Supplemental Online Content

Dahl D, Onishi Y, Norwood P, et al. Effect of Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control in Patients With Type 2 Diabetes. *JAMA.* Published online February 8, 2022. doi:10.1001/jama.2022.0078

Supplement 2. eAPPENDIX

≥5%, ≥10% and ≥15% at week 40 (D) mean 7-point SMBG profiles at baseline and at week 40

eFigure 3. Efficacy measures (treatment-regimen estimand). (A) body weight change from baseline to week 40; and (B) proportion of patients achieving body weight loss targets ≥5%, ≥10%, and ≥15% at week 40

eFigure 4. Daily mean insulin glargine dose changes over time. (A) insulin glargine dose (IU/kg/day) percent change from baseline and (B) insulin glargine dose (IU/kg/day) change from baseline

eFigure 5. Fasting lipid profile at week 40

eFigure 6. Vital parameters (A) pulse rate (bpm), (B) systolic blood pressure (mmHg), and (C) diastolic blood pressure (mmHg)

eFigure 7. BMI and waist circumference over time and change from baseline

eFigure 8. Incidence of diarrhea, nausea, and vomiting over time

eFigure 9. Prevalence of (A) diarrhea, (B) nausea, and (C) vomiting over time

This supplemental material has been provided by the authors to give readers additional information about their work.

Table of Contents

eAPPENDIX
Patient Eligibility Criteria for SURPASS-5 Study

Inclusion Criteria

Patients were eligible to enter the SURPASS-5 study only if they met all the following inclusion criteria at screening.

1. Had been diagnosed with type 2 diabetes (T2D) based on the World Health Organization classification or other locally applicable diagnostic standards and had been treated with insulin glargine (U100), once daily with or without metformin ≥3 months prior to Visit 1
2. Had HbA_{1c} ≥7.0% (53 mmol/mol) to ≤10.5% (91 mmol/mol), as determined by the central laboratory at Visit 1.
3. Had been on stable doses of once-daily insulin glargine (>0.25 IU/kg/day or >20 IU/day) and metformin (if taken) during the 3-month period prior to Visit 1. Insulin glargine dose was considered stable when all doses during this period were within the range defined by ±20% of the most commonly used insulin dose during this same period. Doses of metformin were considered stable if all prescribed doses during this period were in the range between the minimum required dose (≥1500 mg/day) and the maximum approved dose per the locally approved label
4. Required further insulin glargine dose increase at Visit 3 per the treat-to-target (TTT) algorithm based on the self-monitored blood glucose (SMBG) data collected during the prior week
5. Were of stable weight (±5%) ≥3 months prior to Visit 1 and agreed to not initiate a diet and/or exercise program during the study with the intent of reducing body weight other than the lifestyle and dietary measures for diabetes treatment
6. Had body mass index (BMI) ≥23 kg/m^2 at Visit 1
7. Were 18 years old or of an acceptable age to provide informed consent according to local regulations, whichever is older
   (a) Male patients should have been willing to use reliable contraceptive methods throughout the study and for at least three months after last injection
   (b) Female patients:
      - Female patients not of childbearing potential due to surgical sterilization (hysterectomy or bilateral oophorectomy or tubal ligation), congenital anomaly (i.e., Mullerian agenesis) or menopause
         - Women with an intact uterus are deemed postmenopausal if they were 45 years old, and
            - had not taken hormones or oral contraceptives within the last year and had cessation of menses for at least one year, OR
            - had at least six months and less than 12 months of spontaneous amenorrhea with follicle-stimulating hormone (FSH) and estradiol levels consistent with a postmenopausal state (FSH ≥40 mIU/mL and estradiol <30 pg/mL)
      - Female patients of childbearing potential (not surgically sterilized and between menarche and 1-year postmenopausal) must have been:
         - test negative for pregnancy at Visit 1 based on a serum pregnancy test AND
         - if sexually active, agreed to use two forms of effective contraception, where at least one form is highly effective for the duration of the trial and for 30 days thereafter
         - not be breastfeeding
8. In the investigator's opinion, were well-motivated, capable, and willing to:
   - perform fingerstick BG monitoring, including scheduled BG profiles with up to 7 measurements in one day
   - learn how to self-inject study drugs as required for this protocol (visually impaired persons who were not able to perform the injections must have had the assistance of a sighted individual trained to inject the study drug; persons with physical limitations who were not able to perform the injections must have had the assistance of an individual trained to inject the study drug)
   - were willing and able to inject study drugs
   - maintain a study diary, as required for this protocol
   - had a sufficient understanding of one of the provided languages of the country such that they will be able to complete the patient questionnaires
9. Had given written informed consent to participate in this study in accordance with local regulations and the ethical review board (ERB) governing the study site

Exclusion criteria

Patients were excluded from study enrolment if they meet any of the following criteria at screening:

1. Had type 1 diabetes mellitus (T1D)
2. Had chronic or acute pancreatitis any time prior to study entry (Visit 1)
3. Had history of: proliferative diabetic retinopathy or diabetic maculopathy or nonproliferative diabetic retinopathy that requires acute treatment (a dilated fundoscopic examination performed by an ophthalmologist or optometrist between Visit 2 and Visit 3 is required to confirm eligibility)
4. Had a history of severe hypoglycemia and/or hypoglycemia unawareness within the 6 months prior to Visit 1
5. Had a history of diabetic ketoacidosis or hyperosmolar state/coma
6. Had a known clinically significant gastric emptying abnormality (for example, severe diabetic gastroparesis or gastric outlet obstruction), had undergone or plan to undergo during the course of the study: a gastric bypass (bariatric) surgery or restrictive bariatric surgery (for example, Lap-Band®), or chronically took drugs that directly affect gastrointestinal (GI) motility
7. Had any of the following cardiovascular (CV) conditions within two months prior to Visit 1: acute myocardial infarction, or cerebrovascular accident (stroke) or hospitalization due to congestive heart failure (CHF)
8. Had New York Heart Association Functional Classification III and IV CHF
9. Had acute or chronic hepatitis, signs and symptoms of any other liver disease other than non-alcoholic fatty liver disease (NAFLD), or alanine aminotransferase (ALT) level >3.0 times the upper limit of the reference range, as determined by the central laboratory at study entry; patients with NAFLD were eligible for participation in this trial only if their ALT level was ≤3.0 times the upper limit of normal (ULN) for the reference range
10. Had an estimated glomerular filtration rate <30 mL/min/1.73 m^2, calculated by Chronic Kidney Disease-Epidemiology as determined by central laboratory at Visit 1; for patients on metformin, estimated glomerular filtration rate <45 mL/min/1.73 m^2 (or lower than the country-specific threshold for using the protocol-required dose of metformin per local label)
11. Had evidence of a significant, uncontrolled endocrine abnormality (for example, thyrotoxicosis or adrenal crises), in the opinion of the investigator
12. Had family or personal history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2
13. Had a serum calcitonin level of ≥35 ng/L, as determined by central laboratory at Visit 1
14. Had known or suspected hypersensitivity to trial product(s) or related products
15. Had evidence of a significant, active autoimmune abnormality (for example, lupus or rheumatoid arthritis) that, in the opinion of the investigator, was likely to require concurrent treatment with systemic glucocorticoids in the next 12 months
16. Had a transplanted organ (corneal transplants [keratoplasty] allowed) or awaiting an organ transplant
17. Had a history of an active or untreated malignancy or are in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than five years
18. Had a history of any other condition (such as known drug, alcohol abuse, or psychiatric disorder) that, in the opinion of the investigator, may preclude the patient from following and completing the protocol
19. Had any haematological condition that may interfere with HbA_{1c} measurement (for example, haemolytic anaemias and sickle cell disease)
20. Treatment with any glucose-lowering agent(s) other than stated in the inclusion criteria [4] in a period of three months prior to Visit 1 and between Visit 1 and Visit 3
21. Had been treated with prescription drugs that promote weight loss (for example, Saxenda [liraglutide 3.0 mg], Xenical® [orlistat], Meridia® [sibutramine], Acutrim® [phenylpropanolamine], Sanorex® [mazindol], Apidex® [phentermine], BELVIQ® [lorcaserin], Qsymia™ [phentermine/topiramate combination], Contrave® [naltrexone/bupropion], or similar other body weight loss medications including over-the-counter (OTC) medications [for example, alli®]) within three months prior to Visit 1 and/or between study entry (Visit 1) and randomisation (Visit 3)
22. Were receiving chronic (>2 weeks or 14 days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, or inhaled preparations) or had received such therapy within one month of Visit 1 or between Visits 1 and 3
23. Were enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
24. Had participated, within the last 30 days in a clinical study involving an investigational product. If the previous investigational product had a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed

25. Had previously completed or withdrawn from this study or any other study investigating tirzepatide
26. Were investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family was defined as a spouse, parent, child, or sibling, whether biological or legally adopted
27. Were Lilly employees
28. Were unwilling or unable to comply with the use of a paper diary to directly record data from the subject

Criteria for persistent hyperglycemia and initiation of rescue therapy

Add-on glycemic rescue therapy was allowed for patients who met any one of the following prespecified criteria for severe, persistent hyperglycemia and no intercurrent cause of the hyperglycemia could be identified (investigators should first confirm that the patient is fully compliant with the assigned therapeutic regimen and that the patient did not have an acute condition causing severe hyperglycemia):

- average daily blood glucose (BG) from the once-weekly 4-point self-monitored blood glucose (SMBG) profile >270 mg/dL (>15.0 mmol/L) over at least a consecutive 2-week period at any time 16 to 24 weeks post randomization; OR
- average daily BG from the once-weekly 4-point SMBG profile >240 mg/dL (>13.3 mmol/L) over a consecutive 2-week period at any time 25 to 32 weeks post randomization; OR
- average daily BG from the once-weekly 4-point SMBG profile >200 mg/dL (>11.1 mmol/L) over a consecutive 2-week period at any time beyond the first 32 weeks post randomization; OR
- HbA_{1c} ≥8.5% at 24 weeks, with inadequate response to the existing regimen defined as improvement in HbA_{1c} over the last 3 months (Week 12 to Week 24) that is, <0.3%

Rescue therapy option:
The criteria described above for severe, persistent hyperglycemia was only applicable after Week 16. The first choice before initiating any rescue therapy for those patients during the initial 16 weeks was to follow the treat-to-target (TTT) algorithm to increase the dose of insulin glargine. Rescue treatment with pramlintide, DPP-4 inhibitors, GLP-1 receptor agonists or any other basal insulin was not allowed.

Adjudicated events

Pancreatic adverse events

Only cases of pancreatic hyperenzymemia that underwent additional diagnostic follow-up and/or were accompanied by symptoms suggestive of pancreatitis were submitted for adjudication. All suspected cases of acute or chronic pancreatitis were adjudicated by an independent clinical endpoint committee (CEC). In addition, AEs of severe or serious abdominal pain of unknown etiology were also submitted to CEC to assess for possible pancreatitis or other pancreatic disease. Relevant data from patients with acute or chronic pancreatitis and those with severe or serious abdominal pain were entered into a specifically designed eCRF page by study site or Lilly staff. The adjudication committee representative entered the results of adjudication in a corresponding eCRF page.

Major adverse cardiovascular events

Deaths and nonfatal cardiovascular AEs were adjudicated by a committee of physicians external to Lilly with cardiology expertise. The nonfatal cardiovascular AEs to be adjudicated included the following:

- Myocardial infarction
- Hospitalization for unstable angina
- Hospitalization for heart failure
- Coronary interventions (such as coronary artery bypass graft or percutaneous coronary intervention), and
- Cerebrovascular events including cerebrovascular accident (stroke) and transient ischemic attack.

Statistical analysis

In this study, two estimands were prespecified in the protocol and both intended to estimate the treatment effect for all randomized patients. Both estimands are based on the newly released ICH E9 (R1) addendum on estimands and sensitivity analyses in clinical trials.

One estimand was the ‘treatment regimen estimand’, which evaluated the treatment effect of tirzepatide treatments relative to placebo irrespective of adherence to investigational product or introduction of rescue therapy (using a treatment policy strategy to handle intercurrent events per ICH E9 [R1]). For the estimation of this estimand, missing endpoint data were imputed using method of multiple imputation based on the placebo arm.

Another estimand was the 'efficacy estimand', which evaluated the treatment effect of tirzepatide treatments relative to placebo if all patients had adhered to treatment and didn't receive rescue therapy. This estimand used a hypothetical strategy to handle intercurrent events (ICH E9[R1]) and was intended to provide an estimation of the achievable study treatment effect when patients took the treatment as planned and without confounding of other rescue medication use. The resulting missing values (discarded after the use of rescue medication and/or treatment discontinuation, or unobserved) were implicitly handled by the MMRM under the assumption of missing at random.

All patients who were randomized and took at least one dose of study medication (mITT population) were included in the analyses of assessing both estimands. Patients who discontinued study drug due to inadvertent enrollment were excluded from efficacy analyses. The detailed analysis with respective to the two estimands are provided below.

Treatment-regimen estimand

The primary analysis relative to the treatment-regimen estimand was conducted utilizing HbA_{1c} data in the full analysis set (FAS), which included data through the 40-week treatment period using analysis of covariance (ANCOVA) model with treatment, country, baseline metformin use (Yes/No) as fixed effects and baseline HbA_{1c} as a covariate. Missing HbA_{1c} value at week 40 was imputed 100 times using method of multiple imputation based on the placebo arm. Statistical inference over imputed data was guided by Rubin's rule (Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley & Sons Inc.;1987)

A similar approach was used for analysis of change from baseline in body weight and FSG except that baseline HbA_{1c} category (≤8.0%, >8.0% [≤64, >64 mmol/mol]) was included as a fixed effect in place of baseline HbA_{1c} as a covariate and baseline of corresponding variable was used as an additional covariate in the model.

For analysis of proportion of patients achieving HbA1c <7.0%, ≤6.5%, and <5.7% at 40 weeks, logistic regression was used, which included the response variable of dichotomized HbA_{1c} value at week 40, the fixed categorical effects of country, baseline metformin use (Yes/No), treatment, as well as the fixed continuous effect of baseline HbA1c. Before dichotomization, missing continuous value at week 40 was imputed using multiple imputation based on the placebo arm as described above. Statistical inference over imputed data was guided by Rubin's rule.[1]

Efficacy estimand

Primary endpoint analysis was conducted using a mixed model for repeated measures (MMRM) for HbA_{1c} data from baseline through 40 weeks (efficacy analysis set [EAS]), with treatment, visit, treatment-by-visit interaction, country, baseline metformin use (Yes/No) as fixed effects, baseline HbA_{1c} as a covariate, and patient as a random effect. A similar MMRM model was used for other continuous secondary endpoint analyses, with baseline HbA_{1c} category (≤8.0%, >8.0% [≤64, >64 mmol/mol]) as an additional fixed effect and corresponding baseline measure as a covariate.

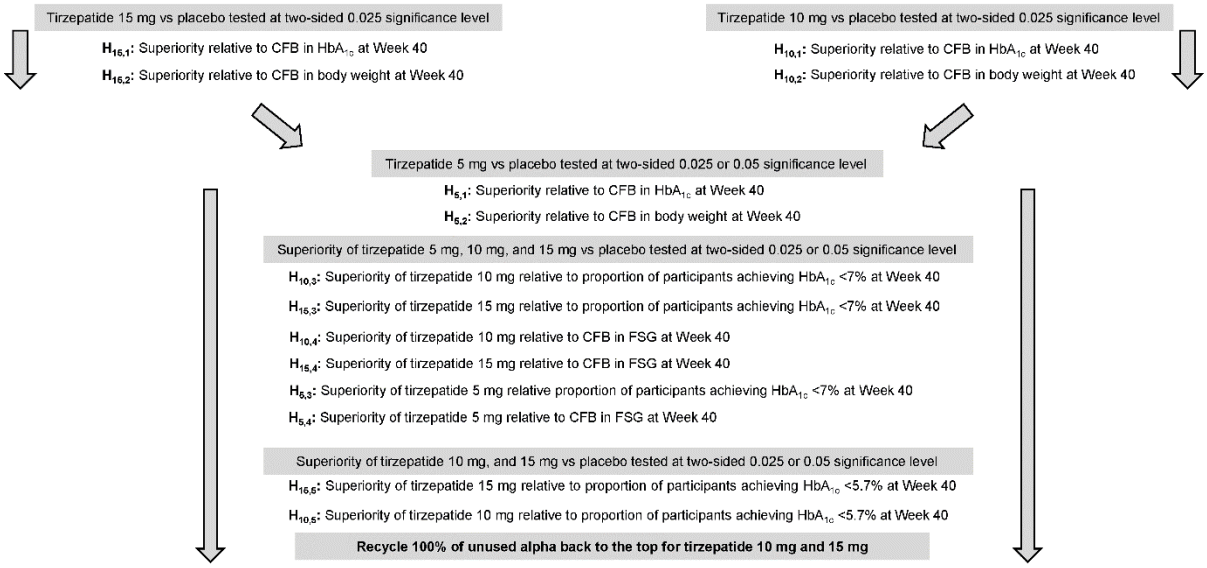
For analysis of proportion of patients achieving HbA_{1c} <7.0%, ≤6.5%, and <5.7% at Week 40, logistic regression was used, which included treatment, country, metformin use (Yes/No) as fixed effects, and baseline HbA_{1c} as a covariate. Missing values were imputed using the predicted value from primary endpoint MMRM analysis and then dichotomised.

Type 1 error rate control strategy for primary and key secondary efficacy analysis

For analyses within each estimand, the type 1 error control strategy for evaluation of the primary and key secondary objectives were as follows:

1. $H_{15,1}$ and $H_{15,2}$ were evaluated hierarchically each at a 2-sided 0.025 significance level conditioned on successfully achieving the preceding objective. In parallel,
2. $H_{10,1}$ and $H_{10,2}$ were evaluated hierarchically each at a 2-sided 0.025 significance level conditioned on successfully achieving the preceding objective.
3. a. If all objectives in #1 and #2 above were successfully established, $H_{5,1}$ and $H_{5,2}$ are evaluated hierarchically, each at a 2-sided 0.05 significance level.
   b. If all objectives in only #1 or only #2 above were successfully established, $H_{5,1}$ and $H_{5,2}$ were evaluated hierarchically, each at a 2-sided 0.025 significance level.

4. If both objectives: $H_{5,1}$ and $H_{5,2}$ were successfully established and
   a. If all objectives in #1 and #2 above are successfully established, then $H_{10,3}$, $H_{15,3}$, $H_{10,4}$, $H_{15,4}$, $H_{5,3}$, $H_{5,4}$, $H_{15,5}$, and $H_{10,5}$ were evaluated hierarchically each at a 2-sided 0·05 significance level conditioned on successfully achieving the preceding objective.
   b. If all objectives in only #1 or only #2 above were successfully established, then $H_{10,3}$, $H_{15,3}$, $H_{10,4}$, $H_{15,4}$, $H_{5,3}$, $H_{5,4}$, $H_{15,5}$, and $H_{10,5}$ were evaluated hierarchically each at a 2-sided 0·025 significance level conditioned on successfully achieving the preceding objective.
5. If all objectives in #3 and #4 above were successfully established, and at least 1 objective from #1 or #2 above was not successfully established, we recycled 100% of the unused alpha back to #1 or #2 above.



Safety and other Measures

Safety was assessed on the safety analysis set, which consisted of all available data, including safety follow-up, from the modified intention-to-treat (mITT) population, irrespective of adherence to study treatment or initiation of antihyperglycemic rescue therapy. Summary statistics were provided for incidence of adverse events (AEs), study and treatment discontinuation due to AEs, and death. Fisher's exact test was used to compare the treatment groups. For continuous laboratory analytes, summary statistics were provided by visit, with statistical comparisons among treatment at each visit conducted using an MMRM analysis. Lipid profile, pancreatic and liver enzymes were analysed on log-transformed data and then converted back to original scale.

Laboratory methods

Serum protein biomarker concentration levels were assessed using ELISA assays as described in Frias et al. 2018.[2]

Supplementary tables and figures

eTable 1. Insulin glargine treat-to-target algorithm

Median Fasting Blood Glucose (Based on last 3 SMBG values)		Adjustment of Insulin Glargine if Dose <20 IU	Adjustment of Insulin Glargine if Dose ≥20 IU
mg/dL	mmol/L		
≤70	≤3.9	-1 or -2 IU[a,b]	-2 to 4 IU[a,b]
71 to 100	4.0 to 5.5	No adjustment	No adjustment
101 to 119	5.6 to 6.6	+1 IU	+2 IU
120 to 139	6.7 to 7.7	+2 IU	+4 IU
140 to 179	7.8 to 9.9	+3 IU	+6 IU
≥180	≥10.0	+4 IU	+8 IU

Algorithm adapted from Riddle, et al., 2003.[3] [a]The insulin dose was also decreased by 1 to 2 IU or 2 to 4 IU if (i) multiple episodes of nonsevere hypoglycemia were recorded during the assessment period at any time during the day; and/or (ii) at least 1 episode that met the criteria for severe hypoglycemia (events requiring assistance of a third person to administer therapy) or was associated with SMBG value <54 mg/dL (<3.0 mmol/L) was recording during the assessment period; [b]If only one hypoglycemic episode with SMBG value ≥54 mg/dL (≥3.0 mmol/L) and ≤70 mg/dL (≤3.9 mmol/L) was recorded, insulin dose was not changed.
Abbreviations: SMBG, self-monitored blood glucose; IU, international units.

eTable 2. Primary and secondary outcomes (efficacy estimand)

Efficacy endpoints[a]	Tirzepatide 5 mg (n = 116)	Tirzepatide 10 mg (n = 119)	Tirzepatide 15 mg (n = 120)	Placebo (n = 120)
Primary endpoint				
HbA_{1c}, %				
Baseline	8.29	8.34	8.22	8.39
Change from baseline at week 40 (95% CI)	-2.23 (-2.39, -2.07)	-2.59 (-2.75, -2.43)	-2.59 (-2.75, -2.42)	-0.93 (-1.09, -0.78)
Difference versus placebo (95% CI)[b]	-1.30 (-1.52, -1.07)	-1.66 (-1.88, -1.43)	-1.65 (-1.88, -1.43)	-
P value	<.001	<.001	<.001	-
HbA_{1c}, mmol/mol				
Baseline	67.1	67.7	66.4	68.2
Change from baseline at week 40 (95% CI)	-24.4 (-26.1, -22.6)	-28.3 (-30.0, -26.5)	-28.3 (-30.1,-26.5)	-10.2 (-11.9, -8.5)
Difference versus placebo (95% CI)	-14.2 (-16.6, -11.7)	-18.1 (-20.6, -15.7)	-18.1 (-20.5, -15.6)	-
Secondary endpoints				
Patients achieving HbA_{1c} targets at week 40				
<7.0% (<53 mmol/mol), No. (%)	107 (93.0)	110 (97.4)	110 (94.0)	40 (33.9)
Absolute difference versus placebo, %	59.1	63.5	60.1	-
Odds ratio versus placebo (95% CI)[b]	37.8 (15.2, 93.7)	100.1 (30.0, 333.6)	43.3 (16.9, 110.8)	-
P value	<.001	<.001	<.001	-
≤6.5% (≤48 mmol/mol), No. (%)	92 (80.0)	107 (94.7)	108 (92.3)	20 (17.0)
Absolute difference versus placebo, %	63.1	77.7	75.4	-
Odds ratio versus placebo (95% CI)[c]	20.5 (10.3, 41.0)	87.8 (34.1, 225.9)	61.4 (26.1, 144.2)	-
P value	<.001	<.001	<.001	-
<5.7% (<39 mmol/mol), No. (%)	30 (26.1)	54 (47.8)	73 (62.4)	3 (2.5)
Absolute difference versus placebo, %	23.6	45.3	59.9	-
Odds ratio versus placebo (95% CI)[d]	12.2 (3.9, 38.0)	32.4 (10.5, 99.5)	56.3 (18.3, 173.3)	-
P value	<.001	<.001	<.001	-
Fasting serum glucose, mg/dL				
Baseline	162.2	162.9	160.4	164.4
Change from baseline at week 40 (95% CI)	-61.4 (-66.39, -56.36)	-67.9 (-72.93, -62.89)	-67.7 (-72.88, -62.51)	-38.9 (-43.82, -34.01)
Difference versus placebo (95% CI)[b]	-22.5 (-29.5, -15.4)	-29.0 (-36.0, -22.0)	-28.8 (-35.9, -21.6)	-
P value	<.001	<.001	<.001	-
7-point self-monitored blood glucose values[e], mg/dL				
Daily mean at baseline	186.6	188.7	183.0	182.0
Daily mean change from baseline at week 40 (95% CI)[c]	-67.1 (-71.1, -63.1)	-71.7 (-75.7, -67.7)	-73.7 (-77.9, -69.6)	-39.4 (-43.5, -35.3)

Difference versus placebo (95% CI)	-27.7 (-33.5, -22.0)	-32.3 (-38.1, -26.6)	-34.3 (-40.1, -28.5)	-
P value	<.001	<.001	<.001	-
Pre-meal daily mean at baseline	162.2	167.0	161.0	158.4
Pre-meal daily mean change from baseline at week 40 (95% CI)[c]	-55.8 (-59.4, -52.3)	-58.9 (-62.5, -55.4)	-58.1 (-61.7, 54.4)	-36.8 (-40.4, -33.3)
Difference versus placebo (95% CI)	-19.0 (-24.0, -14.0)	-22.1 (-27.2, -17.1)	-21.2 (-26.3, -16.1)	-
P value	<.001	<.001	<.001	-
2-h post-meal daily mean at baseline	209.2	207.4	203.3	204.9
2-h post-meal daily mean change from baseline at week 40 (95% CI)[c]	-76.7 (-81.9, -71.4)	-82.3 (-87.5, -77.1)	-87.4 (-92.7, -82.1)	-40.5 (-45.7, -35.3)
Difference versus placebo (95% CI)	-36.2 (-43.6, -28.7)	-41.8 (-49.2, -34.4)	-46.9 (-54.4, -39.5)	-
P value	<.001	<.001	<.001	-
Body weight, kg				
Baseline	95.5	95.4	96.2	94.1
Change from baseline at week 40 (95% CI)[b]	-6.2 (-7.29, -5.01)	-8.2 (-9.37, -7.08)	-10.9 (-12.11, -9.78)	1.7 (0.58, 2.81)
Difference versus placebo (95% CI)	-7.8 (-9.4, -6.3)	-9.9 (-11.5, -8.3)	-12.6 (-14.2, -11.0)	-
P value	<.001	<.001	<.001	-
Patients achieving body weight loss targets at Week 40				
≥5% loss, No. (%)	62 (53.9)	73 (64.6)	99 (84.6)	7 (5.9)
Absolute difference versus placebo, %	48.0	58.7	78.7	-
Odds ratio versus placebo (95% CI)[c]	17.15 (7.55, 38.93)	27.24 (11.87, 62.55)	79.61 (32.76, 193.44)	-
P value	<.001	<.001	<.001	-
≥10% loss, No. (%)	26 (22.6)	53 (46.9)	60 (51.3)	1 (0.9)
Absolute difference versus placebo, %	21.8	46.1	50.4	-
Odds ratio versus placebo (95% CI)[c]	24.03 (4.65, 124.33)	81.55 (15.93, 417.38)	101.81 (19.88, 521.44)	-
P value	<.001	<.001	<.001	-
≥15% loss, No. (%)	8 (7.0)	30 (26.6)	37 (31.6)	0 (0.0)
Absolute difference versus placebo, %	7.0	26.6	31.6	-
Odds ratio versus placebo (95% CI)[c]	19.38 (1.21, 310.99)	93.94 (6.17, 1430.49)	125.41 (8.25, 1905.85)	-
P value	<.036	.001	<.001	-
Patients achieving composite endpoint: HbA_{1c} <7.0% without body weight gain and without clinically significant documented symptomatic hypoglycemia (blood glucose <54 mg/dL) or severe hypoglycemia (%)[f]				
Week 40[c]	77.7	75.5	80.3	11.9
Odds ratio versus placebo (95% CI)	25.88 (12.48, 53.65)	22.92 (11.13, 47.20)	30.22 (14.36, 63.58)	-
P value	<.001	<.001	<.001	-
Patients achieving composite endpoint: HbA_{1c} ≤6.5% without body weight gain and without clinically significant documented symptomatic hypoglycemia (blood glucose <54 mg/dL) or severe hypoglycemia (%)[f]				

Week 40[c]	66.7	72.8	77.9	8.4
Odds ratio versus placebo (95% CI)	21.92 (10.26, 46.83)	29.28 (13.51, 63.47)	38.52 (17.49, 84.83)	-
P value	<.001	<.001	<.001	-

[a]Data presented are estimated mean unless specified otherwise.
[b]Tested for superiority, controlled for type 1 error.
[c]Tested for superiority, not controlled for type 1 error.
[d]Tested for superiority, controlled for type 1 error only for tirzepatide 10 mg and 15 mg versus placebo.
[e]7-point SMBG included fasting premeal, morning 2-hours postmeal, midday premeal, midday 2-hours post meal, evening premeal, evening 2-hours post meal, and bedtime readings. Analysis of covariance model used with treatment, country, baseline metformin use, baseline HbA_{1c} category (≤8.0%, >8.0%) as fixed effects and baseline endpoint value as a covariate.
[f]Results from logistic regression where missing HbA_{1c} and weight at week 40 were imputed and dichotomized after predictions from mixed-model repeated measures model with treatment, visit, treatment-by-visit interaction, country, baseline metformin use, baseline HbA_{1c} category (≤8.0%, >8.0%) [for weight analysis] as fixed effects and baseline endpoint value as a covariate.

Data presented are for the efficacy estimand that evaluated treatment effects using on treatment data without use of rescue therapy.
Abbreviations: CI, confidence interval; HbA_{1c}, glycated hemoglobin A_{1c}; IU, international units; n, number of patients in the specified group; No., number.

eTable 3. Number of patients assessed at each time point for HbA_{1c}, fasting serum glucose and body weight over time (efficacy estimand)

	Number of patients at specified time points															
Week →	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**32**	**40**
HbA_{1c}																
Tirzepatide 5 mg	115	-	-	-	110	-	-	104	-	108	-	105	106	107	-	105
Tirzepatide 10 mg	113	-	-	-	110	-	-	109	-	105	-	105	101	106	-	105
Tirzepatide 15 mg	117	-	-	-	115	-	-	103	-	104	-	102	99	101	-	97
Placebo	118	-	-	-	116	-	-	111	-	113	-	112	112	114	-	111
Total	463															
Fasting serum glucose																
Tirzepatide 5 mg	115	-	112	-	111	-	-	104	-	107	-	105	106	107	-	105
Tirzepatide 10 mg	116	-	114	-	109	-	-	109	-	104	-	105	101	105	-	105
Tirzepatide 15 mg	118	-	115	-	115	-	-	104	-	104	-	102	99	100	-	97
Placebo	118	-	116	-	115	-	-	109	-	112	-	111	111	113	-	109
Total	467															
Body weight																
Tirzepatide 5 mg	115	-	-	-	111	-	-	106		107	-	107	107	106	105	105
Tirzepatide 10 mg	113	-	-	-	110	-	-	109		105	-	105	102	107	106	105
Tirzepatide 15 mg	117	-	-	-	116	-	-	105		104	-	102	99	100	96	97
Placebo	118	-	-	-	116	-	-	109		110	-	112	111	114	112	110
Total	463															
Insulin glargine dose																
Tirzepatide 5 mg	115	115	115	115	115	115	112	111	112	112	112	109	109	107	105	105
Tirzepatide 10 mg	117	117	117	116	113	114	113	113	113	111	109	110	108	107	106	103
Tirzepatide 15 mg	118	118	118	118	118	118	115	113	111	107	106	104	102	100	97	96
Placebo	119	119	119	117	118	117	117	117	117	117	117	117	117	114	112	111
Total	469															

eTable 4. Subgroup analysis of HbA_{1c} at baseline HbA1c ≤8.0% or >8.0%

	Tirzepatide 5 mg		Tirzepatide 10 mg		Tirzepatide 15 mg		Placebo	
	Baseline HbA_{1c} ≤8.0% (n = 52)	**Baseline HbA_{1c} >8.0% (n = 63)**	**Baseline HbA_{1c} ≤8.0% (n = 48)**	**Baseline HbA_{1c} >8.0% (n = 65)**	**Baseline HbA_{1c} ≤8.0% (n = 51)**	**Baseline HbA_{1c} >8.0% (n = 66)**	**Baseline HbA_{1c} ≤8.0% (n = 46)**	**Baseline HbA_{1c} >8.0% (n = 72)**
HbA_{1c}, LS mean (SE), %								
Baseline	7.55 (0.05)	8.90 (0.08)	7.59 (0.05)	8.90 (0.08)	7.44 (0.05)	8.82 (0.08)	7.57 (0.05)	8.91 (0.07)
At week 40	6.03 (0.10)	6.08 (0.11)	5.57 (0.10)	5.84 (0.11))	5.69 (0.10)	5.76 (0.11)	6.93 (0.10)	7.73 (0.10)
Change from baseline to week 40[a]	-1.52 (0.10)**	-2.81 (0.11)**	-1.98 (0.10)**	-3.05 (0.11)**	-1.85 (0.10)**	-3.13 (0.11)**	-0.61 (0.10)**	-1.16 (0.10)**
Difference vs placebo at week 40 (95% CI)	-0.90 (-1.18, -0.62)	-1.66 (-1.94, -1.37)	-1.36 (-1.65, -1.08)	-1.89 (-2.17, -1.61)	-1.24 (-1.53, -0.95)	-1.97 (-2.25, -1.68)	-	-
P value	<.001	<.001	<.001	<.001	<.001	<.001	-	-

Data presented are for the efficacy estimand that evaluated treatment effects using on treatment data without use of rescue therapy. Mixed-model repeated measures model used with treatment, visit, treatment-by-visit interaction, country, baseline metformin use, baseline HbA_{1c} category (≤8.0%, >8.0%), baseline HbA_{1c} category (≤8.0%, >8.0%)-by-visit interaction, baseline HbA_{1c} category (≤8.0%, >8.0%)-by-treatment interaction, and baseline HbA_{1c} category (≤8.0%, >8.0%)-by-Treatment-by-Time interaction as fixed effects and baseline HbA_{1c} value as a covariate.*P <.05 and **P <.001 versus baseline.

Abbreviations: CFB, change from baseline; CI, confidence interval; HbA_{1c}, glycated hemoglobin A_{1c}; mITT, modified intent-to-treat (all randomly assigned patients who took at least 1 dose of study drug); SE, standard error.

eTable 5. Subset analysis of daily mean insulin glargine dose by HbA_{1c} at baseline

	Tirzepatide 5 mg n = 116	Tirzepatide 10 mg n = 119	Tirzepatide 15 mg n = 120	Placebo n = 120
Patients with baseline HbA_{1c} ≤8.0%, No.	52	48	51	47
Insulin glargine dose, estimate (SE), IU/day				
At baseline	33.1 (2.02)	30.4 (1.93)	34.1 (2.10)	30.8 (1.98)
Week 40	35.8 (2.34)	30.0 (2.03)	29.5 (2.03)	54.3 (3.78)
Change from baseline to week 40	4.2 (2.38)	-1.7 (2.06)	-2.2 (2.06)	22.9 (3.83)
Percent change from baseline to week 40	13.0 (7.39)	-5.3 (6.41)	-6.7 (6.41)	71.4 (11.94)**
Estimate difference vs placebo (95% CI); *P* value	-34.1 (-45.4, -20.4); <.001	-44.7 (-54.4, -33.1); <.001	-45.6 (-55.1, -34.0); <.001	-
Patients with baseline HbA_{1c} >8.0%, No.	63	69	67	72
Insulin glargine dose, estimate (SE), IU/day				
At baseline	35.3 (2.05)	33.1 (1.84)	35.7 (2.01)	34.4 (1.87)
Week 40	38.8 (4.39)	40.5 (4.45)	29.4 (3.27)	63.0 (6.54)
Change from baseline to week 40	3.9 (2.66)	6.3 (2.76)	-4.5 (2.05)	27.6 (3.94)
Percent change from baseline to week 40	11.3 (7.69)	18.2 (7.98)*	-13.1 (5.94)*	79.7 (11.40)**
Estimate difference vs placebo (95% CI); *P* value	-38.0 (-48.5, -25.5); <.001	-34.2 (-45.2, -21.1); <.001	-51.6 (-59.7, -41.9); <.001	-

Data presented are for the efficacy estimand that evaluated treatment effects using on treatment data without use of rescue therapy. Insulin doses are log transformed before analysis to account for their skewed distribution and estimated ratio to baseline are transformed back for interpretation expressed as percent change from baseline to week 40 and estimated percent difference vs placebo. Mixed-model repeated measures model used with treatment, visit, treatment-by-visit interaction, country, baseline metformin use,as fixed effects and baseline endpoint value as a covariate within each subset of HbA1c category (≤8.0%, >8.0%).*P<.05, **P<.001 vs baseline.

Abbreviations: CI, confidence interval; HbA_{1c}, glycated hemoglobin A_{1c}; No., number, SE, standard error.

eTable 6. Fasting lipid profile

Parameters (Efficacy Estimand)		Tirzepatide 5 mg n = 116			Tirzepatide 10 mg n = 119			Tirzepatide 15 mg n = 120			Placebo n = 120		
		Baseline	CFB	% CFB	Baseline	CFB	% CFB	Baseline	CFB	% CFB	Baseline	CFB	% CFB
Total cholesterol (mg/dL)	Estimate (SE)	167.1 (3.72)	-14.6 (2.36)	-8.8 (1.42)**	166.3 (3.70)	-17.1 (2.32)	-10.3 (1.39)**	163.4 (3.78)	-21.5 (2.34)	-12.9 (1.41)**	167.7 (3.66)	-0.6 (2.53)	-0.4 (1.52)
	Difference vs placebo for %CFB (95% CI); *P* value	-8.43 (-12.28, -4.42); <.001			-9.93 (-13.71, -5.98); <.001			-12.61 (-16.36, -8.70); <.001			-		
Triglycerides (mg/dL)	Estimate (SE)	153.5 (7.69)	-22.0 (4.17)	-15.2 (2.89)**	144.0 (7.21)	-27.9 (3.96)	-19.3 (2.74)**	138.3 (7.20)	-35.9 (3.84)	-24.9 (2.66)**	141.4 (6.95)	-9.8 (4.50)	-6.8 (3.12)*
	Difference vs placebo for %CFB (95% CI); *P* value	-9.07 (-17.23, -0.12); 0.047			-13.48 (-21.23, -4.97); 0.003			-19.43 (-26.80, -11.33); <.001			-		
LDL cholesterol (mg/dL)	Estimate (SE)	83.6 (3.31)	-7.6 (2.04)	-8.9 (2.39)**	85.7 (3.39)	-10.9 (1.95)	-12.8 (2.29)**	83.9 (3.47)	-13.2 (1.98)	-15.5 (2.32)**	87.5 (3.40)	2.4 (2.26)	2.8 (2.65)
	Difference vs placebo for %CFB (95% CI); *P* value	-11.44 (-17.63, -4.79); .001			-15.23 (-21.15, -8.87); <.001			-17.83 (-23.70, -11.50); <.001			-		
VLDL (mg/dL)	Estimate (SE)	30.5 (1.45)	-4.3 (0.81)	-15.1 (2.86)**	28.6 (1.37)	-5.3 (0.78)	-18.7 (2.73)**	27.2 (1.36)	-6.9 (0.76)	-24.1 (2.67)**	27.7 (1.29)	-1.6 (0.89)	-5.5 (3.11)
	Difference vs placebo for %CFB (95% CI); *P* value	-10.15 (-18.11, -1.42); 0.024			-13.96 (-21.56, -5.62); 0.002			-19.70 (-26.96, -11.72); <.001			-		
HDL cholesterol (mg/dL)	Estimate (SE)	44.1 (1.08)	0.9 (0.68)	2.1 (1.51)	45.2 (1.11)	0.8 (0.67)	1.8 (1.50)	45.5 (1.16)	0.4 (0.70)	0.9 (1.55)	44.8 (1.07)	0.8 (0.66)	1.7 (1.47)
	Difference vs placebo for %CFB (95% CI); *P* value	0.37 (-3.63, 4.54); 0.858			0.09 (-3.90, 4.24); 0.965			-0.80 (-4.83, 3.41); 0.705			-		

Data presented are estimated means (SE) from analysis of covariance using data for the efficacy estimand that evaluated on treatment effects without use of rescue therapy. Lipid data were log transformed before analysis to account for their skewed distribution *P <.05, **P <.001 vs baseline.

Abbreviations: CFB, change from baseline; HDL, high-density lipoprotein; LDL, low-density lipoprotein; n, number of patients in the specified treatment group; SE, standard error; VLDL, very low-density lipoprotein.

eTable 7. Vital signs and additional safety parameters

Parameter	Tirzepatide 5 mg n = 116	Tirzepatide 10 mg n = 119	Tirzepatide 15 mg n = 120	Placebo n = 120
Vital signs				
Systolic blood pressure, LS mean (SE), mmHg				
Baseline	136.9 (1.46)	138.2 (1.44)	136.8 (1.43)	139.8 (1.43)
Change from baseline to week 40	-6.1 (1.24)**	-8.3 (1.21)**	-12.6 (1.23)**	-1.7 (1.21)
***P* value vs placebo at week 40**	.012	<.001	<.001	-
Diastolic blood pressure, LS mean (SE), mmHg				
Baseline	79.2 (1.00)	80.8 (0.99)	80.1 (0.98)	82.6 (0.98)
Change from baseline to week 40	-2.0 (0.73)*	-3.3 (0.72)**	-4.5 (0.73)**	-2.1 (0.71)*
***P* value vs placebo at week 40**	.958	.218	.017	-
Pulse rate, bpm				
Baseline	75.3 (1.04)	74.5 (1.03)	75.6 (1.02)	75.3 (1.02)
Change from baseline to week 40	1.3 (0.83)	3.5 (0.81)**	5.6 (0.82)**	-0.8 (0.81)
***P* value vs placebo at week 40**	.065	<.001	<.001	-
Pancreatic Enzymes, estimate (SE), IU/L				
Amylase				
Baseline	21.3 (0.97)	20.7 (0.93)	20.1 (0.91)	20.6 (0.92)
At week 40	28.4 (0.92)	28.4 (0.90)	29.2 (0.94)	21.8 (0.69)
Percent change from baseline to week 40	37.4 (4.46)**	37.1 (4.34)**	41.3 (4.56)**	5.2 (3.32)
Difference vs placebo (%) (95% CI)	30.6 (19.5, 42.8)	30.3 (19.4, 42.3)	34.3 (22.9, 46.8)	-
***P* value vs placebo**	<.001	<.001	<.001	-
Lipase				
Baseline	33.6 (1.64)	36.0 (1.73)	32.8 (1.58)	34.0 (1.63)
At week 40	45.1 (1.84)	45.0 (1.79)	47.5 (1.93)	32.5 (1.29)
Percent change from baseline at week 40	32.3 (5.40)**	32.1 (5.27)**	39.4 (5.66)**	-4.6 (3.79)
Difference vs placebo (%) (95% CI)	38.6 (24.0, 55.1)	38.4 (23.9, 54.5)	46.0 (30.6, 63.2)	-
***P* value vs placebo**	<.001	<.001	<.001	-

Parameter	Tirzepatide 5 mg n = 116	Tirzepatide 10 mg n = 119	Tirzepatide 15 mg n = 120	Placebo n = 120
Liver Enzymes, estimate (SE), IU/L				
Alanine aminotransferase				
Baseline	25.0 (1.15)	24.9 (1.13)	25.4 (1.16)	23.4 (1.06)
At week 40	19.9 (0.80)	18.9 (0.75)	17.7 (0.71)	22.8 (0.90)
Percent change from baseline to week 40	-19.4 (3.25)*	-23.3 (3.03)*	-28.3 (2.89)**	-7.5 (3.64)
Difference vs placebo (%) (95% CI)	-12.9 (-22.0, -2.7)	-17.1 (-25.7, -7.5)	-22.5 (-30.6, -13.4)	-
***P* value vs placebo**	.015	<.001	<.001	-
Aspartate aminotransferase				
Baseline	20.7 (0.77)	20.4 (0.75)	20.6 (0.76)	19.0 (0.70)
At week 40	19.3 (0.54)	18.4 (0.51)	17.3 (0.49)	20.2 (0.55)
Percent change from baseline to week 40	-4.12 (2.70)	-8.56 (2.52)*	-14.07 (2.41)**	0.02 (2.75)
Difference vs placebo (%) (95% CI)	-4.1 (-11.3, 3.6)	-8.6 (-15.3, -1.3)	-14.1 (-20.5, -7.2)	-
***P* value vs placebo**	.283	.022	<.001	-
Estimated glomerular filtration rate (CKD-EPI calculation), LS mean (SE), ml/min/1.73 m^2				
Baseline	86.0 (1.65)	86.8 (1.63)	83.9 (1.64)	84.6 (1.62)
Change from baseline to Week 40	-6.0 (0.89)**	-4.4 (0.88)**	-3.6 (0.89)**	-4.0 (0.87)**
Difference vs placebo (95% CI)	-2.0 (-4.5, 0.4);	-0.4 (-2.9, 2.0)	0.4 (-2.0, 2.8)	-
***P* value vs placebo**	.106	.731	.746	-

Data presented as estimated mean (SE) unless specified otherwise and used the safety analysis set for analyses. Mixed-model for repeated measures was used with treatment, visit, treatment-by-visit interaction, country, baseline metformin use, baseline HbA_{1c} category (≤8.0%, >8.0%) as fixed effects and baseline endpoint value as a covariate. Data for liver and pancreatic enzymes were log transformed before analysis to account for their skewed distribution.

*P <.05, **P <.001 vs baseline.

Abbreviations: BL, baseline; LS, least squares; n, number of patients in specified treatment group; SE, standard error.

eTable 8. Prevalence of gastrointestinal TEAEs by maximum severity level

	Tirzepatide 5 mg n = 116	Tirzepatide 10 mg n = 119	Tirzepatide 15 mg n = 120	Placebo n = 120
Nausea/Vomiting/Diarrhea, No. (%)				
Mild	10 (8.6)	25 (21.0)	29 (24.2)	10 (8.3)
Moderate	11 (9.5)	5 (4.2)	10 (8.3)	2 (1.7)
Severe	1 (0.9)	1 (0.8)	2 (1.7)	1 (0.8)
Diarrhea, No. (%)				
Mild	8 (6.9)	11 (9.24)	18 (15.0)	9 (7.5)
Moderate	5 (4.3)	3 (2.5)	6 (5.0)	2 (1.7)
Severe	1 (0.9)	1 (0.8)	1 (0.8)	1 (0.8)
Nausea, No. (%)				
Mild	6 (5.2)	17 (14.3)	13 (10.8)	2 (1.7)
Moderate	9 (7.8)	4 (3.4)	8 (6.7)	1 (0.8)
Severe	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Vomiting, No. (%)				
Mild	3 (2.6)	7 (5.9)	10 (8.3)	2 (1.7)
Moderate	4 (3.5)	2 (1.7)	5 (4.2)	1 (0.8)
Severe	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)

Data are prevalence n (%) from safety analysis set. Severity was assessed and reported by investigator.
Abbreviations: n, number of patients in the specified treatment group; No., number of patients who experienced the event after the first treatment dose; TEAE, treatment emergent adverse events.

eTable 9. Hypoglycemia events through safety follow-up[a]

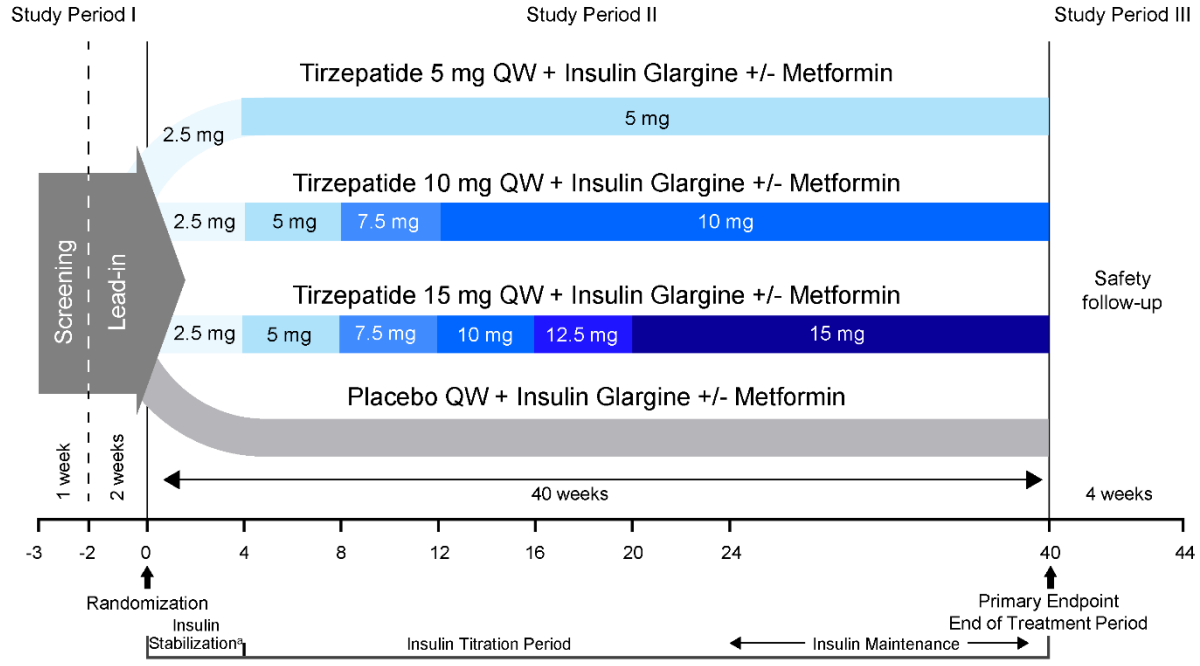
	Tirzepatide 5 mg n = 116	Tirzepatide 10 mg n = 119	Tirzepatide 15 mg n = 120	Placebo n = 120
Severe Hypoglycemia[b]	0 (0.0)	2 (1.6)	1 (0.8)	0 (0.0)
Hypoglycemia incidence (blood glucose <54 mg/dL), No. (%)	18 (15.5)	23 (19.3)	17 (14.2)	15 (12.5)
Number of episodes, No.	61	49	41	44
Aggregated rate per year, events/patient-year	0.64	0.50	0.43	0.44
Hypoglycemia incidence (blood glucose ≤70 mg/dL), No. (%)	70 (60.3)	75 (63.0)	72 (60.0)	73 (60.8)
Number of episodes, No.	737	809	847	669
Aggregated rate per year, events/patient-year	7.73	8.19	8.79	6.63
Nocturnal hypoglycemia incidence (blood glucose <54 mg/dL), No. (%)	8 (6.9)	4 (3.4)	8 (6.7)	8 (6.7)
Number of episodes, No.	25	4	17	23
Aggregated rate per year, events/patient-year	0.26	0.04	0.18	0.23
Nocturnal hypoglycemia incidence (blood glucose ≤70 mg/dL), No. (%)	27 (23.3)	28 (23.5)	22 (18.3)	23 (19.2)
Number of episodes, No.	140	87	192	131
Aggregated rate per year, events/patient-year	1.47	0.88	1.99	1.30

[a]Data are from safety analysis set excluding hypoglycemic events occurring after initiation of new antihyperglycemic therapy.
[b]Severe hypoglycemic events were defined as episodes with severe cognitive impairment requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
Abbreviations: mITT, modified intent-to-treat; n, number of patients in the specified treatment group.

eTable 10. Malignant neoplasms reported during the study

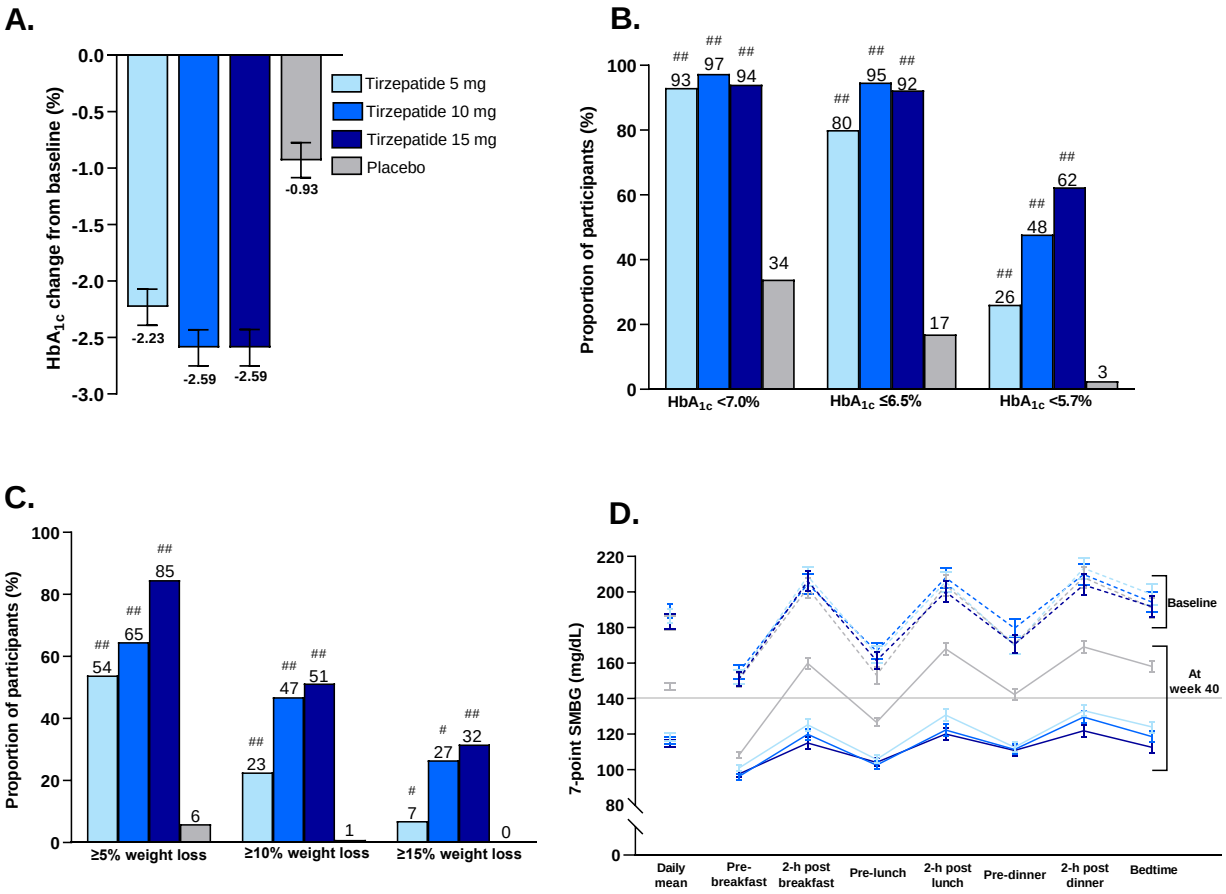
Treatment group	Type of malignant neoplasm	Study day
Tirzepatide 5 mg	Renal neoplasm	Day 192
Tirzepatide 5 mg	Papillary renal cell carcinoma	Day 100
Tirzepatide 10 mg	Uterine cancer	Day 141
Placebo	Transitional cell carcinoma	Day 110
Placebo	Basal cell carcinoma	Day 91

eFigure 1. SURPASS-5 study design



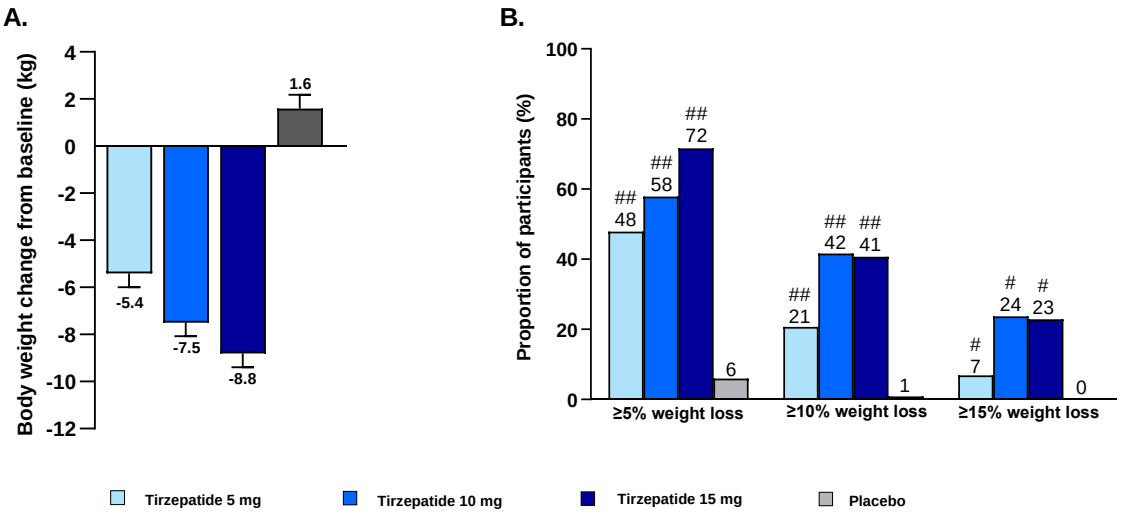
[a]Stabilization period was the first 4 weeks after randomization with restricted insulin dose adjustments. Insulin glargine titration period starts from week 4 to 40 (end of treatment or end of study) with unrestricted insulin dose adjustments. Maintenance period, when insulin glargine dose was expected to be stable, was from week 24 to 40. Abbreviations: QW, once-weekly.

eFigure 2. Secondary efficacy outcomes from efficacy estimand. (A) HbA_{1c} change from baseline at week 40, (B) proportion of patients achieving HbA_{1c} levels <7.0%, ≤6.5%, and <5.7% at week 40, (C) proportion of patients achieving body weight loss ≥5%, ≥10% and ≥15% at week 40 (D) mean 7-point SMBG profiles at baseline and at week 40



All data reflect efficacy estimand (corresponding analyses used the efficacy analysis set) that evaluated treatment effects using on-treatment data without use of rescue therapy.
Panel A: Mixed-model repeated measures analysis was used with treatment, visit, treatment-by-visit interaction, country, baseline metformin use as fixed effects and baseline HbA_{1c} value as a covariate. Error bars represent 95% CI for the estimated mean.
Panel B, C: Logistic regression with the same factor and covariate as Panel A (without interactions) where missing endpoints were dichotomized after they were predicted from the continuous endpoint mixed-model repeated measures analysis in Panel A . $^{\#}P$ <.05 and $^{\#\#}P$ <.001 vs placebo at Week 40.
Panel D: Values are estimated mean (SE) from analysis of covariance with treatment, country, baseline metformin use, baseline HbA_{1c} category (≤8.0%, >8.0%) as fixed effects and baseline value as a covariate.
Abbreviations: SE, standard error; SMBG, self-monitored blood glucose.

eFigure 3. Efficacy measures (treatment-regimen estimand). (A) body weight change from baseline to week 40; and (B) proportion of patients achieving body weight loss targets ≥5%, ≥10%, and ≥15% at week 40



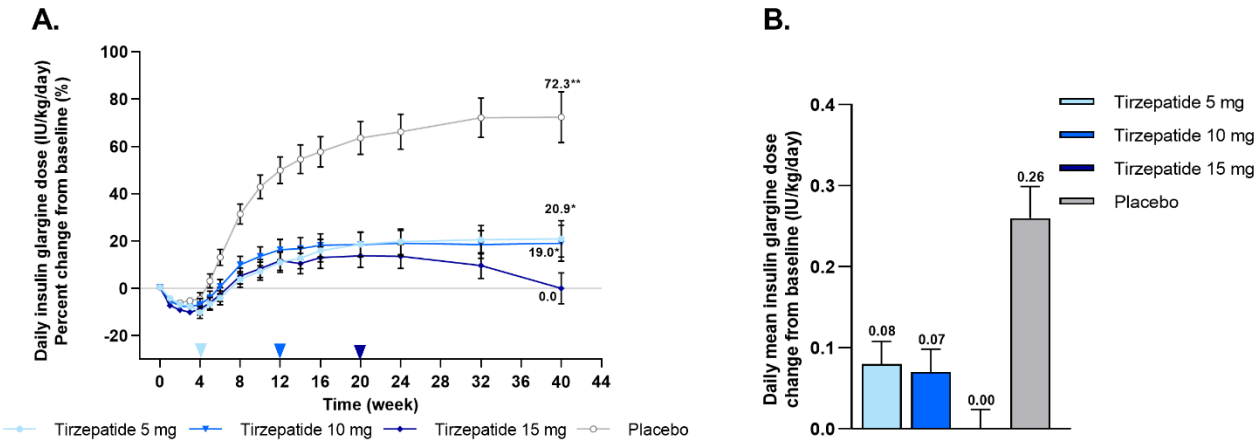
Data reflect treatment-regimen estimand (corresponding analyses used the full analysis set) that evaluated treatment effects regardless of treatment adherence or use of rescue therapy. Missing values at week 40 were imputed 100 times using method of multiple imputation based on the placebo arm.

Panel A: analysis of covariance model was used with treatment, country, baseline metformin use, baseline HbA_{1c} category (≤8.0%, >8.0%) as fixed effects and baseline weight value as a covariate. Data are presented as estimated mean (SE).

For panel B: logistic regression was used with the same fixed effects and covariate as that for analysis of covariance model. $^{\#}P<.05$ and $^{\#\#}P<.001$ vs placebo at 40 weeks.

Abbreviations: $HbA_{1c,}$ glycated hemoglobin A_{1c}; SE, standard error.

eFigure 4. Daily mean insulin glargine dose changes over time. (A) insulin glargine dose (IU/kg/day) percent change from baseline and (B) insulin glargine dose (IU/kg/day) change from baseline

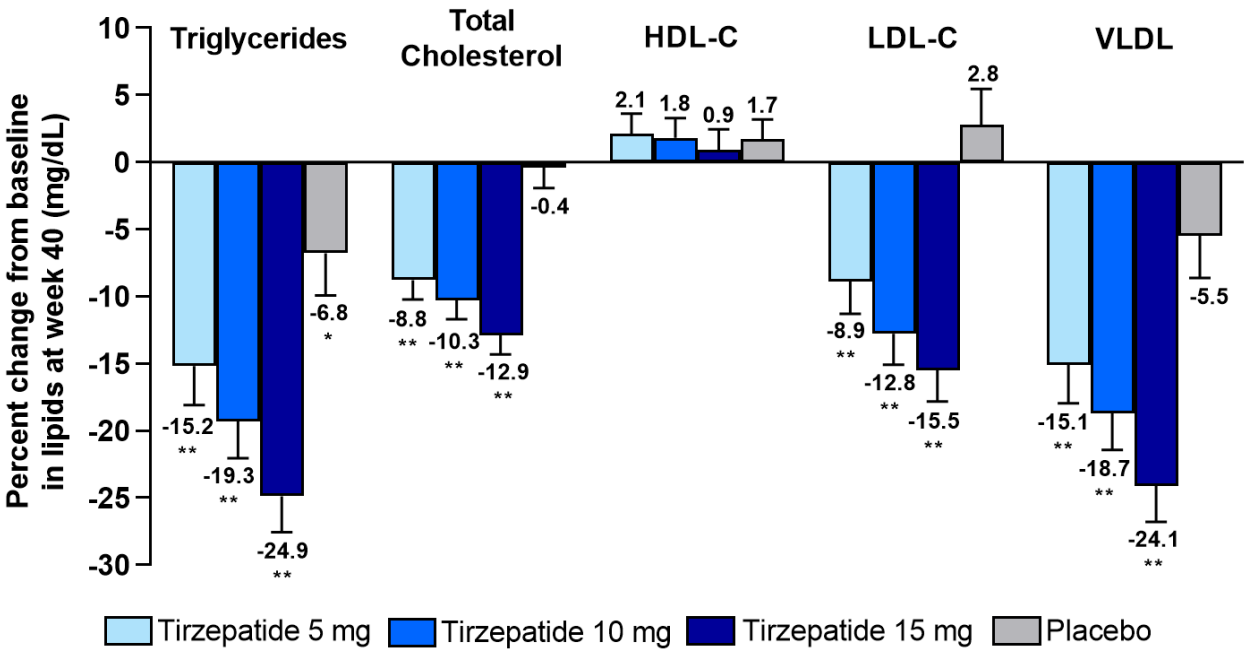


Blue arrows on the X-axis indicate the time points when maintenance doses of tirzepatide 5, 10, and 15 mg were achieved. Error bars represent standard error of the mean. *P<.05 and **P<.001 vs baseline at week 40.

Panel A and B reflect efficacy estimand (corresponding analysis used the efficacy analysis set) that evaluated treatment effects using on-treatment data without use of rescue therapy. Mixed-model for repeated measures was used with treatment, visit, treatment-by-visit interaction, country, baseline metformin use, baseline HbA_{1c} category (≤8.0%, >8.0%) as fixed effects and baseline insulin dose as a covariate.

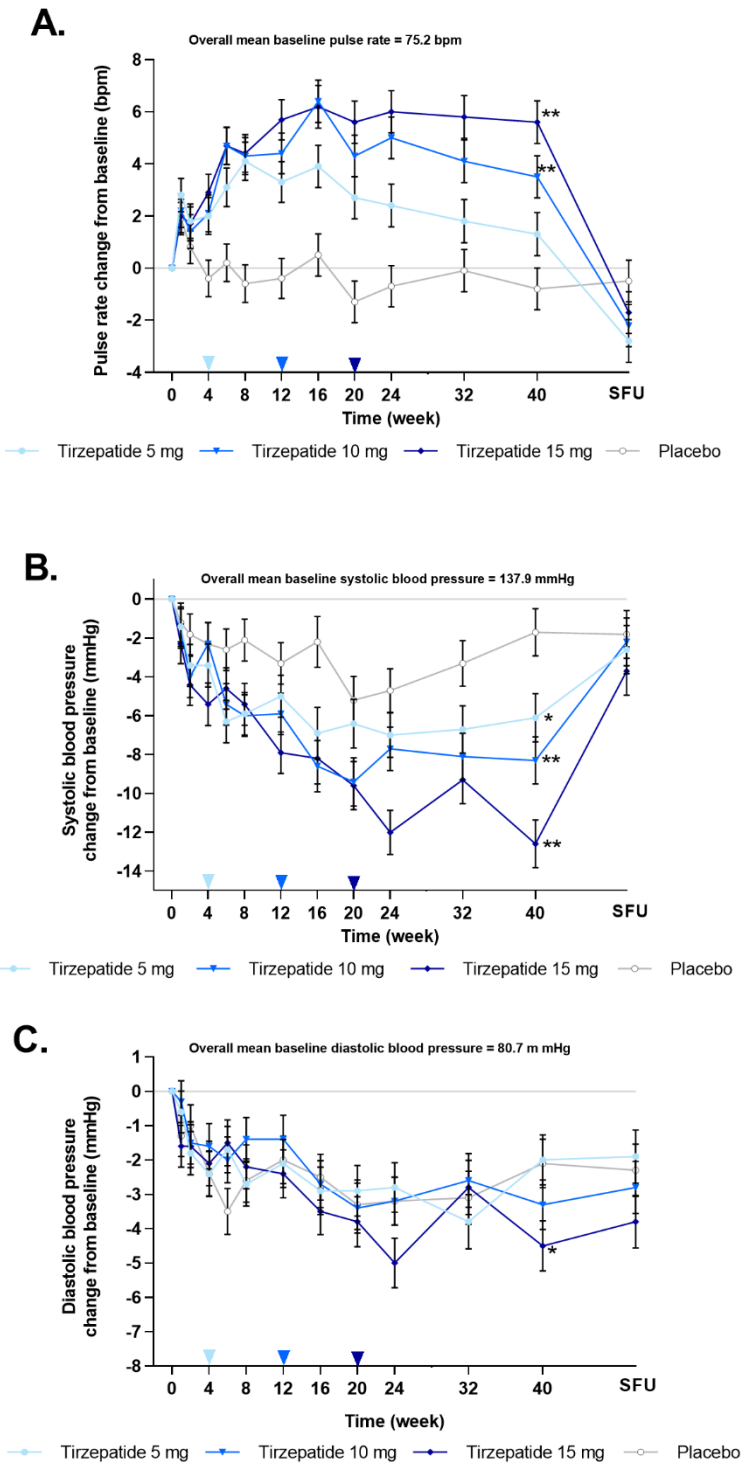
Insulin doses were log transformed before analysis to account for their skewed distribution and estimated ratio to baseline were transformed back for interpretation expressed as percent change from baseline to week 40 and change from baseline to week 40.

eFigure 5. Fasting lipid profile at week 40



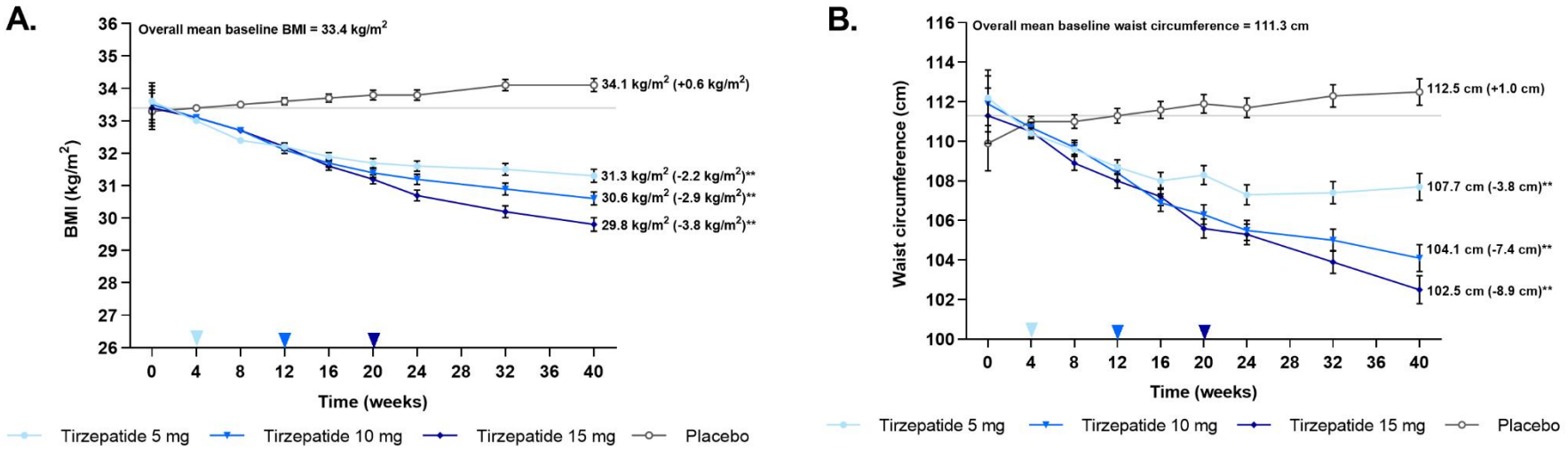
Data reflect efficacy estimand (corresponding analyses used the efficacy analysis set) that evaluated treatment effects using on-treatment data without use of rescue therapy. Values are estimated means (SE) from analysis of covariance of log-transformed data with treatment, country, baseline metformin use, baseline HbA_{1c} category (≤8.0%, >8.0%) as fixed effects and baseline endpoint value as a covariate. *P <.05 and **P <.001 vs baseline at week 40.
Abbreviations: HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; SE, standard error; VLDL, very low density lipoprotein.

eFigure 6. Vital parameters (A) pulse rate (bpm), (B) systolic blood pressure (mmHg), and (C) diastolic blood pressure (mmHg)



Blue arrows on the X-axis indicate the time points when maintenance dose of tirzepatide 5, 10 and 15 mg were achieved.
**P<.001 for change difference versus placebo at 40 weeks.
Data are from the safety analysis set and analyzed using mixed-model for repeated measures analysis with treatment, visit, treatment-by-visit interaction, country, baseline metformin use, baseline HbA_{1c} category (≤8.0%, >8.0%) as fixed effects and baseline endpoint value as a covariate. Values are estimated means; error bars represent standard error of the mean.
Abbreviations: bpm, beats per minute; SE, standard error; SFU, safety follow-up.

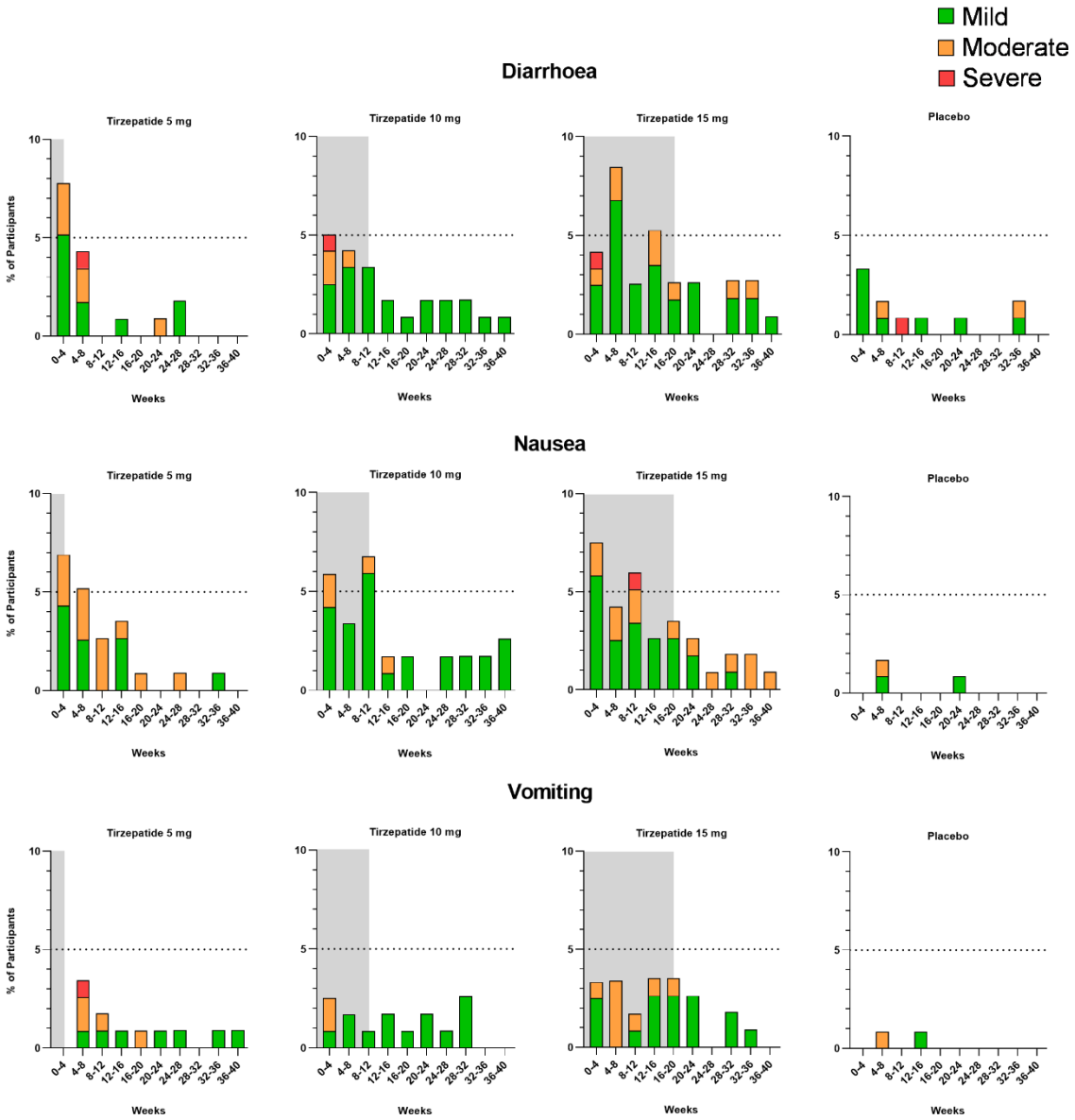
eFigure 7. BMI and waist circumference over time and change from baseline



Blue arrows on the X-axis indicate the time points when maintenance dose of tirzepatide 5, 10 and 15 mg were achieved. ***P*<.001 for change difference versus placebo at 40 weeks.
Data are from the safety analysis set and calculated using mixed-model for repeated measures analysis with treatment, visit, treatment-by-visit interaction, country, baseline metformin use, baseline HbA_{1c} category (≤8.0%, >8.0%) as fixed effects and baseline endpoint value as a covariate. Values are estimated means; error bars represent standard error of the mean; and change in estimated mean values from baseline to 40 weeks are in parentheses.

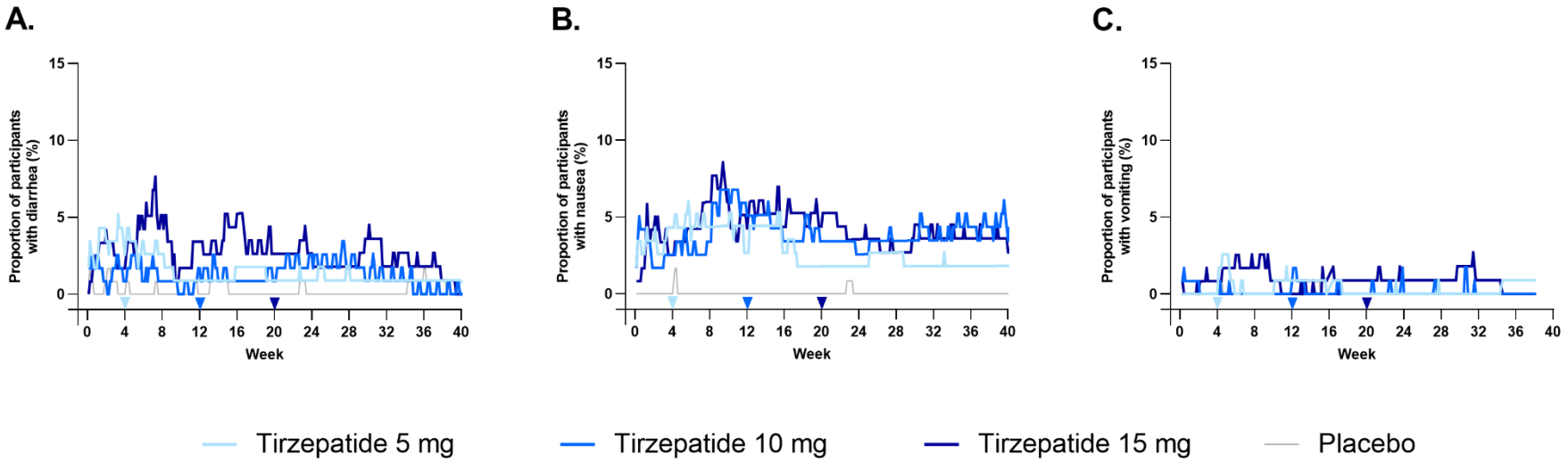
Abbreviations: BMI, body mass index.

eFigure 8. Incidence of diarrhea, nausea, and vomiting over time



Data are from safety analysis set. Values are percentage of patients who reported a new event during a time interval. Severity was assessed and reported by investigator. The grey shaded area signifies the treatment dose escalation period after which the assigned study treatment dose is reached.

eFigure 9. Prevalence of (A) diarrhea, (B) nausea, and (C) vomiting over time



All data are from safety analysis set. Values are percentage of patients who reported an event at a particular time point. Arrows on the x-axis indicate when the assigned treatment dose was reached after dose escalation period for tirzepatide 5 mg, 10 mg, and 15 mg.

References

1. Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley & Sons Inc.; 1987.
2. Frias JP, Nauck MA, Van J, et al. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. *Lancet.* 2018;392(10160):2180-2193. doi:10.1016/s0140-6736(18)32260-8
3. Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care.* 2003;26(11):3080-3086. doi:10.2337/diacare.26.11.3080