Efficacy and safety of co-administered once-weekly cagrilintide 2·4 mg with once-weekly semaglutide 2·4 mg in type 2 diabetes: a multicentre, randomised, double-blind, active-controlled, phase 2 trial

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See Comment page 671

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Summary

Background Combining the GLP-1 receptor agonist semaglutide with the long-acting amylin analogue cagrilintide has weight-loss benefits; the impact on glycated haemoglobin (HbA_{1c}) is unknown. This trial assessed the efficacy and safety of co-administered semaglutide with cagrilintide (CagriSema) in participants with type 2 diabetes.

Methods This 32-week, multicentre, double-blind, phase 2 trial was conducted across 17 sites in the USA. Adults with type 2 diabetes and a BMI of 27 kg/m² or higher on metformin with or without an SGLT2 inhibitor were randomly assigned (1:1:1) to once-weekly subcutaneous CagriSema, semaglutide, or cagrilintide (all escalated to 2·4 mg). Randomisation was done centrally using an interactive web response system and was stratified according to use of SGLT2 inhibitor treatment (yes *vs* no). The trial participants, investigators, and trial sponsor staff were masked to treatment assignment throughout the trial. The primary endpoint was change from baseline in HbA_{1c}; secondary endpoints were bodyweight, fasting plasma glucose, continuous glucose monitoring (CGM) parameters, and safety. Efficacy analyses were performed in all participants who had undergone randomisation, and safety analyses in all participants who had undergone randomisation and received at least one dose of the trial medication. This trial is registered on ClinicalTrials.gov (NCT04982575) and is complete.

Findings Between Aug 2 and Oct 18, 2021, 92 participants were randomly assigned to CagriSema (n=31), semaglutide (n=31), or cagrilintide (n=30). 59 (64%) participants were male; the mean age of participants was 58 years (SD 9). The mean change in HbA_{1c} from baseline to week 32 (CagriSema: –2·2 percentage points [SE 0·15]; semaglutide: –1·8 percentage points [0·16]; cagrilintide: –0·9 percentage points [0·15]) was greater with CagriSema versus cagrilintide (estimated treatment difference –1·3 percentage points [95% CI –1·7 to –0·8]; p<0·0001), but not versus semaglutide (–0·4 percentage points [–0·8 to 0·0]; p=0·075). The mean change in bodyweight from baseline to week 32 (CagriSema: –15·6% [SE 1·26]; semaglutide: –5·1% [1·26]; cagrilintide: –8·1% [1·23]) was greater with CagriSema versus both semaglutide (p<0·0001) and cagrilintide (p<0·0001). The mean change in fasting plasma glucose from baseline to week 32 (CagriSema: –3·3 mmol/L [SE 0·3]; semaglutide: –2·5 mmol/L [0·4]; cagrilintide: –1·7 mmol/L [0·3]) was greater with CagriSema versus cagrilintide (p=0·0010) but not versus semaglutide (p=0·10). Time in range (3·9–10·0 mmol/L) was 45·9%, 32·6%, and 56·9% at baseline and 88·9%, 76·2%, and 71·7% at week 32 with CagriSema, semaglutide, and cagrilintide, respectively. Adverse events were reported by 21 (68%) participants in the CagriSema group, 22 (71%) in the semaglutide group, and 24 (80%) in the cagrilintide group. Mild or moderate gastrointestinal adverse events were most common; no level 2 or 3 hypoglycaemia was reported. No fatal adverse events were reported.

Interpretation In people with type 2 diabetes, treatment with CagriSema resulted in clinically relevant improvements in glycaemic control (including CGM parameters). The mean change in HbA_{1c} with CagriSema was greater versus cagrilintide, but not versus semaglutide. Treatment with CagriSema resulted in significantly greater weight loss versus semaglutide and cagrilintide and was well tolerated. These data support further investigation of CagriSema in this population in longer and larger phase 3 studies.

Funding Novo Nordisk.

Introduction

Approximately 90% of adults with type 2 diabetes have overweight or obesity.[1] In addition to the achievement of glycaemic targets and cardiorenal risk reduction, weight loss between 5% and 15% is an appropriate target for many people with type 2 diabetes.[2–6] Weight loss has benefits beyond glycated haemoglobin (HbA_{1c}) reduction, including improvements in other metabolic (eg, insulin

Research in context

Evidence before this study

We searched PubMed for studies in any language published between July 29, 2011, and July 29, 2021, using the search terms ("semaglutide" OR "glucagon-like peptide-1 receptor agonist" OR "GLP-1") AND ("cagrilintide" or "amylin analog"). One phase 1b clinical trial investigating the therapeutic combination of these mechanisms was identified. Individuals with a BMI of 27·0–39·9 kg/m² received ascending doses of cagrilintide (amylin analogue) or matched placebo, in combination with semaglutide (GLP-1 receptor agonist) 2·4 mg. The combination was well tolerated with an acceptable safety profile. Mean percentage bodyweight reductions at week 20 were greater with cagrilintide doses of 1·2 mg, 2·4 mg, and 4·5 mg than with placebo. Cagrilintide is an investigational therapy that reduced bodyweight in a phase 2 trial when administered as monotherapy in participants without diabetes and with a BMI of at least 30 kg/m², or at least 27 kg/m² with hypertension or dyslipidaemia. Semaglutide is approved for the treatment of type 2 diabetes, for reducing the risk of major adverse cardiovascular events in people with type 2 diabetes and established cardiovascular disease, and for chronic weight management in adults with obesity, or overweight with weight-related comorbidities.

Added value of this study

Our phase 2 clinical trial is the first study to report efficacy and safety data for treatment with the combination of a GLP-1 receptor agonist and an amylin analogue in participants with type 2 diabetes. We found that treatment with co-administered semaglutide 2·4 mg and cagrilintide 2·4 mg (CagriSema) resulted in clinically relevant improvements in glycaemic control, including continuous glucose monitoring parameters, as well as significantly greater weight loss than either semaglutide or cagrilintide alone. The magnitude of the weight loss was greater than previously reported with pharmacotherapies in this population. The combination was well tolerated; the most common adverse events were mild or moderate gastrointestinal events.

Implications of all the available evidence

These data support further investigation of CagriSema in this population in longer and larger phase 3 studies.

resistance, hypertension, and hyperlipidaemia), biomechanical, and psychosocial complications.[2–6] In people with type 2 diabetes, sustained weight loss of 10–15% can have disease-modifying effects, including the potential to improve metabolic health, and can reduce the risk of long-term complications.[2,4,5]

The GLP-1 receptor agonist semaglutide is approved as a once-weekly subcutaneous injection (0·5 mg, 1·0 mg, or 2·0 mg) for the treatment of type 2 diabetes (as an adjunct to diet and exercise)[7] and for reducing the risk of major adverse cardiovascular events in people with type 2 diabetes and established cardiovascular disease.[8] Subcutaneous semaglutide (2·4 mg) is also approved for chronic weight management as an adjunct to diet and exercise for adults with obesity, or overweight with weight-related comorbidities.[9,10]

Amylin is a pancreatic β-cell hormone co-secreted with insulin in response to nutrient intake.[11] Through activation of neurons in the brain, amylin slows gastric emptying and induces satiety.[11–14] Cagrilintide is the first long-acting amylin analogue being investigated for weight management, as a once-weekly treatment in combination with semaglutide.[13,14] In a phase 2 dose-finding trial in people with overweight or obesity and hypertension or dyslipidaemia, and without type 2 diabetes, cagrilintide 2·4 mg, as an adjunct to diet and exercise, resulted in a bodyweight reduction of 10% versus 3% with placebo after 26 weeks.[13] Furthermore, a phase 1b trial investigating doses of cagrilintide up to 4·5 mg co-administered with semaglutide 2·4 mg in people with overweight or obesity reported a mean bodyweight reduction of 17% with cagrilintide 2·4 mg and semaglutide 2·4 mg versus 10% with co-administered semaglutide 2·4 mg and placebo after 20 weeks.[14] Thus, combining these agents with different but complementary mechanisms of action has the potential to increase efficacy. It was, therefore, deemed relevant to investigate whether once-weekly subcutaneous co-administration of semaglutide and cagrilintide (both escalated to 2·4 mg) improves glycaemic and weight control, when compared with cagrilintide or semaglutide alone in people with type 2 diabetes and overweight or obesity.

Methods

Study design and participants

This 32-week, multicentre, randomised, double-blind, parallel-group, active-controlled, phase 2 trial was conducted across 17 sites in the USA from August, 2021, to July, 2022. 12 of the sites were medical practices experienced in clinical research, four were research centres, and one was university-based. The trial protocol was approved by appropriate health authorities according to local guidelines and by an Institutional Review Board/Independent Ethics Committee, and was conducted in accordance with the Declaration of Helsinki and International Council on Harmonisation Good Clinical Practice guidelines. Participants provided written informed consent before commencement of any trial-related activity.

Adults with type 2 diabetes were eligible for participation if they had a BMI of 27·0 kg/m² or higher and HbA_{1c} between 7·5% and 10·0% (53–86 mmol/mol), despite being treated with a stable daily dose of metformin with or without an SGLT2 inhibitor for at least 90 days before screening. Exclusion criteria included

renal impairment (estimated glomerular filtration rate <60 mL/min/1·73 m²) and uncontrolled and potentially unstable diabetic retinopathy or maculopathy verified by a fundus examination performed within 90 days before screening. Full inclusion and exclusion criteria can be found in the appendix (pp 5–6).

See Online for appendix

Randomisation and masking

Following a 2-week screening period, eligible participants were randomly assigned 1:1:1 using a web-based randomisation system to receive separate subcutaneous injections of semaglutide 2·4 mg (PDS290 pre-filled pen injector) and cagrilintide 2·4 mg (NovoPen Echo), hereby referred to as CagriSema, or semaglutide 2·4 mg (PDS290) and cagrilintide placebo (NovoPen Echo), or cagrilintide 2·4 mg (NovoPen Echo) and semaglutide placebo (PDS290; appendix p 15). All pen injectors were manufactured by Novo Nordisk, Denmark. This trial did not include a placebo group. Randomisation was done centrally using an interactive web response system (Calyx, Nottingham, UK) and was stratified according to use of SGLT2 inhibitor treatment (yes *vs* no). Investigators at each site accessed the interactive web response system to randomly assign participants. The semaglutide 2·4 mg and cagrilintide 2·4 mg trial products were identical to the corresponding placebo in appearance, enabling masking of treatment. The trial participants, investigators, and trial sponsor staff remained masked to treatment allocation throughout the trial.

Procedures

All participants received treatment once weekly for 32 weeks. Treatment doses were escalated every 4 weeks from 0·25 mg to 0·5 mg, 1·0 mg, and 1·7 mg until the maintenance dose of 2·4 mg was reached after 16 weeks. Participants then underwent a 16-week maintenance period, followed by a 5-week follow-up period. Rescue medication was offered if fasting plasma glucose exceeded the predefined limits (15·0 mmol/L [270 mg/dL] from randomisation to week 8; 13·3 mmol/L [240 mg/dL] from week 9 to week 20; 11·1 mmol/L [200 mg/dL] from week 21 to end of treatment). In line with standard practice in trials of pharmacological treatment for type 2 diabetes, there was no mandated diet and exercise requirement. Participants were provided with a Dexcom G6 device (San Diego, CA, USA) for collecting continuous glucose monitoring (CGM) profiles, which was to be worn for 10 full days preceding baseline, week 20, and week 32. Both participants and investigators were masked to CGM readings, and these readings were not used for any dose adjustments or hypoglycaemic episode reporting. Mean glucose, as measured by CGM, was based upon measurements taken every 5 min.

All participants were provided with glucometers, to measure blood glucose if symptoms of hypoglycaemia occurred. Participants experiencing symptoms of hypoglycaemia were instructed to measure blood glucose on their glucometer every 15 min until blood glucose was at least 3·9 mmol/mol (≥70 mg/dL) or symptoms had resolved. Hypoglycaemic episodes were recorded in the electronic case report form and participant diaries. Hypoglycaemic episodes were defined according to the American Diabetes Association (ADA) 2018 classification[15] as level 1 (alert value; blood glucose <3·9 mmol/L [<70 mg/dL] and ≥3·0 mmol/L [≥54 mg/dL]), level 2 (clinically significant; blood

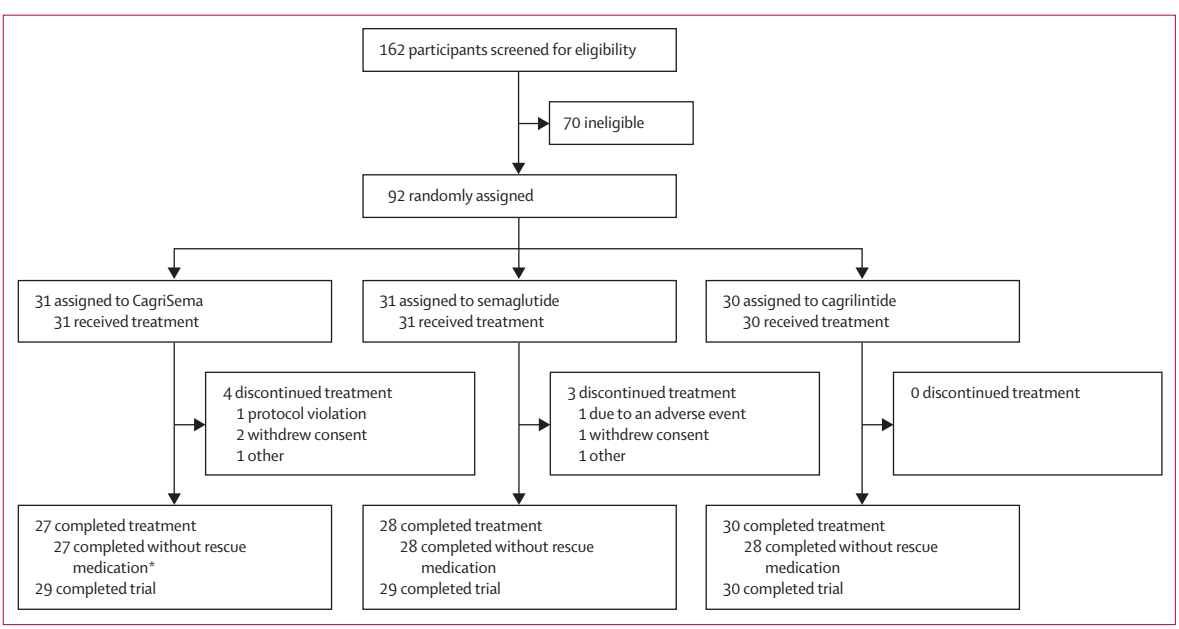

Figure 1: **Trial profile**
CagriSema=co-administered semaglutide and cagrilintide. *One participant in the CagriSema group received rescue medication before discontinuing treatment.

glucose <3·0 mmol/L [<54 mg/dL]), or level 3 (severe; no glucose threshold but requiring assistance from another person for recovery).

Outcomes

The primary objective of this trial was to compare the effect of CagriSema versus semaglutide on the change from baseline to week 32 in HbA_{1c}. The secondary objectives compared the effect of CagriSema versus cagrilintide on the change from baseline to week 32 in HbA_{1c} and the effect of CagriSema versus semaglutide and cagrilintide on other parameters of glycaemic control, bodyweight, safety and tolerability, and hypoglycaemia.

The primary endpoint was change in HbA_{1c} from baseline to week 32 (used to assess both the primary and secondary objectives for HbA_{1c}). Supportive secondary endpoints were change from baseline to week 32 in bodyweight (percent change and change in kg), CGM-related endpoints,[15] and change from baseline to week 32 in fasting plasma glucose (mmol/L). CGM endpoints included time in range (TIR; 3·9–10·0 mmol/L [70–180 mg/dL]; percentage of readings) and time above range (TAR; >10·0 mmol/L [>180 mg/dL]; percentage of readings) at week 32, and change from baseline to week 32 in mean glucose. Additionally, 24-h CGM profiles were collected. Biomarkers including fasting glucagon, fasting serum insulin, high-sensitivity C-reactive protein (hsCRP), leptin, soluble leptin receptor, and a lipid panel were assessed. Post-hoc analyses evaluated the proportion of participants with HbA_{1c} less than 7·0% and 6·5% or below, or a reduction in bodyweight of 10% or higher and 15% or higher at week 32, additional CGM endpoints of time in tight range (TITR; 3·9–7·8 mmol/L [70–140 mg/dL]; percentage of readings) and time below range (TBR; <3·9 mmol/L [<70 mg/dL]; percentage of readings) at week 32, and the ratio of leptin to soluble leptin receptor. Safety assessments included adverse events, hypoglycaemic episodes, blood pressure, heart rate, and relevant laboratory assessments.

Statistical analysis

The sample size calculation aimed at quantifying the magnitude of expected variation in the estimated treatment difference (ETD) for the primary endpoint. Using an expected standard deviation of 1·0%, a planned sample size of 30 participants per treatment group (90 participants in total) would ensure, with 80% probability, that the 95% CI for the ETD would be within 0·56 percentage points of the mean (above or below). Efficacy analyses were performed in the full analysis population (all participants who had undergone randomisation), and safety analyses were assessed in the safety analysis population (all participants who had undergone randomisation and were exposed to at least one dose of the trial medication).

Treatment efficacy was evaluated using two estimands. The trial product estimand (primary estimand) strategy evaluated the treatment effect in all randomly assigned participants based on data collected

	CagriSema (n=31)	Semaglutide (n=31)	Cagrilintide (n=30)	Total (n=92)
Sex				
Female	13 (42%)	13 (42%)	7 (23%)	33 (36%)
Male	18 (58%)	18 (58%)	23 (77%)	59 (64%)
Mean age, years (SD)	56 (10)	57 (10)	62 (7)	58 (9)
Hispanic or Latino ethnicity	10 (32%)	13 (42%)	6 (20%)	29 (32%)
Race				
Black or African American	5 (16%)	5 (16%)	5 (17%)	15 (16%)
White	26 (84%)	24 (77%)	22 (73%)	72 (78%)
Other	0	2 (6%)	3 (10%)	5 (5%)
HbA_{1c}, %				
Mean (SD)	8·5 (0·8)	8·6 (0·7)	8·1 (0·8)	8·4 (0·8)
Range	7·5–10·3	7·5–10·0	6·9–9·9	6·9–10·3
HbA_{1c}, mmol/mol				
Mean (SD)	70 (9)	70 (8)	65 (8)	69 (9)
Range	58–89	58–86	52–85	52–89
Bodyweight, kg				
Mean (SD)	104·3 (23·2)	105·4 (24·9)	107·4 (25·0)	105·7 (24·1)
Range	64·0–179·4	62·7–153·5	63·6–176·2	62·7–179·4
BMI, kg/m²*				
Mean (SD)	35·9 (5·7)	36·2 (7·2)	34·4 (6·1)	35·5 (6·3)
Range	27·6–52·5	26·7–52·9	26·7–48·5	26·7–52·9
Duration of diabetes, years				
Mean (SD)	6·4 (3·8)	9·2 (8·3)	10·7 (9·1)	8·7 (7·5)
Range	0·7–15·8	0·7–30·8	0·7–39·0	0·7–39·0
FPG, mmol/L				
Mean (SD)	10·0 (3·2)	9·8 (2·1)	8·9 (2·7)	9·6 (2·7)
Range	4·8–21·5	6·5–16·1	4·6–14·7	4·6–21·5
FPG, mg/dL				
Mean (SD)	180 (58)	177 (39)	160 (48)	172 (49)
Range	86–387	117–290	83–265	83–387
SBP, mm Hg†				
Mean (SD)	130 (15)	128 (13)	128 (15)	NA
Range	106–171	96–151	105–165	NA
DBP, mm Hg†				
Mean (SD)	80 (7)	79 (11)	78 (10)	NA
Range	64–97	49–99	58–99	NA
eGFR, mL/min/1·73 m²†‡				
Mean (SD)	94 (12)	90 (18)	92 (13)	NA
Range	71–118	61–121	69–122	NA
Metformin	23 (74%)	23 (74%)	21 (70%)	67 (73%)
Metformin and SGLT2 inhibitor	8 (26%)	8 (26%)	9 (30%)	25 (27%)

Data are n (%) unless otherwise stated. Data are for the full analysis population unless otherwise stated. Baseline information is defined as the latest planned assessment before dosing. CagriSema=co-administered semaglutide and cagrilintide. DBP=diastolic blood pressure. eGFR=estimated glomerular filtration rate. FPG=fasting plasma glucose. HbA_{1c}=glycated haemoglobin. NA=not applicable. SBP=systolic blood pressure. *BMI is calculated based on baseline measurements of bodyweight and height. †Observations are based on the safety analysis population. ‡Baseline data for eGFR were collected during the 2-week screening period before initiation of treatment.

Table 1: **Baseline demographics and characteristics**

up to and including week 32 from the on-treatment without rescue medication period, regardless of change in treatment dose. To impute missing data, and for participants who discontinued treatment or initiated rescue medication, a mixed model for repeated measurements (MMRM) was used. The primary analysis for the trial product estimand was based on an MMRM with baseline HbA_{1c} as covariate, and treatment and SGLT2 inhibitor use (yes *vs* no) as factors nested within the factor time using participants as random factor with unstructured within-participant covariance. Data after first non-adherence or rescue intervention were set to missing.

The treatment policy estimand (additional estimand) evaluated the treatment effect for all randomised participants, regardless of trial product discontinuation or use of rescue medication. The primary analysis for the treatment policy estimand was an analysis of covariance

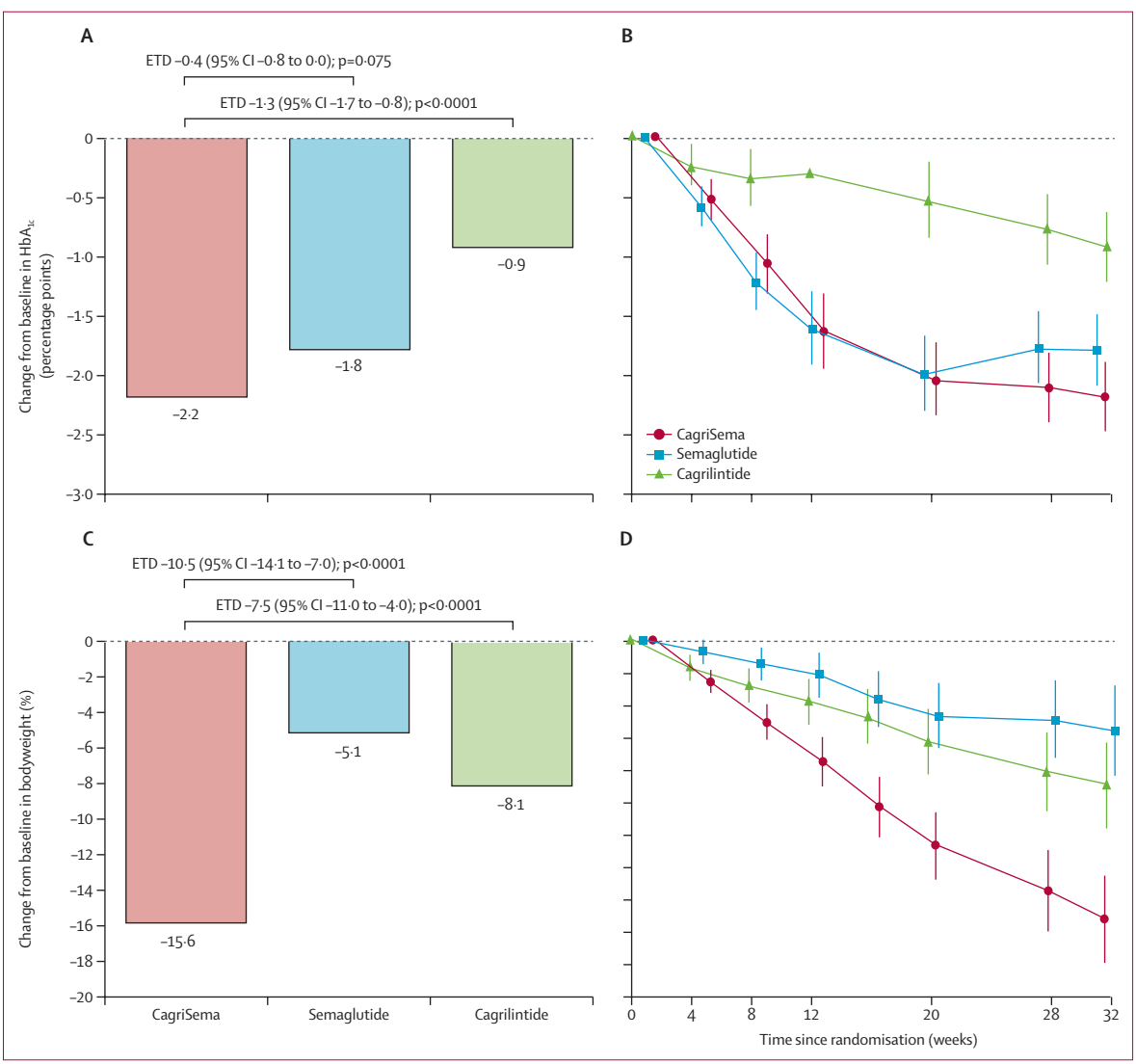

Figure 2: **Change from baseline in HbA_{1c} and bodyweight**

Data are for the full analysis population and trial product estimand, and from the on-treatment observation period. The primary analysis for the trial product estimand was based on a mixed model for repeated measurements with baseline HbA_{1c} as covariate, and treatment and SGLT2 inhibitor use (yes *vs* no) as factors nested within the factor time using participants as random factor with unstructured within-participant covariance. (A) Mean change from baseline to week 32 in HbA_{1c} (percentage points). (B) Mean change over time in HbA_{1c} (percentage points). (C) Mean change from baseline to week 32 in bodyweight (%). (D) Mean change over time in bodyweight (%). For panels A and C, n=27 in the CagriSema group, n=24 in the semaglutide group, and n=27 in the cagrilintide group. Using the treatment policy estimand, mean change in HbA_{1c} from baseline to week 32 was −2·1 percentage points with CagriSema, −1·8 percentage points with semaglutide, and −0·9 percentage points with cagrilintide, and the ETD was −0·3 percentage points (95% CI −0·8 to 0·2; p=0·23) for CagriSema versus semaglutide and −1·2 percentage points (−1·7 to −0·7; p<0·0001) for CagriSema versus cagrilintide. Mean change in bodyweight from baseline to week 32 using the treatment policy estimand was −14·7% (−15·3 kg) for CagriSema, −5·2% (−5·4 kg) for semaglutide, and −8·1% (−8·6 kg) for cagrilintide, and the ETD was −9·5% (95% CI −13·8 to −5·1; p<0·0001) for CagriSema versus semaglutide, and −6·5% (−10·6 to −2·4; p=0·0018) for CagriSema versus cagrilintide. Data for the treatment policy estimand are shown in the appendix (p 16). CagriSema=co-administered semaglutide and cagrilintide. ETD=estimated treatment difference. HbA_{1c}=glycated haemoglobin.

model with baseline HbA_{1c} as covariate, and treatment and SGLT2 inhibitor use (yes *vs* no) as factors. Missing data were imputed using retrieved drop-out multiple imputation with baseline HbA_{1c} as covariate.

A linear mixed model was used for continuous outcome measures. Analyses were performed using SAS 9.4. Further information regarding the statistical analysis can be found in the appendix (p 4).

The trial is registered with ClinicalTrials.gov (NCT04982575).

Role of the funding source

The sponsor of the study had a role in study design, monitoring, data collection, data analysis, and data interpretation. Medical writing and editorial support were funded by the trial sponsor.

Results

Between Aug 2 and Oct 18, 2021, a total of 162 participants were screened; 92 participants were randomly assigned to CagriSema (n=31), semaglutide (n=31), or cagrilintide (n=30). A high proportion of participants completed treatment (27 [87%] with CagriSema, 28 [90%] with semaglutide, and 30 [100%] with cagrilintide) and completed the trial (29 [94%] with CagriSema and semaglutide and 30 [100%] with cagrilintide). The trial product was discontinued by four (13%) of 31 participants treated with CagriSema, three (10%) of 31 participants treated with semaglutide, and none of the 31 participants treated with cagrilintide (figure 1).

Baseline characteristics are presented in table 1 and in the appendix (pp 7–8). 59 (64%) participants were male, the mean age of participants was 58 years, and mean diabetes duration was 9 years. At baseline, mean HbA_{1c} was 8·4% and mean bodyweight was 105·7 kg. Slight imbalances were observed for baseline HbA_{1c} and diabetes duration between treatment groups. The representativeness of the trial population is described in the appendix (p 9).

A significantly greater reduction in HbA_{1c} was observed from baseline to week 32 with CagriSema versus cagrilintide. Using the trial product estimand, mean change in HbA_{1c} from baseline to week 32 was –2·2 percentage points (SE 0·15) with CagriSema, –1·8 percentage points (0·16) with semaglutide, and –0·9 percentage points (0·15) with cagrilintide (figure 2). The ETD was –0·4 percentage points (95% CI –0·8 to 0·0; p=0·075) for CagriSema versus semaglutide and –1·3 percentage points (–1·7 to –0·8; p<0·0001) for CagriSema versus cagrilintide. Consistent results were observed using the treatment policy estimand (appendix p 16). A numerically greater proportion of participants reached the targets of HbA_{1c} less than 7·0% and 6·5% or below with CagriSema compared with semaglutide and cagrilintide (table 2).

A significantly greater reduction in bodyweight was observed from baseline to week 32 with CagriSema versus both semaglutide and cagrilintide. Using the trial product estimand, mean change in bodyweight from baseline to week 32 was –15·6% (SE 1·26; –16·3 kg) with CagriSema, –5·1% (1·26; –5·3 kg) with semaglutide, and –8·1% (1·23; –8·4 kg) with cagrilintide (figure 2). The ETD was –10·5% (95% CI –14·1 to –7·0; p<0·0001) for CagriSema versus semaglutide and –7·5% (–11·0 to –4·0; p<0·0001) for CagriSema versus cagrilintide. Consistent results were observed using the treatment policy estimand (appendix p 16). A numerically greater proportion of participants reached the target

	CagriSema (n=31)	Semaglutide (n=31)	Cagrilintide (n=30)
HbA_{1c}, percentage points			
Observed mean (SD)	6·3 (0·8)*	6·7 (0·8)†	7·3 (0·8)*
Estimated mean change from baseline (SE)	–2·2 (0·2)‡	–1·8 (0·2)§	–0·9 (0·2)‡
ETD (95% CI) *vs* CagriSema	NA	–0·4 (–0·8 to 0·0)	–1·3 (–1·7 to –0·8)
p value	NA	0·075	<0·0001
Bodyweight, %			
Estimated mean change from baseline (SE)	–15·6 (1·3)‡	–5·1 (1·3)§	–8·1 (1·2)‡
ETD (95% CI) *vs* CagriSema	NA	–10·5 (–14·1 to –7·0)	–7·5 (–11·0 to –4·0)
p value	NA	<0·0001	<0·0001
Bodyweight, kg			
Observed mean (SD)	86·7 (18·7)*	101·5 (24·7)†	97·7 (23·1)*
Estimated mean change from baseline (SE)	–16·3 (1·3)‡	–5·3 (1·3)§	–8·4 (1·3)‡
ETD (95% CI) *vs* CagriSema	NA	–10·9 (–14·7 to –7·2)	–7·9 (–11·6 to –4·2)
p value	NA	<0·0001	<0·0001
FPG, mmol/L			
Mean (SD)	6·5 (1·5)*	7·2 (2·2)†	7·7 (1·9)‡
Estimated mean change from baseline (SE)	–3·3 (0·3)¶	–2·5 (0·4)§	–1·7 (0·3)¶
ETD (95% CI) *vs* CagriSema	NA	–0·8 (–1·8 to 0·2)	–1·7 (–2·6 to –0·7)
p value	NA	0·10	0·0010
Mean glucose by CGM, mmol/L			
Mean (SD)	7·4 (1·5)¶	8·7 (2·6)‖	9·0 (1·7)‖
Estimated mean change from baseline (SE)	–3·6 (0·4)¶	–2·4 (0·4)**	–1·3 (0·4)‖
ETD (95% CI) *vs* CagriSema	NA	–1·1 (–2·2 to 0·0)	–2·3 (–3·3 to –1·2)
p value	NA	0·043	<0·0001
Participants with HbA_{1c} ≤6·5%,††‡‡ n (%)	21 (75%)*	14 (48%)†	5 (17%)§§
Participants with HbA_{1c} <7·0%,††‡‡ n (%)	25 (89%)*	20 (69%)†	10 (33%)§§
Participants with ≥10% reduction in bodyweight,†† n (%)	20 (71%)*	4 (14%)†	7 (23%)§§
Participants with ≥15% reduction in bodyweight,†† n (%)	15 (54%)*	0†	2 (7%)§§

Data are for the full analysis population and trial product estimand, and from the on-treatment observation period. CagriSema=co-administered semaglutide and cagrilintide. CGM=continuous glucose measurement. ETD=estimated treatment difference. FPG=fasting plasma glucose. HbA_{1c}=glycated haemoglobin. NA=not applicable. *n=28. †n=29. ‡n=27. §n=24. ¶n=26. ‖n=25. **n=22. ††Endpoints were included in a post-hoc analysis. ‡‡Statistical analyses of between-group differences were not completed for these endpoints due to the small sample size. §§n=30.

Table 2: **Key efficacy endpoints at week 32 using the trial product estimand**

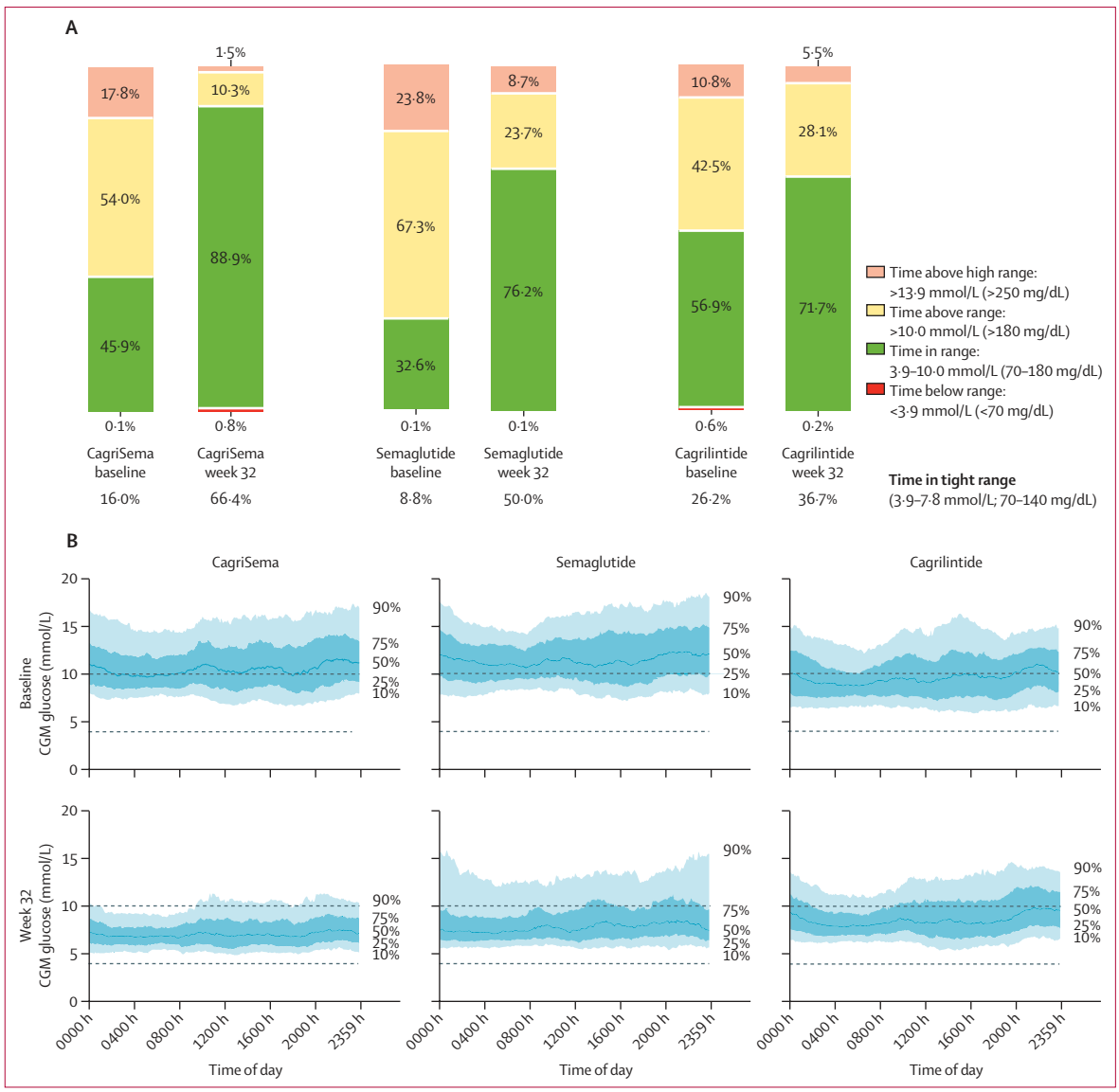

Figure 3: **CGM observations**

(A) Time below range, time in range, time above range, time above high range, and time in tight range (percentage of readings); note that time above high range is a subcategory of time above range. Data are for the full analysis population and from the on-treatment observation period. At baseline: n=31 in the CagriSema group, n=30 in the semaglutide group, and n=30 in the cagrilintide group; at week 32: n=26 in the CagriSema group, n=25 in the semaglutide group, and n=25 in the cagrilintide group. (B) 24-h CGM profiles. The dark blue line signifies the median, the blue bands signify the 10–90th and 25–75th centiles, and the dashed lines signify the blood glucose target range of 3·9–10·0 mmol/L; time since midnight is split into 5-min intervals. Data are for the full analysis population and from the in-trial observation period. CagriSema=co-administered semaglutide and cagrilintide. CGM=continuous glucose monitoring.

of 10% or higher and 15% or higher reduction in bodyweight with CagriSema compared with semaglutide and cagrilintide (table 2).

At week 32, TIR (3·9–10·0 mmol/L [70–180 mg/dL]) measured by CGM was 88·9% with CagriSema, 76·2% with semaglutide, and 71·7% with cagrilintide, and TAR was 10·3% with CagriSema, 23·7% with semaglutide, and 28·1% with cagrilintide (figure 3). Changes from baseline in TIR and TITR were analysed post hoc, and were both significantly greater with CagriSema versus cagrilintide, but not versus semaglutide (appendix p 10). 24-h CGM profiles at baseline and week 32 are presented in figure 3, and within-day glycaemic variability results are presented in the appendix (p 10). Significantly greater reductions in mean CGM-measured glucose from baseline to week 32 were observed with CagriSema versus both semaglutide (p=0·043) and cagrilintide (p<0·0001; table 2). Fasting plasma glucose decreased from baseline to week 32 in all treatment groups; significantly greater reductions were observed with CagriSema versus cagrilintide (p=0·0010), but not versus semaglutide (p=0·10; table 2).

Key observations for hsCRP, leptin, soluble leptin receptor, fasting serum insulin, C-peptide, proinsulin, and fasting glucagon from baseline to week 32 are summarised in the appendix (pp 7–8). As a biomarker of interest, the ratio of leptin to soluble leptin receptor was investigated in a post-hoc analysis and showed a significantly differentiated effect from baseline at week 32 for CagriSema and cagrilintide compared with semaglutide (appendix p 11). Numerical reductions in certain lipids, including total cholesterol, triglycerides, low-density lipoprotein cholesterol, and very-low-density lipoprotein cholesterol, were present among all treatment groups (appendix pp 7–8, 17).

Considering all adverse events, similar proportions of participants reported events across treatment groups (table 3 and appendix p 12). The most common category of adverse events was gastrointestinal adverse events, which occurred in 18 (58%) of 31 participants treated with CagriSema, 10 (32%) of 31 treated with semaglutide, and 10 (33%) of 30 treated with cagrilintide; all were mild or moderate in severity and the majority began during dose escalation (appendix p 18). A total of three participants reported injection-site reactions and no cases of acute gallbladder disease or acute pancreatitis were reported (appendix p 13). Two adverse events of retinal drusen and one adverse event of retinal haemorrhage were captured by a Medical Dictionary for Regulatory Activities (MedDRA) search, were mild in severity, and were assessed as unlikely to be related to the trial products. No additional data were collected for these events as they were not considered events of diabetic retinopathy (appendix p 13). Two participants reported two serious adverse events with semaglutide and four participants reported five serious adverse events with cagrilintide (appendix p 14). No clinically significant or severe hypoglycaemic episodes (level 2 or 3) were

	CagriSema (n=31)			Semaglutide (n=31)			Cagrilintide (n=30)		
	n (%)	Events	Event rate*	n (%)	Events	Event rate*	n (%)	Events	Event rate*
Adverse events and serious adverse events									
Adverse events	21 (68%)	81	409·3	22 (71%)	76	368·5	24 (80%)	89	424·7
Adverse events leading to drug withdrawal†	0	0	0	1 (3%)	2	9·7	0	0	0
Severity of adverse events									
Mild	18 (58%)	59	298·1	13 (42%)	43	208·5	20 (67%)	68	324·5
Moderate	14 (45%)	22	111·2	16 (52%)	32	155·2	13 (43%)	20	95·4
Severe	0	0	0	1 (3%)	1	4·8	1 (3%)	1	4·8
Fatal	0	0	0	0	0	0	0	0	0
Serious adverse events	0	0	0	2 (6%)	2	9·7	4 (13%)	5	23·9
Hypoglycaemic episodes (ADA classification)‡									
Level 1	2 (6%)	2	11·0	0	0	0	2 (7%)	3	15·6
Level 2	0	0	0	0	0	0	0	0	0
Level 3	0	0	0	0	0	0	0	0	0
Adverse events by system organ class§									
Gastrointestinal adverse events (preferred term)¶	18 (58%)	35	176·8	10 (32%)	21	101·8	10 (33%)	16	76·4
Nausea	9 (29%)	10	50·5	5 (16%)	7	33·9	4 (13%)	5	23·9
Constipation	5 (16%)	5	25·3	4 (13%)	5	24·2	4 (13%)	4	19·1
Diarrhoea	5 (16%)	7	35·4	2 (6%)	2	9·7	2 (7%)	2	9·5
Vomiting	3 (10%)	3	15·2	1 (3%)	1	4·8	0	0	0
GORD	3 (10%)	3	15·2	0	0	0	1 (3%)	1	4·8
Infections and infestations	11 (35%)	15	75·8	10 (32%)	16	77·6	12 (40%)	14	66·8
Nervous system disorders	2 (6%)	2	10·1	8 (26%)	9	43·6	4 (13%)	6	28·6
Musculoskeletal and connective tissue disorders	5 (16%)	5	25·3	4 (13%)	6	29·1	4 (13%)	5	23·9
General disorders and administration-site conditions	5 (16%)	8	40·4	0	0	0	5 (17%)	27	128·8

Data are for the safety analysis population and from the on-treatment observation period. ADA=American Diabetes Association. CagriSema=co-administered semaglutide and cagrilintide. GORD=gastro-oesophageal reflux disease. *Events per 100 years of exposure time. †One participant in the semaglutide group discontinued treatment due to an adverse event (diarrhoea). ‡Hypoglycaemic episodes were defined according to the ADA 2018 classification: level 1, blood glucose <3·9 mmol/L and ≥3·0 mmol/L; level 2, blood glucose <3·0 mmol/L; level 3, requiring assistance from another person for recovery. §Five system organ classes in which adverse events were most frequently reported. All remaining adverse events by system organ class are included in the appendix (p 12). ¶Gastrointestinal adverse events are reported by preferred term for adverse events occurring in ≥10% of participants among all treatment groups.

Table 3: **Summary of adverse events**

reported. From baseline to week 32, the mean change in systolic blood pressure was –13 mm Hg with CagriSema, 1 mm Hg with semaglutide, and –3 mm Hg with cagrilintide, and mean change in pulse rate was 3 beats per min with CagriSema, 7 beats per min with semaglutide, and –1 beats per min with cagrilintide (appendix p 19).

Discussion

In this exploratory trial, 32-week treatment with CagriSema resulted in a clinically relevant reduction in HbA_{1c} of 2·2 percentage points versus 1·8 percentage points with semaglutide and 0·9 percentage points with cagrilintide. Furthermore, treatment with CagriSema resulted in significantly greater weight loss versus both semaglutide and cagrilintide.

TIR was 89% at week 32 with CagriSema, a clinically relevant margin[15] greater than the 76% achieved with semaglutide and 72% with cagrilintide, without increasing TBR, which remained low in all treatment groups. TITR at week 32 was 66% for CagriSema, 50% for semaglutide, and 37% for cagrilintide. The numerically higher TIR and TITR observed at week 32 with CagriSema compared with semaglutide indicates a potential to further improve glycaemia versus semaglutide. Visual inspection of the 24-h CGM profiles supported a flattening of the glucose curve from baseline to week 32 in all treatment groups, with the most pronounced improvements observed with CagriSema. Notable flattening was observed around expected mealtimes with CagriSema and cagrilintide, and to a lesser extent with semaglutide, where peaks were still visible, although exact mealtimes were not recorded for any of the participants. These observations are consistent with the postprandial glucose-lowering effect observed with pramlintide, a short-acting amylin analogue approved as an adjunct to mealtime insulin treatment for type 1 and type 2 diabetes.[16] Delayed gastric emptying, which has been previously observed with amylin agonist administration,[17] might have also contributed to the visibly smaller mealtime peaks. The CGM results, alongside an observed decrease from baseline at week 32 in fasting serum insulin and C-peptide with CagriSema and cagrilintide, add to the efficacy of CagriSema[18] and suggest mechanistic differentiation compared with semaglutide alone.

The significant reductions in bodyweight observed with CagriSema during this trial support previous findings of CagriSema and cagrilintide in people with overweight or obesity without type 2 diabetes.[13,14] Weight loss of the magnitude observed with CagriSema, that had not plateaued at 32 weeks, has not been previously observed with pharmacological interventions in people with type 2 diabetes, a population for whom results in weight loss trials have historically been disappointing. Additionally, the weight loss observed with CagriSema (16%) was similar to bodyweight loss observed in populations without type 2 diabetes,[14] which is often not the case for pharmacological treatments, including semaglutide.[19,20] Weight loss of this magnitude can have disease-modifying effects in people with type 2 diabetes.[5] Of note, the weight-loss reduction observed with semaglutide (–5%) was lower in this trial than previously reported (approximately –9% *vs* –3% with placebo at 32 weeks),[21] potentially due to the small sample size, short duration, and absence of mandated diet and exercise counselling, which was implemented in previous trials of subcutaneously administered semaglutide 2·4 mg in people with overweight or obesity and type 2 diabetes.[21] Cagrilintide is expected to reduce bodyweight via similar mechanisms to native amylin, by interacting with the amylin and calcitonin receptors in the brain to control energy homoeostasis.[13,14,22]

While the glucose-lowering effect of semaglutide is well established,[20] this trial suggests that cagrilintide also has glucose-lowering properties. This glucose-lowering effect might be partly attributed to the robust weight loss; a model-based analysis using the results of a systematic literature search for weight-loss trials in people with type 2 diabetes and overweight or obesity estimated that each 1 kg of weight loss correlated with a mean HbA_{1c} reduction of 0·1 percentage points.[23] However, other effects of amylin agonist administration might have contributed, including slowing of gastric emptying, reduction in postprandial glucagon secretion, and synergistic effects with leptin that improve leptin responsiveness, improve insulin sensitivity, and reduce appetite.[24–28] Of note, leptin responsiveness is thought to be reduced in people with obesity compared with those of a healthy weight.[25,29] In this trial, differences were present in the ratio between circulating leptin and soluble leptin receptor with CagriSema and cagrilintide compared with semaglutide, suggesting a potential sensitising effect on leptin responsiveness.[29,30] Indeed, leptin responsiveness has been associated with improvements in insulin sensitivity;[24,26] however, further mechanistic studies are warranted to explore this association. It is of interest that clinically relevant improvements were observed in systolic blood pressure, lipid parameters, and hsCRP with CagriSema treatment after 32 weeks.

The safety profile of CagriSema was generally consistent with the GLP-1 receptor agonist and amylin analogue drug classes. Gastrointestinal adverse events were more common with CagriSema than with semaglutide or cagrilintide; however, all were mild or moderate in severity and most had onset during dose escalation. The possibility that the higher incidence of gastrointestinal adverse events in the CagriSema group contributed to the greater weight loss cannot be discounted. However, a previous mediation analysis of semaglutide 2·4 mg in adults with overweight or obesity suggested that the effect of gastrointestinal adverse events was not a major contributory factor in

semaglutide-induced weight loss.[31] Few serious adverse events were reported in the present trial, and the proportion of participants completing treatment was high among all treatment groups, with only one discontinuation due to an adverse event in the semaglutide group. High on-treatment and in-trial retention was also notable among all treatment groups.

Strengths of this trial include the use of each individual component as a comparator to CagriSema and the use of CGM assessments for a comprehensive assessment of glycaemic parameters. Race and ethnicity demographics were largely representative of the US population in terms of the proportion of people who were of Black or African American race or of Hispanic ethnicity. Furthermore, this trial did not include a placebo group. This avoided the negative ethical considerations of administering a placebo, which would not be expected to affect HbA_{1c}, in people with major metabolic comorbidities. Limitations of this trial include the small sample size, which introduced heterogeneity between treatment groups at baseline, including for sex, age, fasting plasma glucose, and HbA_{1c}. Other limitations include the relatively short treatment duration.

Overall, in this phase 2 trial in people with type 2 diabetes, clinically relevant improvements in glycaemic control—as assessed by HbA_{1c}, TIR, and other CGM measures—were observed with CagriSema, as well as weight loss of a magnitude not previously reported with pharmacotherapies in this population. CagriSema also had an acceptable safety profile. These data support further investigation of CagriSema in this population in longer and larger phase 3 studies.

Contributors

JPF and CM were involved in data acquisition, data interpretation, and manuscript development. SD, FKK, IL, SDP, and MD were involved in data interpretation and manuscript development. LE was involved in trial design, data analysis, trial conduct, data collection, and manuscript development. SM was involved in trial design, data interpretation, trial conduct, data collection, and manuscript development. JPF, SD and LE accessed and verified the underlying data reported in the manuscript. All authors had full access to all the data in the study, actively contributed to all drafts of the manuscript, and had final responsibility for the decision to submit for publication.

Declaration of interests

JPF has received research funding (paid to institution) from 89bio, Akero, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Intercept, IONIS, Janssen, Madrigal, Merck, Metacrine, NorthSea Therapeutics, Novartis, Novo Nordisk, Oramed, Pfizer, Poxel, and Sanofi; is involved with advisory boards and consulting for 89bio, Akero, Altimmune, Becton Dickenson, Boehringer Ingelheim, Carmot Therapeutics, Echosens, Eli Lilly, Gilead, Intercept, Merck, Novo Nordisk, Pfizer, and Sanofi; and has received payment or honoraria for speaker bureaus for Eli Lilly. They are seated on the board of directors in T1D Exchange (non-compensated position). SD, LE, and SM are employed at Novo Nordisk and are stockholders of Novo Nordisk shares. FKK has received research grants (paid to institution) from AstraZeneca, Gubra, Novo Nordisk, Sanofi, and Zealand Pharma; and received personal honoraria for consulting, participating in advisory boards, and/or speaking for 89bio, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Sanofi, Structure Therapeutics, Zealand Pharma, and Zucara. They are a co-founder and minority shareholder in Antag Therapeutics and co-owner of the medical weight-loss clinic Medicinsk Vægttabsbehandling ApS. IL has received research funding (paid to institution) from Boehringer Ingelheim, Merck, Mylan, Novo Nordisk, Pfizer, and Sanofi. They received advisory/consulting fees and/or other support from AstraZeneca, Bayer, Boehringer Ingelheim, Carmot Therapeutics, Eli Lilly, GI Dynamics, Intarcia, Intercept, Johnson and Johnson, Mannkind, Merck, Mylan, Novartis, Novo Nordisk, Pfizer, Sanofi, Shionogi, Structure Therapeutics, TARGETPharma, Valeritas, and Zealand Pharma. CM has received research funding (paid to institution) from the European Commission, FWO, Helmsley Charitable Trust, JDRF, and Novo Nordisk Foundation. They have received honoraria (paid to institution) for consulting, participating in advisory boards, and/or giving lectures/presentations from ActoBio Therapeutics, AstraZeneca, Avotres, Boehringer Ingelheim, Eli Lilly and Company, Imcyse, Insulet, Mannkind, Medtronic, Novartis, Novo Nordisk, Pfizer, Roche, Sandoz, Sanofi, Vertex, and Zealand Pharma; and are Chair of the Board of Hippo and Friends iVZW, Vice President of EUDF, President of EASD, and Chair of the Board of INNODIA iVZW. SDP acted as consultant, advisory board member, and/or speaker for Abbott, AstraZeneca, Bausch, Bayer, Boehringer Ingelheim, Dexcom, Eli Lilly, HLS, Janssen, Merck, Novo Nordisk, Pfizer, and Sanofi. They are/have been an investigator in clinical trials funded by AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Pfizer, Prometic, and Sanofi. MD has acted as consultant, advisory board member, and speaker for Boehringer Ingelheim, Eli Lilly, Novo Nordisk, and Sanofi; an advisory board member for Lexicon, Medtronic, Pfizer, and ShouTi Pharma; and as a speaker for Amgen, AstraZeneca, Napp Pharmaceuticals, and Novartis. MD has received grants in support of investigator and investigator-initiated trials from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Novo Nordisk, and Sanofi-Aventis.

Data sharing

Individual participant data will be shared in datasets in a de-identified, anonymised format. Shared data will include datasets from clinical research sponsored by Novo Nordisk completed after 2001 for product indications approved in both the EU and the USA. The study protocol and redacted clinical study report will be made available according to Novo Nordisk data sharing commitments. These data will be available permanently after research completion and approval of product and product use in both the EU and the USA (no end date). Data will be shared with bona fide researchers submitting a research proposal requesting access to data, for use as approved by the Independent Review Board (IRB) according to the IRB charter. These data can be accessed via an access request proposal form; the access criteria can be found at novonordisk-trials.com. The data will be made available on a specialised SAS data platform.

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