Once-weekly cagrilintide for weight management in people with overweight and obesity: a multicentre, randomised, double-blind, placebo-controlled and active-controlled, dose-finding phase 2 trial

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Summary

Background Natural amylin is a pancreatic hormone that induces satiety. Cagrilintide is a long-acting amylin analogue under investigation for weight management. We assessed the dose–response relationship of cagrilintide regarding the effects on bodyweight, safety, and tolerability.

Methods We conducted a multicentre, randomised, double-blind, placebo-controlled and active-controlled, dose-finding phase 2 trial at 57 sites including hospitals, specialist clinics, and primary care centres in ten countries (Canada, Denmark, Finland, Ireland, Japan, Poland, Serbia, South Africa, the UK, and the USA). Eligible participants were adults aged at least 18 years without diabetes, with a body-mass index of at least 30 kg/m² or at least 27 kg/m² with hypertension or dyslipidaemia. Participants were randomly assigned (6:1) to subcutaneous self-injections of once-weekly cagrilintide (0·3, 0·6, 1·2, 2·4, or 4·5 mg), once-daily liraglutide 3·0 mg, or volume-matched placebo (for six placebo groups). The trial had a 26-week treatment period, including a dose-escalation period of up to 6 weeks, and a 6-week follow-up period without treatment. Participants and investigators were masked to the assigned study treatment with respect to active versus pooled placebo treatment, but not to different active treatments. The primary endpoint was the percentage change in bodyweight from baseline to week 26, assessed in all randomly assigned participants according to the trial product estimand (assuming all participants were adherent to treatment) and to the treatment policy estimand (regardless of adherence to treatment). Safety was assessed in all participants who received at least one dose of randomised treatment. This trial is registered with ClinicalTrials.gov, NCT03856047, and is closed to new participants.

Findings Between March 1 and Aug 19, 2019, we randomly assigned 706 participants to cagrilintide 0·3–4·5 mg (100–102 per dose group), 99 to liraglutide 3·0 mg, and 101 to placebo. Permanent treatment discontinuation (n=73 [10%]) occurred similarly across treatment groups, mostly due to adverse events (n=30 [4%]). In total, 29 participants (4%) withdrew from the trial. According to the trial product estimand, mean percentage weight reductions from baseline were greater with all doses of cagrilintide (0·3–4·5 mg, 6·0%–10·8% [6·4–11·5 kg]) versus placebo (3·0% [3·3 kg]; estimated treatment difference range 3·0%–7·8%; p<0·001). Weight reductions were also greater with cagrilintide 4·5 mg versus liraglutide 3·0 mg (10·8% [11·5 kg] *vs* 9·0% [9·6 kg]; estimated treatment difference 1·8%, p=0·03). Similar weight loss reductions were observed with the treatment policy estimand. The most frequent adverse events were gastrointestinal disorders (eg, nausea, constipation, and diarrhoea) and administration-site reactions. More participants receiving cagrilintide 0·3–4·5 mg had gastrointestinal adverse events compared with placebo (41%–63% *vs* 32%), primarily nausea (20%–47% *vs* 18%).

Interpretation Treatment with cagrilintide in people with overweight and obesity led to significant reductions in bodyweight and was well tolerated. The findings support the development of molecules with novel mechanisms of action for weight management.

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Introduction

Obesity is a prevalent, complex, progressive chronic condition associated with an increased risk of long-term complications, including type 2 diabetes, cancer, hypertension, and cardiovascular disease, which decrease quality of life and life expectancy.[1] Additionally, obesity increases the risk of severe outcomes related to COVID-19, including hospitalisation, admission to an intensive care unit, and mortality.[2]

Modest weight loss of 5–10% is associated with health benefits in individuals with overweight or obesity, reducing the risk of type 2 diabetes and cardiometabolic

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Research in context

Evidence before this study

We did a PubMed search for relevant articles published from January, 2011, to March, 2021, including the search terms "obesity", "anti-obesity", "pharmacotherapy", "weight management", "weight loss", "amylin analogue", and "glucagon-like peptide-1 receptor agonist". Our literature review confirmed the few approved pharmacotherapies currently available for the treatment of obesity.

Added value of this study

This is the first study to investigate the effect of ascending doses of cagrilintide for weight management. Before this study, cagrilintide was shown to promote weight loss in a dose-dependent manner in preclinical studies and one clinical trial. This study compared the effect of cagrilintide with placebo and liraglutide 3·0 mg, a GLP-1 receptor agonist approved for weight management. Using the trial product estimand, cagrilintide led to greater weight loss at all doses (0·3–4·5 mg) versus placebo (estimated treatment difference range: −3·0% [−3·0 kg] to −7·8% [−8·2 kg]), and greater weight loss with cagrilintide 4·5 mg dose versus liraglutide 3·0 mg (estimated treatment difference: −1·8% [−1·9 kg])

Implications of all the available evidence

Our study provides evidence that cagrilintide led to clinically significant, dose-dependent weight loss that was greater with cagrilintide at all doses versus placebo and greater with cagrilintide 4·5 mg versus liraglutide 3·0 mg. In participants with overweight and obesity, treatment with cagrilintide was well tolerated at all tested doses. The data from this study support the further clinical development of cagrilintide for weight management.

disease.[3,4] Greater weight loss (≥10%) is often required to improve some obesity-related complications, including obstructive sleep apnoea and osteoarthritis of the knee.[5]

Most guidelines for chronic weight management recommend a step-wise approach that starts with lifestyle interventions, followed by adjunct pharmacotherapy if sufficient weight loss is not achieved.[5] Despite the prevalence of obesity worldwide and the associated risk of complications, few approved pharmacotherapy options for weight management are available, and these have modest efficacy (3–9% weight loss relative to placebo at 1 year).[6,7] Results from the global phase 3 Semaglutide Treatment Effect in People with Obesity (STEP) trial programme[8–10] showed significant weight losses with the new-generation GLP-1 receptor agonist semaglutide 2·4 mg in people with overweight or obesity, and its use for weight management was approved by the US Food & Drug Administration in June, 2021. However, given the heterogeneity of obesity as a disease and the differential response to treatment, exploring novel molecules with different mechanisms of action is of interest, and might provide effective therapeutic options for its treatment.

See Online for appendix

Amylin is a pancreatic β-cell hormone that is co-secreted with insulin in response to nutrient intake. It functions as a satiety signal, acting upon homoeostatic and hedonic brain regions,[11] slows gastric emptying, and suppresses the post-prandial glucagon response to meals.[12] Amylin operates in the area postrema and nucleus of the solitary tract in the hindbrain to regulate appetite and induce satiety, and is thought to regulate food choices through receptors located in the hypothalamus, ventral tegmental area, and laterodorsal tegmental nucleus.[11] Cagrilintide is a long-acting, acylated amylin analogue with high homology to natural amylin that reduces food intake and bodyweight in a dose-dependent manner.[13–15]

This study assessed the dose–response relationship of cagrilintide regarding the effects on bodyweight, safety, and tolerability of ascending doses of subcutaneous cagrilintide once weekly in participants with overweight or obesity, to determine the optimal dose for weight management. In addition to weight, changes in waist circumference and cardiometabolic parameters with cagrilintide were compared with placebo and the GLP-1 receptor agonist, liraglutide 3·0 mg, which is approved for weight management.[16,17]

Methods

Study design and participants

We conducted a multicentre, randomised, double-blind, placebo-controlled and active-controlled, dose-finding, phase 2 trial at 57 sites including hospitals, specialist clinics, and primary care centres in ten countries (Canada, Denmark, Finland, Ireland, Japan, Poland, Serbia, South Africa, the UK, and the USA). The trial had a 26-week treatment period, including a dose-escalation period of up to 6 weeks, and a 6-week follow-up period without treatment (week 32; appendix p 9).

The protocol and statistical analysis plan were designed by the sponsor (Novo Nordisk) and are available with the full text of this article. The protocol and amendments were approved by the relevant institutional review boards or independent ethics committees for all participating sites.

Eligible participants were male and female adults of non-childbearing potential (ie, postmenopausal, or premenopausal with documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or bilateral tubal ligation), aged at least 18 years, with a body-mass index of at least 30·0 kg/m², or at least 27·0 kg/m² with hypertension or dyslipidaemia. Key exclusion criteria were the presence or history of diabetes (glycated haemoglobin [HbA_{1c}] ≥6·5% [48 mmol/mol]) and

previous or planned obesity treatment with surgery or a weight loss device (except for devices removed or liposuction or abdominoplasty performed more than 1 year before screening). Full eligibility criteria are in the appendix (pp 2–3). All participants provided written informed consent.

Randomisation and masking

Participants were randomly assigned (6:1) to subcutaneous injections of once-weekly cagrilintide (0·3, 0·6, 1·2, 2·4, or 4·5 mg), once-daily liraglutide 3·0 mg, or volume-matched placebo (for six placebo groups). The randomisation was performed using an interactive web response system and on-demand allocation. Participants and investigators were masked to the assigned study treatment with respect to active versus pooled placebo treatment, but not to different active treatments, because of the differences in dose escalations, frequency of treatment, volumes, and devices.

Procedures

Participants received subcutaneous injections of either active treatment (once-weekly cagrilintide at one of the five doses [0·3, 0·6, 1·2, 2·4, or 4·5 mg], or once-daily liraglutide 3·0 mg) or volume-matched placebo for 26 weeks. All six placebo groups were pooled into one placebo group for the main analyses. Cagrilintide was initiated at 0·3 mg (for final dose of 0·3 mg) or 0·6 mg (for all other doses) per week at randomisation and escalated incrementally every 2 weeks until reaching the final dose (appendix p 17). Liraglutide was initiated at 0·6 mg per day and escalated weekly until reaching the maintenance dose of 3·0 mg. Cagrilintide and matching cagrilintide placebo were administered using a NovoPen 4 durable pen-injector (Novo Nordisk A/S, Hillerød, Denmark), and liraglutide 3·0 mg and matching liraglutide placebo were administered using a 3 mL PDS290 pen-injector (Novo Nordisk A/S). Participants self-injected at home. Training on how to use the pen-injector was provided before first use and repeated during the trial at regular intervals. All participants received dietary and physical activity counselling, aiming to achieve a 500-kcal deficit per day and 150 min of physical activity per week. Body weight was assessed at screening, randomisation, and weeks 2, 4, 6, 8, 10, 14, 18, 22, 26, and 32. Details of efficacy and safety assessments conducted at each visit are provided in the protocol.

Outcomes

The primary endpoint was the percentage change in bodyweight from baseline to week 26. Secondary efficacy endpoints were: the proportion of participants with bodyweight reduction from baseline of at least 5% and at least 10% at week 26, and the change from baseline to week 26 in absolute bodyweight (kg), waist circumference (cm), lipids (total cholesterol, HDL, LDL, very-low-density lipoprotein, and triglycerides), and glycaemic variables (HbA_{1c}, fasting plasma glucose, fasting insulin, homoeostatic model assessment of insulin resistance, and β-cell function).

Treatment-emergent adverse events, serious adverse events, and occurrence of anti-cagrilintide antibodies were assessed throughout the trial (weeks 0–32). Additional safety assessments included changes from baseline to week 26 in systolic and diastolic blood pressure, pulse rate, plasma high-sensitivity C-reactive protein, renin activity, and aldosterone. Exploratory endpoints included the proportion of participants achieving at least 15% and 20% weight loss at week 26, and changes in patient-reported outcomes (Short-Form 36 [SF-36] v2.0 acute and the Three-Factor Eating Questionnaire Revised 18-item version 2 [TFEQ-R18 v2]).[18] Because none of the participants achieved at least 20% weight loss in the cagrilintide 0·3 mg and pooled placebo groups, the planned analysis of this endpoint comparing cagrilintide and placebo could not be performed and was therefore not included. Other exploratory endpoints are listed in the appendix (p 4).

Statistical analysis

For the primary endpoint, a sample size of 100 participants in each active treatment group was calculated to be sufficient to provide the trial with a power of more than 99% to show a significant difference between the optimal dose of cagrilintide versus pooled placebo, and a power of 98% between the optimal dose of cagrilintide versus liraglutide 3·0 mg.

For the primary endpoint, the superiority of each cagrilintide dose versus pooled placebo was assessed in hierarchical order starting with the treatment difference between the highest cagrilintide dose and pooled placebo, with superiority at a significance level of 5%. Comparisons with liraglutide 3·0 mg were not adjusted for multiplicity and are therefore not considered confirmatory. Data are presented as estimated treatment differences with respective 95% CIs. All matched placebo groups were pooled for the main analyses.

Two estimands (the trial product estimand and the treatment policy estimand) were used to assess treatment efficacy, and accounted differently for intercurrent events and missing data, as described previously.[19] Primary and secondary efficacy endpoints were analysed in all randomly assigned participants (full analysis set), according to the trial product estimand, which assumes that participants had adhered to their assigned treatment throughout the trial. A participant was categorised as adherent to treatment until the first time of non-adherence, which was defined as not receiving their assigned treatment within the previous 14 days, receiving other weight management drug or bariatric surgery, not reaching the target dose at the pre-specified week, or not receiving the target dose (plus or minus 10%) within the 14 days following the pre-specified evaluation week. As such, available data from assigned participants with

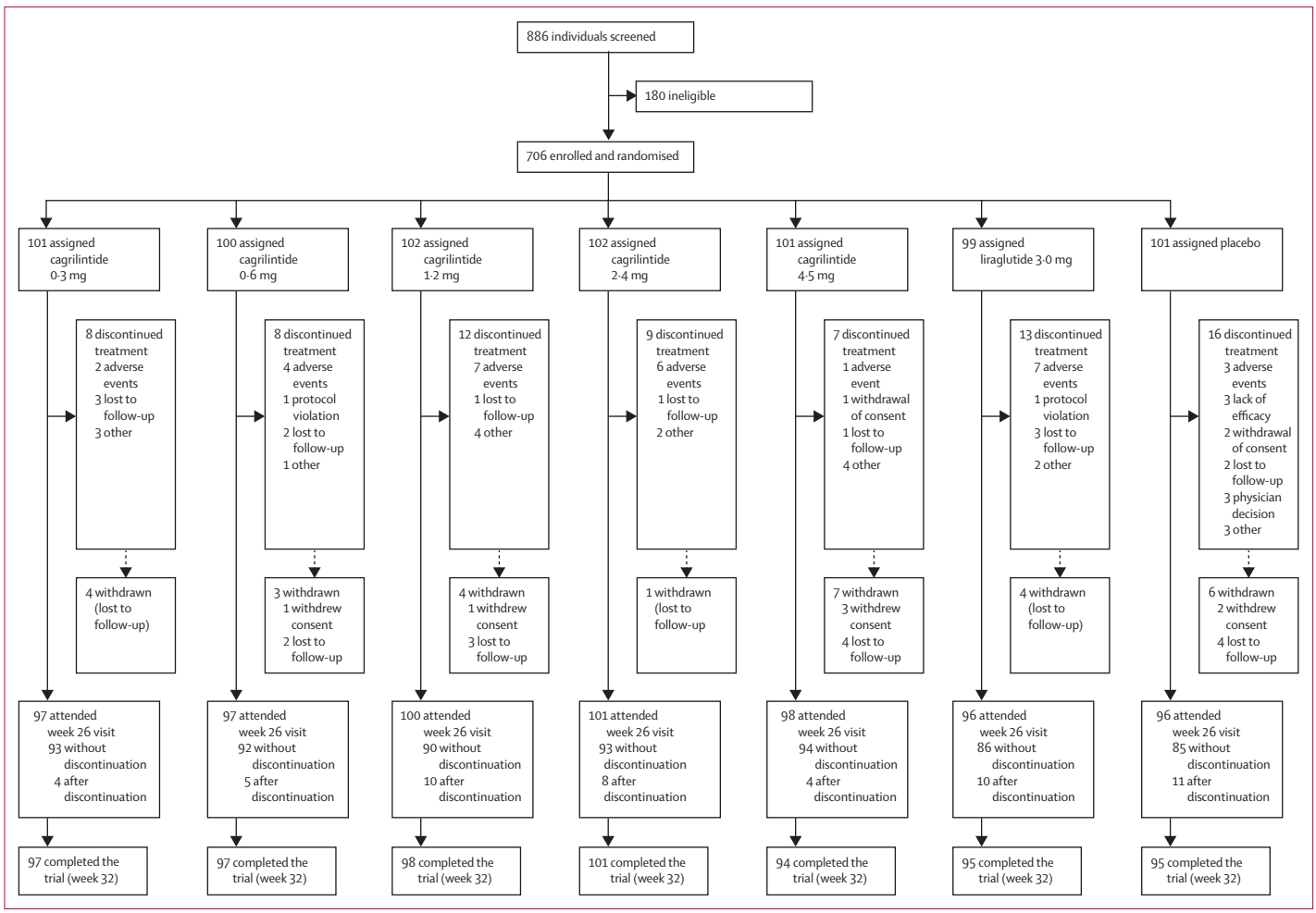


Figure 1: **Trial profile**
Participants who completed the trial include those assigned treatment minus those who were withdrawn. Not all participants who attended the week 26 visit completed the trial.

bodyweight measurements while treatment-adherent were included in the analyses for the trial product estimand, and missing data and data from non-adherence periods were handled with the multiple imputation method using data from the same treatment arm while treatment-adherent, under the assumption that participants who were not adherent to treatment would have responded similarly to those who adhered to treatment. Multiple imputation of missing data was done using Markov Chain Monte Carlo, followed by sequential regression for monotone missing values, including sex and region as factors. Therefore, the primary analysis estimated the treatment effect in the hypothetical situation in which all randomly assigned participants had continued their randomised treatment until week 26, and where those participants discontinuing the treatment prematurely would have had a trajectory (for the endpoint in question) mimicking the average of those who did not discontinue. In line with previous publications,[8–10] we refer to this statistical approach as the trial product estimand, but it should be noted that these imputation-based estimates cannot be interpreted as causal effects of the trial product per se. Therefore, a post-hoc analysis using the complier average causal effect was conducted to explore the full effect of compliance on treatment effect for the primary endpoint, as suggested during the peer-review process of this manuscript. The assumption behind this analysis was that the intention-to-treat effect as estimated with the treatment policy estimand (effect of being offered the treatment) is proportional to the actual treatment compliance score, defined as the number of weeks that a participant was on treatment divided by 26 (corresponding to the number of weeks on treatment when fully compliant). Continuous data were assessed with an ANCOVA model, using randomised treatment as a factor and baseline bodyweight (kg) as a covariate. Categorical data were evaluated with a binary logistic-regression model with randomised treatment as a factor and baseline bodyweight as a covariate.

	Cagrilintide					Liraglutide 3·0 mg (n=99)	Placebo pooled (n=101)	Total (n=706)
	0·3 mg (n=101)	0·6 mg (n=100)	1·2 mg (n=102)	2·4 mg (n=102)	4·5 mg (n=101)			
Age (years)	53·5 (10·3)	53·2 (11·0)	52·1 (8·7)	52·7 (9·8)	51·5 (12·7)	51·5 (9·3)	51·4 (11·9)	52·3 (10·6)
Sex								
Male	45 (45%)	38 (38%)	39 (38%)	27 (26%)	45 (45%)	34 (34%)	42 (42%)	270 (38%)
Female	56 (55%)	62 (62%)	63 (62%)	75 (74%)	56 (55%)	65 (66%)	59 (58%)	436 (62%)
Race or ethnic group								
White	77 (76%)	75 (75%)	75 (74%)	80 (78%)	83 (82%)	82 (83%)	71 (70%)	543 (77%)
Asian	13 (13%)	14 (14%)	15 (15%)	11 (11%)	9 (9%)	13 (13%)	17 (17%)	92 (13%)
Black or African American	9 (9%)	5 (5%)	8 (8%)	9 (9%)	5 (5%)	0	9 (9%)	45 (6%)
Native American or Alaska Native	1 (1%)	1 (1%)	0	0	0	0	0	2 (<1%)
Hispanic or Latino	2 (2%)	1 (1%)	4 (4%)	2 (2%)	3 (3%)	5 (5%)	4 (4%)	21 (3%)
Other	1 (1%)	5 (5%)	4 (4%)	2 (2%)	4 (4%)	4 (4%)	4 (4%)	24 (3%)
Bodyweight (kg)	109·8 (25·1)	106·2 (23·8)	104·4 (21·5)	106·8 (24·1)	111·0 (28·6)	107·8 (24·1)	106·2 (21·6)	107·4 (24·2)
Height (m)	1·69 (0·09)	1·68 (0·09)	1·67 (0·09)	1·68 (0·10)	1·69 (0·11)	1·67 (0·10)	1·68 (0·10)	1·68 (0·10)
Body-mass index (kg/m²)	38·4 (7·5)	37·2 (6·9)	37·1 (6·2)	37·9 (7·6)	38·4 (7·7)	38·4 (7·4)	37·4 (5·7)	37·8 (7·0)
Waist circumference (cm)	116·2 (16·0)	114·5 (15·1)	113·5 (15·0)	113·7 (14·6)	118·9 (17·6)	116·3 (15·4)	114·7 (13·7)	115·4 (15·4)
HbA_{1c} (%; mmol/mol)	5·6% (0·4); 38·1 (4·1)	5·6% (0·4); 37·3 (3·9)	5·6% (0·4); 37·9 (3·9)	5·6% (0·4); 37·8 (3·9)	5·6% (0·3); 38·1 (3·8)	5·6% (0·4); 37·3 (4·3)	5·6% (0·4); 37·8 (4·2)	5·6% (0·4); 37·8 (4·0)
Fasting plasma glucose (mmol/L)	5·8 (0·8)	5·6 (0·6)	5·7 (0·6)	5·6 (0·6)	5·8 (1·1)	5·6 (0·7)	5·6 (0·6)	5·7 (0·8)
Blood pressure (mm Hg)								
Systolic	134·1 (15·7)	131·9 (15·9)	132·5 (14·8)	129·4 (12·6)	132·7 (15·7)	131·8 (13·7)	131·9 (13·2)	132·0 (14·6)
Diastolic	82·4 (9·9)	83·0 (9·6)	83·7 (10·3)	80·2 (8·9)	82·1 (10·2)	84·5 (7·9)	82·8 (7·9)	82·7 (9·6)

Data are mean (SD), n (%), or mean % (SD). HbA_{1c}=glycated haemoglobin.

Table 1: **Baseline characteristics of the study participants**

For the primary endpoint, an additional analysis was performed to estimate the treatment effect on all randomised participants regardless of adherence to treatment (treatment policy estimand). For the treatment policy estimand, bodyweight data for all participants regardless of adherence to treatment were included, and missing data for participants without bodyweight data at week 26 were handled using the multiple imputation method (missing data were handled by imputing data from participants who permanently discontinued treatment but attended the week 26 visit from the same randomised treatment group). We did two pre-specified sensitivity analyses to evaluate the robustness of the primary analysis: a mixed-effects model for repeated measurements analysis and an analysis in which post-baseline measurements were excluded for participants with treatment non-adherence. Safety endpoints were analysed using descriptive statistics in all randomly assigned participants exposed to at least one dose of their randomised treatment (safety analysis set). Additional details regarding the statistical analysis are in the appendix (pp 5–8).

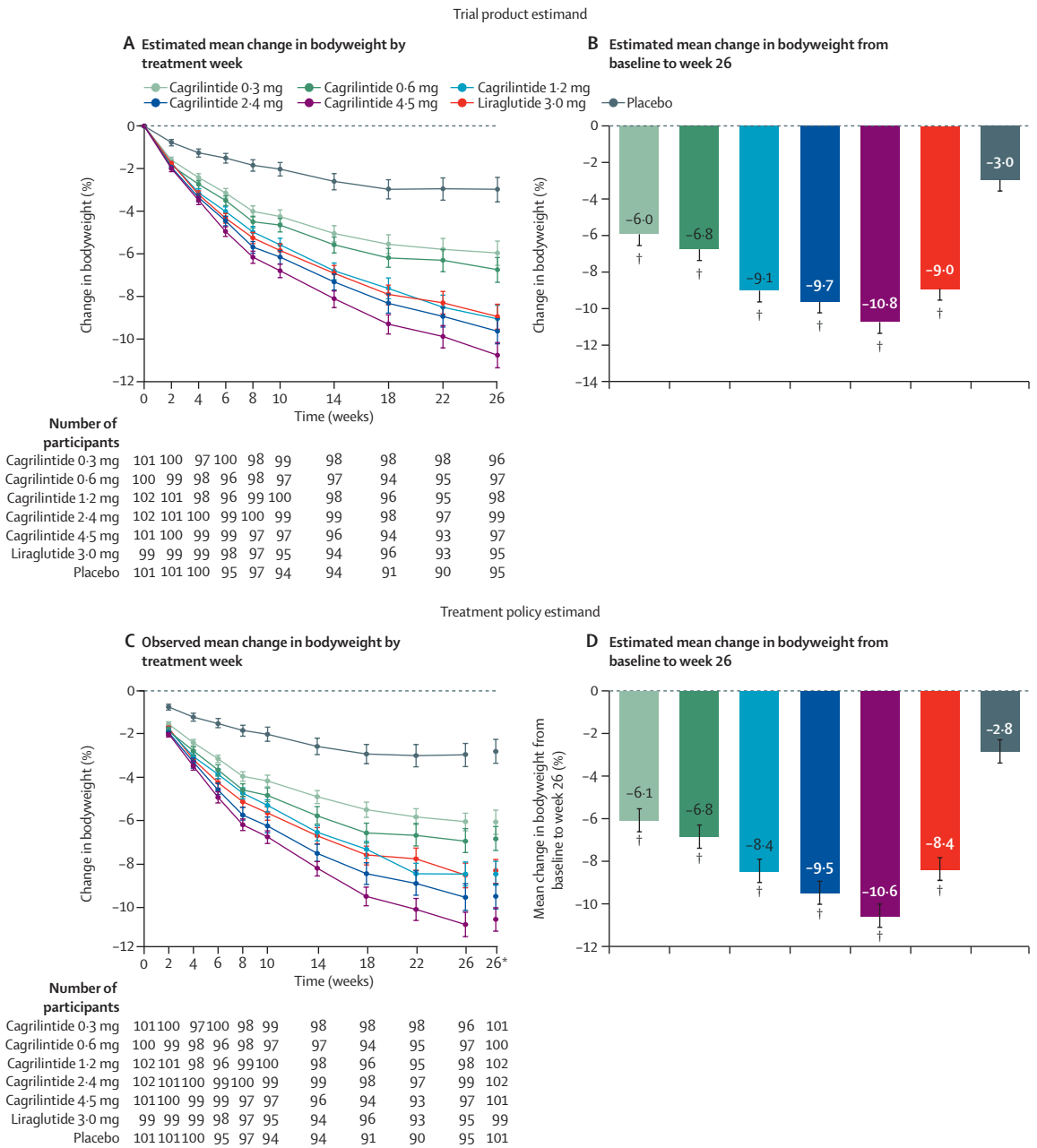
Role of the funding source

The funder of the study had a role in study design, study oversight, data collation, data analysis and interpretation, and writing of the report.

Results

Between March 1 and Aug 19, 2019, we screened 886 participants and randomly assigned 706 to treatment: cagrilintide 0·3–4·5 mg (100–102 participants per dose group), liraglutide 3·0 mg (99 participants), or volume-matched placebo (101 participants; figure **1**). All randomly assigned participants were exposed to trial product and were included in the full and safety analysis sets. 73 participants (10%) permanently discontinued treatment and 29 (4%) withdrew from the trial. Of those who discontinued treatment prematurely, 43 participants remained in the trial and had their data collected. Permanent discontinuation was similar across treatment groups, mostly due to adverse events (30 participants [4%] across treatment groups). 552 (78%) participants adhered to treatment up to week 26. The main reason for trial withdrawal was being lost to follow-up. 677 (96%) participants, including participants who had permanently discontinued treatment, attended the follow-up visit at week 32 (figure 1). Baseline characteristics were similar across treatment arms (table **1**).

For the primary analysis using the trial product estimand, bodyweight decreased progressively in all active treatment groups, and did not appear to reach a plateau by week 26 (figure **2**). At week 26, mean weight reductions from baseline were greater with all doses of cagrilintide



(Figure 2 continues on next page)

compared with pooled placebo (–6·0%, –6·8%, –9·1%, –9·7%, and –10·8% for cagrilintide 0·3 mg, 0·6 mg, 1·2 mg, 2·4 mg, and 4·5 mg, respectively, *vs* –3·0% for pooled placebo; estimated treatment difference range –3·0% to –7·8%; p<0·001). Weight reductions were greater with cagrilintide 4·5 mg versus liraglutide 3·0 mg (–10·8% *vs* –9·0%; estimated treatment difference –1·8%; p=0·03; table **2**, figure 2). Similar weight reductions from baseline were observed when analysing data from all participants regardless of adherence to treatment (ie, according to treatment policy estimand; figure 2). Absolute weight reductions (kg) from baseline were similar to percentage weight reductions (table 2). The results of the sensitivity analyses were similar to those of the primary analysis (appendix p 18). Adherence to treatment was high throughout the trial (mean compliance scores ranged from 0·95 to 0·97 across active treatment groups), and the complier average causal effect post-hoc analysis showed similar weight changes to the primary analysis (appendix p 18). Some weight regain

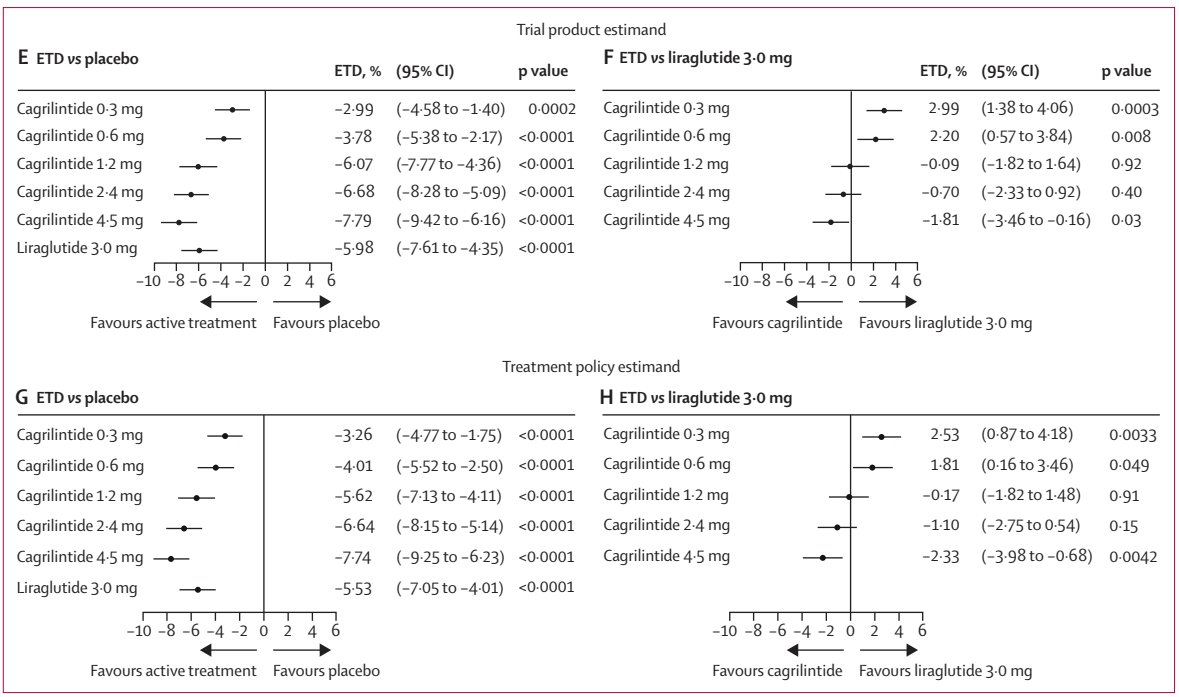


Figure 2: **Change in bodyweight from baseline to week 26**

Mean (SE) estimated change from baseline in bodyweight (%) by treatment week according to the trial product estimand (A) and mean (SE) observed change from baseline in bodyweight (%) by treatment week according to the treatment policy estimand (C). Mean estimated change in bodyweight (%) from baseline to week 26 according to the trial product estimand (B), and the treatment policy estimand (D). Mean ETDs for active treatment versus placebo (E) and cagrilintide versus liraglutide 3·0 mg (F). Mean ETDs for active treatment versus placebo (G) and cagrilintide liraglutide 3·0 mg analysed according to the treatment policy estimand (H), which assessed the effect of treatment in all randomly assigned participants regardless of adherence to treatment. Comparisons with liraglutide 3·0 mg have not been adjusted for multiplicity. Error bars indicate SEs. ETD=estimated treatment difference. *Estimated change in bodyweight using ANCOVA with imputation of missing data and data during treatment non-adherence. †p<0·001 versus placebo.

in the cagrilintide and liraglutide 3·0 mg groups was noted at week 32, following treatment cessation at week 26. Observed mean weight loss with cagrilintide 0·3 to 4·5 mg ranged from –5·0 to –9·8% at week 32 (appendix p 19) compared with –6·1% to –10·8% at week 26. Observed mean weight loss with liraglutide 3·0 mg was –7·2% at week 32, compared with –8·5% at week 26.

The number of participants achieving a categorical weight loss of at least 5%, 10%, and 15% at week 26 are shown in figure 3, table 2, and the appendix (pp 20–21). Waist circumference reductions with cagrilintide 1·2–4·5 mg were dose-dependent, greater than pooled placebo, and similar to liraglutide 3·0 mg (table 2).

No apparent change in HbA_{1c} and fasting glucose concentrations was observed from baseline to week 26 across all cagrilintide groups and pooled placebo; liraglutide 3·0 mg improved these parameters (table 2). Across all treatment groups, fasting insulin concentrations decreased from baseline to week 26 (table 2, appendix pp 10–11). Reductions in triglycerides and very-low-density cholesterol with cagrilintide 2·4 and 4·5 mg were greater versus pooled placebo, and similar to reductions with liraglutide 3·0 mg; changes from baseline in other lipid variables were similar across treatment groups (appendix pp 22–23). TFEQ-R18 scores improved from baseline in all treatment groups, with greater improvements with cagrilintide versus pooled placebo in cognitive restraint (with the 1·2 and 4·5 mg doses), emotional eating (0·3 and 2·4 mg doses), and uncontrolled eating (1·2–4·5 mg doses); cagrilintide results were similar to those observed with liraglutide 3·0 mg (appendix pp 20–21). Changes from baseline in SF-36 physical and mental component summary scores were small across treatment groups (appendix pp 20–21).

Across cagrilintide groups, the number of participants with adverse events was numerically higher than with pooled placebo and similar to that with liraglutide 3·0 mg (table 3). There were numerically fewer adverse events per 100 patient-years of exposure across all cagrilintide groups compared with liraglutide 3·0 mg (table 3). Between two and six (2–6%) participants in the cagrilintide groups discontinued treatment prematurely because of adverse events, compared with seven (7%) participants in the liraglutide 3·0 mg group and three (3%) in the pooled placebo group. The most frequent adverse events were gastrointestinal disorders (eg, nausea, constipation, and diarrhoea) and administration-site reactions (table 3). Few serious

	Cagrilintide					Liraglutide 3·0 mg (n=99)	Placebo pooled (n=101)
	0·3 mg (n=101)	0·6 mg (n=100)	1·2 mg (n=102)	2·4 mg (n=102)	4·5 mg (n=101)		
Primary endpoint							
Bodyweight (% change from baseline at week 26)	−6·0% (0·6)	−6·8% (0·6)	−9·1% (0·7)	−9·7% (0·6)	−10·8% (0·6)	−9·0% (0·6)	−3·0% (0·6)
Estimated treatment difference (95% CI) *vs* placebo	−3·0 (−4·6 to −1·4)	−3·8 (−5·4 to −2·2)	−6·1 (−7·8 to −4·4)	−6·7 (−8·3 to −5·1)	−7·8 (−9·4 to −6·2)	−6·0 (−7·6 to −4·4)	NA
Estimated treatment difference (95% CI) *vs* liraglutide 3·0 mg	3·0 (1·4 to 4·6)	2·2 (0·6 to 3·8)	−0·1 (−1·8 to 1·6)	−0·7 (−2·3 to 0·9)	−1·8 (−3·5 to −0·2)	NA	NA
Selected secondary endpoints							
Bodyweight (kg change from baseline at week 26)	−6·4 (0·6)	−7·1 (0·6)	−9·7 (0·7)	−10·3 (0·6)	−11·5 (0·6)	−9·6 (0·6)	−3·3 (0·6)
Estimated treatment difference (95% CI) *vs* placebo	−3·0 (−4·7 to −1·3)	−3·6 (−5·5 to −2·1)	−6·4 (−8·9 to −4·6)	−6·9 (−8·7 to 5·2)	−8·2 (−9·9 to −6·4)	−6·2 (−8·0 to −4·5)	NA
Estimated treatment difference (95% CI) *vs* liraglutide 3·0 mg	3·2 (1·5 to 5·0)	2·5 (0·7 to 4·2)	−0·2 (−2·0 to 1·7)	−0·7 (−2·4 to 1·1)	−1·9 (−3·7 to −0·2)	NA	NA
Estimated proportion of participants achieving bodyweight reduction ≥5% at week 26*	59 (58%)	62 (62%)	78 (76%)	75 (74%)	90 (89%)	75 (76%)	31 (31%)
Estimated proportion of participants achieving bodyweight reduction ≥10% at week 26*	15 (15%)	24 (24%)	37 (36%)	45 (44%)	55 (54%)	39 (39%)	10 (10%)
Waist circumference (cm change from baseline at week 26)	−5·8 (0·7)	−6·0 (0·7)	−7·9 (0·7)	−8·6 (0·7)	−9·2 (0·7)	−7·8 (0·7)	−4·4 (0·7)
Estimated treatment difference (95% CI) *vs* placebo	−1·4 (−3·4 to 0·6)	−1·6 (−3·6 to 0·4)	−3·4 (−5·5 to −1·4)	−4·2 (−6·2 to −2·2)	−4·8 (−6·8 to −2·8)	−3·4 (−5·4 to −1·4)	NA
Estimated treatment difference (95% CI) *vs* liraglutide 3·0 mg	2·0 (0·1 to 3·9)	1·8 (−0·2 to 3·7)	−0·1 (−2·1 to 2·0)	−0·8 (−2·8 to 1·2)	−1·4 (−3·3 to 0·6)	NA	NA
HbA_{1c} (change from baseline to week 26, %; mmol/mol)	0·0% (0·2); −0·5 (2·4)	−0·1% (0·2); −0·6 (2·2)	−0·1% (0·3); −0·8 (3·0)	−0·1% (0·3); −1·0 (2·9)	−0·1% (0·2); −1·2 (2·4)	−0·3% (0·2); −2·9 (2·7)	−0·1% (0·2); −0·6 (2·7)
Fasting plasma glucose (mmol/L change from baseline to week 26)	0·0 (0·6)	0·0 (0·5)	−0·2 (0·5)	0·0 (0·7)	−0·2 (1·0)	−0·5 (0·7)	0·0 (0·6)
Systolic blood pressure† (mm Hg change from baseline to week 26)	−4·7 (1·3)	−4·9 (1·3)	−5·5 (1·4)	−8·0 (1·3)	−6·5 (1·3)	−4·3 (1·3)	−3·6 (1·3)
Estimated treatment difference (95% CI) *vs* placebo	−1·0 (−4·5 to 2·5)	−1·3 (−4·9 to 2·3)	−1·8 (−5·5 to 1·9)	−4·3 (−7·8 to −0·8)	−2·8 (−6·4 to 0·7)	−0·7 (−4·2 to 2·9)	NA
Estimated treatment difference (95% CI) *vs* liraglutide 3·0 mg	−0·4 (−3·9 to 3·2)	−0·6 (−4·2 to 2·9)	−1·2 (−4·9 to 2·5)	−3·7 (−7·2 to −0·1)	−2·2 (−5·7 to 1·3)	NA	NA
Diastolic blood pressure† (mm Hg change from baseline to week 26)	−2·6 (0·8)	−2·5 (0·8)	−2·2 (0·8)	−5·7 (0·8)	−3·6 (0·8)	−1·6 (0·8)	−2·1 (0·8)
Estimated treatment difference (95% CI) *vs* placebo	−0·5 (−2·7 to 1·8)	−0·4 (−2·7 to 1·9)	−0·1 (−2·4 to 2·2)	−3·5 (−5·8 to −1·2)	−1·5 (−3·8 to 0·8)	0·5 (−1·8 to 2·8)	NA
Estimated treatment difference (95% CI) *vs* liraglutide 3·0 mg	−1·0 (−3·2 to 1·3)	−0·9 (−3·2 to 1·3)	−0·6 (−2·9 to 1·7)	−4·1 (−6·4 to −1·8)	−2·0 (−4·3 to 0·3)	NA	NA
Pulse† (beats per min change from baseline to week 26)	−1·9 (0·9)	−0·2 (0·9)	−1·7 (1·0)	−1·6 (0·9)	−5·1 (0·9)	2·1 (0·9)	−0·6 (0·9)
Estimated treatment difference (95% CI) *vs* placebo	−1·3 (−3·8 to 1·2)	0·4 (−2·1 to 2·9)	−1·1 (−3·7 to 1·5)	−1·1 (−3·6 to 1·5)	−4·5 (−7·1 to −2·0)	2·7 (0·1 to 5·2)	NA
Estimated treatment difference (95% CI) *vs* liraglutide 3·0 mg	−4·0 (−6·5 to −1·4)	−2·3 (−4·8 to 0·3)	−3·8 (−6·4 to −1·1)	−3·7 (−6·3 to −1·1)	−7·2 (−9·8 to −4·6)	NA	NA

Data are % (SE), n (%) or estimated mean (SE) change from baseline to week 26, unless otherwise stated. Data presented were analysed according to the trial product estimand, assuming all participants were adherent to treatment, using analysis of covariance for continuous endpoints and logistic regression for binary endpoints. Data collected after the first two consecutive missed doses of trial product were excluded. HbA_{1c}=glycated haemoglobin. NA=not applicable. *Estimated using logistic regression with multiple imputation of missing data for bodyweight data outside the treatment adherent period. †Values from blood pressure and pulse presented were taken at the trial site.

Table 2: **Primary and selected secondary endpoints**

adverse events occurred with cagrilintide and were not dependent on dose (table 3, appendix p 24). No fatal events occurred.

Across treatment groups, most participants had their first gastrointestinal disorders within 4–6 weeks after starting treatment (appendix p 12). The number of participants with gastrointestinal disorders was numerically higher with cagrilintide than pooled placebo and similar to that with liraglutide 3·0 mg. There were fewer gastrointestinal disorder events per 100 patient-years of exposure across all cagrilintide doses compared with liraglutide 3·0 mg. The number of gastrointestinal disorders reported increased with cagrilintide dose; most were non-serious and mild or moderate (table 3). The most common gastrointestinal disorders were nausea, constipation, diarrhoea, and vomiting. Reporting of

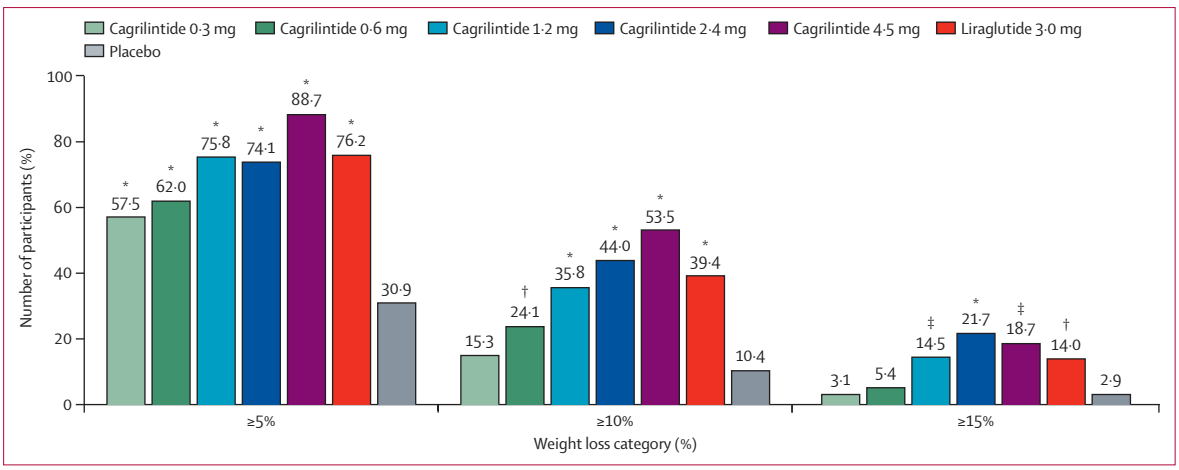


Figure 3: **Categorical weight loss**
Mean categorical weight loss of at least 5%, 10%, and 15% or more in all randomly assigned participants from baseline to week 26 according to the trial product estimand (assuming all participants were adherent to treatment). Data from all participants who had adhered to treatment at week 26 and imputed data for participants who had not adhered to treatment at week 26 were included. *p<0·001 versus placebo. †p<0·05 versus placebo. ‡p<0·01 versus placebo.

vomiting across cagrilintide groups was infrequent and none of the events led to permanent treatment discontinuation. Permanent treatment discontinuation due to gastrointestinal disorders with cagrilintide was low and not dose-dependent (occurring in two participants receiving 1·2 mg and one participant receiving 2·4 mg). One case of pancreatitis was reported with liraglutide 3·0 mg.

Occurrence of administration-site reactions in the cagrilintide groups was dose-dependent and higher than in the liraglutide 3·0 mg or pooled placebo groups (table 3). The most common administration-site reactions were injection-site reaction (150 events in 38 [5%] participants) and injection-site erythema (64 events in 42 [6%] participants). None of the administration-site reaction events were serious, none were severe with cagrilintide, and few led to treatment discontinuation (two participants receiving cagrilintide 0·6 mg, one participant receiving cagrilintide 2·4 mg, and one participant receiving liraglutide 3·0 mg).

The presence of anti-cagrilintide antibodies increased with cagrilintide dose and time of exposure, occurring in 46–73% of participants by week 26 (appendix p 25). At follow-up, antibodies were present in 40–70% of participants; of these, most were cross-reactive with native amylin and few were neutralising against cagrilintide or native amylin (appendix p 25). The presence of antibodies and the magnitude of titres did not seem to affect changes in bodyweight (appendix p 13). No serious allergic reactions were reported.

Few cardiovascular events were reported and the number of participants with an event was similar across treatment groups; most events were non-serious and mild or moderate, with no evidence of clustering of event types (table 3). No significant differences in blood pressure or pulse rate were recorded (table 2; appendix pp 14–15). Mean concentrations of plasma renin and aldosterone showed a transient increase in all active treatment groups, which reduced to near baseline concentrations towards the end of treatment (appendix p 16). Mean sodium and potassium concentrations remained within normal ranges throughout the trial. Overall, reductions in high-sensitive C-reactive protein were observed in all treatment groups, with greater numerical reductions observed in the cagrilintide and liraglutide 3·0 mg groups (appendix pp 22–23). 19 neoplasms occurred in 17 participants (2%), with five malignant neoplasms reported (one participant on cagrilintide 0·6 mg, two participants on cagrilintide 1·2 mg, one participant on liraglutide 3·0 mg, and one participant on placebo). There was no evidence of dose dependence or clustering of event types (table 3). No safety concerns were identified within the categories of renal, hepatic, gallbladder, or psychiatric disorders, and there were no unexpected findings in biochemical and haematological variables, electrocardiograms, or physical examinations (table 3).

Discussion

Cagrilintide is the first long-acting amylin analogue to be investigated for weight management. In this study, treatment with cagrilintide for 26 weeks in participants with overweight or obesity without type 2 diabetes, as adjunct to lifestyle interventions, led to dose-dependent, clinically relevant reductions in bodyweight and waist circumference.

In our study, the 7·8% mean weight loss achieved with cagrilintide 4·5 mg at week 26 using the trial product estimand (versus placebo) was greater than the 6·0% mean weight loss achieved with liraglutide 3·0 mg. The trial product estimand models the treatment effect of the different doses of cagrilintide in the hypothetical

	Cagrilintide 0·3 mg (n=101)			Cagrilintide 0·6 mg (n=100)			Cagrilintide 1·2 mg (n=102)			Cagrilintide 2·4 mg (n=102)			Cagrilintide 4·5 mg (n=101)			Liraglutide 3·0 mg (n=99)			Placebo pooled (n=101)		
	n (%)	Events	Events per 100 patient-years*	n (%)	Events	Events per 100 patient-years*	n (%)	Events	Events per 100 patient-years*	n (%)	Events	Events per 100 patient-years*	n (%)	Events	Events per 100 patient-years*	n (%)	Events	Events per 100 patient-years*	n (%)	Events	Events per 100 patient-years*
Any adverse event	72 (71%)	335	570·8	78 (78%)	291	505·0	88 (86%)	361	620·9	79 (78%)	449	757·4	89 (88%)	460	787·1	80 (81%)	470	828·5	67 (66%)	276	495·9
Serious adverse events	6 (6%)	8	13·6	2 (2%)	3	5·2	7 (7%)	8	13·8	3 (3%)	6	10·1	4 (4%)	4	6·8	4 (4%)	4	7·1	3 (3%)	4	7·2
Severe adverse events	4 (4%)	6	10·2	7 (7%)	12	20·8	9 (9%)	11	18·9	7 (7%)	12	20·2	6 (6%)	7	12·0	6 (6%)	8	14·1	4 (4%)	8	14·4
Fatal adverse events	0	..	..	0	..	..	0	..	..	0	..	..	0	..	..	0	..	..	0	..	..
Adverse event leading to permanent discontinuation of study drug	2 (2%)	2	3·4	4 (4%)	4	6·9	6 (6%)	6	10·3	6 (6%)	6	10·1	1 (1%)	1	1·7	7 (7%)	7	12·3	3 (3%)	3	5·4
Adverse events in ≥10% of participants by preferred term†																					
Nausea	20 (20%)	26	44·3	27 (27%)	32	55·5	37 (36%)	45	77·4	32 (31%)	41	69·2	47 (47%)	61	104·4	39 (39%)	56	98·7	18 (18%)	26	46·7
Constipation	11 (11%)	12	20·4	9 (9%)	9	15·6	8 (8%)	8	13·8	17 (17%)	17	28·7	21 (21%)	25	42·8	26 (26%)	30	52·9	7 (7%)	10	18·0
Diarrhoea	15 (15%)	22	37·5	10 (10%)	12	20·8	8 (8%)	9	15·5	18 (18%)	20	33·7	7 (7%)	9	15·4	18 (18%)	28	49·4	9 (9%)	10	18·0
Headache	10 (10%)	15	25·6	5 (5%)	5	8·7	11 (11%)	13	22·4	11 (11%)	17	28·7	7 (7%)	10	17·1	13 (13%)	24	42·3	12 (12%)	22	39·5
Decreased appetite	4 (4%)	4	6·8	9 (9%)	9	15·6	8 (8%)	8	13·8	13 (13%)	13	21·9	17 (17%)	18	30·8	9 (9%)	10	17·6	4 (4%)	4	7·2
Fatigue	8 (8%)	8	13·6	5 (5%)	5	8·7	8 (8%)	9	15·5	10 (10%)	12	20·2	20 (20%)	21	35·9	8 (8%)	8	14·1	3 (3%)	3	5·4
Vomiting	6 (6%)	6	10·2	6 (6%)	7	12·1	5 (5%)	5	8·6	9 (9%)	11	18·6	8 (8%)	8	13·7	20 (20%)	31	54·6	3 (3%)	4	7·2
Nasopharyngitis	6 (6%)	7	11·9	9 (9%)	12	20·8	13 (13%)	14	24·1	4 (4%)	7	11·8	3 (3%)	3	5·1	10 (10%)	12	21·2	10 (10%)	12	21·6
Injection-site erythema	5 (5%)	5	8·5	4 (4%)	5	8·7	6 (6%)	6	10·3	7 (7%)	23	38·8	17 (17%)	22	37·6	3 (3%)	3	5·3	0		
Injection-site reaction	4 (4%)	26	44·3	4 (4%)	10	17·4	7 (7%)	30	51·6	12 (12%)	44	74·2	10 (10%)	39	66·7	1 (1%)	1	1·8	0		
Dyspepsia	3 (3%)	4	6·8	2 (2%)	2	3·5	3 (3%)	3	5·2	3 (3%)	3	5·1	4 (4%)	4	6·8	10 (10%)	10	17·6	4 (4%)	4	7·2

(Table 3 continues on next page)

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situation in which all participants had adhered to treatment. Therefore, it is useful to estimate the full effect of the different doses of cagrilintide on bodyweight, and the results support further investigation of the higher doses of cagrilintide in future phase 3 trials, either as monotherapy or in combination with semaglutide as previously reported.[20] An additional analysis using the treatment policy estimand including all randomly assigned participants regardless of adherence to treatment showed similar weight loss with cagrilintide at all doses, which was greater than with liraglutide 3·0 mg. This additional analysis reflects the intention-to-treat principle as defined in the International Council for Harmonisation guideline.[21] Although comparisons with other trials should be made with caution because of differences in treatment duration, statistical analysis, and trial design, placebo-subtracted weight loss with cagrilintide 4·5 mg at 26 weeks was greater than that reported in 52–56-week trials with other approved obesity pharmacotherapies (by intention-to-treat analysis), including liraglutide 3·0 mg (5·4%),[22] naltrexone–bupropion (4·8%),[23] and orlistat (3·0%),[24] but lower than with semaglutide 2·4 mg (10·2–12·4%) after 68 weeks of treatment (semaglutide 2·4 mg is currently approved for weight management in the UK and USA),[8–10] or phentermine–topiramate (9·0%).[6,25] In another study, weight loss with cagrilintide 4·5 mg was also greater compared with the amylin analogue pramlintide (indicated for use in patients with type 1 and type 2 diabetes as an adjunct to meal-time insulin);[26] the study reported placebo-subtracted weight reductions of 5·6–6·8% in a 1-year trial in individuals with obesity.[27]

By contrast with placebo, reductions in weight with cagrilintide continued throughout the 26 weeks of treatment and did not appear to reach a plateau. As sustained weight loss is crucial for improvements in obesity-related complications, longer studies are needed to establish the full weight-loss potential of cagrilintide and determine whether weight loss is sustained long term.

All doses of cagrilintide were well tolerated. The most common adverse events were gastrointestinal disorders (primarily nausea), followed by administration-site reactions; these were mostly mild or moderate, and all administration-site reactions were non-serious. More anti-cagrilintide antibodies were detected with higher doses of cagrilintide, but very few were neutralising against cagrilintide or native amylin; these did not seem to affect efficacy and were not associated with any serious allergic reactions. Similarly to natural human amylin,[28] cagrilintide led to a transient activation of renin and aldosterone, although with no accompanying increase in blood pressure or change in electrolytes.

Although most approved pharmacotherapies for weight management act on the hypothalamus to reduce appetite and energy intake,[7] preclinical studies indicate that amylin reduces weight by targeting both homoeostatic and hedonic regions of the brain.[11,13–15]

	Cagrilintide 0·3 mg (n=101)			Cagrilintide 0·6 mg (n=100)			Cagrilintide 1·2 mg (n=102)			Cagrilintide 2·4 mg (n=102)			Cagrilintide 4·5 mg (n=101)			Liraglutide 3·0 mg (n=99)			Placebo pooled (n=101)		
	n (%)	Events	Events per 100 patient-years*	n (%)	Events	Events per 100 patient-years*	n (%)	Events	Events per 100 patient-years*	n (%)	Events	Events per 100 patient-years*	n (%)	Events	Events per 100 patient-years*	n (%)	Events	Events per 100 patient-years*	n (%)	Events	Events per 100 patient-years*
(Continued from previous page)																					
Safety areas of interest‡																					
Gastrointestinal disorders	41 (41%)	92	156·8	45 (45%)	80	138·8	49 (48%)	94	161·7	52 (51%)	130	219·3	64 (63%)	125	213·9	59 (60%)	205	361·4	32 (32%)	69	124·0
Cardiovascular disorders	4 (4%)	5	8·5	4 (4%)	4	6·9	5 (5%)	10	17·2	8 (8%)	12	20·2	5 (5%)	5	8·6	7 (7%)	9	15·9	5 (5%)	5	9·0
Acute gallbladder disease	1 (1%)	2	3·4	1 (1%)	1	1·7	2 (2%)	2	3·4	1 (1%)	1	1·7	1 (1%)	1	1·7	1 (1%)	1	1·8	0		
Hepatic disorders	4 (4%)	4	6·8	3 (3%)	4	6·9	0			2 (2%)	2	3·4	1 (1%)	2	3·4	1 (1%)	2	3·5	2 (2%)	2	3·6
Administration-site reaction	17 (17%)	44	75·0	13 (13%)	22	38·2	17 (17%)	48	82·6	26 (26%)	87	146·7	43 (43%)	87	148·9	13 (13%)	14	24·7	3 (3%)	3	5·4
Allergic reactions	2 (2%)	2	3·4	8 (8%)	8	13·9	5 (5%)	7	12·0	6 (6%)	9	15·2	10 (10%)	14	24·0	8 (8%)	9	15·9	4 (4%)	4	7·2
Neoplasms§	4 (4%)	4	6·5	1 (1%)	2	3·3	3 (3%)	3	4·8	1 (1%)	1	1·6	5 (5%)	6	9·8	2 (2%)	2	3·3	1 (1%)	1	1·6
Psychiatric disorders	7 (7%)	11	18·7	6 (6%)	6	10·4	3 (3%)	3	5·2	8 (8%)	8	13·5	6 (6%)	6	10·3	9 (9%)	11	19·4	8 (8%)	15	27·0

Data are adverse events and serious adverse events that occurred from week 0 to week 26 in participants in the safety population, unless otherwise specified. n (%)=the number of participants who had at least one event. *Calculated as (number of events/number of patient-years) × 100. †Adverse events with an incidence of at least 10% in any treatment group. ‡Determinedaccording to a list of terms specified by a predefined Medical Dictionary for Regulatory Activities search. §In-trial period.

Table 3: **On-treatment adverse events**

Acting on the hindbrain, amylin induces satiety and satiation, reducing food intake,[12] and might regulate food preferences via the ventral tegmental area,[29] although the mechanism is not fully understood. Additionally, natural amylin slows gastric emptying and has synergistic effects with leptin, which contribute to reduced appetite.[12] Accordingly, weight reductions following cagrilintide treatment in our study were accompanied by a general improvement in TFEQ scores for cognitive restraint, emotional eating, and uncontrolled eating, similar to results with liraglutide 3·0 mg. Further studies are needed to fully understand the mechanism of action of cagrilintide on eating behaviours and food preferences.

A strength of this study was the high number of participants who completed the trial (96%), which led to few participants with missing data, contributing to the robustness of these results. A limitation was the absence of masking between active treatment groups because of differences in volumes, devices, and dose-escalation periods, which might have introduced bias in the reporting of adverse events. Additionally, the 26-week duration of the study and the duration of treatment at target dose in some treatment groups might have been insufficient for weight loss to plateau, particularly in participants assigned to cagrilintide 4·5 mg, who did not reach the target dose until week 6. Another limitation of the study was the high proportion of individuals who were white, which will affect the generalisability of the study results.

The use of the trial product estimand for the main analysis is also associated with limitations. With this estimand, data outside the treatment-adherence period are replaced by estimates of what participants' behaviour would have been if they had stayed on treatment, assuming they would have behaved similarly to participants who adhered to treatment throughout the trial. How participants who discontinued would behave if they had continued their randomised treatment is a counterfactual question that is not possible to address using the collected data. For this reason, the trial product estimates can be challenging to interpret. A more precise estimation of the causal effect of treatment on bodyweight and other endpoints in randomised trials requires different statistical approaches. The complier average causal effect analysis, conducted post hoc, showed similar changes in bodyweight to those of the primary and secondary analyses because of the high adherence to treatment during the trial. Finally, the use of descriptive statistics for the analysis of safety endpoints does not account for the accumulated effect of multiple dosing on safety outcomes. Therefore, using estimands such as the trial product estimand in the analysis of safety endpoints could be informative and will be explored in future weight management trials.

Given its novel mechanism of action and the known heterogeneity of response to currently approved pharmacotherapies,[30] cagrilintide presents an opportunity to expand the range of existing pharmacotherapies for weight management. Moreover, cagrilintide could be explored in combination with other agents with different mechanisms of action, for a potential additive weight-loss effect. In a phase 1 trial in participants with overweight and obesity, cagrilintide in combination with semaglutide 2·4 mg for 20 weeks led to weight reductions of up to 17·1%.[20] In conclusion, in adults with overweight or obesity, treatment with cagrilintide 0·3–4·5 mg for 26 weeks as an adjunct to lifestyle interventions showed dose-dependent, clinically meaningful weight loss, and was well tolerated. These data support further development of cagrilintide as a novel pharmacotherapy for weight management.

Contributors

LE was involved in the concept and design of the trial and conducted the statistical analyses. DCWL, CWlR, BMcG, SDP, KHP, DR, and RLB conducted the trial and collected the data. All authors had full access to all the data in the study, and analysed and interpreted the data. DCWL and AS verified the underlying data. The manuscript was drafted with support from a medical writer (funded by the sponsor), under the direction of the authors. All authors were involved in the writing or critical revision of the manuscript, approved the final draft, had final responsibility for the decision to submit the manuscript for publication, and vouch for the accuracy of the data presented.

Declaration of interests

DCWL is a consultant for, and has received speaker honoraria from, Amgen, AstraZeneca, Bausch Health, Boehringer Ingelheim, Eli Lilly, HLS Therapeutics, and Novo Nordisk; and has received research funding from AstraZeneca and Novo Nordisk. AS, AMF, and LE are employees and shareholders at Novo Nordisk A/S. CWlR is an advisory board member and speaker for Boehringer Ingelheim, GI Dynamics, Herbalife, Johnson & Johnson (J&J), Keyron, Novo Nordisk, and Sanofi; and has shares in Keyron. BMcG has served on advisory boards for Boehringer Ingelheim, J&J, and Novo Nordisk; received grants for educational work from AstraZeneca, Biogen, Boehringer Ingelheim, J&J, Janssen, Lilly, MSD, Novo Nordisk, Orexigen, and Sanofi; and received institutional research grant support from Novo Nordisk. SDP has received consulting fees or speaking honoraria from Abbott, AstraZeneca, Bausch, Boehringer Ingelheim, Dexcom, HLS, Janssen, Lilly, Merck, Novo Nordisk, and Sanofi; and research funding from Abbott, AstraZeneca, Bausch, Boehringer Ingelheim, Janssen, Lilly, Merck, Novo Nordisk, and Sanofi. KHP is a consultant, advisory board member, speaker, and clinical investigator for Novo Nordisk, and has received funding from the Novo Nordisk Foundation. DR is a consultant, advisory board member, speaker, clinical investigator for, and shareholder of Novo Nordisk; a clinical investigator for AstraZeneca and Boehringer Ingelheim; has received research funding from Obesinov; and received honoraria from Medscape. RLB has consulted for Boehringer Ingelheim, Novo Nordisk, and Pfizer; participates in advisory boards for ViiV and Gila Therapeutics; and participates in speaker bureau for Novo Nordisk, ViiV, and International Medical Press.

Data sharing

Data will be shared with researchers who submit a research proposal approved by an independent review board. Individual patient data will be shared in datasets in a de-identified and anonymised format. Data will be made available after research completion and approval of the product and product use in the EU and USA. Information about proposals for data access requests can be found at novonordisk-trials.com.

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