Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial

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Summary

Background Tirzepatide is a novel dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist under development for the treatment of type 2 diabetes. We aimed to assess the efficacy and safety of tirzepatide versus titrated insulin degludec in people with type 2 diabetes inadequately controlled by metformin with or without SGLT2 inhibitors.

Methods In this open-label, parallel-group, multicentre (122 sites), multinational (13 countries), phase 3 study, eligible participants (aged ≥18 years) had a baseline glycated haemoglobin (HbA_{1c}) of 7·0–10·5%, body-mass index of at least 25 kg/m², stable weight, and were insulin-naive and treated with metformin alone or in combination with an SGLT2 inhibitor for at least 3 months before screening. Participants were randomly assigned (1:1:1:1), using an interactive web-response system, to once-weekly subcutaneous injection of tirzepatide (5, 10, or 15 mg) or once-daily subcutaneous injection of titrated insulin degludec, and were stratified by country, HbA_{1c}, and concomitant use of oral antihyperglycaemic medications. Tirzepatide was initially given at 2·5 mg and the dose was escalated by 2·5 mg every 4 weeks until the assigned dose was reached. Insulin degludec was initially given at 10 U per day and was titrated once weekly to a fasting self-monitored blood glucose of less than 5·0 mmol/L (<90 mg/dL), following a treat-to-target algorithm, for 52 weeks. The primary efficacy endpoint was non-inferiority of tirzepatide 10 mg or 15 mg, or both, versus insulin degludec in mean change from baseline in HbA_{1c} at week 52. Key secondary efficacy endpoints were non-inferiority of tirzepatide 5 mg versus insulin degludec in mean change from baseline in HbA_{1c} at week 52, superiority of all doses of tirzepatide versus insulin degludec in mean change from baseline in HbA_{1c} and bodyweight, and the proportion of participants achieving HbA_{1c} of less than 7·0% (<53 mmol/mol) at week 52. We used a boundary of 0·3% to establish non-inferiority in HbA_{1c} difference between treatments. Efficacy and safety analyses were assessed in the modified intention-to-treat population (all participants who received at least one dose of study drug). This trial is registered with ClinicalTrials.gov, number NCT03882970, and is complete.

Findings Between April 1 and Nov 15, 2019, we assessed 1947 participants for eligibility, 1444 of whom were randomly assigned to treatment. The modified intention-to-treat population was 1437 participants from the tirzepatide 5 mg (n=358), tirzepatide 10 mg (n=360), tirzepatide 15 mg (n=359), and insulin degludec (n=360) groups. From a mean baseline HbA_{1c} of 8·17% (SD 0·91), the reductions in HbA_{1c} at week 52 were 1·93% (SE 0·05) for tirzepatide 5 mg, 2·20% (0·05) for tirzepatide 10 mg, and 2·37% (0·05) for tirzepatide 15 mg, and 1·34% (0·05) for insulin degludec. The non-inferiority margin of 0·3% was met. The estimated treatment difference (ETD) versus insulin degludec ranged from –0·59% to –1·04% for tirzepatide (p<0·0001 for all tirzepatide doses). The proportion of participants achieving a HbA_{1c} of less than 7·0% (<53 mmol/mol) at week 52 was greater (p<0·0001) in all three tirzepatide groups (82%–93%) versus insulin degludec (61%). At week 52, from a baseline of 94·3 kg (SD 20·1), all three tirzepatide doses decreased bodyweight (–7·5 kg to –12·9 kg), whereas insulin degludec increased bodyweight by 2·3 kg. The ETD versus insulin degludec ranged from –9·8 kg to –15·2 kg for tirzepatide (p<0·0001 for all tirzepatide doses). The most common adverse events in tirzepatide-treated participants were mild to moderate gastrointestinal events that decreased over time. A higher incidence of nausea (12–24%), diarrhoea (15–17%), decreased appetite (6–12%), and vomiting (6–10%) was reported in participants treated with tirzepatide than in those treated with insulin degludec (2%, 4%, 1%, and 1%, respectively). Hypoglycaemia (<54 mg/dL or severe) was reported in five (1%), four (1%), and eight (2%) participants on tirzepatide 5, 10, and 15 mg, respectively, versus 26 (7%) on insulin degludec. Treatment discontinuation due to an adverse event was more common in the tirzepatide groups than in the insulin degludec group. Five participants died during the study; none of the deaths were considered by the investigators to be related to the study treatment.

Interpretation In patients with type 2 diabetes, tirzepatide (5, 10, and 15 mg) was superior to titrated insulin degludec, with greater reductions in HbA_{1c} and bodyweight at week 52 and a lower risk of hypoglycaemia. Tirzepatide showed a similar safety profile to that of GLP-1 receptor agonists.

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See Comment page 560

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Introduction

Type 2 diabetes is a chronic metabolic condition characterised by hyperglycaemia that requires stepwise addition of medications as the disease progresses.[1,2] Current guidelines recommend basal insulin or GLP-1 receptor agonists as the first-line injectable therapy in patients with type 2 diabetes.[1,2] Basal insulin is effective in controlling hyperglycaemia, but is associated with weight gain and increased risk of hypoglycaemia.[3,4] GLP-1 receptor agonists have shown similar or greater efficacy than basal insulin on glycaemic control, with weight loss and lower risk of hypoglycaemia,[5–10] but are associated with gastrointestinal side-effects.[11]

Glucose-dependent insulinotropic polypeptide (GIP) is the incretin hormone responsible for the majority of the insulinotropic incretin effect in healthy individuals.[12] It regulates insulin secretion in a glucose-dependent manner, inhibits glucagon secretion during hyperglycaemia, and signals glucagon secretion during hypoglycaemia and in normoglycaemic states. Because GIP receptors, in contrast to GLP-1 receptors, are abundant in adipose tissue, GIP exerts additional actions beyond its incretin role that contribute to the therapeutic efficacy by improving insulin sensitivity, lipid homoeostasis, and whole-body energy metabolism.[13,14]

Tirzepatide is a 39-amino acid synthetic peptide with agonist activity at both GIP and GLP-1 receptors.[15] Its structure is based on the GIP amino acid sequence and includes a C20 fatty di-acid moiety. It has a half-life of about 5 days, allowing once-weekly subcutaneous administration. The results from the SURPASS-1 and SURPASS-2 phase 3 trials showed the superiority of tirzepatide in reducing glycated haemoglobin (HbA_{1c}) and bodyweight, as monotherapy versus placebo (SURPASS-1)[16] and as an add-on to metformin compared with once-weekly administration of the selective GLP-1 receptor agonist semaglutide 1 mg (SURPASS-2).[17] Further, tirzepatide was associated with reductions in blood pressure, triglyceride concentrations, and VLDL concentrations, and an increase in HDL concentrations.[16,17] The most commonly reported adverse events were gastrointestinal in nature and mild to moderate in severity, usually occurring during the dose-escalation period.[16,17]

In this trial, we aimed to assess the effects on glycaemic control, bodyweight, and safety of once-weekly tirzepatide (5, 10, and 15 mg) versus titrated once-daily insulin degludec in patients with type 2 diabetes with inadequate glycaemic control on a stable dose of metformin with or without SGLT2 inhibitors.

Research in context

Evidence before this study

We searched PubMed on May 6, 2021, using the terms "albiglutide", "dulaglutide", "exenatide", "liraglutide", "lixisenatide", "semaglutide", "tirzepatide", "glucagon-like peptide-1 receptor agonist (GLP-1 RA)", "glucose-dependent insulinotropic polypeptide (GIP)", "basal insulin", "insulin degludec", "insulin glargine", and "type 2 diabetes", with no date or study duration restrictions. Non-English references were excluded. Current guidelines recommend either basal insulin or GLP-1 receptor agonists as the first-line injectable therapy in the treatment of type 2 diabetes. Tirzepatide is a novel once-weekly dual GIP and GLP-1 receptor agonist representing a first-in class drug for the treatment of type 2 diabetes. It has shown clinically meaningful improvements in glycated haemoglobin (HbA_{1c}) and bodyweight as monotherapy compared to placebo and as add-on to metformin compared to the GLP-1 receptor agonist semaglutide in phase 3 trials. Its safety profile is similar to that of GLP-1 receptor agonists.

Added value of this study

To our knowledge, this trial is the first to compare the efficacy and safety of a dual GIP and GLP-1 receptor agonist with basal insulin. Treatment with 5, 10, or 15 mg of tirzepatide for 52 weeks resulted in greater reductions in HbA_{1c} and bodyweight than did insulin degludec, with larger proportions of participants achieving the recommended HbA_{1c} treatment targets. The most frequent adverse events with tirzepatide were gastrointestinal symptoms that were mild to moderate in severity and decreased over time. Overall, the safety and tolerability profile of tirzepatide is similar to that of GLP-1 receptor agonists and results in lower risk of hypoglycaemia than does insulin degludec.

Implications of all the available evidence

Once-weekly tirzepatide provides meaningful benefits in glycaemic control in patients with type 2 diabetes inadequately controlled by metformin with or without an SGLT2 inhibitor. The broader metabolic benefit of tirzepatide, with improvements in bodyweight, blood pressure, and lipid profile, along with the low risk of clinically relevant hypoglycaemia, should be taken into consideration in patients with inadequate glycaemic control on oral antihyperglycaemic medication who require therapy intensification with an injectable medication.

Methods

Study design and participants

This multicentre, randomised, active-controlled, open-label, parallel-group, phase 3 trial (SURPASS-3) was done at 122 medical research centres and hospitals in Argentina, Austria, Greece, Hungary, Italy, Poland, Puerto Rico, Romania, South Korea, Spain, Taiwan, Ukraine, and the USA.

Eligible participants (aged ≥18 years) were insulin-naive and had type 2 diabetes that was inadequately controlled (HbA_{1c} 7·0–10·5%) on stable treatment with metformin alone or in combination with an SGLT2 inhibitor for at least 3 months before screening, a body-mass index (BMI) of at least 25 kg/m², and stable weight (no change outside of 5%) during the previous 3 months. Key exclusion criteria included patients with type 1 diabetes, history of pancreatitis, history of proliferative diabetic retinopathy or maculopathy (or non-proliferative diabetic retinopathy requiring acute treatment), and an estimated glomerular filtration rate of less than 45 mL/min per 1·73 m². Full eligibility criteria are in the appendix (p 3).

The protocol for this study is available in the appendix (p 27). The protocol was approved by the institutional review boards at each site and the trial was done in accordance with local regulations, the principles of the Declaration of Helsinki, the Council of International Organizations of Medical Sciences International Ethical Guidelines, and Good Clinical Practice guidelines. All participants provided written informed consent.

Randomisation and masking

Participants were randomly assigned (1:1:1:1) to receive once-weekly tirzepatide (5, 10, or 15 mg), or once-daily insulin degludec. Assignment to treatment group was determined by a computer-generated random sequence using the Eli Lilly and Company interactive web-response system. This system is externally validated and compliant with the Code of Federal Regulations 21 part 11.

Participants were stratified at randomisation based on country, baseline HbA_{1c} (≤8·5% [≤69 mmol/mol] or >8·5% [>69 mmol/mol]), and current use of concomitant oral antihyperglycaemic medications (metformin alone or metformin plus an SGLT2 inhibitor). We used an open-label design owing to the different dosing frequencies, titration schemes, and injection devices of insulin degludec and tirzepatide. Every attempt was made to retain participants in the study regardless of whether they decided to discontinue study treatment. All cases of suspected pancreatitis and major adverse cardiovascular events were adjudicated by an independent clinical endpoint committee (appendix p 7) in a masked manner.

Procedures

After a 1-week screening and 2-week lead-in period, participants were treated with either tirzepatide or insulin degludec for 52 weeks, followed by a 4-week safety follow-up period (appendix p 19).

Tirzepatide (Eli Lilly and Company, Indianapolis, IN, USA) was administered once weekly via subcutaneous injection with a single-dose pen, preferably on the same day and time each week. The starting dose of tirzepatide was 2·5 mg once weekly for 4 weeks, followed by dose increases at 2·5-mg increments every 4 weeks until the allocated treatment dose of 5, 10, or 15 mg was reached (appendix p 19). If intolerable gastrointestinal symptoms or events (eg, nausea, diarrhoea, and vomiting) occurred and persisted when the tirzepatide dose was escalated despite mitigating measures (such as eating smaller meals, symptomatic medications, or temporary interruption of the treatment by omitting one dose), the investigator could decide to continue the treatment at a lower, tolerated maintenance dose of tirzepatide (5 mg or 10 mg). De-escalation was not allowed in patients randomly allocated to 5 mg tirzepatide. Participants who had their dose de-escalated remained on that dose for the remainder of the study. If intolerable gastrointestinal adverse events persisted after dose de-escalation, participants discontinued tirzepatide treatment. Dose de-escalation was not allowed after the escalation period (week 24).

See Online for appendix

Insulin degludec (Novo Nordisk, Bagsværd, Denmark) was administered once daily via subcutaneous injection with a prefilled pen containing 3 mL (U100/mL), ideally at bedtime. The initial dose of insulin degludec was 10 U per day, titrated weekly to a fasting blood glucose of less than 5·0 mmol/L (<90 mg/dL), following a treat-to-target algorithm based on the median value of the last three self-monitored blood glucose (SMBG) values (appendix p 11).[3,18,19] Investigators could decide on insulin adjustments that deviated from the treat-to-target algorithm recommendation if there were safety concerns.

Initiation of new antihyperglycaemic medications (other than study drugs and background metformin and SGLT2 inhibitors) during the study was only allowed for rescue therapy for persistent hyperglycaemia on the basis of prespecified criteria (appendix p 6) or after early study drug discontinuation. GLP-1 receptor agonists, DPP-4 inhibitors, and pramlintide were prohibited medications and were not allowed as rescue therapies. No other basal insulins were allowed throughout the study, except for the tirzepatide groups as rescue therapy.

During the safety follow-up period (ie, 4 weeks), participants could be treated with another glucose-lowering therapy at the investigator's discretion, and this treatment was not considered as rescue therapy.

Outcomes

The primary efficacy endpoint was mean change from baseline in HbA_{1c} at week 52 to determine non-inferiority of tirzepatide 10 mg or 15 mg, or both, versus

insulin degludec. We used a boundary of 0·3% to establish non-inferiority. Key secondary efficacy endpoints were change from baseline in HbA_{1c} and bodyweight, and proportion of participants achieving an HbA_{1c} target of less than 7·0% (<53 mmol/mol) at week 52. Other secondary efficacy endpoints at week 52 included change from baseline in fasting serum glucose (FSG); proportion of participants achieving an HbA_{1c} target of 6·5% or lower (≤48 mmol/mol) and less than 5·7% (<39 mmol/mol); change from baseline in 7-point SMBG profiles; and proportion of participants achieving weight loss (≥5%, ≥10%, and ≥15% of bodyweight). Exploratory efficacy outcomes included changes in lipids (total cholesterol, LDL, HDL, VLDL, and triglycerides), waist circumference, and BMI. Composite endpoints of proportion of participants achieving the HbA_{1c} targets of less than 7·0% or 6·5% or lower without weight gain and clinically significant documented symptomatic hypoglycaemia or severe hypoglycaemia at week 52 were also assessed. The proportion of participants achieving an FSG target of less than 5·0 mmol/L (<90 mg/dL) at week 52 was also reported.

Safety endpoints were treatment-emergent adverse events (TEAEs), early discontinuation of study treatment due to adverse events, adjudicated pancreatic adverse events, serum calcitonin, allergic and hypersensitivity reactions, treatment-emergent antidrug antibodies for tirzepatide, mean change from baseline in pulse rate and systolic and diastolic blood pressure, hypoglycaemic events (≤70 mg/dL [≤3·9 mmol/L], including severe hypoglycaemic events, defined as episodes with severe cognitive impairment requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions), and initiation of rescue therapy for persistent hyperglycaemia. The adjudicated major adverse cardiovascular events will contribute to a meta-analysis across all SURPASS trials for the establishment of cardiovascular disease safety.

Statistical analysis

Our primary objective was non-inferiority of tirzepatide 10 mg or 15 mg versus insulin degludec (0·3% non-inferiority boundary) relative to the primary efficacy endpoint. Key secondary objectives, controlled for type I error, included non-inferiority of tirzepatide 5 mg compared to insulin degludec relative to HbA_{1c} and superiority of all doses of tirzepatide versus insulin degludec relative to HbA_{1c}.

We designed this study to assess both non-inferiority and superiority of tirzepatide versus insulin degludec. Since superiority is more restrictive than non-inferiority, the study was powered to compare superiority of all doses of tirzepatide versus insulin degludec. The sample size calculation assumed at least a –0·35% change from baseline in HbA_{1c} between tirzepatide groups and insulin degludec, a common SD of 1·1%, and dropout rate of up to 28%. A sample size of 1420 participants provided at least 90% power to establish superiority for a tirzepatide dose compared with insulin degludec at a two-sided significance level of 0·025. Using the assumed –0·35% difference of change from baseline in HbA_{1c} between tirzepatide groups and insulin degludec along with the 0·3% non-inferiority boundary, and assuming the same common SD and dropout rate, the sample size of 1420 participants also provided more than 99% power to achieve non-inferiority relative to the primary efficacy endpoint at a one-sided significance level of 0·0125. Full details of our type I error control strategy are given in the appendix (p 8).

Two estimands—the efficacy estimand and the treatment-regimen estimand—were used to assess treatment efficacy from different perspectives and accounted for intercurrent events differently. The efficacy estimand is the treatment effect between tirzepatide and insulin degludec among all randomised participants who continued to receive the study drug without rescue medication. The treatment-regimen estimand is the treatment effect among all participants, including the effect of any additional antihyperglycaemic medication, for all randomised participants regardless of premature study drug discontinuation and use of rescue medication.

All participants who received at least one dose of study drug (ie, the modified intention-to-treat [mITT] population) were included in the analyses of assessing both estimands. Participants who discontinued study drug due to inadvertent enrolment were excluded from efficacy analyses. Type I error rate was strongly controlled within each estimand for the evaluation of primary and key secondary objectives via a graphical approach. All reported results are for the efficacy estimand, unless stated otherwise. The results were described by the estimated treatment difference (ETD) with associated two-sided CIs and p values corresponding to two-sided tests of no difference. Results for the primary and key secondary analyses on the treatment-regimen estimand are in the appendix (p 23). Safety analyses were done on the mITT population, using all data from the start of treatment to the end of the safety follow-up period.

We used SAS software (version 9.4) for all statistical analyses. This trial is registered with ClinicalTrials.gov, number NCT03882970.

Role of the funding source

The funder of the study was involved in the study design, data collection, data review, data analysis, and drafting of the report by providing medical writing support.

Results

The trial started on April 1, 2019, and finished on Jan 4, 2021, with participants recruited between April 1

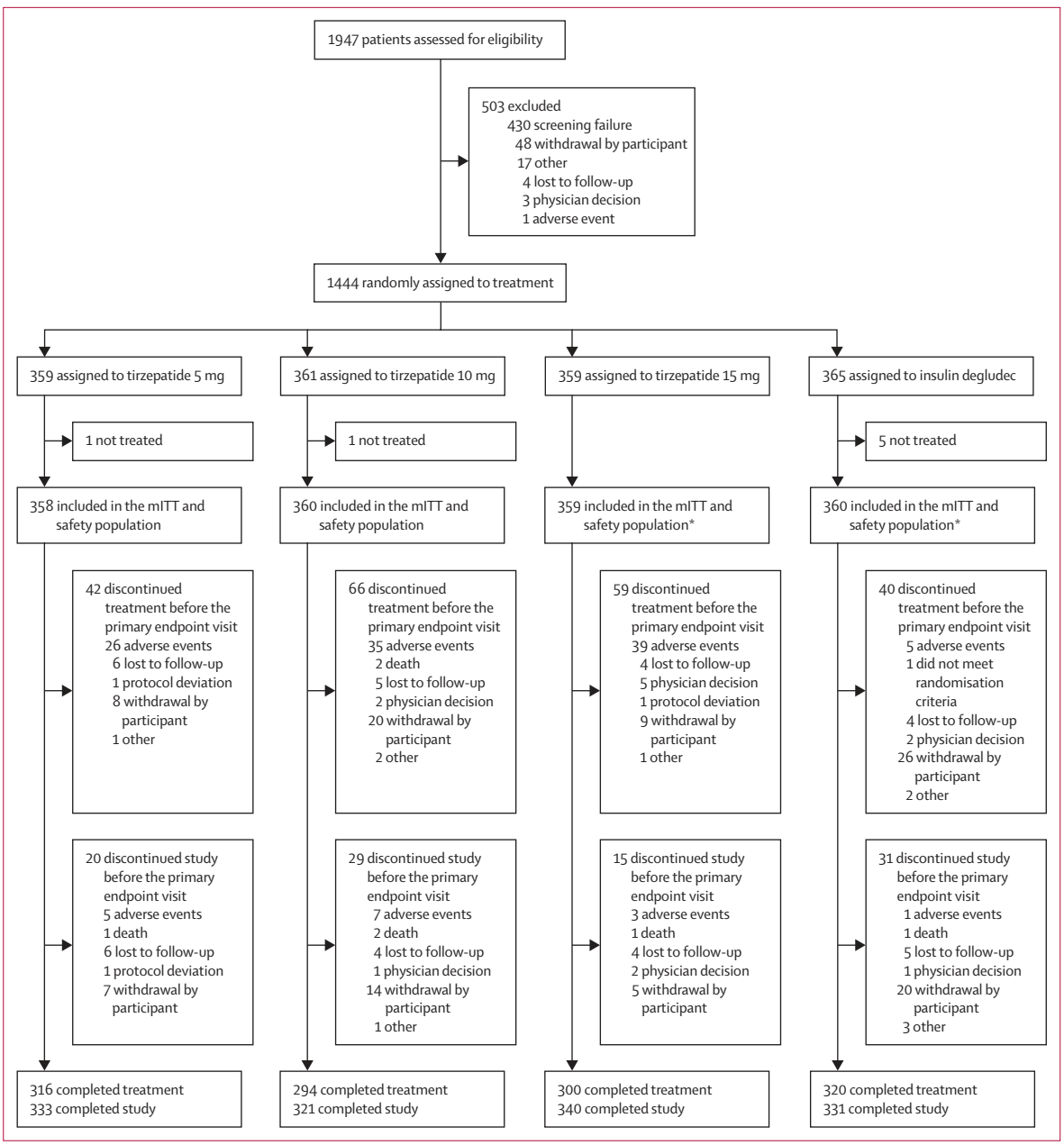

Figure 1: **Trial profile**
mITT=modified intention-to-treat. *One patient in the tirzepatide 15 mg group and one patient in the insulin degludec group were discontinued from treatment owing to inadvertent enrolment and were excluded from the efficacy estimand and treatment-regimen estimand.

and Nov 15, 2019. 1947 participants were assessed for eligibility, of whom 1444 were randomly assigned to treatment and 1437 received at least one dose of study drug and were included in the mITT and safety population (figure 1). 1230 (85%) of 1437 participants completed the study and treatment and 1325 (92%) participants completed the study, whether or not they remained on treatment. Having an adverse event was the most common reason for early discontinuation of treatment in the tirzepatide groups; withdrawal by participant was the most common reason in the insulin degludec group (figure 1).

Baseline demographics and clinical characteristics were similar across the tirzepatide and insulin degludec groups (table 1). The majority of participants were White (91%), 44% were women, the mean age was 57·4 years (SD 10·0), and the mean duration of type 2 diabetes was 8·4 years (6·2). The overall mean HbA_{1c} was 8·17% (0·91), bodyweight was 94·3 kg (20·1), and BMI was 33·5 kg/m² (6·1). 1005 (70%) of

	Tirzepatide 5 mg (n=358)	Tirzepatide 10 mg (n=360)	Tirzepatide 15 mg (n=359)	Insulin degludec (n=360)	Overall (n=1437)
Age, years	57·2 (10·1)	57·4 (9·7)	57·5 (10·2)	57·5 (10·1)	57·4 (10·0)
Sex					
Male	200 (56%)	195 (54%)	194 (54%)	213 (59%)	802 (56%)
Female	158 (44%)	165 (46%)	165 (46%)	147 (41%)	635 (44%)
Race					
American Indian or Alaska Native	0	1 (<1%)	1 (<1%)	2 (1%)	4 (<1%)
Asian	20 (6%)	19 (5%)	20 (6%)	17 (5%)	76 (5%)
Black or African American	13 (4%)	12 (3%)	8 (2%)	11 (3%)	44 (3%)
Multiple	1 (<1%)	0	1 (<1%)	0	2 (<1%)
Native Hawaiian or other Pacific Islander	1 (<1%)	0	2 (1%)	1 (<1%)	4 (<1%)
White	323 (90%)	328 (91%)	327 (91%)	329 (91%)	1307 (91%)
Ethnic origin					
Hispanic or Latino	109 (30%)	108 (30%)	96 (27%)	108 (30%)	421 (29%)
Not Hispanic or Latino	246 (69%)	252 (70%)	259 (72%)	252 (70%)	1009 (70%)
Not reported	3 (1%)	0	4 (1%)	0	7 (1%)
Duration of diabetes, years	8·5 (5·8)	8·4 (6·6)	8·5 (6·5)	8·1 (6·0)	8·4 (6·2)
HbA_{1c} concentration					
Values in %	8·17% (0·89)	8·18% (0·89)	8·21% (0·94)	8·12% (0·94)	8·17% (0·91)
Values in mmol/mol	65·81 (9·69)	65·91 (9·76)	66·18 (10·24)	65·20 (10·28)	65·78 (9·99)
Patients with ≤8·5%	248 (69%)	249 (69%)	252 (70%)	256 (71%)	1005 (70%)
Patients with >8·5%	110 (31%)	111 (31%)	107 (30%)	104 (29%)	432 (30%)
Fasting serum glucose concentration					
Values in mmol/L	9·53 (2·66)	9·46 (2·64)	9·35 (2·55)	9·26 (2·33)	9·40 (2·55)
Values in mg/dL	171·7 (47·9)	170·4 (47·6)	168·4 (46·0)	166·7 (41·9)	169·3 (45·9)
Diabetes medication at randomisation*					
Metformin alone	246 (69%)	242 (67%)	247 (69%)	244 (68%)	979 (68%)
Metformin plus SGLT2 inhibitor	112 (31%)	118 (33%)	112 (31%)	116 (32%)	458 (32%)
Bodyweight, kg	94·4 (18·9)	93·8 (19·8)	94·9 (21·0)	94·0 (20·6)	94·3 (20·1)
Body-mass index, kg/m²	33·6 (5·9)	33·4 (6·2)	33·7 (6·1)	33·4 (6·1)	33·5 (6·1)
Blood pressure, mm Hg					
Systolic	130·73 (13·59)	131·10 (13·12)	131·85 (12·85)	132·45 (13·63)	131·53 (13·30)
Diastolic	78·59 (8·52)	79·22 (8·69)	79·25 (9·16)	79·57 (9·18)	79·16 (8·89)
Pulse rate, beats per min	74·87 (9·85)	75·22 (9·46)	75·68 (9·52)	75·11 (9·93)	75·22 (9·69)
eGFR (CKD-EPI calculation, mL/min per 1·73 m²)	95·1 (17·2)	93·7 (16·9)	93·1 (17·3)	94·6 (16·8)	94·1 (17·0)
<60 mL/min per 1·73 m²	16 (5%)	13 (4%)	12 (3%)	15 (4%)	56 (4%)
≥60 mL/min per 1·73 m²	342 (96%)	347 (96%)	347 (97%)	345 (96%)	1381 (96%)
Urine albumin:creatinine ratio, g/kg					
<30	250 (70%)	274 (76%)	250 (70%)	258 (72%)	1032 (72%)
≥30 to ≤300	88 (25%)	67 (19%)	98 (27%)	85 (24%)	338 (24%)
>300	19 (5%)	19 (5%)	11 (3%)	15 (4%)	64 (4%)

Data are mean (SD) or n (%), unless otherwise specified. Percentages might not sum to 100 owing to rounding. CKD-EPI=chronic kidney disease epidemiology collaboration. eGFR=estimated glomerular filtration rate. HbA_{1c}=glycated haemoglobin. *Metformin doses of ≥1500 mg per day.

Table 1: **Baseline demographics and clinical characteristics**

1437 participants had an HbA_{1c} of 8·5% or below at baseline, and 458 (32%) participants were being treated with metformin plus SGLT2 inhibitor.

Mean baseline HbA_{1c} was decreased after 52 weeks of treatment by 1·93% (SE 0·05), 2·20% (0·05), and 2·37% (0·05) in the tirzepatide 5, 10, and 15 mg groups, respectively, compared with a decrease of 1·34% (0·05) in the insulin degludec group (table 2; figure 2A,B). The ETD versus insulin degludec was –0·86% (multiplicity adjusted 97·5% CI –1·02 to –0·70) for

10 mg tirzepatide and –1·04% (–1·19 to –0·88) for tirzepatide 15 mg. Given that the upper limits of the CIs are less than 0·3 for tirzepatide 10 and 15 mg, non-inferiority was achieved versus insulin degludec for the primary efficacy endpoint. These 97·5% CIs also indicate superiority of tirzepatide 10 and 15 mg versus insulin degludec for the primary efficacy endpoint (p<0·0001 for both doses). The ETD versus insulin degludec was –0·59% (95% CI –0·73 to –0·45) for tirzepatide 5 mg (p<0·0001). The mean insulin degludec dose at week 52 was 48·8 U per day (SD 30·4; 0·5 U/kg per day [SD 0·3]; appendix p 20). No differences were noted regarding HbA_{1c} reduction at week 52 in the subgroup of participants on metformin plus SGLT2 inhibitor versus those on metformin alone (appendix p 12). Additional results from the

	Tirzepatide 5 mg (n=358)	Tirzepatide 10 mg (n=360)	Tirzepatide 15 mg (n=358)	Insulin degludec (n=359)
Glycaemia endpoints				
HbA_{1c}, %				
Baseline	8·17% (0·05)	8·19% (0·05)	8·21% (0·05)	8·13% (0·05)
At week 52	6·26% (0·05)	5·99% (0·05)	5·81% (0·05)	6·85% (0·05)
Change from baseline at week 52*†	–1·93% (0·05)	–2·20% (0·05)	–2·37% (0·05)	–1·34% (0·05)
ETD *vs* insulin degludec (95% CI); p value‡	–0·59% (–0·73 to –0·45); p<0·0001	–0·86% (–1·00 to –0·72); p<0·0001	–1·04% (–1·17 to –0·90); p<0·0001	..
HbA_{1c}, mmol/mol				
Baseline	65·8 (0·5)	66·0 (0·5)	66·3 (0·5)	65·4 (0·5)
At week 52	44·9 (0·5)	41·9 (0·6)	40·0 (0·6)	51·3 (0·5)
Change from baseline at week 52*†	–21·1 (0·5)	–24·0 (0·6)	–26·0 (0·6)	–14·6 (0·5)
ETD *vs* insulin degludec (95% CI); p value‡	–6·4 (–7·9 to –4·9); p<0·0001	–9·4 (–10·9 to –7·9); p<0·0001	–11·3 (–12·8 to –9·8); p<0·0001	..
Participants achieving HbA_{1c} targets at week 52				
<7·0% (<53 mmol/mol)†	291 (82%)	314 (90%)	327 (93%)	215 (61%)
OR *vs* insulin degludec (95% CI); p value	3·45 (2·38 to 5·01); p<0·0001	7·02 (4·55 to 10·84); p<0·0001	10·79 (6·65 to 17·48); p<0·0001	..
≤6·5% (≤48 mmol/mol)	252 (71%)	281 (80%)	301 (85%)	156 (44%)
OR *vs* insulin degludec (95% CI); p value	3·62 (2·59 to 5·06); p<0·0001	6·36 (4·42 to 9·14); p<0·0001	9·59 (6·48 to 14·19); p<0·0001	..
<5·7% (<39 mmol/mol)	91 (26%)	135 (39%)	171 (48%)	19 (5%)
OR *vs* insulin degludec (95% CI); p value	7·11 (4·17 to 12·12); p<0·0001	14·14 (8·34 to 23·96); p<0·0001	22·09 (13·02 to 37·47); p<0·0001	..
Fasting serum glucose, mmol/L				
Baseline	9·54 (0·14)	9·48 (0·14)	9·35 (0·14)	9·24 (0·14)
At week 52	6·75 (0·10)	6·38 (0·10)	6·13 (0·10)	6·33 (0·10)
Change from baseline at week 52	–2·68 (0·10)	–3·04 (0·10)	–3·29 (0·10)	–3·09 (0·10)
ETD *vs* insulin degludec (95% CI); p value	0·41 (0·14 to 0·69); p=0·0036	0·05 (–0·24 to 0·33); p=0·7510	–0·20 (–0·48 to 0·08); p=0·1682	..
Fasting serum glucose, mg/dL				
Baseline	171·8 (2·4)	170·7 (2·4)	168·4 (2·4)	166·4 (2·4)
At week 52	121·6 (1·8)	114·9 (1·9)	110·5 (1·9)	114·1 (1·8)
Change from baseline at week 52	–48·2 (1·8)	–54·8 (1·9)	–59·2 (1·9)	–55·7 (1·8)
ETD *vs* insulin degludec (95% CI); p value	7·5 (2·4 to 12·5); p=0·0036	0·8 (–4·3 to 5·9); p=0·7510	–3·6 (–8·7 to 1·5); p=0·1682	..
7-point SMBG, daily mean mg/dL				
Baseline	179·2 (2·2)	180·1 (2·2)	181·4 (2·1)	173·2 (2·1)
Change from baseline at week 52	–52·6 (1·2)§	–59·7 (1·2)¶	–60·6 (1·2)¶	–48·0 (1·2)
Pre-meal				
Baseline	165·5 (2·1)	165·3 (2·1)	167·6 (2·1)	159·8 (2·1)
Change from baseline at week 52	–44·7 (1·1)	–51·3 (1·1)‖	–52·3 (1·1)¶	–46·2 (1·1)
2-h post-meal				
Baseline	192·8 (2·4)	194·1 (2·5)	195·2 (2·4)	186·7 (2·4)
Change from baseline at week 52	–60·3 (1·5)¶	–67·2 (1·5)¶	–68·2 (1·5)¶	–50·2 (1·5)

(Table 2 continues on next page)

	Tirzepatide 5 mg (n=358)	Tirzepatide 10 mg (n=360)	Tirzepatide 15 mg (n=358)	Insulin degludec (n=359)
(Continued from previous page)				
Bodyweight endpoints				
Bodyweight (kg)				
Baseline	94·5 (1·1)	94·3 (1·1)	94·9 (1·1)	94·2 (1·1)
At week 52	87·3 (0·4)	84·2 (0·4)	81·9 (0·4)	97·1 (0·4)
Change from baseline at week 52†	−7·5 (0·4)	−10·7 (0·4)	−12·9 (0·4)	2·3 (0·4)
ETD *vs* insulin degludec (95% CI); p value	−9·8 (−10·8 to −8·8); p<0·0001	−13·0 (−14·0 to −11·9); p<0·0001	−15·2 (−16·2 to −14·2); p<0·0001	..
Participants achieving bodyweight loss targets at week 52				
≥5% loss	233 (66%)	293 (84%)	310 (88%)	22 (6%)
OR *vs* insulin degludec (95% CI); p value	29·78 (18·35 to 48·35); p<0·0001	79·88 (47·56 to 134·17); p<0·0001	110·77 (64·73 to 189·55); p<0·0001	..
≥10% loss	132 (37%)	195 (56%)	245 (69%)	10 (3%)
OR *vs* insulin degludec (95% CI); p value	20·61 (10·77 to 39·44); p<0·0001	44·67 (23·34 to 85·51); p<0·0001	82·26 (42·70 to 158·48); p<0·0001	..
≥15% loss	44 (13%)	99 (28%)	150 (43%)	0
OR *vs* insulin degludec (95% CI); p value	104·50 (6·73 to 1622·53); p<0·0001	293·07 (19·02 to 4515·65); p<0·0001	564·49 (36·68 to 8686·39); p<0·0001	..
Participants achieving composite endpoints at week 52				
Met HbA_{1c} target of <7·0%, without weight gain and without clinically significant documented symptomatic hypoglycaemia (BG <54 mg/dL) or severe hypoglycaemia	79·54% (2·21)	88·48% (1·70)	91·61% (1·43)	15·32% (1·93)
OR *vs* insulin degludec (95% CI); p value	21·48 (14·35 to 32·16); p<0·0001	42·47 (27·06 to 66·66); p<0·0001	60·38 (37·31 to 97·71); p<0·0001	..
Met HbA_{1c} target of ≤6·5%, without weight gain and without clinically significant documented symptomatic hypoglycaemia (BG <54 mg/dL) or severe hypoglycaemia	68·92% (2·58)	80·72% (2·16)	85·99% (1·85)	11·83% (1·69)
OR *vs* insulin degludec (95% CI); p value	16·53 (11·07 to 24·69); p<0·0001	31·22 (20·35 to 47·88); p<0·0001	45·75 (29·17 to 71·75); p<0·0001	..

Data are estimated mean (SE) or n (%), unless otherwise specified. p values are for superiority *vs* insulin degludec comparison, unless otherwise specified. Modified intention-to-treat population (efficacy analysis set). BG=blood glucose. ETD=estimated treatment difference. HbA_{1c}=glycated haemoglobin. OR=odds ratio. SMBG=self-monitored blood glucose. *Tested for non-inferiority, controlled for type 1 error. †Tested for superiority, controlled for type 1 error. ‡p value for both non-inferiority and superiority comparison. §p=0·0068 *vs* insulin degludec. ¶p<0·0001 *vs* insulin degludec. ||p=0·0012 *vs* insulin degludec.

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

subgroup analysis based on baseline HbA_{1c} (≤8·5% [≤69 mmol/mol] or >8·5% [>69 mmol/mol]) at week 52 are provided in the appendix (p 13).

More participants in the tirzepatide groups (82–93%) than in the insulin degludec group (61%) achieved the HbA_{1c} target of less than 7·0% (<53 mmol/mol) at week 52 (p<0·0001 for all tirzepatide doses *vs* insulin degludec; table 2). This trend was also seen for the targets of 6·5% or lower (≤48 mmol/mol; 71–85% *vs* 44%) and less than 5·7% (<39 mmol/mol; 26–48% *vs* 5%) at week 52 (p<0·0001 for all tirzepatide doses *vs* insulin degludec; table 2, figure 2C).

More participants in the tirzepatide groups than in the insulin degludec group achieved the composite endpoints of the HbA_{1c} targets of less than 7·0% (80–92% *vs* 15%) or 6·5% or lower (69–86% *vs* 12%) without weight gain and without clinically significant documented symptomatic hypoglycaemia or severe hypoglycaemia at week 52 (p<0·0001 for all tirzepatide doses *vs* insulin degludec; table 2).

Participants in all four groups had reduced FSG from baseline at week 52 (all p<0·0001); the reductions seen in the tirzepatide 10 and 15 mg groups did not differ from that of the insulin degludec group (table 2, figure 2D,E). The reductions in FSG versus baseline were significant for all treatment groups as early as 2 weeks after treatment initiation. A greater proportion of participants receiving insulin degludec (25·7% [SE 2·8]) achieved the FSG target of less than 5·0 mmol/L (<90 mg/dL) at week 52 compared with participants receiving tirzepatide (6·9% [1·3] to 16·3% [2·1]). Compared with the insulin degludec group at week 52, the tirzepatide groups showed significantly greater decreases from baseline in 7-point SMBG daily mean and SMBG 2-h post-meal daily mean (table 2). All tirzepatide doses resulted in mean SMBG 2-h post-meal

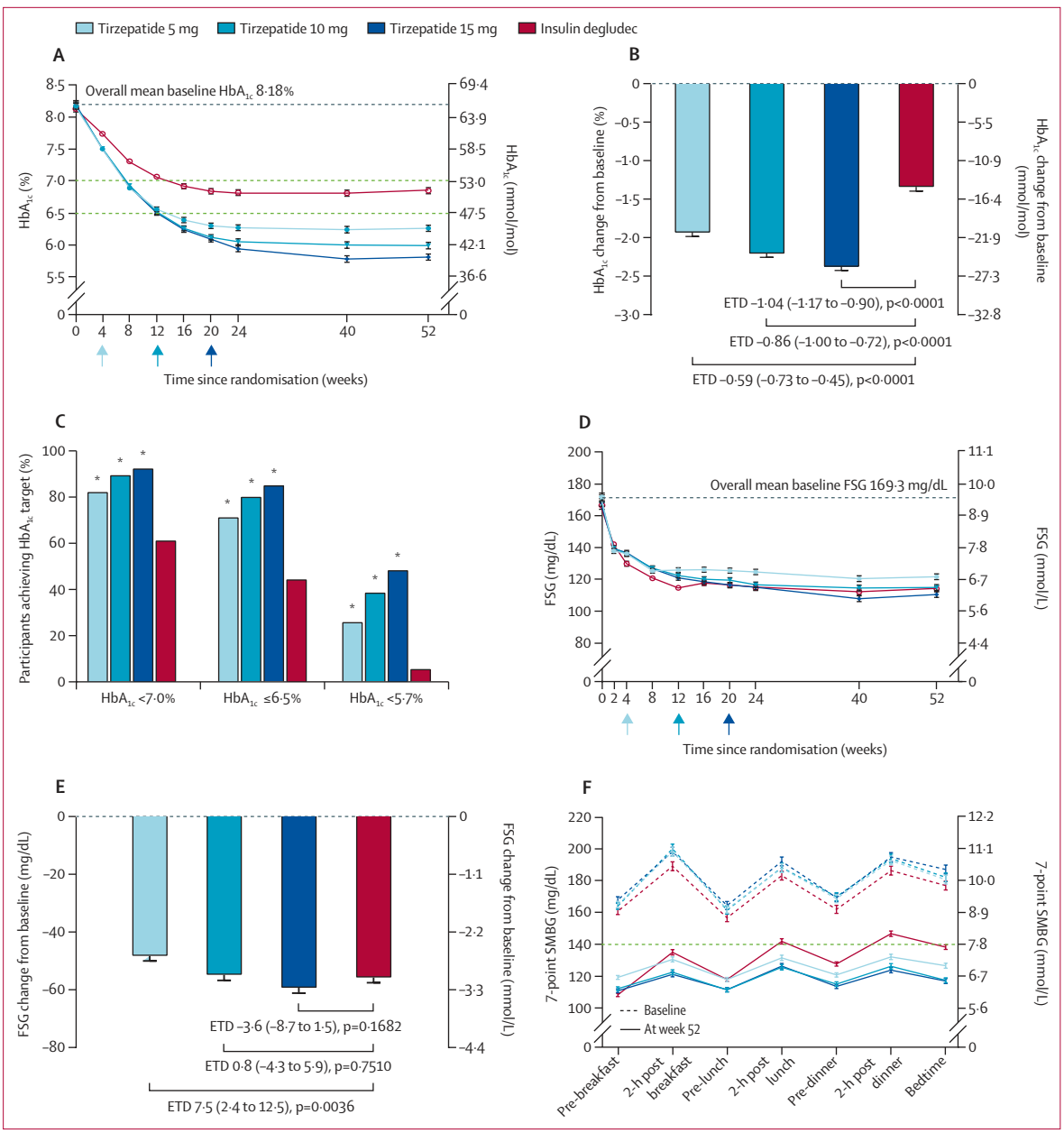

Figure 2: **HbA$_{1c}$, HbA$_{1c}$ targets, FSG, and 7-point SMBG**

Modified intention-to-treat population (efficacy analysis set). Tirzepatide 5, 10, and 15 mg once weekly, compared with insulin degludec: HbA$_{1c}$ values over time (A); change from baseline in HbA$_{1c}$ at week 52 (B); proportion of participants achieving HbA$_{1c}$ targets of <7·0%, ≤6·5%, and <5·7% at week 52 (C); FSG values over time (D); change from baseline in FSG at week 52 (E); and 7-point SMBG at baseline and week 52 (F). (A, B, D–F) Data are estimated means (error bars are SE) from a mixed model for repeated measurements analysis; ETD versus insulin degludec are least squares means (95% CI) at week 52. Arrows show when the maintenance doses of tirzepatide 5, 10, and 15 mg were started for the respective treatment groups. (C) Data are proportions (%) from logistic regression analysis. Black horizontal dashed lines show baseline values and green horizontal dashed lines show target values. ETD=estimated treatment difference. FSG=fasting serum glucose. HbA$_{1c}$=glycated haemoglobin. SMBG=self-monitored blood glucose. *p<0·0001 *vs* insulin degludec at week 52.

values of less than 7·8 mmol/L (140 mg/dL) at week 52 (figure 2F).

Tirzepatide reduced mean bodyweight from baseline at week 52 by –7·5 kg to –12·9 kg (8·1–13·9% of baseline bodyweight); insulin degludec caused a weight gain of 2·3 kg (table 2, figure 3A,B). The ETD versus insulin degludec ranged from –9·8 kg to –15·2 kg (p<0·0001 for all doses). Bodyweight loss of at least 5%, 10%, and 15% was achieved in more participants in the tirzepatide groups versus the insulin degludec group (p<0·0001 for all tirzepatide doses *vs* insulin degludec; table 2, figure 3D).

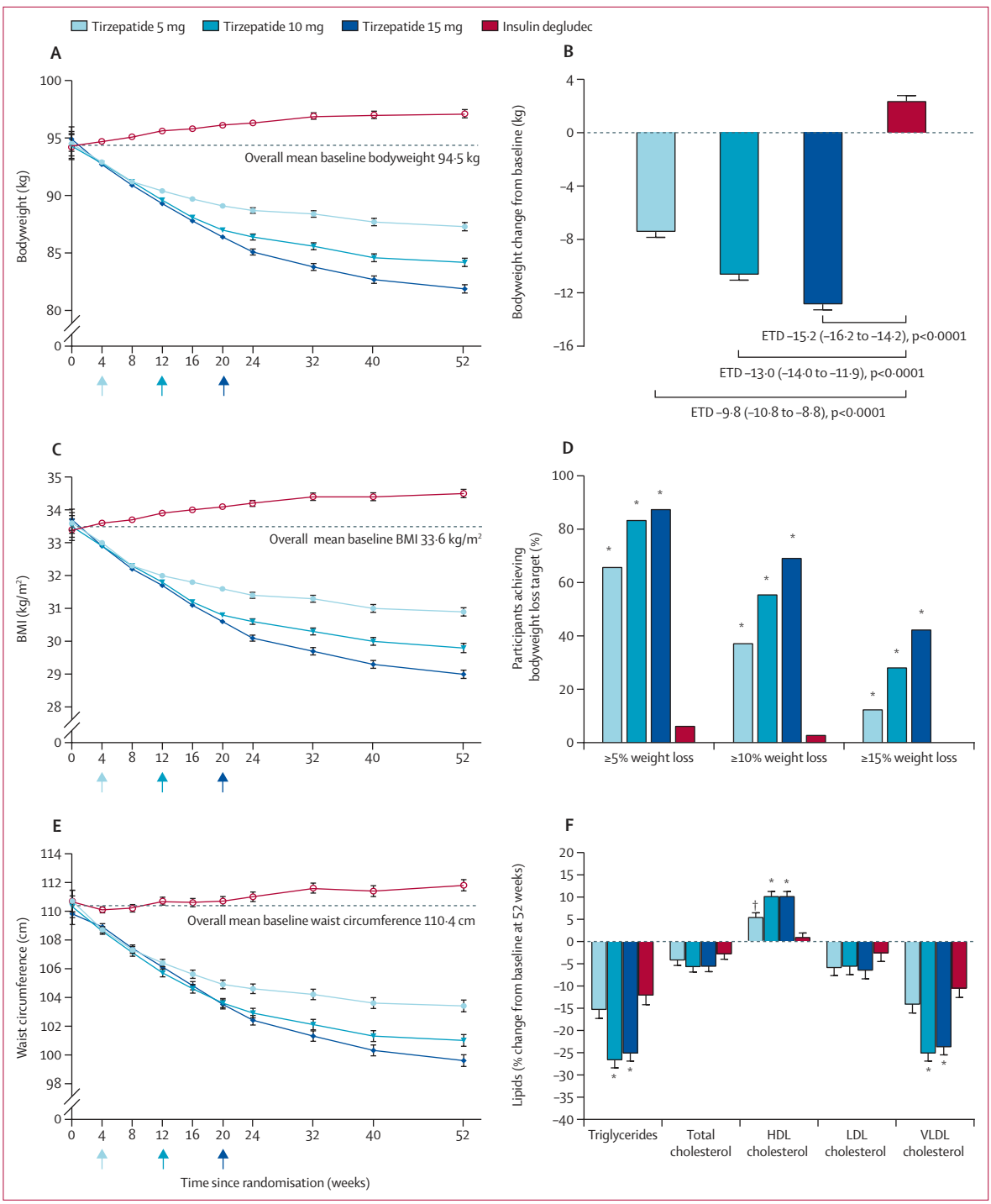

Figure 3: **Bodyweight, weight loss targets, BMI, waist circumference, and fasting lipid profile**
mITT population (efficacy analysis set). Tirzepatide 5, 10, and 15 mg once weekly, compared with insulin degludec: bodyweight over time (A); change from baseline in bodyweight at week 52 (B); mean BMI over time (C); proportion of participants achieving bodyweight loss targets of ≥5%, ≥10%, and ≥15% at week 52 (D); mean waist circumference over time (E); and fasting lipid profile at week 52 (F). (A–C and E) Data are estimated means (error bars are SE) from a MMRM analysis; ETD versus insulin degludec are least squares means (95% CI) at week 52. Arrows show when the maintenance doses of tirzepatide 5, 10, and 15 mg were started in the respective treatment groups. (D) Data are proportions (%) from logistic regression analysis. (F) Data are estimated means (error bars are SE) from MMRM analysis using log transformation. BMI=body-mass index. ETD=estimated treatment difference. mITT population=modified intention-to-treat population. MMRM=mixed-effects model repeated measures. *p<0·0001 and †p=0·0006 *vs* insulin degludec at week 52.

All doses of tirzepatide reduced BMI (by –2·7 to –4·6 kg/m²; figure 3C) and waist circumference (by –7·1 to –10·9 cm; figure 3E) from baseline at week 52, while insulin degludec increased both parameters. The cumulative distribution curve for bodyweight change shows that nearly all tirzepatide-treated participants lost weight during the study (appendix p 21). Bodyweight reduction at week 52 did not differ between participants on metformin plus an SGLT2 inhibitor and those on metformin alone (appendix p 12).

Tirzepatide 10 and 15 mg significantly decreased triglycerides and VLDL cholesterol at week 52 to a larger extent than did insulin degludec (figure 3F; appendix p 14). All tirzepatide doses significantly increased HDL cholesterol, whereas insulin degludec had no notable effect. Total cholesterol and LDL cholesterol did not differ among treatments.

At week 52, significant decreases in mean systolic (–4·9 to –6·6 mm Hg) and diastolic (–1·9 to –2·5 mm Hg) blood pressure were observed for tirzepatide; no changes were seen for insulin degludec (appendix pp 16, 22). There were transient increases from baseline in mean pulse rate in all tirzepatide groups (appendix p 22), with an ETD of 2·1 bpm (95% CI 1·0–3·3) in the tirzepatide 15 mg group versus insulin degludec group at week 52 (p=0·0003).

Mean values of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations decreased from baseline to week 52 to a greater extent in the tirzepatide groups than in the insulin degludec group. The urine albumin-to-creatinine ratio decreased from baseline with tirzepatide 15 mg (p<0·0008), with no significant changes seen for the rest of the groups at week 52 (appendix p 17).

97 (7%) of 1437 participants reported serious adverse events, with the proportion of participants similarly distributed across the treatment groups (table 3). There were five deaths during the study, which were similarly distributed across the treatment groups. None of the deaths were considered by the investigators to be related to the study treatment: one was from metastatic gastric cancer in the tirzepatide 5 mg group, one from COVID-19-related pneumonia and one from cardiorespiratory arrest in the tirzepatide 10 mg group, one from suicidal depression in the tirzepatide 15 mg group 8 months after treatment discontinuation, and one from infection-related multiorgan failure in the insulin degludec group. Treatment discontinuation due to an adverse event was more common in the tirzepatide groups than in the insulin degludec group, mainly due to gastrointestinal events.

Gastrointestinal events (nausea, diarrhoea, and vomiting) and decreased appetite were the most frequent TEAEs in the tirzepatide groups. A higher incidence of nausea, diarrhoea, decreased appetite, and vomiting throughout the entire study period was reported in participants treated with tirzepatide versus insulin degludec (table 3). When gastrointestinal events were analysed within 4-week intervals, these events were most frequent during the dose-escalation period and were mostly mild to moderate in severity (appendix p 24). 47 (13%) of 360 participants randomised to tirzepatide 10 mg and 57 (16%) of 359 participants randomised to tirzepatide 15 mg had their dose de-escalated, of whom 11 (3%) and 13 (4%), respectively, discontinued treatment after dose de-escalation.

The incidence of severe hypoglycaemia and blood glucose less than 54 mg/dL was 1–2% in the tirzepatide groups versus 7% in insulin degludec group (table 3). One patient in the tirzepatide 15 mg group had one episode of severe hypoglycaemia while receiving 2·5 mg at day 28, during the dose-escalation period. The participant recovered and completed the study on treatment without another clinically significant hypoglycaemic event. Four (1%) participants each in the tirzepatide 5 and 10 mg groups, five (1%) in the tirzepatide 15 mg group, and two (1%) in the insulin degludec group had persistent hyperglycaemia that required rescue therapy.

There were no adjudication-confirmed cases of pancreatitis. Mean values of amylase and lipase concentrations increased from baseline to week 52 in all tirzepatide groups, compared with the insulin degludec group, and decreased towards the baseline during the safety follow-up period (appendix p 16; data not shown for safety follow-up period). Two (1%) participants in the tirzepatide 5 mg group, and one each (<1%) in the tirzepatide 10 and 15 mg groups reported cholelithiasis. One (<1%) participant in the tirzepatide 15 mg group had cholecystitis.

There were no clinically relevant changes in mean calcitonin values from baseline. No cases of medullary thyroid carcinoma or C-cell hyperplasia were reported. Three participants (two in the tirzepatide 5 mg group and one in the tirzepatide 15 mg group) had treatment-emergent diabetic retinopathy.

Across study groups, there were ten major adverse cardiovascular events confirmed by adjudication and they were reported in similar proportions across treatment groups (table 3).

Malignant neoplasms were reported in three (1%) participants in the tirzepatide 5 mg group, five (1%) in the tirzepatide 10 mg group, three (1%) in the tirzepatide 15 mg group, and one (<1%) in the insulin degludec group. None of these events were considered by the investigators to be related to the study treatment, and no particular trends were seen (appendix p 18).

Hypersensitivity reactions occurred in 3% of participants treated with tirzepatide compared with 1% with insulin degludec. Injection site reactions occurred in <1–2% of participants treated with tirzepatide and 2% of participants treated with insulin degludec and

	Tirzepatide 5 mg (n=358)	Tirzepatide 10 mg (n=360)	Tirzepatide 15 mg (n=359)	Insulin degludec (n=360)
Any serious adverse event	29 (8%)	20 (6%)*	26 (7%)	22 (6%)
Deaths†	1 (<1%)	2 (1%)	1 (<1%)	1 (<1%)
Adverse events leading to treatment discontinuation‡	25 (7%)	37 (10%)	39 (11%)	5 (1%)
Nausea	3 (1%)	7 (2%)	9 (3%)	1 (<1%)
Vomiting	3 (1%)	6 (2%)	3 (1%)	0
Diarrhoea	4 (1%)	1 (<1%)	3 (1%)	0
Decreased appetite	1 (<1%)	4 (1%)	1 (<1%)	0
Decreased weight	1 (<1%)	1 (<1%)	4 (1%)	0
Participants with at least one TEAE	219 (61%)	248 (69%)	263 (73%)	193 (54%)
TEAEs occurring in ≥5% of participants in any treatment group, by preferred term				
Nausea	41 (12%)	81 (23%)	85 (24%)	6 (2%)
Diarrhoea	55 (15%)	60 (17%)	56 (16%)	14 (4%)
Decreased appetite	22 (6%)	37 (10%)	43 (12%)	2 (1%)
Vomiting	21 (6%)	34 (9%)	36 (10%)	4 (1%)
Dyspepsia	15 (4%)	32 (9%)	18 (5%)	0
Increased lipase	21 (6%)	16 (4%)	20 (6%)	7 (2%)
Nasopharyngitis	11 (3%)	14 (4%)	15 (4%)	22 (6%)
Abdominal pain	7 (2%)	17 (5%)	23 (6%)	4 (1%)
Hypertension	11 (3%)	7 (2%)	11 (3%)	21 (6%)
Other adverse events				
Hypoglycaemia (BG ≤70 mg/dL)	30 (8%)	49 (14%)	51 (14%)	170 (48%)
Hypoglycaemia (BG <54 mg/dL)	5 (1%)	4 (1%)	7 (2%)	26 (7%)
Severe hypoglycaemia	0	0	1 (<1%)	0
Injection site reaction	1 (<1%)	6 (2%)	8 (2%)	6 (2%)
Hypersensitivity	10 (3%)	12 (3%)	9 (3%)	5 (1%)
Cholelithiasis	2 (1%)	1 (<1%)	1 (<1%)	0
Cholecystitis	0	0	1 (<1%)	0
Diabetic retinopathy	2 (1%)	0	1 (<1%)	0
Adjudicated pancreatitis	0	0	0	0
Adjudicated MACE-4§	3 (1%)	3 (1%)	1 (<1%)	3 (1%)
Malignant neoplasms	3 (1%)	5 (1%)	3 (1%)	1 (<1%)

Data are n (%) in the safety population. Participants might be counted in more than one category. BG=blood glucose. MACE=major adverse cardiovascular event. TEAE=treatment-emergent adverse event. *One serious adverse event included here is not valid because it occurred before randomisation. †Deaths are also included as serious adverse events and adverse events leading to treatment discontinuation. ‡Only events occurring in ≥1% of participants in any treatment group are shown. §MACE-4 is a composite endpoint of death from cardiovascular or undetermined causes, myocardial infarction, stroke, and admission to hospital for unstable angina.

Table 3: **Adverse events**

were mild or moderate in severity (table 3). No severe cases of hypersensitivity or injection site reactions were reported. Overall, in SURPASS-3, the samples with antidrug antibodies detected had similar pharmacokinetics to samples with antidrug antibodies not detected (data not shown). Participants with treatment-emergent antidrug antibodies had similar efficacy to those without such antibodies, and none of the antibody-positive patients had severe or serious hypersensitivity or injection site reactions.

The efficacy outcomes at week 52 for HbA_{1c}, bodyweight, and proportion of participants achieving HbA_{1c} and bodyweight loss targets were consistent in both efficacy and treatment-regimen estimand (figures 2, 3; appendix p 23).

Discussion

SURPASS-3 is the first study comparing the efficacy and safety of once-weekly tirzepatide, a novel dual GIP and GLP-1 receptor agonist, versus a daily basal insulin regimen in patients with type 2 diabetes. All three doses of tirzepatide (5, 10, and 15 mg) led to statistically superior and clinically meaningful changes in HbA_{1c} after 52 weeks (–1·93% to –2·37%) compared with titrated insulin degludec (–1·34%) in participants on metformin with or without an SGLT2 inhibitor. Furthermore, participants on tirzepatide had mean bodyweight reductions of –7·5 to –12·9 kg (8·1–13·9% of baseline bodyweight) in comparison to a modest bodyweight increase with insulin degludec (2·3 kg). The observed tirzepatide results are consistent with

published reports in similar populations, including the head-to-head trial comparing tirzepatide with semaglutide 1 mg (SURPASS-2 study).[17,20] 32% of participants were on a stable dose of an SGLT2 inhibitor plus metformin in this study. The reductions in HbA_{1c} and bodyweight at week 52 in all tirzepatide groups were similar between the subgroup on metformin alone and the subgroup on metformin plus an SGLT2 inhibitor (appendix p 12).

In this study, up to 93% of participants on tirzepatide achieved the HbA_{1c} target of less than 7·0% (<53 mmol/mol),[21] and 26–48% of participants treated with tirzepatide achieved an HbA_{1c} level of less than 5·7% (<39 mmol/mol), indicating normoglycaemia. Moreover, 69–86% of participants treated with tirzepatide achieved HbA_{1c} target values of 6·5% or lower (≤48 mmol/mol) without weight gain and clinically significant hypoglycaemia, which indicates it is possible to achieve well established, but stringent, HbA_{1c} goals for type 2 diabetes in a safe manner.

Although caution should be used when comparing findings across trials since the patient populations often differ (eg, in the concomitant medication and the duration of the intervention), the HbA_{1c} reductions achieved at week 52 with all tirzepatide doses in this study were greater than those achieved with GLP-1 receptor agonist drugs in other trials with similar populations.[5,6,17]

The effect of tirzepatide on FSG was apparent in all the treatment groups at the first timepoint measured (week 2). This observation suggests that the starting dose of 2·5 mg of tirzepatide is already efficacious on hyperglycaemia shortly after treatment initiation. All three treatment doses of tirzepatide were superior to insulin degludec in reducing 2-h post-meal SMBG at week 52 with all mean postprandial values remaining below the normal glucose level of 7·8 mmol/L (140 mg/dL). This marked improvement in daytime hyperglycaemia with tirzepatide contributes to the differences in overall glycaemic control versus intensively titrated insulin degludec in the absence of differences in FSG. Furthermore, the effect on postprandial glycaemic excursions might have a greater effect on HbA_{1c} as it decreases.[22] The near-normalisation of the SMBG profiles with low risk of hypoglycaemia is consistent with previous studies with tirzepatide,[20] and might be partially explained by the optimisation of the incretin effect with the dual agonism of GIP and GLP-1, potentially allowing for near normoglycaemia without increasing hypoglycaemia.[23] Future studies will provide further evidence on the role of dual GIP and GLP-1 receptor agonism in glucose regulation in this population of patients (NCT03951753).

We do not consider slowed gastric emptying to be the major driver of the marked improvement in postprandial hyperglycaemia in SMBG data, given the persistence of improved postprandial hyperglycaemia at 52 weeks, which is probably well after the transient effect of tirzepatide in delaying gastric emptying has waned.[24] However, long-term studies are needed to confirm if complete tachyphylaxis occurs with tirzepatide, given that even residual effects on gastric emptying or small intestinal motility could still produce meaningful effects on postprandial glucose response.[25] The SURPASS-3 continuous glucose monitoring substudy will provide further data on the effect of tirzepatide on glycaemic variability measures, such as time in range, which is becoming a more relevant metric for the assessment of overall glycaemic control.

One of the key challenges in studies using an insulin comparator is ensuring a fair comparison between treatment strategies. In this study, insulin degludec was titrated to a fasting blood glucose of less than 5 mmol/L (<90 mg/dL) via a treat-to-target algorithm used in previous trials. More participants treated with insulin degludec than with tirzepatide achieved the FSG target of less than 5·0 mmol/L (<90 mg/dL) at week 52. As expected, most of the titration occurred during the first half of the study and a mean dose of 48·8 U per day (SD 30·4; 0·5 U/kg per day [0·3]) was reached at week 52. These doses are similar to those achieved in previous studies of insulin degludec using a treat-to-target algorithm in similar patient populations.[3,4] The glycaemic outcomes—ie, mean HbA_{1c} and FSG values, and proportion of participants achieving the HbA_{1c} target of less than 7·0% (<53 mmol/mol)—at week 52 in insulin degludec-treated participants were also similar to previous findings with insulin degludec.[3,4]

Bodyweight reduction was observed for all doses of tirzepatide as early as 4 weeks after treatment initiation, and this continued until week 52 without reaching a plateau for any of the doses, irrespective of the occurrence of gastrointestinal adverse events. Additional analyses will be done to evaluate the influence of gastrointestinal adverse events on the weight loss, because this issue has been previously described for GLP-1 receptor agonist molecules.[26] The decrease in bodyweight of 12·9 kg (13·9% of total weight) is the highest observed in tirzepatide-treated patients thus far, which might be explained by the longer duration of this trial.[17,20] The proportions of participants achieving the different weight loss targets in this study were similar to those observed in SURPASS-2.[17]

All three tirzepatide doses led to an improvement in the fasting lipid profile (substantial reduction in triglycerides and VLDL concentrations, and increase in HDL cholesterol) of tirzepatide-treated participants, in line with the findings in a phase 2 study of tirzepatide[20] and the SURPASS-2 trial.[17] These changes might partly be explained by weight loss; however, they could also reflect the effects of GIP receptor agonism on adipose tissue metabolism, potentially resulting in reduced ectopic liver fat and improvement of dyslipidaemia.[27,28]

There was also a clinically meaningful decrease in systolic blood pressure in the tirzepatide groups (4·9–6·6 mm Hg).

There was a small, transient increase in pulse rate, as previously reported for GLP-1 receptor agonists, which has not been associated with increased cardiovascular risk in patients with type 2 diabetes treated with those agents.[29] The reductions in HbA_{1c}, bodyweight, and systolic blood pressure and improved lipid profile with tirzepatide suggest an overall amelioration of cardiovascular risk. The SURPASS-4 trial (NCT03730662), which enrolled patients with increased cardiovascular risk, and specifically the SURPASS-CVOT trial (NCT04255433) comparing tirzepatide with dulaglutide, will provide a more comprehensive assessment of the cardiovascular outcomes and potential cardioprotective effects of this dual GIP and GLP-1 receptor agonist.

The decreases in ALT and AST concentrations seen with tirzepatide were consistent with those reported previously for GLP-1 receptor agonists, and also for tirzepatide.[17] A post-hoc analysis of a phase 2 study of tirzepatide[20] showed improvement in non-alcoholic steatohepatitis (NASH)-related biomarkers.[30] The SURPASS-3 MRI substudy will provide further data on the effect of tirzepatide on liver fat content in a subpopulation of study participants at high risk for hepatic steatosis. In addition, the therapeutic potential of tirzepatide in NASH will be explored in studies specifically designed for that purpose (eg, SYNERGY-NASH NCT04166773).

The most common TEAEs in participants who received tirzepatide were gastrointestinal side-effects that decreased with continued dosing. The incidences of nausea, diarrhoea, and vomiting were lower than those in a phase 2 study of tirzepatide,[20] and similar to those in SURPASS-2 and GLP-1 receptor agonist class.[5,6,17] In participants who had their dose of tirzepatide de-escalated, the incidence of gastrointestinal events reported was decreased after de-escalation (data not shown). However, more data are needed to better understand the impact of de-escalation on the tolerability profile of tirzepatide-treated patients.

Our study has several strengths. First, the relatively long duration of the intervention, which provided enough time to assess the effect of all three doses of tirzepatide after steady state was reached, and for the optimisation of the insulin degludec dose. Second, the titration of the insulin degludec dose and the related glycaemic efficacy results achieved in that treatment group would support the choice as a valid comparator. Finally, the study had a large sample size, with a heterogeneous population and a high proportion of participants who completed treatment and completed the trial.

Our study has limitations. First, the open-label design, owing to the different dosing frequency, titration scheme, and injection device of insulin degludec compared with tirzepatide. This design should be considered when interpreting endpoints that are susceptible to subjectivity, such as gastrointestinal adverse events. Second, gastrointestinal adverse events were self-reported, including their severity. Although this approach is standard practice in most clinical trials, using self-report assessment alone has limitations,[31] and an increased risk of nocebo effect (ie, the expectation of adverse gastrointestinal effects) or precebo effect (ie, the influence of preconceived notions or communications about the trial) should be considered.[32] Third, patients with asymptomatic gastroparesis were not excluded and its potential effect on glycaemic control should be taken into account. Finally, owing to the global nature of the study and the countries participating in it, the proportion of Black and African American participants in this study was low.

In summary, tirzepatide-treated participants had clinically meaningful and superior improvements in glycaemic control and bodyweight, with lower risk of hypoglycaemia, than did participants treated with titrated insulin degludec, in a population with type 2 diabetes inadequately controlled by metformin with or without an SGLT2 inhibitor. These results support the use of tirzepatide for the treatment of type 2 diabetes and provide further evidence for the potential role of this dual GIP and GLP-1 receptor agonist as the next step in the treatment continuum when injectable therapy is considered.

Contributors

AR, RB, and LFL designed the study. AR and KB provided medical oversight. BL, FG, EJ, and JPF acquired the data. RB did the statistical analyses. AR, RB, KB, and LFL verified the data and are the guarantors of this work and, as such, take responsibility for the integrity of the data and the accuracy of the data analysis. All authors participated in data interpretation and critical review of the manuscript, had full access to all the data in the study, and approved of this manuscript to be submitted for publication.

Declaration of interests

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Data sharing

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymisation, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at https://www.vivli.org.

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