Safety, tolerability, pharmacokinetics, and pharmacodynamics of concomitant administration of multiple doses of cagrilintide with semaglutide 2·4 mg for weight management: a randomised, controlled, phase 1b trial

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Lancet 2021; 397: 1736–48
Published Online April 22, 2021 https://doi.org/10.1016/S0140-6736(21)00845-X

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Summary

Background Cagrilintide, a long-acting amylin analogue, and semaglutide 2·4 mg, a glucagon-like peptide-1 analogue, are both being investigated as options for weight management. We aimed to determine the safety, tolerability, pharmacokinetics, and pharmacodynamics of this drug combination.

Methods In this randomised, placebo-controlled, multiple-ascending dose, phase 1b trial, individuals aged 18–55 years with a body-mass index 27·0–39·9 kg/m² and who were otherwise healthy were recruited from a single centre in the USA. The trial included six sequential overlapping cohorts, and in each cohort eligible participants were randomly assigned (3:1) to once-weekly subcutaneous cagrilintide (0·16, 0·30, 0·60, 1·2, 2·4, or 4·5 mg) or matched placebo, in combination with once-weekly subcutaneous semaglutide 2·4 mg, without lifestyle interventions. In each cohort, the doses of cagrilintide and semaglutide were co-escalated in 4-week intervals to the desired dose over 16 weeks, participants were treated at the target dose for 4 weeks, and then followed up for 5 weeks. Participants, investigators, and the sponsor were masked to treatment assignment. The primary endpoint was number of treatment-emergent adverse events from baseline to end of follow-up. Secondary pharmacokinetic endpoints assessed from day of last dose (week 19) to end of treatment (week 20) were area under the plasma concentration-time curve from 0 to 168 h ($AUC_{0–168\ h}$) and maximum concentration [C_{max}] of cagrilintide and semaglutide; exploratory pharmacokinetic endpoints were half-life, time to C_{max} [t_{max}], plasma clearance, and volume of distribution of cagrilintide and semaglutide; and exploratory pharmacodynamic endpoints were changes in bodyweight, glycaemic parameters, and hormones. Safety, pharmacokinetic, and pharmacodynamic endpoints were assessed in all participants who were exposed to at least one dose of study drug. This study is registered with ClinicalTrials.gov, NCT03600480, and is now complete.

Findings Between July 25, 2018, and Dec 17, 2019, 285 individuals were screened and 96 were randomly assigned to cagrilintide (0·16–2·4 mg group n=12; 4·5 mg group n=11) or placebo (n=24), in combination with semaglutide 2·4 mg, of whom 95 were exposed to treatment (one patient in 0·60 mg cagrilintide group was not exposed) and included in the safety and full analysis datasets. The mean age was 40·6 years (SD 9·2), 56 (59%) of 95 participants were men and 51 (54%) were Black or African American. Of 566 adverse events reported in 92 participants (69 [97%] of 71 participants assigned to 0·16–4·5 mg cagrilintide and 23 [96%] of 24 assigned to placebo), 207 (37%) were gastrointestinal disorders. Most adverse events were mild to moderate in severity and the proportion of participants with one or more adverse event was similar across treatment groups. Exposure was proportional to cagrilintide dose and did not affect semaglutide exposure or elimination. $AUC_{0–168\ h}$ ranged from 926 nmol×h/L to 24 271 nmol×h/L, and C_{max} ranged from 6·14 nmol/L to 170 nmol/L with cagrilintide 0·16–4·5 mg. $AUC_{0–168\ h}$ ranged from 12 757 nmol×h/L to 15 305 nmol×h/L, and C_{max} ranged from 96·4 nmol/L to 120 nmol/L with semaglutide 2·4 mg. Cagrilintide 0·16–4·5 mg had a half-life of 159–195 h, with a median t_{max} of 24–72 h. Semaglutide 2·4 mg had a half-life of 145–165 h, with a median t_{max} of 12–24 h. Plasma clearance and volume of distribution for both cagrilintide and semaglutide were similar across treatment groups. At week 20, mean percentage bodyweight reductions were greater with cagrilintide 1·2 and 2·4 mg than with placebo (15·7% [SE 1·6] for cagrilintide 1·2 mg and 17·1% [1·5] for cagrilintide 2·4 mg *vs* 9·8% [1·2] for pooled placebo cohorts 1–5; estimated treatment difference of –6·0% [95% CI –9·9 to –2·0] for cagrilintide 1·2 mg and –7·4% [–11·2 to –3·5] for cagrilintide 2·4 mg *vs* pooled placebo), and with cagrilintide 4·5 mg than with matched placebo (15·4% [1·3] *vs* 8·0% [2·2]; estimated treatment difference –7·4% [–12·8 to –2·1]), all in combination with semaglutide 2·4 mg. Glycaemic parameters improved in all treatment groups, independently of cagrilintide dose. Changes in hormones were similar across treatment groups.

Interpretation Concomitant treatment with cagrilintide and semaglutide 2·4 mg was well tolerated with an acceptable safety profile. Future larger and longer trials are needed to fully assess the efficacy and safety of this treatment combination.

Funding Novo Nordisk A/S.

Introduction

Obesity is a chronic, multifactorial condition that decreases quality of life and is associated with numerous complications, including type 2 diabetes, cardiovascular disease, cancer, osteoarthritis, chronic back pain, and asthma.[1,2]

Weight loss of at least 5% has been associated with improvements in cardiovascular risk factors, prevention of type 2 diabetes,[3] and improvements in obesity-associated complications, such as osteoarthritis and non-alcoholic fatty liver disease.[4] These improvements often correlate with the magnitude of weight loss. For some complications, greater weight loss (of at least 10%) is required for clinically significant improvements in health (eg, asthma, sleep apnoea, and type 2 diabetes remission).[5,6]

Despite the high prevalence of obesity worldwide and associated disease burden, few treatment options are available for weight management, including pharmacotherapy.[7] Approved non-surgical weight loss interventions result in a mean weight loss of 3–9% relative to placebo, which might not be sufficient for improvements in some obesity-associated complications.[8,9] Combining obesity medications with different mechanisms of action might be beneficial for individuals with overweight or obesity, providing more effective treatment options for weight management.

Semaglutide is a glucagon-like peptide-1 (GLP-1) analogue that is approved for the treatment of type 2 diabetes,[10] and is being studied for weight management in the phase 3 STEP programme.[11] In individuals with overweight or obesity, treatment with semaglutide was associated with significant reductions in bodyweight,[12,13] with mean reductions of 12·4% relative to placebo after 68 weeks reported in the STEP 1 trial.[14] Weight reductions with semaglutide are due to the reduction of *ad libitum* energy intake caused by reduced appetite, increased satiety, and improved control of eating and food preferences.[15,16]

Cagrilintide (recommended international non-proprietary name for NNC0174-0833)[17] is a long-acting acylated amylin analogue with agonistic effects on both native amylin and calcitonin receptors[18–20] that is being investigated for weight management. Native amylin is a glucoregulatory pancreatic hormone co-secreted with insulin that is involved in the delay of gastric emptying and suppression of postprandial glucagon release.[21] Additionally, native amylin reduces energy intake and is involved in the regulation of appetite and satiation through activation of receptors in the area postrema and nucleus of the solitary tract of the hindbrain.[21] Amylin has been suggested to have a role in the regulation of food choices and preferences via the hypothalamus, ventral tegmental area, and laterodorsal tegmental nucleus.[21] A phase 2 trial published in 2020 found dose-dependent reductions in bodyweight of up to 10·8% in participants with overweight and obesity after treatment with once-weekly subcutaneous cagrilintide at doses of 0·30–4·5 mg.[22]

We aimed to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics (including weight change from baseline) of six multiple-ascending doses of once-weekly subcutaneous cagrilintide (final dose 0·16, 0·30, 0·60, 1·2, 2·4, and 4·5 mg) versus placebo, both in combination with once-weekly subcutaneous semaglutide 2·4 mg, in participants with overweight or obesity.

Methods

Study design and participants

In this randomised, double-blind, placebo-controlled, multiple-ascending dose, phase 1b trial with sequential overlapping cohorts and sentinel dosing, we recruited participants at a single centre in Kansas, USA. We used a sequential cohort design with sentinel dosing to minimise the risk of unforeseen adverse events because of the potential risk for exacerbated gastrointestinal side-effects

Research in context

Evidence before this study

We searched PubMed for articles in English published between Jan 1, 2010, and Nov 30, 2020, using the terms "obesity", "anti-obesity", "pharmacotherapy", "combination pharmacotherapy", "weight management", "weight loss", "amylin analogue", AND "glucagon-like peptide-1 receptor agonist". Our literature review confirmed the small number of pharmacotherapies currently available for the treatment of obesity. Cagrilintide had been found to promote weight loss in a dose-dependent manner in preclinical and clinical studies, and semaglutide 2·4 mg had been shown to promote weight loss in individuals with obesity or overweight with comorbidities in the STEP programme.

Added value of this study

To our knowledge, this is the first study to investigate the use of cagrilintide in combination with semaglutide 2·4 mg for weight management. We found use of cagrilintide in combination with semaglutide 2·4 mg was well tolerated in participants with overweight and obesity with an acceptable safety profile, and that this treatment combination can promote clinically significant dose-dependent weight loss.

Implications of all the available evidence

Our data support the further clinical development of this drug combination for weight management.

with concomitant treatment with cagrilintide and semaglutide 2·4 mg. The trial was done at one site, Altasciences Clinical Kansas, Overland Park, KS, USA, and had a 20-week treatment period, comprising a 16-week dose co-escalation period, a 4-week treatment period at target doses, and a 5-week follow-up period (appendix p 11). Eligible individuals were women of non-childbearing potential (not menstruating for 12 months or permanently sterile) or men using appropriate contraception, aged 18–55 years, with a body-mass index (BMI) of 27·0–39·9 kg/m², and considered otherwise healthy, as verified by medical history, physical examination, clinical laboratory tests, and electrocardiogram (ECG). Individuals aged 40 years or older with an estimated 10-year atherosclerotic cardiovascular disease risk of 5% or higher at screening were excluded from the trial. A full list of inclusion and exclusion criteria is in the appendix (pp 2–4).

See Online for appendix

The study was done in accordance with Good Clinical Practice guidelines and the ethical principles originating in the Declaration of Helsinki. Participants provided written informed consent to participate after a full explanation of the study had been given. The trial was approved by Midlands Independent Review Board. The protocol is included in the appendix (pp 15–127).

Randomisation and masking

Eligible participants were randomly assigned to treatment if they fulfilled all the prespecified randomisation criteria, including no consumption of alcohol within 48 h or smoking tobacco within 24 h before randomisation. A full list of randomisation criteria is in the appendix (p 5).

The trial included six sequential overlapping cohorts (appendix p 11). In each of the six cohorts, participants were randomly assigned (3:1) to once-weekly subcutaneous injections of cagrilintide at one of the six doses (0·16 mg [cohort 1], 0·30 mg [cohort 2], 0·60 mg [cohort 3], 1·2 mg [cohort 4], 2·4 mg [cohort 5], or 4·5 mg [cohort 6]) in combination with semaglutide 2·4 mg, or matched placebo of equal injection volume in combination with semaglutide 2·4 mg. The randomisation schedule was prepared by the sponsor using computer-generated randomisation lists printed on paper. Eligible participants were assigned a unique randomisation number in ascending numerical order at the trial site. Participants, investigators, and the sponsor were masked to treatment assignment. Treatment with semaglutide 2·4 mg was not masked.

Procedures

Participants were asked to maintain their usual lifestyle (diet, physical activity, and sleeping pattern) throughout the trial. In cohort 1, cagrilintide was initiated at 0·01 mg and escalated in 4-week intervals until the final dose was reached at week 16 (appendix p 6). Safety, tolerability, and pharmacokinetic parameters for the first 8–10 weeks of treatment were assessed before proceeding to each subsequent cohort. In cohorts 2–6, cagrilintide was initiated at 0·02, 0·04, 0·08, 0·16, and 0·45 mg, and escalated incrementally every 4 weeks until reaching the final doses of 0·30 mg in cohort 2, 0·60 mg in cohort 3, 1·2 mg in cohort 4, 2·4 mg in cohort 5, and 4·5 mg in cohort 6 at week 16.

Matched placebo was cagrilintide without drug substance but with the same excipients. Cagrilintide and placebo were administered using a NovoPen4 durable device (NovoFine Autocover needles 30G, 8 mm, Novo Nordisk A/S, Denmark), and semaglutide was administered using a PDS290 pre-filled pen-injector (NovoFine Autocover needles 30G, 8 mm, Novo Nordisk A/S, Denmark). Study medications were administered by investigators (MK) in the right side (cagrilintide or placebo) and the left side (semaglutide 2·4 mg) of the abdomen.

All treatment cohorts received once-weekly subcutaneous semaglutide (target dose of 2·4 mg) in addition to their randomised treatment. Both cagrilintide and semaglutide were co-escalated to their target doses over 16 weeks as simultaneous separate injections (appendix p 6). In cohorts 1–5, due to the potentially increased risk of gastrointestinal events with cagrilintide in combination with semaglutide 2·4 mg, the escalation regimen used for semaglutide 2·4 mg was more conservative than that used in the phase 3 trials investigating semaglutide 2·4 mg for weight management (STEP programme).[11] Semaglutide was initiated at 0·15 mg once weekly and escalated every 4 weeks (to 0·30, 0·60, and 1·2 mg) until the final dose of 2·4 mg was reached at week 16 (appendix p 6). In cohort 6 (cagrilintide 4·5 mg plus semaglutide 2·4 mg), the dose-escalation regimen used for semaglutide was similar to that used in the STEP programme, where semaglutide was initiated at 0·24 mg per week and escalated every 4 weeks (to 0·5, 1·0, and 1·7 mg) until the final dose of 2·4 mg was reached at week 16.

Initially the trial was designed to include five cohorts, but the protocol was amended on Oct 28, 2019, to include a sixth cohort to allow the investigation of exposure to a higher dose of cagrilintide (4·5 mg) in combination with semaglutide 2·4 mg. As mentioned, the semaglutide dose escalation in this cohort is different to that used in the other five cohorts to investigate if the escalation regimen used in the STEP programme could be applied successfully in combination with cagrilintide. This change in the escalation regimen was substantiated by the assessment of preliminary blinded safety and tolerability data from cohorts 1–5.

The dose ratio of cagrilintide to semaglutide 2·4 mg was fixed within each cohort and ranged from 0·07:1 in cohort 1 to around 1·9:1 in cohort 6 (appendix p 6). Within each cohort, sentinel dosing was used to minimise the risk of any unforeseen adverse events, such that four randomly selected participants were

initially given the dose of study drug (three with cagrilintide in combination with semaglutide 2·4 mg and one with matching placebo in combination with semaglutide 2·4 mg) and only after 72 h of monitoring were other participants in the cohort given the dose of study drug.

The participants attended six in-house visits, scheduled to take place at baseline and at weeks 4, 8, 12, 16, and 19. The remaining visits (21 in total) were once-weekly outpatient visits. For cohort 6, two planned in-house visits (at weeks 16 and 19) were converted into daily outpatient visits due to disruptions caused by the COVID-19 pandemic. All assessments were done as planned, except on day 134 (week 19), when pharmacokinetic samples at 8 h and 12 h were not collected. Reporting of adverse events and concomitant medications were assessed via telephone 8 h after dosing.

Blood samples for pharmacokinetic testing were collected before dosing at baseline (week 0) and at weekly visits, and after the last dose (week 19) at 4, 8, 12, 24, 48, 72, 96, 168, 336, 504, 672, 840, and 1008 h after dosing. For testing of semaglutide pharmacokinetic parameters, blood samples were collected in K3EDTA tubes (Vacuette, Greiner Bio-One North America, Monroe, NC, USA) and analysed at Celerion Switzerland AG (Fehraltorf Switzerland), and for cagrilintide, blood samples were collected in K2EDTA tubes (BD P800 Hemogard, BD Biosciences, San Jose, CA, USA) and analysed at Novo Nordisk A/S (Måløv, Denmark). Plasma concentrations were assayed using in-house assays validated according to US Food and Drug Administration and Europen Medicines Agency guidelines.

Physical examinations, done by the investigator (MK) and sub-investigators at the site (physicians and nurses), were done at baseline and at weeks 4, 8, 12, 16, 20, and at follow-up, and included assessments of general appearance, thyroid gland, lymph node palpation, head, ears, eyes, nose, throat, neck, and skin, and respiratory, cardiovascular, gastrointestinal (including mouth), musculoskeletal, central, and peripheral nervous system. Vital signs (body temperature [ear], systolic and diastolic blood pressure, and pulse rate) were measured at baseline and every week throughout the trial. 12-lead ECG was done at baseline and at weeks 4, 8, 12, 16, and 20, and at follow-up. Injection-site reactions were assessed at baseline and every week until week 20 and at follow-up. Bodyweight measurements were taken at baseline and every 2 weeks until week 20, and again at follow-up. Haematology, biochemistry, coagulation parameters, lipids, hormones (including aldosterone and renin activity levels), and urinalysis were measured at baseline, and every 2 weeks until week 20, and again at follow-up, and analysed at Quest Diagnostics (Overland Park, KS, USA). Fasting plasma glucose, insulin, C-peptide, glucagon (all analysed at Quest Diagnostics), and fasting leptin and soluble leptin receptor (analysed at Celerion Switzerland AG) were measured at baseline and weeks 4, 8, 12, 16, and 20, and at follow-up. Glycated haemoglobin was measured at baseline, weeks 8 and 20, and at follow-up, and analysed at Quest Diagnostics. Anticagrilintide antibodies were measured at baseline and at follow-up and were analysed at Novo Nordisk A/S. Participants completed paper-based patient-reported outcomes questionnaires (Columbia – Suicide Severity Rating Scale [C-SSRS] and Patient Health Questionnaire [PHQ-9]) at baseline and at weeks 6, 13, and 20, and at follow-up.

Outcomes

The primary endpoint was the number of treatment-emergent adverse events from baseline (week 0) to the end of the follow-up period (week 25). Adverse events were either observed by the investigator or reported by the participant (spontaneously in-person or via telephone call to site staff and at each trial visit). Adverse events were defined using prespecified criteria, which are detailed in the protocol (appendix pp 97–98).

Secondary pharmacokinetic endpoints were assessed from the day of last dose (week 19) until the end of treatment (week 20) and were: area under the plasma concentration-time curve from 0 to 168 h at steady state ($AUC_{0–168\ h}$) for cagrilintide and semaglutide, and the maximum concentration (C_{max}) of cagrilintide and semaglutide in plasma at steady state.

Exploratory pharmacokinetic endpoints were assessed from the day of last dose (week 19) to the follow-up visit (week 25) and were: cagrilintide and semaglutide half-life at steady state, time to C_{max} in plasma at steady state, plasma clearance, and volume of distribution during elimination and at steady state. Exploratory pharmacodynamic endpoints included change from baseline to week 20 in bodyweight, glucose metabolism (glycated haemoglobin and fasting glucose, insulin, C-peptide, and glucagon), and hormones (fasting leptin and soluble leptin receptor). Endogenous amylin was also prespecified as an exploratory pharmacodynamic endpoint but could not be analysed due to limitations of the available assays. Additional exploratory safety endpoints were change from baseline to week 20 in clinical laboratory tests, vital signs, ECG, physical examinations, and patient-reported outcomes (C-SSRS and PHQ-9). The occurrence of anticagrilintide antibodies from baseline to the end of follow-up (week 25) was also assessed to determine the functional activity of cagrilintide in relation to pharmacokinetic and pharmacodynamic parameters, and immunogenic response to cagrilintide treatment.

Statistical analysis

The sample size of this study was not based on a formal statistical assessment because of the exploratory nature of the trial. Nevertheless, a sample size of 96 participants with an estimated withdrawal rate of 25% was considered sufficient to assess the safety and tolerability results. We summarised baseline characteristics using descriptive statistics, using number and proportion for categorical

data, and mean (SD) for continuous data. We analysed safety endpoints in all participants who were exposed to at least one dose of trial product (safety analysis dataset) and summarised these data using descriptive statistics. All participants in the safety analysis dataset contributed to the assessment as treated.

We analysed pharmacokinetic and pharmacodynamic endpoints in all participants randomly assigned to treatment who received at least one dose of trial product (full analysis dataset) using descriptive statistics. All participants in the full analysis dataset contributed to the assessment as treated. We plotted individual and mean curves for the concentration-time profiles over time using both linear and log-linear concentration scales. For $AUC_{0-168\ h}$ and C_{max}, we logarithmically transformed the values and analysed them using an analysis-of-variance model with randomly assigned treatment as factor, where the residual variance was allowed to depend on treatment group. We back-transformed the estimated least square means and present them along with the respective 95% CIs. We present treatment ratios for $AUC_{0-168\ h}$ and C_{max} with corresponding 95% CIs. We assessed the dose

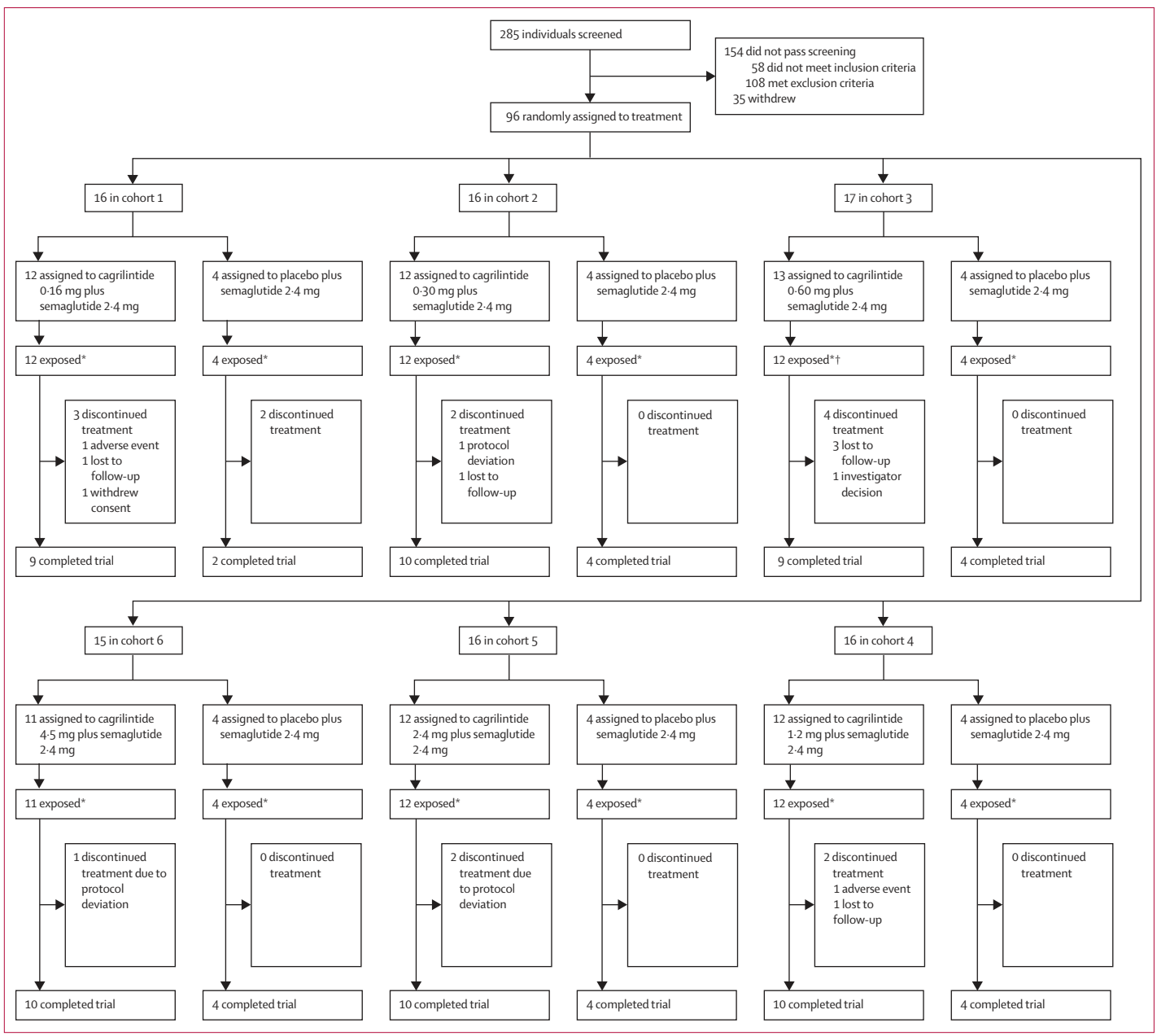

Figure 1: **Trial profile**
*Full and safety analysis datasets. †One participant randomly assigned to treatment was not exposed to their assigned treatment.

proportionality of cagrilintide for $AUC_{0-168\ h}$ and C_{max} by estimating the slope β in the linear regression model of the logarithm of the relevant endpoint versus log(dose), where β=1 indicates dose-proportional increases in $AUC_{0-168\ h}$ or C_{max}. We report the estimated quantity 2^{β} with 95% CI.

For analyses of the primary endpoint and the secondary and exploratory endpoints of safety, pharmacokinetics, and pharmacodynamics, except for changes in bodyweight, participants who were given placebo in combination with semaglutide 2·4 mg were pooled across cohorts. We analysed changes in bodyweight using a mixed model for repeated measurements, where all changes in bodyweight measurements were entered as dependent variables, using randomly assigned treatment, visit number, and the interaction between them as factors, and baseline bodyweight (in kg) as a covariate. We present data as least square means with SEs, and we calculated the estimated treatment differences with corresponding 95% CIs. We did two main analyses of bodyweight data. The primary analysis included bodyweight data for cohorts 1–5, which were compared with the cohorts 1–5 pooled placebo in combination with semaglutide 2·4 mg group, and for cohort 6, which was compared with its matched placebo in combination with semaglutide 2·4 mg group. The secondary analysis included joint bodyweight data from all six cohorts compared with the cohorts 1–6 pooled placebo in combination with semaglutide 2·4 mg group. We decided to separately analyse cohort 6 to account for the different escalation regimen of semaglutide in this cohort. For bodyweight analyses of cohort 6, we incorporated within-participant repeated measurements using a Toeplitz covariance model because of the small number of observations in a single cohort. For the remaining analyses of bodyweight, we used an unstructured covariance matrix.

We used a 5% significance level, but no testing of hypotheses was prespecified. We used SAS version 9.4 for all analyses. This study is registered with ClinicalTrials.gov, NCT03600480.

Role of the funding source

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

Results

Between July 25, 2018, and Dec 17, 2019, 285 individuals were screened and 96 were eligible and randomly assigned to treatment. 95 (99%) of 96 were exposed to treatment and were included in the full and safety analysis

	Cohort 1: cagrilintide 0·16 mg plus semaglutide 2·4 mg (n=12)	Cohort 2: cagrilintide 0·30 mg plus semaglutide 2·4 mg (n=12)	Cohort 3: cagrilintide 0·60 mg plus semaglutide 2·4 mg (n=12)	Cohort 4: cagrilintide 1·2 mg plus semaglutide 2·4 mg (n=12)	Cohort 5: cagrilintide 2·4 mg plus semaglutide 2·4 mg (n=12)	Cohort 6: cagrilintide 4·5 mg plus semaglutide 2·4 mg (n=11)	Pooled placebo cohorts 1–6: placebo plus semaglutide 2·4 mg (n=24)	Total (n=95)
Age, years	43·0 (9·2)	38·4 (10·4)	40·0 (8·3)	41·3 (11·1)	43·0 (8·1)	37·0 (9·7)	41·0 (8·8)	40·6 (9·2)
Sex								
Female	4 (33%)	5 (42%)	6 (50%)	6 (50%)	7 (58%)	3 (27%)	8 (33%)	39 (41%)
Male	8 (67%)	7 (58%)	6 (50%)	6 (50%)	5 (42%)	8 (73%)	16 (67%)	56 (59%)
Race								
Black or African American	5 (42%)	4 (33%)	8 (67%)	8 (67%)	6 (50%)	6 (55%)	14 (58%)	51 (54%)
White	7 (58%)	7 (58%)	3 (25%)	3 (25%)	6 (50%)	5 (45%)	10 (42%)	41 (43%)
American Indian or Alaska Native	0	1 (8%)	1 (8%)	0	0	0	0	2 (2%)
Other	0	0	0	1 (8%)	0	0	0	1 (1%)
Ethnicity								
Hispanic or Latino	1 (8%)	3 (25%)	0	0	0	1 (9%)	0	5 (5%)
Other	11 (92%)	9 (75%)	12 (100%)	12 (100%)	12 (100%)	10 (91%)	24 (100%)	90 (95%)
Bodyweight, kg	93·0 (10·6)	92·9 (11·7)	95·3 (11·7)	95·1 (14·4)	92·1 (11·9)	98·0 (17·3)	99·6 (15·6)	95·7 (13·6)
BMI, kg/m²	31·0 (3·2)	30·8 (2·3)	33·3 (3·7)	32·6 (4·4)	32·2 (2·5)	33·0 (4·2)	32·2 (3·0)	32·1 (3·4)
HbA_{1c}								
%	5·4 (0·4)	5·3 (0·3)	5·4 (0·4)	5·5 (0·4)	5·2 (0·4)	5·2 (0·4)	5·4 (0·4)	5·3 (0·4)
mmol/mol	35·0 (4·0)	34·8 (3·8)	35·2 (4·9)	36·4 (4·4)	33·0 (4·1)	33·6 (3·9)	35·7 (3·9)	34·9 (4·1)
Lipids								
HDL-C, mmol/L	1·3 (0·3)	1·2 (0·5)	1·3 (0·3)	1·3 (0·3)	1·4 (0·4)	1·2 (0·3)	1·3 (0·3)	1·3 (0·3)
LDL-C, mmol/L	3·2 (0·5	3·2 (0·7)	2·8 (0·7)	3·3 (0·7)	3·2 (0·6)	3·1 (0·5)	3·4 (0·6)	3·2 (0·6)
Triglycerides, mmol/L	1·48 (0·77)	1·69 (0·69)	1·32 (1·25)	1·19 (0·35)	1·19 (0·37)	1·22 (0·31)	1·33 (0·86)	1·35 (0·74)

Data are mean (SD) or n (%), unless otherwise specified. Data for participants receiving treatment with placebo in combination with semaglutide 2·4 mg were pooled across cohorts; subset analyses of placebo groups for cohorts 1–5 (n=20) and cohort 6 (n=4) did not identify any differences in baseline characteristics (data not shown). BMI=body-mass index. HbA_{1c}=glycated haemoglobin. HDL-C=high-density lipoprotein cholesterol. LDL-C=low-density lipoprotein cholesterol.

Table 1: **Demographics and baseline characteristics of participants who received at least one dose of study drug (safety and full analysis datasets)**

	Cohort 1: cagrilintide 0·16 mg plus semaglutide 2·4 mg (n=12)		Cohort 2: cagrilintide 0·30 mg plus semaglutide 2·4 mg (n=12)		Cohort 3: cagrilintide 0·60 mg plus semaglutide 2·4 mg (n=12)		Cohort 4: cagrilintide 1·2 mg plus semaglutide 2·4 mg (n=12)		Cohort 5: cagrilintide 2·4 mg plus semaglutide 2·4 mg (n=12)		Cohort 6: cagrilintide 4·5 mg plus semaglutide 2·4 mg (n=11)		Pooled placebo cohorts 1–6: placebo plus semaglutide 2·4 mg (n=24)	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Adverse event	11 (92%)	37	12 (100%)	84	11 (92%)	88	12 (100%)	60	12 (100%)	89	11 (100%)	76	23 (96%)	132
Severity														
Mild	11 (92%)	36	12 (100%)	77	11 (92%)	80	12 (100%)	53	12 (100%)	82	11 (100%)	66	23 (96%)	116
Moderate	1 (8%)	1	4 (33%)	7	4 (33%)	8	5 (42%)	6	4 (33%)	7	4 (36%)	10	8 (33%)	15
Severe*	0	0	0	0	0	0	1 (8%)	1	0	0	0	0	1 (4%)	1
Serious adverse event†	0	0	0	0	0	0	1 (8%)	1	0	0	0	0	0	0
Participants with ≥1 adverse event leading to withdrawal	1 (8%)	1	0	0	0	0	1 (8%)	1	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Adverse events of gastrointestinal disorders system organ class	7 (58%)	12	10 (83%)	38	7 (58%)	30	10 (83%)	19	11 (92%)	33	9 (82%)	25	19 (79%)	50
Most common events by preferred term‡§														
Injection-site reaction	4 (33%)	7	4 (33%)	8	2 (17%)	19	2 (17%)	4	6 (50%)	17	3 (27%)	7	7 (29%)	10
Nausea	6 (50%)	6	9 (75%)	13	6 (50%)	10	6 (50%)	7	10 (83%)	12	8 (73%)	10	8 (33%)	9
Decreased appetite	7 (58%)	8	8 (67%)	9	7 (58%)	7	6 (50%)	6	12 (100%)	12	9 (82%)	9	14 (58%)	14
Early satiety	1 (8%)	1	3 (25%)	3	4 (33%)	4	8 (67%)	8	8 (67%)	8	10 (91%)	10	9 (38%)	9
Vomiting	0	0	4 (33%)	8	2 (17%)	5	1 (8%)	2	9 (75%)	12	4 (36%)	11	3 (13%)	5
Headache	1 (8%)	1	6 (50%)	7	3 (25%)	4	2 (17%)	2	2 (17%)	3	2 (18%)	8	6 (25%)	9
Dyspepsia	2 (17%)	3	4 (33%)	4	5 (42%)	5	2 (17%)	2	4 (33%)	4	2 (18%)	2	8 (33%)	12
Diarrhoea	0	0	2 (17%)	6	2 (17%)	4	1 (8%)	2	2 (17%)	2	0	0	9 (38%)	14
Abdominal pain	1 (8%)	1	3 (25%)	4	1 (8%)	2	1 (8%)	1	1 (8%)	1	0	0	2 (8%)	2
Fatigue	0	0	0	0	3 (25%)	3	3 (25%)	3	0	0	3 (27%)	3	1 (4%)	1
Dizziness	0	0	3 (25%)	3	2 (17%)	3	0	0	0	0	0	0	2 (8%)	2

Data are n (%), where n is participants with one or more adverse event, and number of events. Data for participants receiving treatment with placebo in combination with semaglutide 2·4 mg were pooled across cohorts; subset analyses of placebo groups for cohorts 1–5 (n=20) and cohort 6 (n=4) did not identify any differences in frequency of adverse events (data not shown). *Severe adverse events included meningitis (cohort 4) and serum creatinine increased (pooled placebo). †The serious adverse event was meningitis (cohort 4). ‡Adverse events occurring in at least 20% of participants in any group. §Adverse event definitions are listed in the protocol (appendix pp 97–98).

Table 2: **Treatment-emergent adverse events**

datasets (figure 1). Overall, 80 (83%) of 96 participants completed the trial. Of those randomly assigned to treatment, 16 (17%) withdrew or were withdrawn from the trial and two (2%) discontinued treatment due to adverse events. Withdrawal from the trial occurred similarly across all treatment groups (figure 1).

56 (59%) of 95 participants were men, 51 (54%) were Black or African American, and 41 (43%) were White. The mean age was 40·6 years (SD 9·2), mean bodyweight was 95·7 kg, (13·6), and mean BMI was 32·1 kg/m² (3·4). Baseline characteristics were generally balanced across treatment groups (table 1).

566 treatment-emergent adverse events were reported (table 2). The number of adverse events with cagrilintide 0·16–4·5 mg in combination with semaglutide 2·4 mg ranged from 37 events in 11 (92%) of 12 participants given cagrilintide 0·16 mg to 89 events in 12 (100%) of 12 participants given cagrilintide 2·4 mg, both in combination with semaglutide 2·4 mg. The number of events with placebo in combination with semaglutide 2·4 mg was 132, reported in 23 (96%) of 24 participants (table 2). Most adverse events reported were mild or moderate in severity, with no apparent differences between treatment groups. Two severe adverse events were reported in two (2%) participants, one with cagrilintide 1·2 mg in combination with semaglutide 2·4 mg (cohort 4; viral meningitis) and one in the pooled placebo in combination with semaglutide 2·4 mg group (serum creatinine increased). Both the events were deemed unlikely to be related to study treatment by the study investigator (MK). The severe adverse event of viral meningitis was also a serious adverse event that led to treatment withdrawal. No other serious adverse events were reported. One other adverse event occurred that led to treatment withdrawal, which was non-cardiac chest pain in one participant given cagrilintide 0·16 mg in combination with semaglutide 2·4 mg (cohort 1). The event was mild in severity, and assessed by the study

investigator as possibly related to trial product. For both events leading to treatment withdrawal, the participants recovered fully and the events were resolved. Generally, we did not observe any patterns in the duration of adverse events between treatment groups (data not shown). Few events reoccurred in the same participants, but some had the same adverse event for a longer period. No deaths were reported during the trial period.

The most common adverse events reported were gastrointestinal disorders (207 events in 73 [77%] of 95 participants), most frequently nausea (67 events in 53 [56%] participants), vomiting (43 events in 23 [24%] participants), and dyspepsia (32 events in 27 [28%] participants; table 2). Gastrointestinal disorders were not dependent on cagrilintide dose, with 12–38 events occurring in seven (58%) of 12 participants to 11 (92%) of 12 participants given cagrilintide 0·16–4·5 mg in combination with semaglutide 2·4 mg, compared with 50 events occurring in 19 (79%) of 24 pooled participants given placebo in combination with semaglutide 2·4 mg. All gastrointestinal disorder events were mild to moderate in severity.

Decreased appetite was reported as an adverse event more frequently with higher doses of cagrilintide (with 12 events occurring in 12 [100%] of 12 participants given cagrilintide 2·4 mg in combination with semaglutide 2·4 mg and nine events occurring in nine [82%] of 11 participants given cagrilintide 4·5 mg in combination with semaglutide 2·4 mg) than with placebo in combination with semaglutide 2·4 mg (14 events in 14 [58%] participants; table 2). Early satiety was more frequently reported with cagrilintide at doses equal to or higher than 1·2 mg in combination with semaglutide 2·4 mg than with placebo in combination with semaglutide 2·4 mg (table 2). All injection-site reactions were mild in severity and most were deemed possibly or probably related to cagrilintide administration. Injection-site reactions were not dose-dependent (table 2). The most common injection site-reactions were ecchymosis (34 events in 22 [79%] of 28 participants who reported injection-site reactions) and redness (30 events in nine [32%] participants).

Mean plasma-concentration profiles of cagrilintide show that exposure to cagrilintide increased with increasing doses and was proportional for both $AUC_{0-168\ h}$ and C_{max}

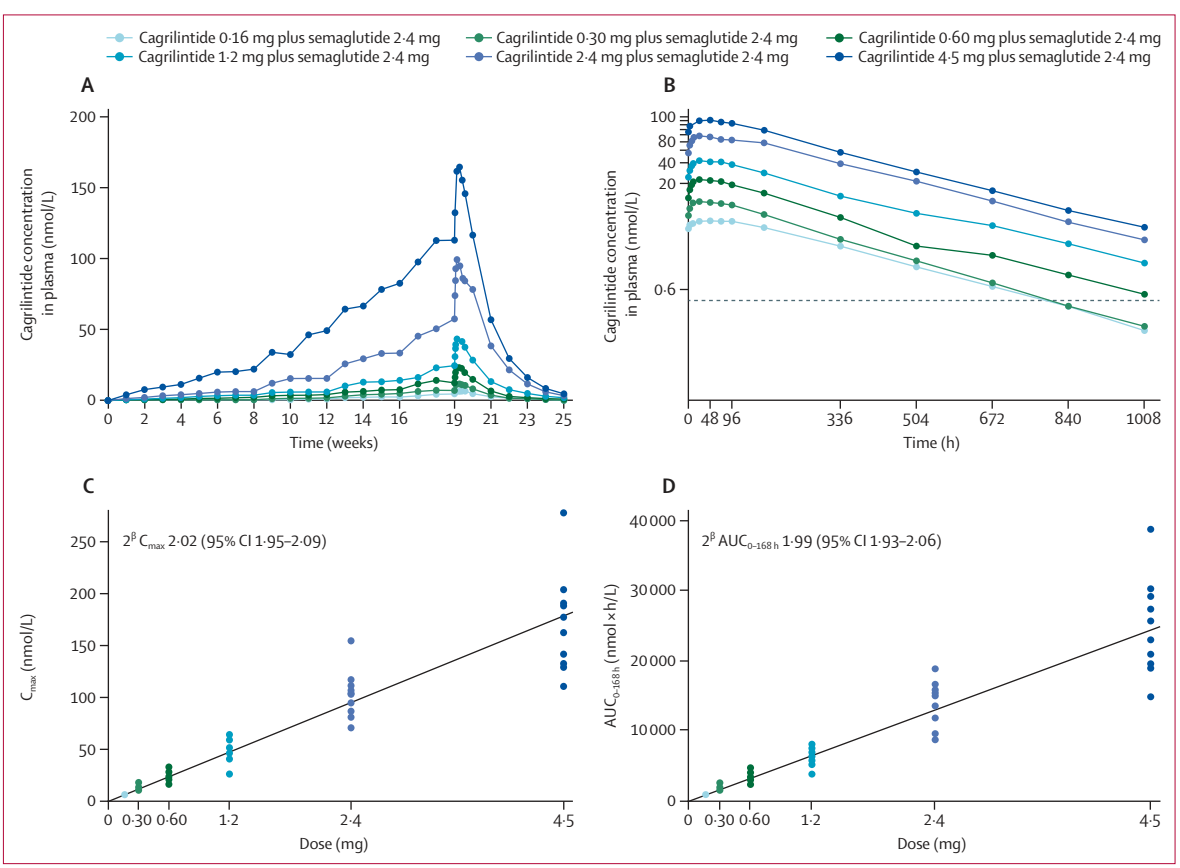

Figure 2: **Selected pharmacokinetic endpoints of cagrilintide**
Mean plasma concentration (A) and elimination (B) profiles after subcutaneous administration of six different doses of cagrilintide (0·16, 0·30, 0·60, 1·2, 2·4, and 4·5 mg) in combination with semaglutide 2·4 mg. Scatter plots showing dose versus C_{max} (C) and $AUC_{0-168\ h}$ (D) of cagrilintide. Horizontal dotted lines show the lower limit of quantification. Values below the lower limit of quantification were imputed. $AUC_{0-168\ h}$=area under the plasma concentration-time curve from baseline to 168 h. C_{max}=maximum concentration.

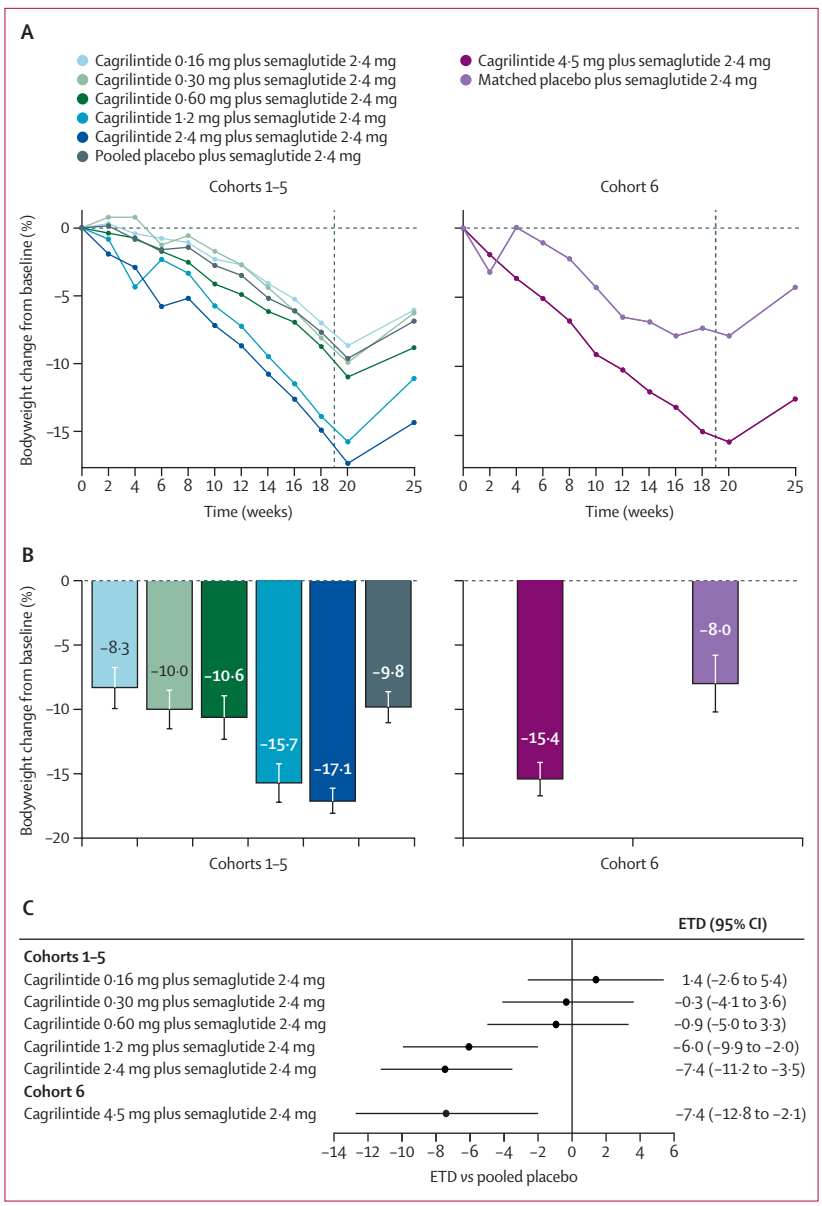

Figure 3: **Changes in bodyweight from baseline (primary analysis)**
Mean observed changes in bodyweight with cagrilintide 0·16–4·5 mg in combination with semaglutide 2·4 mg from baseline by treatment week (A) and mean estimated changes in bodyweight from baseline to week 20 (B) in cohorts 1–5 versus pooled placebo and cohort 6 versus matched placebo. (C) ETD in percentage bodyweight with cagrilintide 0·16–4·5 mg in combination with semaglutide 2·4 mg in cohorts 1–5 versus pooled placebo and cohort 6 versus matched placebo. In panel A, first dosing of cagrilintide and semaglutide was on week 0 and the vertical dotted line shows the last dosing of cagrilintide and semaglutide. In panel B, bars show percentage bodyweight changes, and error bars show SEs. ETD=estimated treatment difference.

(figure 2). Despite the variability within groups, treatment ratios for comparisons of $AUC_{0–168\ h}$ and C_{max} were within the 95% CIs, supporting dose proportionality. $AUC_{0–168\ h}$ ranged from 926 nmol×h/L to 24271 nmol×h/L, and C_{max} ranged from 6·14 nmol/L to 170 nmol/L with cagrilintide 0·16–4·5 mg in weeks 19–20 (appendix p 7). $AUC_{0–168\ h}$ ranged from 12757 nmol×h/L to 15305 nmol×h/L, and C_{max} ranged from 96·4 nmol/L to 120 nmol/L with semaglutide 2·4 mg (appendix p 7). Cagrilintide dose did not affect semaglutide exposure and elimination (appendix p 12).

Cagrilintide was slowly absorbed after administration, with median time to achieve C_{max} between 24 h and 25 h for cagrilintide 0·30–4·5 mg and 72 h for cagrilintide 0·16 mg. For semaglutide, median time to C_{max} ranged 12–24 h. Cagrilintide half-life ranged 159–195 h and semaglutide half-life ranged 145–165 h across treatment groups (appendix p 7). Plasma clearance and volume of distribution for both cagrilintide and semaglutide were similar across treatment groups (appendix p 7).

We analysed bodyweight data separately for cohorts 1–5, which were compared with the cohorts 1–5 pooled placebo in combination with semaglutide 2·4 mg group, and for cohort 6, which was compared with its matched placebo in combination with semaglutide 2·4 mg group, due to the different escalation regimen used for semaglutide (primary analysis; figure 3, table 3). Data from all six cohorts were also compared with the cohorts 1–6 pooled placebo in combination with semaglutide 2·4 mg group for the secondary analysis (table 3; appendix p 13). In both analyses, across all treatment groups, bodyweight reductions from baseline to the end of treatment (week 20) were continuous and generally greater with higher cagrilintide doses than with lower doses (figure 3; appendix p 13). At week 20, in cohorts 1–5, participants who were given cagrilintide 0·16–2·4 mg in combination with semaglutide 2·4 mg had mean bodyweight changes ranging –8·3% (SE 1·6; –8·0 kg [SE 1·5]) to –17·1% (1·5; –15·9 kg [1·4]) and were highest with cagrilintide 1·2 or 2·4 mg in combination with semaglutide 2·4 mg compared with pooled placebo in combination with semaglutide 2·4 mg (figure 3; table 3). In cohort 6, mean bodyweight changes with cagrilintide 4·5 mg in combination with semaglutide 2·4 mg were –15·4% (1·3; –15·0 kg [1·3]) *vs* –8·0% (2·2; –7·8 kg [2·2]) with matched placebo in combination with semaglutide 2·4 mg (figure 3, table 3).

Glycaemic parameters improved in all treatment groups, independently of cagrilintide dose (table 3). Changes from baseline in fasting leptin and fasting soluble leptin receptor did not depend on cagrilintide dose across treatment groups (table 3).

At week 20, across all treatment groups, systolic and diastolic blood pressure reduced from baseline, whereas heart rate increased from baseline in all treatment groups, independent of cagrilintide dose (appendix p 14). Mean aldosterone levels increased from baseline with cagrilintide in combination with semaglutide 2·4 mg in a dose-dependent manner but remained within the normal reference ranges and decreased after approximately 2 weeks of receiving treatment, reaching near baseline levels at follow-up. The increase in aldosterone did not lead to dose-dependent changes in sodium or potassium levels (data not shown). No changes in renin activity were observed during the trial (appendix p 14). Total cholesterol,

	Cohort 1: cagrilintide 0·16 mg plus semaglutide 2·4 mg (n=12)	Cohort 2: cagrilintide 0·30 mg plus semaglutide 2·4 mg (n=12)	Cohort 3: cagrilintide 0·60 mg plus semaglutide 2·4 mg (n=12)	Cohort 4: cagrilintide 1·2 mg plus semaglutide 2·4 mg (n=12)	Cohort 5: cagrilintide 2·4 mg plus semaglutide 2·4 mg (n=12)	Pooled placebo cohorts 1–5: placebo plus semaglutide 2·4 mg (n=20)	Cohort 6: cagrilintide 4·5 mg plus semaglutide 2·4 mg (n=11)	Matched placebo (cohort 6): placebo plus semaglutide 2·4 mg (n=4)	Pooled placebo cohorts 1–6: placebo plus semaglutide 2·4 mg (n=24)
Bodyweight, %									
Mean (SE) change from baseline to week 20	−8·3 (1·6)	−10·0 (1·5)	−10·6 (1·7)	−15·7 (1·6)	−17·1 (1·5)	−9·8 (1·2)	−15·4 (1·3)	−8·0 (2·2)	−9·5 (1·0)
Minimum change	−16·2	−14·9	−17·7	−22·4	−24·8	−20·5	−22·4	−13·2	−20·5
Maximum change	−1·3	−2·4	−4·4	−8·0	−9·4	2·5	−8·4	−3·8	2·5
ETD (95% CI) *vs* matched placebo	1·4 (−2·6 to 5·4)	−0·3 (−4·1 to 3·6)	−0·9 (−5·0 to 3·3)	−6·0 (−9·9 to −2·0)	−7·4 (−11·2 to −3·5)	..	−7·4 (−12·8 to −2·1)	..	..
Bodyweight, kg									
Mean (SE) change from baseline to week 20	−8·0 (1·5)	−9·3 (1·4)	−10·1 (1·6)	−14·6 (1·5)	−15·9 (1·4)	−8·9 (1·1)	−15·0 (1·3)	−7·8 (2·2)	−8·7 (1·0)
Minimum change	−16·9	−12·8	−15·7	−21·0	−23·3	−20·2	−22·4	−13·0	−20·2
Maximum change	−1·1	−2·4	−3·7	−7·6	−9·3	2·4	−9·4	−3·7	2·4
ETD (95% CI) *vs* matched placebo	0·9 (−2·9 to 4·7)	−0·4 (−4·0 to 3·1)	−1·2 (−5·1 to 2·7)	−5·7 (−9·5 to −2·0)	−7·0 (−10·6 to −3·4)	..	−7·3 (−12·5 to −2·0)	..	..
BMI, kg/m²	−2·6 (1·4)	−3·0 (1·1)	−3·7 (1·6)	−4·9 (1·2)	−5·6 (1·7)	−3·1 (2·1)	−5·0 (1·2)	−2·5 (1·3)	−3·0 (2·0)
HbA_{1c}									
%	0·0 (0·3)	−0·2 (0·1)	−0·4 (0·1)	−0·3 (0·1)	−0·3 (0·2)	NA	−0·3 (0·1)	NA	−0·2 (0·2)
mmol/mol	−0·5 (3·1)	−1·8 (1·6)	−4·0 (1·5)	−2·8 (1·4)	−2·7 (1·8)	NA	−3·3 (1·3)	NA	−2·4 (2·0)
Fasting plasma glucose, mmol/L	−0·3 (0·6)	−0·3 (0·5)	−0·3 (0·7)	−0·2 (0·4)	−0·6 (0·5)	NA	−0·2 (0·3)	NA	−0·3 (0·5)
Fasting insulin, pmol/L	−7·9 (47·1)	−5·9 (64·0)	−19·1 (26·5)	15·8 (26·1)	−22·4 (26·5)	NA	−17·2 (24·8)	NA	−11·2 (47·7)
Fasting C-peptide, nmol/L	−0·02 (0·16)	0·06 (0·23)	−0·06 (0·17)	0·13 (0·14)	−0·12 (0·17)	NA	−0·08 (0·11)	NA	−0·01 (0·27)
Fasting glucagon, ng/L	−19 (24)	−20 (13)	−7 (21)	−12 (17)	−5 (18)	NA	−7 (14)	NA	−15 (25)
Fasting leptin, ng/mL	−14·6 (11·0)	−15·0 (10·1)	−17·7 (17·0)	−15·8 (7·7)	−21·6 (17·0)	NA	−12·1 (19·9)	NA	−12·8 (9·9)
Fasting soluble leptin receptor, ng/mL	−0·9 (6·2)	1·9 (4·5)	0 (7·4)	5·7 (8·6)	5·8 (7·5)	NA	1·6 (4·7)	NA	−0·7 (5·2)

Data are mean (SD) change from baseline to week 20, unless otherwise specified. BMI=body-mass index. ETD=estimated treatment difference. HbA_{1c}=glycated haemoglobin. NA=not applicable.

Table 3: **Selected exploratory pharmacodynamic endpoints**

high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides decreased in all treatment groups, independent of cagrilintide dose (appendix p 9).

One severe event of increased blood creatinine was reported with placebo in combination with semaglutide 2·4 mg and was assessed to not be related to treatment. No clinically relevant changes were noted in electrolytes or other biochemistry or haematology parameters (data not shown). No clinically relevant changes were seen in physical examinations or ECG across treatment groups (data not shown). Patient-reported outcomes did not indicate any safety concerns, although one participant given cagrilintide 0·60 mg in combination with semaglutide 2·4 mg showed signs of moderate depression during the trial (data not shown).

The proportion of participants with anticagrilintide antibodies increased with cagrilintide dose and time of exposure and were confirmed at week 20 in one (11%) of 12 participants to seven (64%) of 11 participants given cagrilintide 0·16–4·5 mg in combination with semaglutide 2·4 mg. At follow-up (week 25), most antibodies were cross-reactive with native amylin and none were neutralising against cagrilintide (appendix p 10).

Discussion

To our knowledge, this is the first randomised trial to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of different doses of the novel long-acting once-weekly amylin analogue, cagrilintide, in combination with semaglutide 2·4 mg in adults with overweight or obesity. In this small, single-centre, phase 1b trial, treatment with cagrilintide 0·16–4·5 mg in combination with semaglutide 2·4 mg for 20 weeks (including a 16-week co-escalation period) was generally well tolerated in participants with overweight or obesity without complications.

Overall, no unexpected safety concerns were identified in the trial and no apparent difference was seen in the number of adverse events across treatment groups. Most adverse events were mild or moderate in severity. The occurrence of gastrointestinal disorders was expected because of the known effect of semaglutide and cagrilintide on gastrointestinal motility, and was in line

with previous observations with semaglutide and cagrilintide in individuals with overweight or obesity.[22,23] The addition of cagrilintide to semaglutide was associated with increased nausea and vomiting, but these events were mild or moderate in severity and the proportion of participants reporting gastrointestinal disorders did not increase with cagrilintide dose, by contrast with observations from a previous phase 2 trial investigating the efficacy and safety of cagrilintide as monotherapy for weight loss.[22] The conventional semaglutide dose-escalation regimen used in cohort 6, which was used in the STEP programme,[11] did not seem to affect the occurrence of gastrointestinal side-effects compared with the more conservative dose-escalation regimen used in cohorts 1–5. Thus, these data support the use of the conventional semaglutide dose-escalation regimen for the further investigation of treatment combination with cagrilintide. All injection-site reactions were mild in severity and did not depend on cagrilintide dose. The only serious adverse event reported in the trial (viral meningitis) occurred in a participant in the cagrilintide 1·2 mg in combination with semaglutide 2·4 mg group and was resolved and deemed unlikely to be related to the study treatment. An increased proportion of participants had anticagrilintide antibodies present with increasing doses of cagrilintide and longer time of exposure, but none of the antibodies were neutralising and were not thought to be associated with reduced efficacy or any safety concerns.

Similar to the mode of action of native amylin,[24] the addition of cagrilintide was associated with dose-dependent increases in mean aldosterone concentrations, indicating activation of the renin-angiotensin-aldosterone system (RAAS). These increases, which were within the normal range, occurred at cagrilintide treatment initiation and dose escalation, but were transient and decreased after approximately 2 weeks, with near baseline levels recorded at follow-up. Importantly, RAAS activation did not lead to increases in blood pressure or changes in electrolytes, consistent with human studies of native amylin[24] and a previous phase 2 clinical trial using cagrilintide as monotherapy for weight management in individuals with overweight or obesity.[22] Increases in heart rate were observed in all treatment groups regardless of cagrilintide treatment, consistent with semaglutide effects described in previous studies in individuals with obesity[13] and type 2 diabetes.[25]

The elimination half-life of cagrilintide was around 7–8 days, with maximum exposure 24–25 h after administration, making it suitable for once-weekly dosing. Semaglutide exposure and elimination were not affected by concomitant cagrilintide administration, supporting further clinical development of the cagrilintide and semaglutide 2·4 mg combination for weight management.

In the large, phase 3 STEP 1 trial, treatment with semaglutide 2·4 mg for 68 weeks led to significant mean weight loss of 12·4% (12·7 kg) relative to placebo.[14] In our study, we assessed changes in bodyweight as an exploratory endpoint and found mean weight reductions with cagrilintide in combination with semaglutide 2·4 mg and without lifestyle interventions were as high as 17·1% (15·9 kg; with cagrilintide 2·4 mg plus semaglutide 2·4 mg) after 20 weeks of treatment. Thus, the combination of cagrilintide with semaglutide 2·4 mg has the potential to further close the gap between the available pharmacological options for weight management and bariatric surgery,[26] with clinically significant weight reductions in just 20 weeks. Notably, in cohort 6, weight loss in the placebo in combination with semaglutide 2·4 mg group seemed to plateau at approximately 16 weeks, which is earlier than that seen in the STEP trials,[14,27] and could have been driven by the small sample size. Mean bodyweight reductions in this trial were also greater than those found in 26 weeks with cagrilintide alone (up to 7·8% reduction in bodyweight relative to placebo with 4·5 mg dose).[22]

Decreased appetite and increased satiety were more frequently reported with cagrilintide and semaglutide 2·4 mg in a dose-dependent manner than with placebo in combination with semaglutide 2·4 mg and at higher doses of cagrilintide, consistent with the role of semaglutide and native amylin as satiation signals.[15,21] The effects of semaglutide on bodyweight are mediated by a reduction in appetite and energy intake, primarily through its action on GLP-1 receptors in the hypothalamus,[15] but also other regions of the brain (area postrema, nucleus of the solitary tract, and parabrachial nuclei).[28] Cagrilintide induces satiety and satiation, and is thought to affect food choices by targeting both homoeostatic and hedonic regions of the brain.[21] Although both semaglutide and cagrilintide induce satiety, they operate in different regions of the brain, which might result in an additive effect on appetite regulation. Moreover, the potential for cagrilintide to affect food choices might contribute to the modification of eating behaviours, further improving treatment efficacy. Thus, combining treatments with different but complementary mechanisms of action has the potential to increase efficacy. Furthermore, given the heterogeneity of obesity and the different body size phenotypes, influencing different pathophysiological mechanisms might result in increased weight loss.[29]

Our trial had some limitations. First, the trial was designed to primarily assess the safety and tolerability of cagrilintide in combination with semaglutide, and weight loss was assessed as an exploratory endpoint. Therefore, weight loss data should be interpreted with caution. Second, the short duration of the trial (20 weeks) and the short time that participants were treated at final target dose (4 weeks) might have restricted treatment efficacy and safety assessments. Longer trials are needed to fully assess the efficacy and safety of this treatment combination and assess whether weight loss is sustained. Third, the sample

size and power might limit the generalisation of our findings, and might not have been sufficient to differentiate weight loss with cagrilintide 1·2, 2·4, and 4·5 mg, for which no dose response was noted after 20 weeks of treatment. Fourth, participants with a BMI of more than 40 kg/m² and high cardiovascular risk were excluded from the trial because of potential complications that could act as confounding factors. Similarly, only males and females of non-childbearing potential could be included at the time of trial design, because of the potential risk of cagrilintide for a fetus. This concern has now been mitigated (unpublished) and women of childbearing potential can be included in future trials. Finally, the global COVID-19 pandemic also affected trial conduct, affecting trial visit schedules for participants in cohort 6. All outpatient visits for cohort 6 were done as planned, but two planned in-house visits were converted into outpatient visits, with follow-up via telephone. Nevertheless, the data from this trial are robust and acceptable for further interpretation.

Treatment with once-weekly cagrilintide (0·16, 0·30, 0·60, 1·2, 2·4, and 4·5 mg) in combination with semaglutide 2·4 mg for 20 weeks was not associated with an increase in adverse events compared with placebo in combination with semaglutide 2·4 mg, with no unexpected safety or tolerability findings. Pharmacokinetic parameters support once-weekly dosing of cagrilintide in combination with semaglutide 2·4 mg, and this dosing regimen was associated with clinically meaningful weight loss of up to 17·1% bodyweight, without lifestyle interventions. These data support the further clinical development of cagrilintide and semaglutide 2·4 mg as a potential novel and effective combination therapy for weight management.

Contributors

LBE, KKB, MK, and MTL contributed to the study design. MK contributed to the recruitment of study participants and the collection of data. LBE, KKB, MTL, AS, DCWL, and DMR contributed to the data analysis. All authors participated in the interpretation of the data and drafting and revision of the manuscript. LBE, KKB, and MK had full access to and verified the underlying study data. All authors reviewed and approved the final submitted version. All authors had full access to the data, were involved in the development and approval of the manuscript, made the decision to submit for publication, and vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol. The manuscript was drafted with support of a medical writer (funded by the sponsor), under the direction of the authors.

Declaration of interests

LBE, KKB, MTL, and AS are employees and shareholders at Novo Nordisk A/S. MK is the principal investigator for the study and received sponsorship from Novo Nordisk. DMR is a consultant, advisory board member, speaker, clinical investigator for, and shareholder of Novo Nordisk; a clinical investigator for Boehringer Ingelheim; has received research funding from Obesinov and honoraria from Medscape. DCWL is a consultant for and has received speaker honoraria from Amgen, AstraZeneca, Bausch Health, Boehringer Ingelheim, Eli Lilly, HLS Therapeutics, and Novo Nordisk.

Data sharing

Data will be shared with bona fide 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 the USA. Information about data access request proposals can be found at novonordisk-trials.com.

For more on **data access** see https://www.novonordisk-trials.com/

Acknowledgments

This study was funded by Novo Nordisk A/S. We thank all participants, investigators, and trial staff who were involved in the conduct of the trial. We also thank Diana Marouco of Axis, a division of Spirit Medical Communications Group, for medical writing and editorial assistance, funded by Novo Nordisk A/S.

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