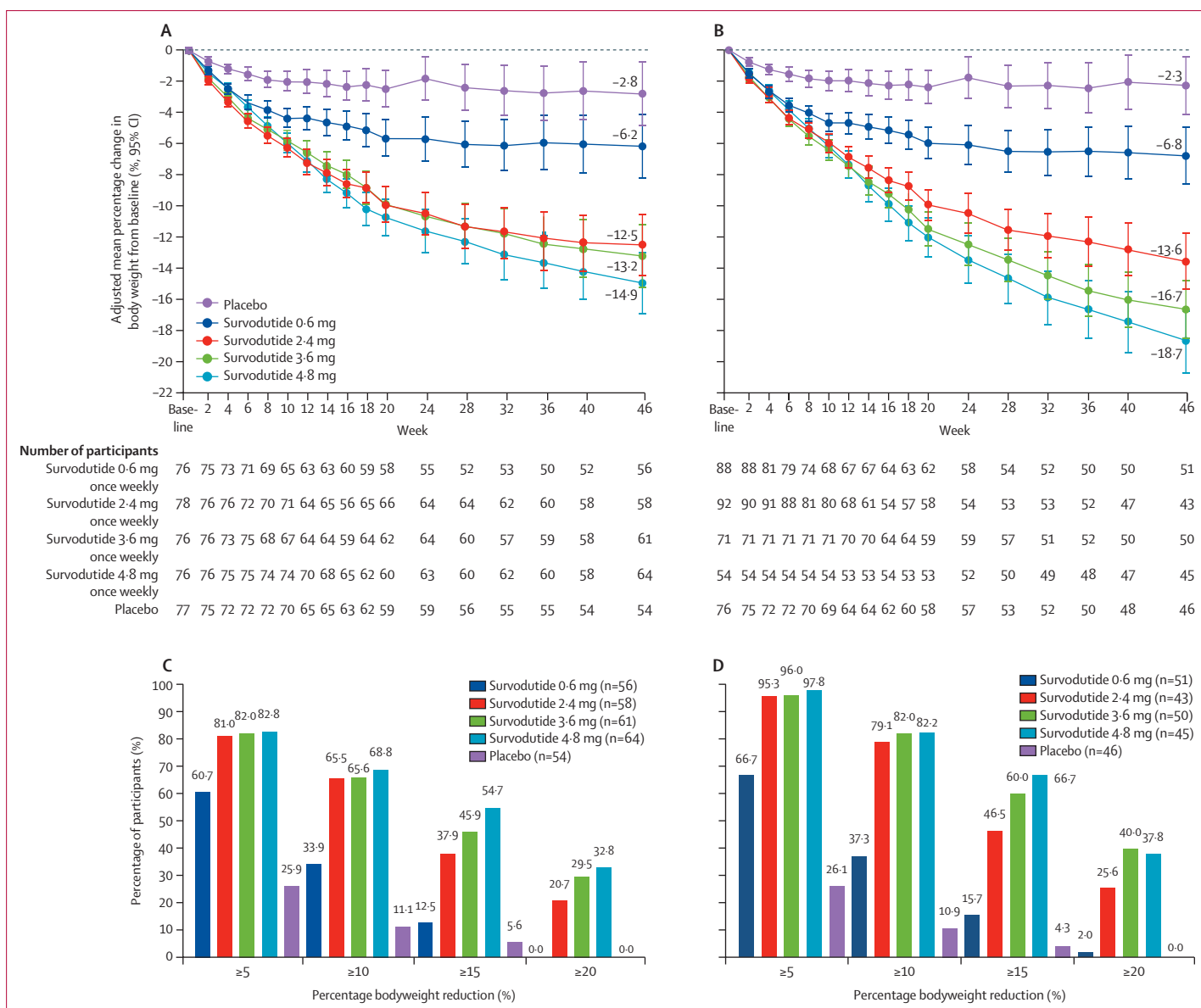
This trial is closed, completed, and registered with ClinicalTrials.gov (NCT04667377) and EudraCT (2020–002479–37).

### Role of the funding source

The funder was involved in the study design, data collection, and analysis, oversaw its conduct, monitored trial sites, and were given the opportunity to review this manuscript for medical and scientific accuracy, as well as intellectual property considerations. Investigators were responsible for the 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 funder.

### Results

Participants were recruited between March 8, 2021 and Nov 11, 2021; the last participant completed the trial on Oct 7, 2022. In total, 520 participants were screened for eligibility, and 387 participants were randomly assigned (approximately 77 per trial arm), of whom 386 received survodutide or matched placebo during the dose-escalation phase, and 286 during the dose-maintenance phase (approximately 57 per trial arm). Overall, 308 (80%) of



**Figure 2: Comparison of bodyweight parameters**

Change from baseline in bodyweight to week 46; mixed model for repeated measures estimates for percentage changes in bodyweight from baseline to week 46 according to planned treatment (A) and actual treatment received during the dose-maintenance phase (B; modified intention-to-treat population). Percentage of participants achieving 5% or more, 10% or more, 15% or more, and 20% or more bodyweight reductions over time according to planned treatment (C) and actual treatment received during the dose-maintenance phase (D; modified intention-to-treat population).

386 participants completed the trial, which included participants who prematurely discontinued the trial medication but completed the week 46 visit (249 [81%] of 309 receiving survodutide; 46 [77%] of 77 receiving placebo), with 233 (60%) of 386 completing the 46-week treatment period (187 [61%] of 309 receiving survodutide; 46 [60%] of 77 receiving placebo; figure 1). The treated set comprised 386 participants and the modified intention-to-treat population comprised 384 participants; two participants did not provide any post-baseline efficacy data. Analyses based on planned treatment and actual treatment were predefined for this trial. The majority of the participants

(92%) randomly assigned to the survodutide 2.4 mg dose received that same dose during the maintenance phase. In the highest survodutide dose group (4.8 mg), 70% of the participants received the maintenance dose as assigned at randomisation (appendix p 7).

Mean age at trial entry was 49.1 years (SD 12.9), approximately two-thirds of participants were female (n=262, 68%) and 301 (78%) of participants were White. Mean (SD) BMI was 37.1 kg/m<sup>2</sup> (6.1), waist circumference was 113.4 cm (14.5), systolic blood pressure was 125.6 mm Hg (13.4), and diastolic blood pressure was 81.3 mm Hg (7.8; table 1).

	Change from baseline to week 46					Comparison versus placebo			
	Survodutide 0.6 mg	Survodutide 2.4 mg	Survodutide 3.6 mg	Survodutide 4.8 mg	Placebo	Survodutide 0.6 mg	Survodutide 2.4 mg	Survodutide 3.6 mg	Survodutide 4.8 mg
<b>Planned treatment</b>									
Primary endpoint (all data), n/N	56/76	58/78	61/76	64/76	57/77	56/76	58/78	61/76	64/76
Bodyweight, %	-6.2 (-8.3 to -4.1)	-12.5 (-14.5 to -10.5)	-13.2 (-15.3 to -11.2)	-14.9 (-16.9 to -13.0)	-2.8 (-4.9 to -0.7)	-3.4 (-6.3 to -0.4)	-9.7 (-12.6 to -6.8)	-10.4 (-13.3 to -7.5)	-12.1 (-15.0 to -9.2)
p value	..	..	..	..	..	0.026	<0.0001	<0.0001	<0.0001
Secondary endpoints (on-treatment)	47/75	45/78	50/76	47/76	46/76	47/75	45/78	50/76	47/76
Bodyweight, kg	-7.2 (-9.3 to -5.1)	-14.8 (-16.8 to -12.7)	-15.6 (-17.7 to -13.6)	-18.5 (-20.5 to -16.4)	-2.7 (-4.7 to -0.6)	-4.5 (-7.4 to -1.6)	-12.1 (-14.9 to -9.2)	-13.0 (-15.9 to -10.1)	-15.8 (-18.7 to -12.9)
p value	..	..	..	..	..	0.0025	<0.0001	<0.0001	<0.0001
Waist circumference, cm	-8.3 (-10.7 to -5.9)	-15.0 (-17.4 to -12.6)	-15.0 (-17.3 to -12.6)	-16.0 (-18.4 to -13.7)	-4.0 (-6.3 to -1.6)	-4.4 (-7.7 to -1.0)	-11.0 (-14.4 to -7.7)	-11.0 (-14.3 to -7.7)	-12.1 (-15.4 to -8.7)
p value	..	..	..	..	..	0.012	<0.0001	<0.0001	<0.0001
Systolic blood pressure, mm Hg	-6.2 (-9.1 to -3.3)	-8.1 (-11.0 to -5.2)	-8.7 (-11.5 to -5.8)	-8.6 (-11.5 to -5.7; n=48)	-2.5 (-5.3 to 0.4; n=47)	-3.7 (-7.8 to 0.4)	-5.6 (-9.7 to -1.5)	-6.2 (-10.2 to -2.2)	-6.2 (-10.3 to -2.1)
p value	..	..	..	..	..	0.073	0.0072	0.0027	0.0033
Diastolic blood pressure, mm Hg	-3.3 (-5.1 to -1.5)	-4.4 (-6.1 to -2.6)	-4.3 (-6.0 to -2.6)	-4.8 (-6.6 to -3.1; n=48)	-1.9 (-3.6 to -0.1; n=47)	-1.4 (-3.9 to 1.1)	-2.5 (-5.0 to 0.0)	-2.4 (-4.9 to 0.0)	-2.9 (-5.4 to -0.5)
p value	..	..	..	..	..	0.257	0.050	0.051	0.020
<b>Actual treatment</b>									
Primary endpoint (on-treatment), n/N	51/88	43/92	50/71	45/54	46/76	51/88	43/92	50/71	45/54
Bodyweight, %	-6.8 (-8.7 to -5.0)	-13.6 (-15.4 to -11.7)	-16.7 (-18.6 to -14.8)	-18.7 (-20.8 to -16.6)	-2.3 (-4.2 to -0.4)	-4.6 (-7.2 to -1.9)	-11.3 (-14.0 to -8.7)	-14.4 (-17.1 to -11.7)	-16.4 (-19.3 to -13.6)
p value	..	..	..	..	..	0.0009	<0.0001	<0.0001	<0.0001
Secondary endpoints (on-treatment), n/N	51/88	43/92	50/71	45/54	46/76	51/88	43/92	50/71	45/54
Bodyweight, kg	-7.2 (-9.2 to -5.3)	-13.8 (-15.8 to -11.9)	-17.1 (-19.1 to -15.1)	-19.5 (-21.7 to -17.2)	-2.7 (-4.7 to -0.7)	-4.5 (-7.4 to -1.7)	-11.1 (-14.0 to -8.3)	-14.4 (-17.3 to -11.5)	-16.8 (-19.8 to -13.8)
p value	..	..	..	..	..	0.0018	<0.0001	<0.0001	<0.0001
Waist circumference, cm	-8.6 (-10.9 to -6.3)	-14.6 (-17.0 to -12.2)	-15.2 (-17.5 to -12.9)	-16.6 (-19.1 to -14.2)	-4.0 (-6.3 to -1.6)	-4.6 (-7.9 to -1.3)	-10.6 (-14.0 to -7.2)	-11.3 (-14.6 to -8.0)	-12.7 (-16.1 to -9.2)
p value	..	..	..	..	..	0.0061	<0.0001	<0.0001	<0.0001
Systolic blood pressure, mm Hg	-6.3 (-9.0 to -3.5)	-8.0 (-10.9 to -5.1)	-9.2 (-12.0 to -6.4)	-8.3 (-11.3 to -5.3; n=46)	-2.5 (-5.4 to 0.4; n=47)	-3.8 (-7.8 to 0.2)	-5.5 (-9.6 to -1.4)	-6.7 (-10.8 to -2.7)	-5.8 (-10.0 to -1.6)
p value	..	..	..	..	..	0.063	0.0086	0.0011	0.0066
Diastolic blood pressure, mm Hg	-3.4 (-5.1 to -1.8)	-4.4 (-6.2 to -2.6)	-4.3 (-6.0 to -2.5)	-4.7 (-6.5 to -2.9; n=46)	-1.9 (-3.6 to -0.1; n=47)	-1.6 (-4.0 to 0.9)	-2.5 (-5.0 to -0.0)	-2.4 (-4.8 to 0.1)	-2.8 (-5.4 to -0.3)
p value	..	..	..	..	..	0.20	0.048	0.056	0.028

Data are given as mean (95% CI), unless otherwise stated, for the modified intention-to-treat population. N numbers per dose group are given as n at week 46/n at baseline. No confirmatory hypothesis testing was performed. The p values reported are considered nominal. Planned treatment was defined as the maintenance dose assigned at randomisation, and included all data censored for COVID-19-related treatment discontinuations. Actual treatment was defined as the actual dose participants received during the dose maintenance phase, and included on-treatment data only.

Table 2: Mixed model for repeated measures estimates for the primary and secondary endpoints from baseline to week 46 by planned and actual treatment

The therapeutic effect of survodutide versus placebo was shown by a non-flat dose-response curve of percentage change in bodyweight from baseline to week 46, indicative of continued bodyweight loss. Significant bodyweight reductions were observed at all tested doses (0.6 mg, p=0.026; ≥2.4 mg, p<0.0001) compared with placebo (figure 2, table 2). When

participants were analysed according to the planned survodutide treatment, mean changes in bodyweight from baseline to week 46 (mixed model for repeated measures estimates) ranged from -6.2% (95% CI -8.3 to -4.1; survodutide 0.6 mg) to -14.9% (-16.9 to -13.0; survodutide 4.8 mg) versus -2.8% (-4.9 to -0.7) for placebo; this range increased to -6.8% (-8.7 to -5.0;

survodutide 0.6 mg) to  $-18.7\%$  ( $-20.8$  to  $-16.6$ ; survodutide 4.8 mg) when participants were analysed according to the actual treatment ( $-2.3\%$  [ $-4.2$  to  $-0.4$ ] for placebo).

At week 46, bodyweight losses of 5% or greater, 10% or greater, and 15% or greater were achieved by 53 (83%;  $\geq 5\%$  bodyweight loss), 44 (69%;  $\geq 10\%$  bodyweight loss), and 35 (55%;  $\geq 15\%$  bodyweight loss) of 64 participants who were randomly assigned to receive survodutide 4.8 mg, and by 14 (26%), six (11%), and three (6%) of 54 participants who were randomly assigned to placebo (planned treatment; figure 2C). Consistently, bodyweight losses were achieved by 44 (98%;  $\geq 5\%$  bodyweight loss), 37 (82%;  $\geq 10\%$  bodyweight loss), and 30 (67%;  $\geq 15\%$  bodyweight loss) of 45 participants who received survodutide 4.8 mg for the duration of the dose-maintenance phase, and 12 (26%), 5 (11%), and 2 (4%) of 46 participants who received placebo (actual treatment; figure 2D). Additionally, bodyweight reductions of 20% or greater were assessed at week 46. By planned treatment, up to one third of participants receiving survodutide 4.8 mg (21 [33%] of 64 participants) and 3.6 mg (18 [30%] of 61 participants) achieved bodyweight losses of 20% or more; this increased to 17 (38%) of 45 participants receiving survodutide 4.8 mg for the duration of the dose-maintenance phase (actual treatment), and 20 (40%) of 50 receiving survodutide 3.6 mg (figure 2). No participants receiving placebo achieved bodyweight reductions of 20% or more.

At week 46, all tested survodutide doses resulted in substantial absolute reductions in bodyweight and waist circumference from baseline, with greatest mean reductions observed in participants receiving survodutide 4.8 mg (95% CI  $-18.5$  kg [ $-20.5$  to  $-16.4$ ; bodyweight] and  $-16.0$  cm [ $-18.4$  to  $-13.7$ ; waist circumference]; placebo:  $-2.7$  kg [ $-4.7$  to  $-0.6$ ] and  $-4.0$  cm [ $-6.3$  to  $-1.6$ ]; planned treatment; table 2). Substantial reductions in blood pressure were also achieved at week 46; the greatest mean reductions were  $-8.7$  mm Hg (95% CI  $-11.5$  to  $-5.8$ ) for systolic blood pressure (with survodutide 3.6 mg; vs  $-2.5$  mm Hg [ $-5.3$  to  $0.4$ ] with placebo; planned treatment) and  $-4.8$  mm Hg ( $-6.6$  to  $-3.1$ ) for diastolic blood pressure (with survodutide 4.8 mg; vs  $-1.9$  mm Hg [ $-3.6$  to  $-0.1$ ] with placebo; planned treatment; table 2). When participants were analysed according to actual treatment received, greatest mean absolute reductions in bodyweight and waist circumference were observed at week 46 with survodutide 4.8 mg ( $-19.5$  kg [ $-21.7$  to  $-17.2$ ] and  $-16.6$  cm [ $-19.1$  to  $-14.2$ ]; placebo:  $-2.7$  kg [ $-4.7$ ,  $-0.7$ ] and  $-4.0$  cm [ $-6.3$  to  $-1.6$ ]; table 2). The mean reductions in blood pressure at week 46 by actual treatment were similar, if not slightly lower in the survodutide 4.8 mg group compared with planned treatment (systolic blood pressure,  $-8.3$  mm Hg [ $-11.3$  to  $-5.3$ ]; diastolic blood pressure,  $-4.7$  mm Hg [ $-6.5$  to  $-2.9$ ]; table 2).

Treatment with survodutide led to reductions in plasma triglyceride levels, VLDL, HbA<sub>1c</sub>, and alanine aminotransferase concentrations (appendix p 8). Changes from baseline in BMI and clinical obesity staging were consistent with the primary endpoint results, and no changes from baseline were observed in the use of anti-hypertensive and lipid-lowering medications. The changes from baseline in plasma glucagon and amino acids were consistent with target engagement of the glucagon receptor and GLP-1 receptor. Further exploratory results are described in the appendix (p 2).

The incidence of treatment-emergent adverse events was higher with survodutide (all doses pooled; 281 [91%] of 309 participants) compared with the placebo group (58 [75%] of 77 participants; table 3). However, the incidence of serious (defined in accordance with good clinical practice; assessed by the investigator as medically significant or requiring hospitalisation, or resulting in death, persistent disability, or is life threatening) treatment-emergent adverse events was lower among participants receiving survodutide than those receiving placebo (survodutide 13 [4%] of 309, placebo 5 [7%] of 77). Gastrointestinal disorders were the most common treatment-emergent adverse event, occurring in 232 [75%] of 309 participants receiving survodutide and 32 [42%] of 77 participants receiving placebo; these were primarily nausea (survodutide, 174 [56%] of 309 vs placebo, 15 [20%] of 77), vomiting (83 [27%] of 309 vs 4 [5%] of 77), diarrhoea (69 [22%] of 309 vs 8 [10%] of 77), and constipation (65 [21%] of 309 vs 4 [5%] of 77). There were no treatment-emergent adverse events of special interest (pancreatitis and hepatic injury), life-threatening treatment-emergent adverse events, or deaths in the trial. There was a higher rate of investigator-defined, drug-related adverse events in the survodutide group (77% of all dose groups,  $n=237/309$  [0.6 mg, 61%; 2.4 mg, 85%; 3.6 mg, 81%; 4.8 mg, 81%]) compared with the placebo group (38%,  $n=29/77$ ), mostly gastrointestinal-related adverse events. Serious drug-related adverse events were reported by two participants, one receiving survodutide 0.6 mg (nausea, vomiting, dehydration, and renal failure) and one receiving survodutide 3.6 mg (angioedema). No unexpected tolerability concerns were identified.

Adverse events led to treatment discontinuation in 76 (25%) of 309 participants receiving survodutide and three (4%) of 77 participants receiving placebo. These adverse events were most commonly gastrointestinal disorders (51 [67%] of 76 patients who discontinued survodutide due to adverse events; one [33%] of three patients that discontinued placebo due to adverse events) and occurred primarily during the rapid dose-escalation phase. In participants receiving survodutide, 56 (74%) of 76 discontinuations due to adverse events occurred during rapid dose-escalation (appendix p 10). When analysed by planned treatment, the proportion of participants discontinuing treatment due to adverse

	Placebo (n=77)	Survodutide dose group				Survodutide total (n=309)
		0.6 mg (n=77)	2.4 mg (n=78)	3.6 mg (n=77)	4.8 mg (n=77)	
Any treatment-emergent adverse event	58 (75%)	70 (91%)	70 (90%)	71 (92%)	70 (91%)	281 (91%)
Gastrointestinal disorders	32 (42%)	44 (57%)	67 (86%)	58 (75%)	63 (82%)	232 (75%)
Nausea*	15 (20%)	26 (34%)	51 (65%)	48 (62%)	49 (64%)	174 (56%)
Vomiting*	4 (5%)	7 (9%)	23 (30%)	26 (34%)	27 (35%)	83 (27%)
Diarrhoea*	8 (10%)	14 (18%)	22 (28%)	18 (23%)	15 (20%)	69 (22%)
Constipation*	4 (5%)	9 (12%)	17 (22%)	19 (25%)	20 (26%)	65 (21%)
Infections and infestations	33 (43%)	34 (44%)	29 (37%)	35 (46%)	33 (43%)	131 (42%)
Coronavirus disease (COVID-19)*	17 (22%)	16 (21%)	11 (14%)	16 (21%)	10 (13%)	53 (17.2%)
Leading to treatment discontinuation	3 (4%)	15 (20%)	20 (26%)	19 (25%)	22 (29%)	76 (25%)
Gastrointestinal disorders	1 (1%)	5 (7%)	13 (17%)	13 (17%)	20 (26%)	51 (17%)
Nausea†	0	3 (4%)	12 (15%)	8 (10%)	9 (12%)	11 (4%)
Vomiting†	0	1 (1%)	4 (5%)	9 (12%)	10 (13%)	24 (8%)
Infections and infestations	0	4 (5%)	3 (4%)	3 (4%)	1 (1%)	11 (4%)
Coronavirus disease (COVID-19)†	0	4 (5%)	2 (3%)	2 (3%)	1 (1%)	9 (3%)
Serious‡	5 (7%)	1 (1%)	2 (3%)	6 (8%)	4 (5%)	13 (4%)
Requiring or prolonging hospitalisation	4 (5%)	0	1 (1%)	3 (4%)	4 (5%)	8 (3%)
Other medically important serious event	1 (1%)	1 (1%)	1 (1%)	3 (4%)	0	5 (2%)
Life-threatening	0	0	0	0	0	0
Leading to death	0	0	0	0	0	0
Investigator defined, drug related	29 (38%)	47 (61%)	66 (85%)	62 (81%)	62 (81%)	237 (77%)
Serious‡	0	0	0	2 (3%)	0	2 (1%)

Data are n (%). Safety was analysed in the treated set, comprising all randomised participants who received at least one dose of trial treatment, and based on planned treatment. \*Treatment-emergent adverse events listed according to Medical Dictionary for Regulatory Activities preferred term occurred in 20% or more participants in any one study group. †Treatment-emergent adverse events leading to treatment discontinuation events listed according to Medical Dictionary for Regulatory Activities preferred term occurred in 5% or more participants in any one study group. ‡Assessed by the investigator based on pre-defined definition of serious adverse events.

**Table 3: Summary of treatment-emergent adverse events**

events was highest in the survodutide 4.8 mg group compared with the other dose groups (4.8 mg, 22 [29%] of 77; 0.6 mg, 15 [20%] of 77; 2.4 mg, 20 [26%] of 78; 3.6 mg, 19 [25%] of 77). However, when analysed by actual treatment received, less than 10% of participants in the survodutide 4.8 mg group reported adverse events leading to treatment discontinuation (n=5/54, 9.3%; appendix p 11). The difference here is due to discontinuations mostly occurring during the dose-escalation phase, before the maintenance dose of 4.8 mg was reached, but still being reported with the 4.8 mg dose when analysed by planned treatment. In participants receiving 4.8 mg survodutide, 18 of 22 discontinuations due to adverse events occurred during the rapid dose escalation phase (figure 1).

The mean heart rate was higher on average in participants receiving survodutide than those receiving placebo (appendix p 14). At week 46, the mean increase in heart rate from baseline was 2.7 (SD 9.1) bpm for survodutide (all doses pooled) and 0.1 (7.1) bpm for placebo; the mean increases from baseline did not exceed 10 bpm in any survodutide dose groups for the duration of the trial.

## Discussion

In this phase 2 trial, all tested survodutide doses significantly reduced bodyweight in a dose-dependent manner relative to placebo in participants with a BMI of 27 kg/m<sup>2</sup> or greater (0.6 mg, p=0.026; ≥2.4 mg, p<0.0001). Survodutide doses 2.4 mg or greater resulted in substantial, clinically relevant bodyweight losses of 5%<sup>19</sup> or more in over half of participants within 8 weeks of treatment initiation. The effect of survodutide on bodyweight was sustained throughout the treatment period. According to the planned treatment, participants receiving survodutide reached a maximum mean bodyweight reduction from baseline of -14.9% at week 46, which increased to -18.7% when participants were analysed according to the actual treatment dose received. This corresponded to absolute bodyweight reductions of up to -19.5 kg with survodutide 4.8 mg (actual treatment, on-treatment data only) and -18.5 kg (planned treatment).

In a study of the GLP-1 receptor agonist semaglutide (2.4 mg weekly), mean changes in bodyweight after 68 weeks of treatment received reached up to -16.9% (vs -2.4% with placebo) for the trial product estimand.<sup>8</sup> This

shows the potential enhanced bodyweight lowering efficacy of targeting both glucagon receptor and GLP-1 receptor with survodutide. Furthermore, the proportion of participants receiving survodutide 4.8 mg who reached clinically significant bodyweight reductions of 5% or greater, 10% or greater, and 15% or greater at week 46 (actual on-treatment: 97.8% [ $\geq 5\%$ ], 82.2% [ $\geq 10\%$ ], and 66.7% [ $\geq 15\%$ ]) was numerically greater in the current study compared with those seen following 68 weeks treatment with semaglutide (on-treatment: 92.4%, 74.8%, and 54.8%).<sup>8</sup> In the current study, up to 40% of participants (3.6 mg) in the actual treatment set, also achieved at least 20% bodyweight reduction, a greater proportion than that seen in the phase 3 semaglutide study (34.8%).<sup>8</sup> As the dose–response curves in the current phase 2 trial suggest that participant bodyweight loss did not reach a plateau at week 46, it is possible that further bodyweight reductions might be seen in the phase 3 survodutide trials with longer treatment durations.

The potential for increased bodyweight lowering efficacy has been investigated with other glucagon receptor–GLP-1 receptor dual agonists, such as NN1177, which was discontinued following safety concerns associated with treatment.<sup>20</sup> Across three phase 1 trials, treatment with NN1177 showed bodyweight decreases of up to 12.6% (NN1177 4200  $\mu\text{g}$ ), but was accompanied by increases in heart rate, inflammatory markers, and liver enzymes (eg, alanine transaminase), and decreases in glucose tolerance and levels of most amino acids to below the lower limit of normal.<sup>20</sup> Despite the similar mode of action of survodutide and NN1177, these safety signals were not observed with survodutide treatment. Furthermore, previous studies of survodutide have shown improvements in glucose tolerance and decreases in HbA<sub>1c</sub> in participants with type 2 diabetes.<sup>15</sup> The disparities observed between these treatments is likely due to differences in target engagement, with NN1177 showing a receptor ratio of approximately 1:3 compared with a ratio of 1:8 for survodutide.<sup>11,20</sup> This suggests that the balance of receptor ratios of survodutide may be more favourable for a glucagon receptor–GLP-1 receptor agonist in clinical development.

In a recent phase 2 study of the glucose-dependent insulinotropic polypeptide/GLP-1 receptor/glucagon receptor triple agonist retatrutide, participants receiving the highest dose (12 mg) achieved a mean weight loss of –24.2% after 48 weeks of treatment, with 83% of participants achieving at least 15% weight loss.<sup>21</sup> These results exemplify the potential for therapies targeting multiple pathways to have improved efficacy over current GLP-1 receptor agonists.<sup>9</sup> Treatments promoting weight loss of this magnitude are likely required for people with class III obesity (a BMI of 40 or greater) or those who need substantial weight loss to improve the complications of obesity.

In people with obesity, hypertension and hypercholesterolaemia are associated with an increased risk of cardiovascular disease.<sup>22</sup> In this trial, survodutide treatment substantially reduced systolic and diastolic blood pressure, and other cardiovascular risk factors in adults with a BMI of 27 kg/m<sup>2</sup> or greater. GLP-1 receptor agonists are known to provide cardiovascular benefits, particularly in patients with type 2 diabetes.<sup>23</sup> Multiple cardiovascular outcome trials have been performed for GLP-1 receptor agonists, with reductions in three-point major adverse cardiovascular events observed for liraglutide,<sup>24</sup> semaglutide,<sup>25</sup> albiglutide,<sup>26</sup> dulaglutide,<sup>27</sup> and efpeglenatide,<sup>28</sup> when tested in people with obesity and type 2 diabetes. The phase 3 trials of liraglutide and semaglutide in obesity have shown reductions in blood pressure;<sup>6,7</sup> however, few trials directly assessing cardiovascular outcomes have been performed in people with obesity without diabetes. The recently published results of the SELECT study examining semaglutide 2.4 mg in people with obesity with pre-existing cardiovascular disease found that semaglutide was superior to placebo in reducing incidence of major adverse cardiovascular events.<sup>29</sup>

The tolerability profile of survodutide was similar to that of GLP-1 receptor mono-agonists and glucose-dependent insulinotropic polypeptide–GLP-1 receptor dual agonists, with gastrointestinal disorders being the most frequent drug-related adverse events.<sup>7,10</sup> Treatment discontinuation due to adverse events was more frequent in participants receiving survodutide than those receiving placebo. These were most frequent in the first 10 weeks of the trial, coinciding with the initial part of the dose escalation phase. The dose-escalation schemes used in this trial were rapid, with dose increases mostly occurring up to every 2 weeks. Although treatment discontinuations in this trial occurred at a higher rate than seen in phase 3 trials of GLP-1 receptor mono-agonists and glucose-dependent insulinotropic polypeptide–GLP-1 receptor dual agonists,<sup>7,10</sup> the differences in study design and duration between the current phase 2 trial and phase 3 trials means that direct comparisons are not possible. For example, in the phase 3 trials, dose escalations occurred every 4 weeks due to the increased length of the trials (68 and 72 weeks, respectively), while faster escalations were done in the current phase 2 trial, which could explain the differences observed.<sup>7,10</sup> This suggests that adjustments to the dose-escalation phase in future studies might help to minimise rates of treatment discontinuation. In addition, when analysed by actual treatment, the discontinuation rate in the highest survodutide dose group (4.8 mg) was in line with the rates seen in phase 3 trials of other incretin agonists<sup>7,10</sup> and lower than observed with the highest dose of retatrutide (9.3% vs 16.1%).<sup>21</sup> This suggests that in participants who reach the target maintenance dose of 4.8 mg survodutide, the discontinuation rate is similar to other GLP-1 receptor-based therapies. Overall, no unexpected tolerability concerns were identified.

There are several limitations that should be considered when interpreting these results. The relatively short duration of this phase 2 trial did not permit long term assessment of efficacy, safety, and outcomes; thus, phase 3 studies are planned to evaluate the long-term effects of survodutide. Obesity is a chronic and progressive disease that requires long-term management,<sup>1,2</sup> and therefore long-term assessments of potential pharmacotherapies are required. The STEP 5 trial of semaglutide 2.4 mg assessed the effects of treatment over 2 years in participants with obesity, showing that weight loss of up to -15.2% was sustained over longer treatment periods, provided the medications were continued.<sup>30</sup> An extension of the STEP 1 phase 3 trial of semaglutide 2.4 mg showed that participants regained two-thirds of their previous weight loss 1 year after treatment withdrawal, and weight regain had not reached a plateau at the end of the observation period.<sup>30</sup> This effect reversal was also observed for the cardiometabolic improvements seen with 68 weeks' treatment, proving the chronicity of obesity.<sup>8</sup>

Other limitations include the fact that participants with complications associated with obesity, such as diabetes or non-alcoholic steatohepatitis, were excluded from the current trial; therefore, the efficacy of survodutide in people with these conditions requires further investigation. In addition, 78% of participants in this trial were White and 68% were female; increased diversity of the trial population will be a focus in future studies. The results from this phase 2 trial build upon the existing positive evidence for GLP-1 receptor agonism in the treatment of obesity, and highlight the potential for improved treatment efficacy through the use of glucagon receptor–GLP-1 receptor dual agonism. Survodutide appears to be a promising new anti-obesity treatment and warrants further investigation in phase 3 trials.

#### Contributors

AMH and CIR designed the trial. OS and KJL were trial investigators and enrolled participants. AU, ES, and CIR analysed the data. AMH, AU, ES, and CIR interpreted the data. AU and ES accessed and verified the underlying manuscript data. This article was drafted under the guidance of the authors, with medical writing and editorial support paid for by the funder. All authors were permitted access to the study data, contributed to manuscript writing (assisted by a medical writer paid for by the funder), approved the final version of the manuscript, and vouch for data accuracy and fidelity to the protocol.

#### Declaration of interests

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE) and did not receive payment related to the development of this manuscript. CIR has received personal fees from Boehringer Ingelheim, Eli Lilly, GI Dynamics, Gila Pharmaceuticals, Herbalife, Johnson & Johnson, Keyron, Novo Nordisk, and Zealand Pharma outside the submitted work. OS has received research support from Alnylam, Anji, AstraZeneca, Boehringer Ingelheim, CRISPR Therapeutics, Eli Lilly, Gilead, Janssen, Kowa, Medicigo, Moderna, Novartis, Novo Nordisk, Pfizer, Sanofi, ViaCyte, and Zucara Therapeutics; speaker bureau fees from Amgen, AstraZeneca, Bausch Health, HLS Therapeutics, Janssen, LMC, Novo Nordisk, and Sanofi; and consultancy fees from Amgen,

Bayer, Eli Lilly, Novo Nordisk, and Sanofi. ES, AMH, and AU are employees of Boehringer Ingelheim. KJL declares no competing interests.

#### Data sharing

To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data after publication of the primary manuscript and secondary analyses in peer-reviewed journals and regulatory and reimbursement activities are completed, normally within 1 year after the marketing application has been granted by major Regulatory Authorities. Researchers should use the <https://vivli.org/> link to request access to study data, and visit <https://www.mystudywindow.com/msw/datasharing> for further information.

#### Acknowledgments

The authors would like to acknowledge the contributions of Michele Brun (clinical trial lead, Boehringer Ingelheim) and Robert Toorawa (trial statistician, Boehringer Ingelheim) to this study. The authors thank the study participants, and the investigators and study site staff who contributed to the study. Medical writing support in the preparation of this manuscript was provided by Susie Eaton, and Anna Wydra, of Callisto, OPEN Health Communications (London, UK), and was funded by Boehringer Ingelheim. Survodutide was co-invented with Zealand Pharma. Under the terms of the glucagon/GLP-1 licensing agreement, Boehringer Ingelheim funds all research, development, and commercialisation activities.

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