



Once-weekly IcoSema versus once-daily insulin glargine U100 in type 2 diabetes management (COMBINE 4): an open-label, multicentre, treat-to-target, randomised, phase 3b trial

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Summary

Background Stepwise treatment intensification is recommended for managing type 2 diabetes, including insulin initiation when non-insulin glucose-lowering medications are insufficient. Guidelines recommend combining a GLP-1 receptor agonist with basal insulin to improve glycaemic efficacy while reducing weight gain and hypoglycaemia risk. COMBINE 4 evaluated the efficacy and safety of IcoSema, a once-weekly combination therapy of basal insulin icodec and semaglutide (a GLP-1-receptor agonist) versus insulin glargine U100 (glargine U100) in people with type 2 diabetes on oral glucose-lowering medications.

Methods COMBINE 4 was a 40-week, randomised, open-label, treat-to-target, phase 3b trial conducted across 97 sites in nine countries. Adults (aged ≥ 18 years) with type 2 diabetes ($HbA_{1c} \geq 8.0\%$) receiving oral glucose-lowering medications were randomly allocated in a 1:1 ratio without stratification to IcoSema or once-daily glargine U100. The titration target was $3.9\text{--}5.0$ mmol/L ($70\text{--}90$ mg/dL). The primary endpoint was change in HbA_{1c} and the secondary confirmatory endpoint was change in bodyweight, both from baseline to week 40, evaluated in all randomly allocated participants. Adverse events were recorded during weeks 0–45. This trial is registered with ClinicalTrials.gov (NCT06269107) and is complete.

Findings Of 653 individuals screened between Feb 15 and Aug 6, 2024, 151 did not meet screening criteria and 17 withdrew before initiating treatment; 243 were randomised to IcoSema and 242 to glargine U100. Of the 485 randomly allocated participants, 286 (59%) were male and 199 (41%) were female, and median age was 58 years (range 26–82). For HbA_{1c} from baseline (9.57% for IcoSema and 9.50% for glargine U100), mean change to week 40 was greater with IcoSema versus glargine U100 (-3.32 vs -2.44 percentage points; estimated treatment difference [ETD] -0.88 percentage points [95% CI -1.12 to -0.63]), confirming superiority of IcoSema ($p < 0.001$). From baseline to week 40, mean bodyweight decreased with IcoSema and increased with glargine U100 (-0.79 vs 3.81 kg; ETD -4.61 kg [95% CI -5.46 to -3.75]), confirming superiority of IcoSema ($p < 0.001$). Rate of combined clinically significant (blood glucose < 3.0 mmol/L [< 54 mg/dL], confirmed with a blood glucose meter) or severe hypoglycaemia (severe cognitive impairment requiring external assistance for recovery) was statistically significantly lower with IcoSema versus glargine U100 (0.29 vs 0.59 episodes per person-year of exposure; estimated rate ratio 0.56 [95% CI 0.32 to 0.97]; $p = 0.04$). Gastrointestinal disorders were the most frequently reported adverse events with IcoSema.

Interpretation Once-weekly IcoSema demonstrated superior HbA_{1c} reduction and bodyweight change, with lower rates of clinically significant or severe hypoglycaemia, versus glargine U100, suggesting that IcoSema might be an effective once-weekly treatment option for insulin-naïve individuals with type 2 diabetes inadequately controlled on oral glucose-lowering medications.

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Introduction

Stepwise treatment intensification is recommended for managing type 2 diabetes.^{1,2} When several non-insulin glucose-lowering medications become inadequate, insulin therapy remains an important option.^{1,2} For insulin therapy intensification, guidelines recommend using a GLP-1 receptor agonist combined with a basal insulin to improve glycaemic efficacy and provide hypoglycaemia risk and weight management benefits over basal insulin alone.^{1,2}

IDegLira (insulin degludec plus liraglutide) and iGlarLixi (insulin glargine U100 plus lixisenatide), once-daily fixed-ratio combinations of basal insulins plus GLP-1 receptor agonists, afford the benefits of combined therapy while reducing injection frequency versus free combination therapy;^{3,4} once-weekly administration of combination therapy would further reduce this burden.

In the phase 3a COMBINE 1–3 trials, the efficacy and safety of IcoSema, a once-weekly combination therapy of basal insulin icodec and semaglutide (a GLP-1 receptor

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Research in context

Evidence before this study

Current international guidelines recommend using basal insulin in combination with a GLP-1 receptor agonist to afford greater glycaemic efficacy and provide benefits related to hypoglycaemia risk and weight management. To identify clinical publications related to combination therapies of basal insulin and a GLP-1 receptor agonist, we searched PubMed for articles published in English between Jan 1, 2000, and Feb 3, 2026, using the terms ("fixed ratio combination" AND "basal insulin" AND "glucagon-like peptide 1 receptor agonist" AND "type 2 diabetes") OR ("icodec" AND "type 2 diabetes") OR ("semaglutide" AND "type 2 diabetes"). Currently, two once-daily fixed-ratio combinations of basal insulin and a GLP-1 receptor agonist are available: IDegLira (insulin degludec with liraglutide) and iGlarLixi (insulin glargine U100 with lixisenatide). In phase 3 trials, once-daily fixed-ratio combinations showed non-inferior or greater HbA_{1c} reductions compared with daily basal insulin, basal-bolus insulin therapy, or GLP-1 receptor agonists. Furthermore, treatment with these therapies was associated with greater decreases in bodyweight and similar or lower risks of hypoglycaemia versus daily basal insulin or basal-bolus insulin therapy. Despite these improvements, and a lower injection frequency than with free combinations of basal insulin and a GLP-1 receptor agonist, these fixed-ratio combinations still require daily administration, while individuals with type 2 diabetes might value less frequent administration (eg, by using once-weekly combination therapies). More recently, IcoSema, a once-weekly combination therapy of insulin icodec (icodec) and semaglutide (a GLP-1 receptor agonist), has been developed for the management of type 2 diabetes. The efficacy and safety of the mono-components of IcoSema, namely once-weekly icodec and semaglutide, were evaluated in the phase 3a ONWARDS 1-5 and SUSTAIN trials, respectively, while semaglutide has also been investigated in real-world studies. Icodec showed superior reductions in HbA_{1c} compared with once-daily basal insulin and non-inferior reductions compared with basal-bolus insulin therapy, alongside low rates of hypoglycaemia. Semaglutide showed significant reductions in HbA_{1c} and bodyweight versus comparators. The efficacy and safety of IcoSema versus

comparators have been investigated in three phase 3a trials, COMBINE 1-3. In COMBINE 1 and 3, which enrolled insulin-experienced individuals, IcoSema showed superior or non-inferior reductions in HbA_{1c}, as well as superior bodyweight reductions, compared with icodec and daily basal-bolus insulin therapy, while hypoglycaemia rates were statistically significantly lower with IcoSema than with either comparator. In COMBINE 2, which enrolled insulin-naïve, GLP-1 receptor agonist-experienced individuals, IcoSema showed a superior reduction in HbA_{1c} compared with semaglutide 1.0 mg, while bodyweight increased slightly with IcoSema and decreased with semaglutide; the rate of combined clinically significant or severe hypoglycaemia was similar between treatment groups.

Added value of this study

COMBINE 4 (NCT06269107) investigated the efficacy and safety of once-weekly IcoSema versus insulin glargine U100 (glargine U100) in insulin-naïve individuals (aged ≥18 years) with type 2 diabetes inadequately controlled with oral glucose-lowering medications (HbA_{1c} ≥8.0% [≥64.0 mmol/mol]). Compared with glargine U100, IcoSema demonstrated a superior reduction in HbA_{1c} and a superior change in bodyweight, with a statistically significantly lower rate of combined clinically significant hypoglycaemia (blood glucose <3.0 mmol/L [<54 mg/dL], confirmed with a blood glucose meter) or severe hypoglycaemia (severe cognitive impairment requiring external assistance for recovery).

Implications of all the available evidence

In this phase 3b trial, IcoSema led to a statistically significant greater improvement in HbA_{1c} versus glargine U100, which was accompanied by a weight management benefit and a lower rate of clinically significant or severe hypoglycaemia. Taken together, these findings indicate that IcoSema might be a highly effective treatment option for insulin-naïve individuals with type 2 diabetes inadequately controlled with oral glucose-lowering medications. They also provide reassurance regarding weight gain or hypoglycaemia that might follow treatment intensification with injectable therapy, while reducing the injection burden associated with once-daily therapies.

agonist) were investigated in insulin-experienced (COMBINE 1 and 3) and insulin-naïve, GLP-1-receptor agonist-experienced (COMBINE 2) individuals with type 2 diabetes.⁵⁻⁷ For change in HbA_{1c}, IcoSema showed superiority to icodec (COMBINE 1) and 1.0 mg semaglutide (COMBINE 2), and non-inferiority to daily basal-bolus therapy (COMBINE 3). IcoSema was also superior to icodec (COMBINE 1) and daily basal-bolus therapy (COMBINE 3) for change in bodyweight. Rates of combined clinically significant or severe hypoglycaemia were lower with IcoSema versus icodec (COMBINE 1) or daily basal-bolus therapy (COMBINE 3), confirming superiority of IcoSema.

COMBINE 4 assessed the efficacy and safety of IcoSema versus glargine U100 in insulin-naïve individuals with type 2 diabetes inadequately controlled with oral glucose-lowering medications.

Methods

Study design and participants

COMBINE 4 was an open-label, treat-to-target, randomised, phase 3b trial conducted across 97 sites (nine countries: mainland China, Greece, India, Italy, Japan, Poland, South Africa, Türkiye, and the USA). The trial comprised a 2-week screening period, a 40-week treatment period, and a 5-week follow-up (appendix p 18).

See Online for appendix

Eligible adults (aged ≥ 18 years) had type 2 diabetes inadequately controlled with oral glucose-lowering medications ($\text{HbA}_{1c} \geq 8.0\%$ [≥ 64.0 mmol/mol]), and a BMI of 40 or below. Participants were insulin-naïve and GLP-1 receptor agonist-naïve. The full inclusion and exclusion criteria are listed in the appendix (pp 13–14).

The trial was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference for Harmonisation.^{8,9} The protocol, consent form, and other relevant documents were reviewed and approved by the appropriate institutional review boards or independent ethics committees; all participants provided written informed consent before trial entry.

Procedures

Participants were centrally randomised in a 1:1 ratio without stratification to once-weekly IcoSema or once-daily glargine U100 using a randomisation and trial supply management system. IcoSema was administered subcutaneously once weekly; glargine U100 was administered subcutaneously once daily. Starting doses were 40 dose-steps per week for IcoSema (equivalent to icodex 40 units [U] and semaglutide 0.114 mg) and 10 U per day for glargine U100. IcoSema and glargine U100 were titrated weekly by the investigator based on three pre-breakfast self-measured blood glucose (SMBG) values, measured on the 2 days before and on the day of titration (target: 3.9 – 5.0 mmol/L [70 – 90 mg/dL]) according to a pre-specified algorithm (appendix p 10). After randomisation, dipeptidyl peptidase 4 inhibitors, sulfonylureas, and glinides were discontinued; other pre-trial oral glucose-lowering medications were maintained. Participants were given a blood glucose meter (Accu-Chek, Roche Diabetes Care, Basel, Switzerland) at randomisation to record daily SMBG measurements. Additionally, participants were required to record their blood glucose level in an electronic diary when a hypoglycaemic episode was suspected; upon onset of the episode, participants were recommended to measure blood glucose every 15 min until the value was 3.9 mmol/L (70 mg/dL) or higher or symptoms had resolved. A continuous glucose monitoring (CGM) device (Dexcom G6, Dexcom, San Diego, CA, USA) was worn during weeks 35–40 (data from weeks 36–40 were analysed). CGM data were masked to both participants and investigators to avoid confounding and to minimise behaviour changes in participants unfamiliar with CGM. These data were not used for dose titration or hypoglycaemia reporting. Further details can be found in the appendix (pp 10, 23).

Outcomes

The primary endpoint was change in HbA_{1c} from baseline to week 40. Secondary endpoints included one confirmatory secondary endpoint and several supportive secondary endpoints. The confirmatory secondary endpoint

(included in the prespecified testing hierarchy) was change in bodyweight from baseline to week 40. Supportive secondary endpoints were first, percentages of CGM-based time in range (3.9 – 10.0 mmol/L [70 – 180 mg/dL] at weeks 36–40), time below range (<3.0 mmol/L [<54 mg/dL] at weeks 36–40), and time above range (>10.0 mmol/L [>180 mg/dL] at weeks 36–40); second, mean weekly basal insulin dose (weeks 38–40); third, changes in fasting plasma glucose (FPG) and Diabetes Treatment Satisfaction Questionnaire status version (DTSQs); fourth, the total treatment satisfaction score from baseline to week 40; and fifth, number of episodes of clinically significant hypoglycaemia (level 2; blood glucose <3.0 mmol/L [<54 mg/dL], confirmed with a blood glucose meter), severe hypoglycaemia (level 3; severe cognitive impairment requiring external assistance for recovery), and combined clinically significant or severe hypoglycaemia during weeks 0–45. Additional assessments included mean pre-breakfast SMBG used for dose titration by visit; reaching HbA_{1c} below 7.0% (<53.0 mmol/mol) at week 40; reaching HbA_{1c} below 7.0% (<53.0 mmol/mol) at week 40 without weight gain and without clinically significant or severe hypoglycaemia in the prior 12 weeks; and changes in waist circumference, blood pressure, and lipid parameters from baseline to week 40. Adverse events were recorded during weeks 0–45.

Statistical analysis

Efficacy endpoints were evaluated using the full analysis set (all randomised participants) and the in-trial or on-treatment period (appendix pp 10, 15). CGM endpoints were evaluated using the CGM full analysis set (all randomly allocated participants, except those from mainland China as the CGM device used was not available in this country at the time of the trial) and the on-treatment period (appendix p 15). Safety endpoints were evaluated using the on-treatment period, with descriptive statistics based on the safety analysis set (participants exposed to trial treatment) and statistical analyses based on the full analysis set, unless otherwise specified.

The objective was to show that IcoSema is superior to glargine U100 for change in HbA_{1c} from baseline to week 40. If superiority was confirmed, hierarchical confirmatory testing would assess superiority of IcoSema to glargine U100 for change in bodyweight from baseline to week 40. *p* values for endpoints outside the hierarchical testing sequence are not adjusted for multiplicity and are provided for descriptive purposes only.

Continuous efficacy endpoints (HbA_{1c} , bodyweight, FPG, DTSQ, and weekly basal insulin dose) were analysed using an ANCOVA model with region, personal CGM device (yes or no), and randomised treatment as fixed factors, and baseline value (baseline HbA_{1c} for change in weekly basal insulin dose) as the covariate. The model generated least-squares mean changes for each treatment group. Between-group comparisons are

presented as estimated treatment differences (ETDs) with associated 95% CIs. An ANOVA was used to analyse time in range, while a negative binomial regression model with a log-link function and the logarithm of the total number of recorded measurements as offset was used for time above and below range; both models included randomly allocated treatment, region, and personal CGM as factors. Hypoglycaemic episodes were also analysed using a negative binomial regression model with log-link function, including region, randomly allocated treatment and personal CGM as fixed factors and the logarithm of the time period in which a participant was exposed to trial product as offset. Adverse events were reported descriptively.

Missing data were imputed using multiple imputation for all endpoints analysed, except for the time below range (<3.0 mmol/L [<54 mg/dL]) and time above range (>10.0 mmol/L [>180 mg/dL]), as outlined in the appendix (p 11). Observed HbA_{1c} values at week 40 were used when available; multiple imputation was applied only for participants with missing HbA_{1c} values for

week 40, in accordance with the prespecified analysis plan. Each imputed dataset was analysed separately and combined using Rubin's rules. For the primary endpoint, a two-dimensional tipping point sensitivity analysis was performed to evaluate the robustness of the results towards the missing data assumption. In this sensitivity analysis, participants with imputed HbA_{1c} values at week 40 were assumed to have a worse outcome in the IcoSema group and a better outcome in the glargine U100 group compared with what was imputed in the primary analysis; this was achieved by adding to or subtracting values from the imputed HbA_{1c} values, independently in the two treatment groups, before analysing the data. The plausibility of the values where the conclusion of the primary analysis changed was evaluated to assess the robustness of the primary analysis results.

Based on previous semaglutide and IDegLira studies,^{10–16} 474 participants were required to ensure at least 90%

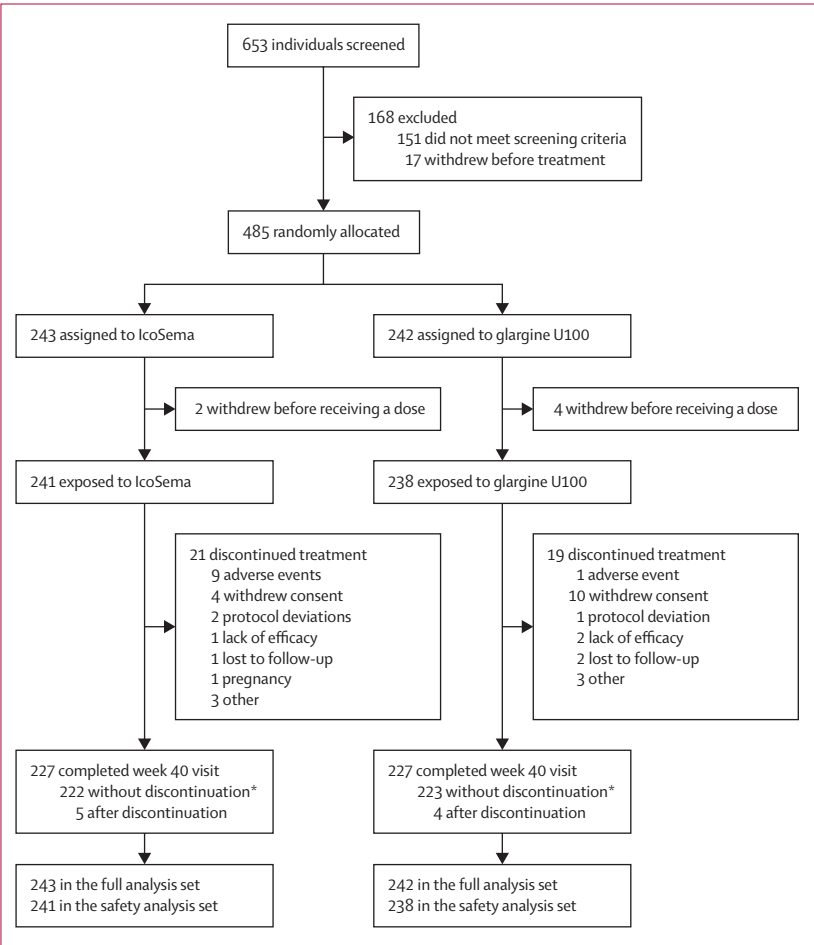


Figure 1: Trial profile
*The number of participants completing the week 40 visit without discontinuation includes those who withdrew before receiving a dose.

	IcoSema (n=243)	Glargine U100 (n=242)
Sex		
Male	140 (58%)	146 (60%)
Female	103 (42%)	96 (40%)
Age, years	58.1 (10.7)	57.7 (10.9)
Ethnicity		
Non-Hispanic or Latino	225 (93%)	216 (89%)
Hispanic or Latino	16 (7%)	25 (10%)
Not reported	2 (1%)	1 (<1%)
Race		
American Indian or Alaska Native	0	1 (<1%)
Asian	106 (44%)	95 (39%)
Black or African American	21 (9%)	19 (8%)
White	111 (46%)	124 (51%)
Multiple	2 (1%)	1 (<1%)
Other	3 (1%)	2 (1%)
Diabetes duration, years	10.9 (7.21)	11.2 (7.19)
Bodyweight, kg	82.4 (17.71)	81.7 (17.64)
Body mass index, kg/m ²	29.6 (5.14)	29.4 (4.95)
HbA _{1c} , %	9.57 (1.43)	9.50 (1.38)
HbA _{1c} , mmol/mol	81.1 (15.6)	80.3 (15.1)
FPG, mmol/L*	11.6 (3.67)	11.4 (3.54)
FPG, mg/dL*	209.2 (66.2)	205.6 (63.8)
Oral glucose-lowering medication	228 (94%)	226 (93%)
Metformin	212 (87%)	211 (87%)
SGLT2 inhibitors	73 (30%)	96 (40%)
Thiazolidinediones	16 (7%)	12 (5%)
α-glucosidase inhibitors	9 (4%)	9 (4%)
Sulfonylureas	1 (<1%)	2 (1%)
DPP-4 inhibitors	0	1 (<1%)

Data are n (%) or mean (SD). Baseline is defined as week 0, except for oral glucose-lowering medication, for which baseline is the day the first dose of randomised treatment was taken. DPP-4=dipeptidyl peptidase 4. FPG=fasting plasma glucose. SGLT2=sodium-glucose co-transporter-2. *Some values were missing at baseline.

Table 1: Participant demographics and baseline characteristics

power for superiority of IcoSema to glargine U100 for change in HbA_{1c} , assuming a treatment difference of -0.299 percentage points (SD 1 percentage point), and at least 90% marginal power for superiority of IcoSema to glargine U100 for change in bodyweight, assuming a treatment difference of -1.577 kg (SD 4.5 kg). This sample size allows marginal power for the primary and confirmatory secondary endpoints ($\geq 90\%$) and joint power for both (87.2%) assuming an intercurrent rate of 17%.

Role of the funding source

Investigators were responsible for trial conduct and trial-related medical decisions; data collection and interpretation; manuscript drafting; and decisions related to publication. Investigators and statisticians remained masked to the trial provisioned CGM throughout the trial. Novo Nordisk representatives were involved in trial design and conduct; data collection, management, analysis, and interpretation; and manuscript preparation, review, and approval. A medical writer, funded by Novo Nordisk, provided writing support under the authors' direction. Novo Nordisk did not have the right to veto publication or to control the decision regarding to which journal the manuscript was submitted; these decisions were taken by the authors.

Results

Of 653 individuals screened between Feb 15 and Aug 6, 2024, 151 did not meet screening criteria and 17 withdrew before initiating treatment; 243 were randomised to IcoSema and 242 to glargine U100. Overall, 222 (91%) of 243 participants receiving IcoSema and 223 (92%) of 242 receiving glargine U100 completed the week 40 visit without permanent treatment discontinuation (figure 1). Of the 485 randomly allocated participants, 286 (59%) were male and 199 (41%) were female, and median age was 58 years (range 26–82). The majority of participants were White (235 [48%]) or Asian (201 [41%]). Participant demographics and baseline characteristics are given in table 1. Four (2%) of

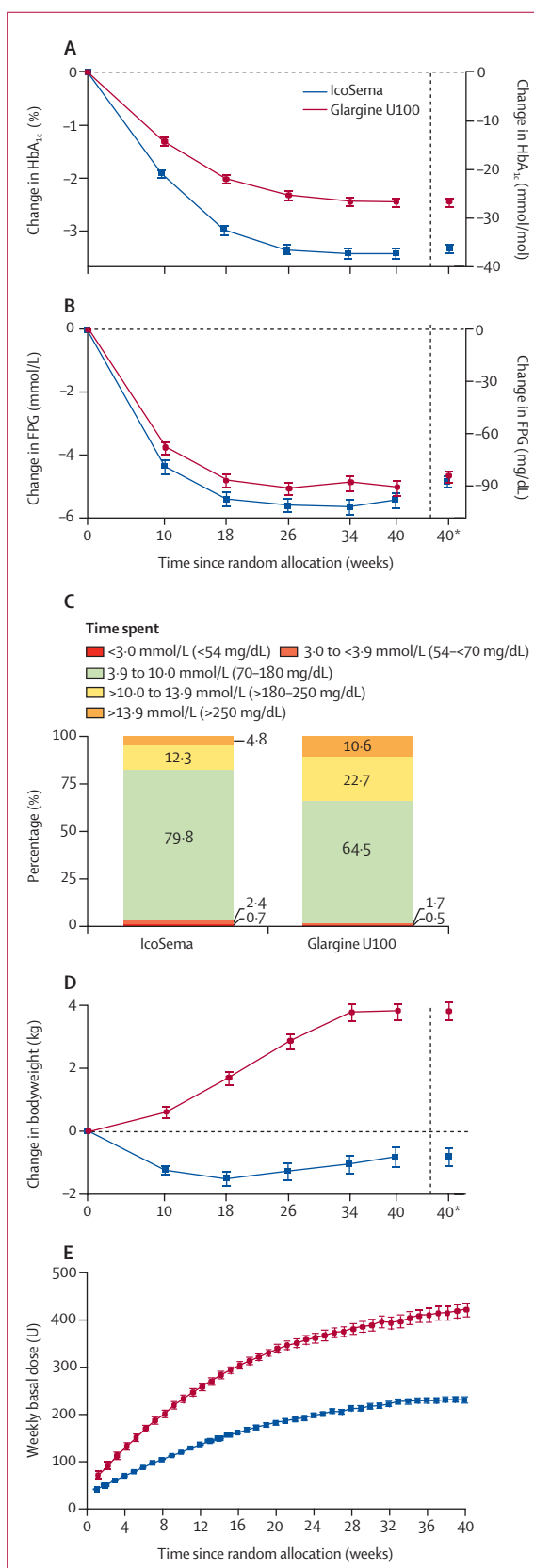


Figure 2: Key efficacy outcomes in the full analysis set
Change in HbA_{1c} from baseline to week 40 (A). Change in FPG from baseline to week 40 (B). CGM outcomes during weeks 36–40 (C). Change in bodyweight from baseline to week 40 (D). Mean weekly basal insulin dose throughout the trial (E). For change in HbA_{1c} , FPG, and bodyweight, observed mean and standard error of the mean (error bars) are shown; data obtained after premature treatment discontinuation were included for change in HbA_{1c} and bodyweight analyses but not for the FPG analysis. For CGM outcomes, participants were included in the analysis only if at least 70% of their planned CGM measurements were available. The analysis was based on observed CGM data. Time spent is defined as 100 times the number of recorded measurements in a given range, divided by the total number of recorded measurements. Basal insulin dose over time represents observed mean and standard error of the mean (error bars) data. CGM=continuous glucose monitoring. FPG=fasting plasma glucose. U=units. *Estimated mean values and standard error of the mean at week 40 were based on multiple imputation.

243 participants receiving IcoSema and eight (3%) of 242 receiving glargine U100 initiated treatment with non-randomised glucose-lowering medication for more than 2 weeks during the trial (appendix p 16).

From baseline to week 40, observed mean HbA_{1c} decreased from 9.57% (SD 1.43) to a model estimate of 6.22% (SE 0.09) with IcoSema and from 9.50% (SD 1.38) to a model estimate of 7.10% (SE 0.09) with glargine U100. Estimated mean changes from baseline to week 40 were -3.32 (SE 0.09) and -2.44 (SE 0.09) percentage points with IcoSema and glargine U100, respectively (ETD -0.88 percentage points [95% CI -1.12 to -0.63]), confirming superiority of IcoSema ($p<0.001$; figure 2A and table 2). A tipping-point sensitivity analysis for the primary endpoint confirmed robustness of the findings (appendix p 19).

From baseline to week 40, mean FPG showed similar decreases in both groups with an ETD of -0.18 mmol/L (95% CI -0.74 to 0.39) or -3.22 mg/dL (95% CI -13.4 to 6.95; $p=0.54$; figure 2B and table 2). Mean pre-breakfast SMBG used for dose adjustment were comparable between groups throughout the trial, decreasing immediately from random allocation until approximately week 20, before remaining relatively stable for the remaining treatment period (appendix p 20).

Odds of reaching HbA_{1c} below 7.0% (<53.0 mmol/mol) at week 40 were statistically significantly greater for IcoSema versus glargine U100 (estimated odds ratio [OR] 4.08 [95% CI 2.58–6.44]; $p<0.001$), as were the odds of reaching HbA_{1c} below 7.0% (<53.0 mmol/mol) without weight gain and without clinically significant or severe hypoglycaemia (estimated OR 7.75 [95% CI 4.63–13.0]; $p<0.001$; table 2). During weeks 36–40,

compared with participants receiving glargine U100, those receiving IcoSema spent a statistically significantly greater percentage of time in range (ETD 13.3 percentage points [95% CI 9.46–17.2]; $p<0.001$) and a statistically significantly lower percentage of time above range (>10.0 mmol/L [>180 mg/dL]; estimated treatment ratio 0.46 [95% CI 0.38–0.56]; $p<0.001$; figure 2C and table 2). Percentage of time below range (<3.0 mmol/L [<54 mg/dL]) was similar between groups (estimated treatment ratio 1.35 [95% CI 0.94–1.94]; $p=0.11$; figure 2C and table 2).

From baseline to week 40, estimated mean changes in bodyweight were -0.79 kg (SE 0.31) and 3.81 kg (SE 0.31) with IcoSema and glargine U100, respectively (ETD -4.61 kg [95% CI -5.46 to -3.75]), confirming superiority of IcoSema ($p<0.001$; figure 2D and table 2). Estimated mean weekly basal insulin dose during weeks 38–40 was statistically significantly lower with IcoSema versus glargine U100 (ETD -126 U [95% CI -154 to -98]; $p<0.001$; figure 2E and table 2). In the IcoSema group, mean semaglutide dose at week 40 was 0.66 mg (SD 0.27).

From baseline to week 40, there was a statistically significantly greater improvement in DTSQs total treatment satisfaction score for IcoSema versus glargine U100 (ETD 1.90 [95% CI 0.84–2.97]; $p<0.001$; table 2).

Overall, 21 (9%) of 241 participants receiving IcoSema and 52 (22%) of 238 receiving glargine U100 had at least one episode of clinically significant hypoglycaemia. Three severe hypoglycaemic episodes were reported in two participants receiving IcoSema, whereas six episodes were reported in five participants receiving glargine

	IcoSema (n=243)	Glargine U100 (n=242)	Estimate (95% CI)	p value
Primary endpoint				
Mean change in HbA _{1c} from baseline to week 40 (SE), percentage points	-3.32 (0.09)	-2.44 (0.09)	ETD -0.88 (-1.12 to -0.63)	<0.001
Confirmatory secondary endpoint				
Mean change in bodyweight from baseline to week 40 (SE), kg	-0.79 (0.31)	3.81 (0.31)	ETD -4.61 (-5.46 to -3.75)	<0.001
Secondary efficacy endpoints				
Observed mean time in range (3.9–10.0 mmol/L [70–180 mg/dL]) during weeks 36–40 (SD)	79.8% (19.6)	64.5% (18.8)	ETD 13.3 (9.46 to 17.2)	<0.001
Observed mean time below range (<3.0 mmol/L [<54 mg/dL]) during weeks 36–40 (SD)	0.69% (1.05)	0.53% (0.96)	ETR 1.35 (0.94 to 1.94)	0.11
Observed mean time above range (>10.0 mmol/L [>180 mg/dL]) during weeks 36–40 (SD)	17.1% (20.8)	33.3% (19.7)	ETR 0.46 (0.38 to 0.56)	<0.001
Mean weekly basal insulin dose during weeks 38–40 (SE), U	234 (10)	360 (10)	ETD -126 (-154 to -98)	<0.001
Mean change in FPG from baseline to week 40 (SE), mmol/L	-4.85 (0.20)	-4.68 (0.20)	ETD -0.18 (-0.74 to 0.39)	0.54
Mean change in DTSQs total treatment satisfaction score from baseline to week 40 (SE)	5.24 (0.38)	3.34 (0.39)	ETD 1.90 (0.84 to 2.97)	<0.001
Additional assessments at week 40				
Percentage of participants who reached HbA _{1c} level $<7.0\%$ (<53.0 mmol/mol) [†]	80.0%	49.5%	EOR 4.08 (2.58 to 6.44)	<0.001
Percentage of participants who reached HbA _{1c} $<7.0\%$ (<53.0 mmol/mol) without weight gain or clinically significant [‡] or severe [§] hypoglycaemic episodes in the previous 12 weeks	43.1%	8.9%	EOR 7.75 (4.63 to 13.0)	<0.001

Values are estimates unless otherwise specified. DTSQs=Diabetes Treatment Satisfaction Questionnaire status version. EOR=estimated odds ratio. ETD=estimated treatment difference. ETR=estimated treatment ratio. FPG=fasting plasma glucose. U=units. *The full analysis set (all randomly assigned participants) was used for all endpoints except the continuous glucose monitoring endpoints, which were analysed using the continuous glucose monitoring full analysis set (all randomly allocated participants except those from mainland China). [†]For participants who discontinued trial treatment, the dichotomous outcome was set to no. [‡]Clinically significant hypoglycaemia (level 2): blood glucose value <3.0 mmol/L (<54 mg/dL), confirmed with a blood glucose meter. [§]Severe hypoglycaemia (level 3): hypoglycaemia with severe cognitive impairment requiring external assistance for recovery.

Table 2: Summary of key outcomes in the full analysis set*

U100. From baseline to week 45, the overall rates of combined clinically significant or severe hypoglycaemia were 0.29 and 0.59 per person-year of exposure with IcoSema and glargine U100, respectively (estimated rate ratio 0.56 [95% CI 0.32 to 0.97]; $p=0.04$; table 3). The cumulative incidence of observed number of combined clinically significant or severe hypoglycaemia episodes per participant is shown in the appendix (p 21).

Overall, 199 (83%) of 241 participants in the IcoSema group and 170 (71%) of 238 participants in the glargine U100 group had 1469 and 671 adverse events (excluding hypoglycaemia), respectively. Most events were mild or moderate in severity (table 3). The most frequently reported adverse events were within the system organ classes for gastrointestinal disorders (IcoSema) and infections and infestations (glargine U100).

	IcoSema (n=241)		Glargine U100 (n=238)		ERR (95% CI)‡	p value
	Participants*	Events, rate per person-year of exposure†	Participants*	Events, rate per person-year of exposure†		
Hypoglycaemia (baseline to week 45)						
Hypoglycaemia alert value§	135 (56%)	1043 (5.21)	180 (76%)	1565 (7.89)	..	..
Clinically significant hypoglycaemia¶	21 (9%)	55 (0.27)	52 (22%)	111 (0.56)	0.57 (0.32 to 1.02)	0.06
Severe hypoglycaemia**	2 (1%)	3 (0.02)	5 (2%)	6 (0.03)	..	..
Combined clinically significant or severe hypoglycaemia	23 (10%)	58 (0.29)	55 (23%)	117 (0.59)	0.56 (0.32 to 0.97)	0.04
Summary of adverse events (baseline to week 45)						
Total	199 (83%)	1469 (7.34)	170 (71%)	671 (3.38)	NA	NA
Serious	16 (7%)	19 (0.09)	23 (10%)	29 (0.15)	NA	NA
Severity						
Mild	186 (77%)	1071 (5.35)	153 (64%)	482 (2.43)	NA	NA
Moderate	82 (34%)	346 (1.73)	69 (29%)	160 (0.81)	NA	NA
Severe	13 (5%)	52 (0.26)	21 (9%)	29 (0.15)	NA	NA
Relation to trial treatment						
Possibly	94 (39%)	269 (1.34)	39 (16%)	85 (0.43)	NA	NA
Probably	84 (35%)	699 (3.49)	31 (13%)	66 (0.33)	NA	NA
Deaths	1 (<1%)	1 (0.01)††	0	0	NA	NA
Most frequently reported (≥5%) adverse events by preferred term‡‡	159 (66%)	918 (4.59)	92 (39%)	170 (0.86)	NA	NA
Gastrointestinal disorders	136 (56%)	818 (4.09)	51 (21%)	84 (0.42)	NA	NA
Nausea	73 (30%)	225 (1.12)	10 (4%)	13 (0.07)	NA	NA
Diarrhoea	52 (22%)	191 (0.95)	13 (5%)	18 (0.09)	NA	NA
Vomiting	44 (18%)	128 (0.64)	7 (3%)	9 (0.05)	NA	NA
Constipation	35 (15%)	58 (0.29)	7 (3%)	10 (0.05)	NA	NA
Abdominal distension	17 (7%)	70 (0.35)	1 (<1%)	1 (0.01)	NA	NA
Dyspepsia	16 (7%)	35 (0.17)	4 (2%)	4 (0.02)	NA	NA
Infections and infestations	93 (39%)	136 (0.68)	81 (34%)	120 (0.61)	NA	NA
Upper respiratory tract infection	27 (11%)	35 (0.17)	25 (11%)	33 (0.17)	NA	NA
Nasopharyngitis	22 (9%)	25 (0.12)	22 (9%)	27 (0.14)	NA	NA
Influenza	16 (7%)	21 (0.10)	8 (3%)	10 (0.05)	NA	NA
Metabolism and nutrition disorders	39 (16%)	79 (0.39)	29 (12%)	32 (0.16)	NA	NA
Decreased appetite	27 (11%)	53 (0.26)	1 (<1%)	1 (0.01)	NA	NA
Nervous system disorders	43 (18%)	87 (0.43)	47 (20%)	66 (0.33)	NA	NA
Headache	18 (7%)	31 (0.15)	9 (4%)	12 (0.06)	NA	NA
Dizziness	15 (6%)	31 (0.15)	19 (8%)	24 (0.12)	NA	NA
General disorders and administration site conditions	46 (19%)	80 (0.40)	39 (16%)	54 (0.27)	NA	NA
Fatigue	13 (5%)	15 (0.08)	7 (3%)	8 (0.04)	NA	NA

Data are n (%), unless otherwise specified. Statistical analyses for hypoglycaemia outcomes were assessed using the full analysis set. ERR=estimated rate ratio.

NA=not applicable. *Participants refers to the number of participants experiencing at least one event. †1 person-year of exposure is 365.25 days. ‡ERR calculated for hypoglycaemia rates only. §Hypoglycaemia alert value (level 1): blood glucose value <3.9 mmol/L (<70 mg/dL) but at least 3.0 mmol/L (≥54 mg/dL), confirmed with a blood glucose meter. ¶Clinically significant hypoglycaemia (level 2): blood glucose value <3.0 mmol/L (<54 mg/dL), confirmed with a blood glucose meter. **Severe hypoglycaemia (level 3): hypoglycaemia with severe cognitive impairment requiring external assistance for recovery. ††Preferred term: arteriosclerosis. ‡‡Identified using a predefined Medical Dictionary for Regulatory Activities (version 28.0) search.

Table 3: Summary of secondary safety endpoints in the safety analysis set

Overall, nine participants receiving IcoSema and one receiving glargine U100 experienced adverse events leading to treatment discontinuation. In addition, 183 adverse events in 35 (15%) of 241 participants in the IcoSema group and 38 adverse events in 20 (8%) of 238 participants in the glargine U100 group led to dose reductions. In total, 19 serious adverse events occurred in 16 participants receiving IcoSema, and 29 occurred in 23 participants receiving glargine U100. One person receiving IcoSema died, but this was considered unlikely to be related to IcoSema; no deaths were reported for glargine U100.

Gastrointestinal adverse events were reported by 136 (56%) of 241 participants receiving IcoSema and 51 (21%) of 238 receiving glargine U100; the most common preferred terms in both groups were nausea, diarrhoea, and vomiting. Gastrointestinal adverse events were reported throughout the trial, with prevalence remaining below 25% with IcoSema and below 5% with glargine U100 (appendix p 22). Gastrointestinal adverse events led to treatment discontinuation for four participants receiving IcoSema and none receiving glargine U100. With IcoSema, median durations of the most frequently reported gastrointestinal adverse events were 4 days for nausea, 3 days for diarrhoea, and 2 days for vomiting. Five participants receiving IcoSema accounted for 267 gastrointestinal adverse events (33% of those reported).

Diabetic retinopathy rates (identified using a predefined Medical Dictionary for Regulatory Activities search) were similar between groups; 11 (5%) of 241 participants receiving IcoSema had 14 events, and ten (4%) of 238 receiving glargine U100 had 13 events (rate of 0.07 events per person-year of exposure for both groups). None of these events were serious; one, in the glargine U100 group, was severe.

Changes in waist circumference, blood pressure, and lipid parameters from baseline to week 40 are shown in the appendix (p 17).

Discussion

In insulin-naïve adults with type 2 diabetes, inadequately controlled with oral glucose-lowering medications, IcoSema demonstrated superiority to glargine U100 in reduction in HbA_{1c} and change in bodyweight from baseline to week 40. Furthermore, the rates of clinically significant or severe hypoglycaemia during weeks 0–45 were low in both groups, and statistically significantly favoured IcoSema over glargine U100 for the combined clinically significant or severe hypoglycaemia rate. The improvement in DTSQs total treatment satisfaction score also statistically significantly favoured IcoSema over glargine U100.

There were substantial and clinically meaningful reductions in HbA_{1c} during the 40-week treatment period: -3.32 and -2.44 percentage points with IcoSema and glargine U100, respectively; these are greater than those reported in COMBINE 1–3.^{5–7} However, unlike

COMBINE 1–3, COMBINE 4 included an insulin-naïve, GLP-1 receptor agonist-naïve population with higher baseline HbA_{1c}; in COMBINE 1–3, eligible participants had an HbA_{1c} between 7.0–10.0% while in COMBINE 4, the inclusion criteria was an HbA_{1c} greater than 8.0%. As a result of this, baseline HbA_{1c} was higher in this trial versus COMBINE 1–3.

It is also important to consider these reductions in the context of the tighter dose titration target used in COMBINE 4 versus COMBINE 1–3 (target pre-breakfast SMBG: 3.9–5.0 mmol/L [70–90] vs 4.4–7.2 mmol/L [80–130 mg/dL]). Notably, low proportions of individuals in both groups initiated additional glucose-lowering therapies during the trial (2% for IcoSema vs 3% for glargine U100), suggesting that most individuals were reaching adequate glycaemic control. Reductions in HbA_{1c} were accompanied by reductions in pre-breakfast SMBG immediately after random allocation in both groups, contrary to observations in COMBINE 1 and 3.^{5,7} This is probably due to differences in pre-trial treatments between trials; in COMBINE 1 and 3, participants switched from pre-trial daily basal insulin to IcoSema, whereas in COMBINE 4, IcoSema was an add-on to pre-trial treatment.

A statistically significantly greater percentage of time in range was observed with IcoSema versus glargine U100, along with a statistically significantly lower percentage of time above range (>10.0 mmol/L [>180 mg/dL]); time below range (<3.0 mmol/L [<54 mg/dL]) was similar between groups. All three outcomes for IcoSema met internationally recommended targets: 70% time in range, less than 25% time above 10.0 mmol/L (180 mg/dL), and less than 1% time below 3.0 mmol/L (54 mg/dL). For glargine U100, only time below 3.0 mmol/L (54 mg/dL) met the target.¹⁷

IcoSema was superior to glargine U100 for change in bodyweight, with an overall decrease reported for IcoSema from baseline to week 40, suggesting a weight management benefit, in contrast to the increase in weight that can be associated with insulin therapy. Furthermore, the statistically significantly lower basal insulin dose reported with IcoSema versus glargine U100 at the end of the trial might be indicative of IcoSema having an insulin dose-sparing effect.

No new safety concerns were reported for IcoSema; its safety profile reflected that of its mono-components. As expected for IcoSema, which includes a GLP-1 receptor agonist,^{1,18,19} gastrointestinal disorders were the main type of adverse event, but most were mild or moderate in severity and of limited duration. Furthermore, prevalence of these events remained below 25% throughout the trial, and only four out of eight adverse events leading to IcoSema discontinuation were due to gastrointestinal disorders. Notably, five participants receiving IcoSema experienced 267 gastrointestinal adverse events, possibly indicating greater sensitivity to recurring events in these individuals.

The rate of combined clinically significant or severe hypoglycaemia was statistically significantly lower with IcoSema versus glargine U100, aligning with previous reports for IcoSema versus basal or basal-bolus insulin,^{5,7} as well as the similar or lower hypoglycaemia risks for IDegLira and iGlarLixi versus basal insulin.²⁰ Diabetic retinopathy rates were similar between groups.

There are some limitations to note. COMBINE 4 had an open-label design, which might have led to detection or reporting bias, although use of objective endpoints probably minimised this effect. Furthermore, CGM data were only collected during the last 4 weeks of treatment, precluding analysis of the change in parameters from baseline to end of treatment. The DTSQ findings reflect treatment satisfaction only and cannot be used to infer effects on adherence or broader quality-of-life outcomes. Real-world assessments are required to evaluate these patient-driven measures. The trial also has notable strengths. COMBINE 4 recruited a large, multinational cohort, probably forming a representative population of insulin-naïve and GLP-1 receptor agonist-naïve participants initiating insulin treatment. Furthermore, although CGM data collection was restricted, the data collected were masked, providing an unbiased representation of relevant metrics.

In conclusion, once-weekly IcoSema showed a superior reduction in HbA_{1c}, a superior change in bodyweight, and a statistically significantly lower rate of combined clinically significant or severe hypoglycaemia versus glargine U100 in insulin-naïve individuals with type 2 diabetes, suggesting that IcoSema might be a feasible treatment option for such individuals. It also provides reassurance regarding concerns around hypoglycaemia and weight gain that may accompany insulin intensification after oral glucose-lowering medications while reducing the injection burden associated with once-daily therapies.

Contributors

LJ, VM, FP, HW, and RRR were trial investigators and helped to obtain data. NW had access to the raw data and was responsible for the statistical considerations in the analysis. LJ, MB, LP-B, and NW accessed and verified the data. All authors participated in reviewing and interpreting the data outputs and in developing the manuscript. All authors had permission to access the raw data and had final responsibility for the decision to submit for publication.

Declaration of interests

LJ has received research support and consultant fees from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Fosun Pharma, Gan & Lee, Haisco Pharmaceutical, Innovent Biologics, Merck, MSD, Novo Nordisk, Sanofi-Aventis, Sibionics, and Sinocare; has served on advisory panels for Haisco Pharmaceutical and received honoraria from Eli Lilly, Innovent Biologics, Novo Nordisk and Sanofi-Aventis. MB, LP-B, and NW are employees of Novo Nordisk and hold stock options. VM has acted as consultant and speaker for, and received research or educational grants from Abbott, Alembic Pharmaceuticals, Apex Pharma, Aventis, Bayer, Biocon, Boehringer Ingelheim, Cipla, Dr Reddy's, Eli Lilly, Emcure, Fourrts India, Franco Indian, Glenmark Pharmaceuticals, GSK, Intas Pharmaceuticals, Ipca Laboratories, Johnson & Johnson, LifeScan, Lupin, Mankind Pharma, Medtronic, MSD, Novartis, Novo Nordisk, Primus Pharmaceuticals, Roche, Sanofi, Servier, Sun Pharma, Torrent Pharma, USV, Wockhardt, and Zydus Lifesciences. FP has received research support or consultant and speaker fees from, or has participated

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Data sharing

Bona fide researchers can request access to data by submitting a research proposal for approval by Novo Nordisk and an independent review panel. Data sharing requests may be considered after research completion and primary publication, or, if the trial is intended for regulatory submission, after approval of product and product use in both the EU and USA. Individual participant data will be shared in data sets in anonymised format. Information about the data sharing process can be found at the Novo Nordisk Trials website.

For the information about the data sharing process see novonordisk-trials.com

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