Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes

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Objectives

SURPASS-2

- **Primary Objective**
  - To demonstrate that tirzepatide 10 mg and/or 15 mg once-weekly are noninferior to semaglutide 1 mg once-weekly for mean change in HbA1c at 40 weeks
- **Key Secondary Objectives (Controlled for Type 1 Error)**
  - To demonstrate that tirzepatide 5 mg once-weekly is noninferior to semaglutide 1 mg once-weekly for glycemic control at 40 weeks for:
    - Mean change from baseline in HbA1c
  - To demonstrate that tirzepatide 5 mg, 10 mg, and/or 15 mg once-weekly is superior to semaglutide 1 mg once-weekly at 40 weeks for:
    - Mean change from baseline in body weight
    - Mean change from baseline in HbA1c
    - Proportion of patients with HbA1c target values of <7.0% (<53 mmol/mol)
  - To demonstrate that tirzepatide 10 mg and/or 15 mg once-weekly are superior to semaglutide 1 mg once-weekly for the proportion of patients with HbA1c target values of <5.7% (<39 mmol/mol) at 40 weeks

HbA1c=Glycated Haemoglobin.

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Study Design

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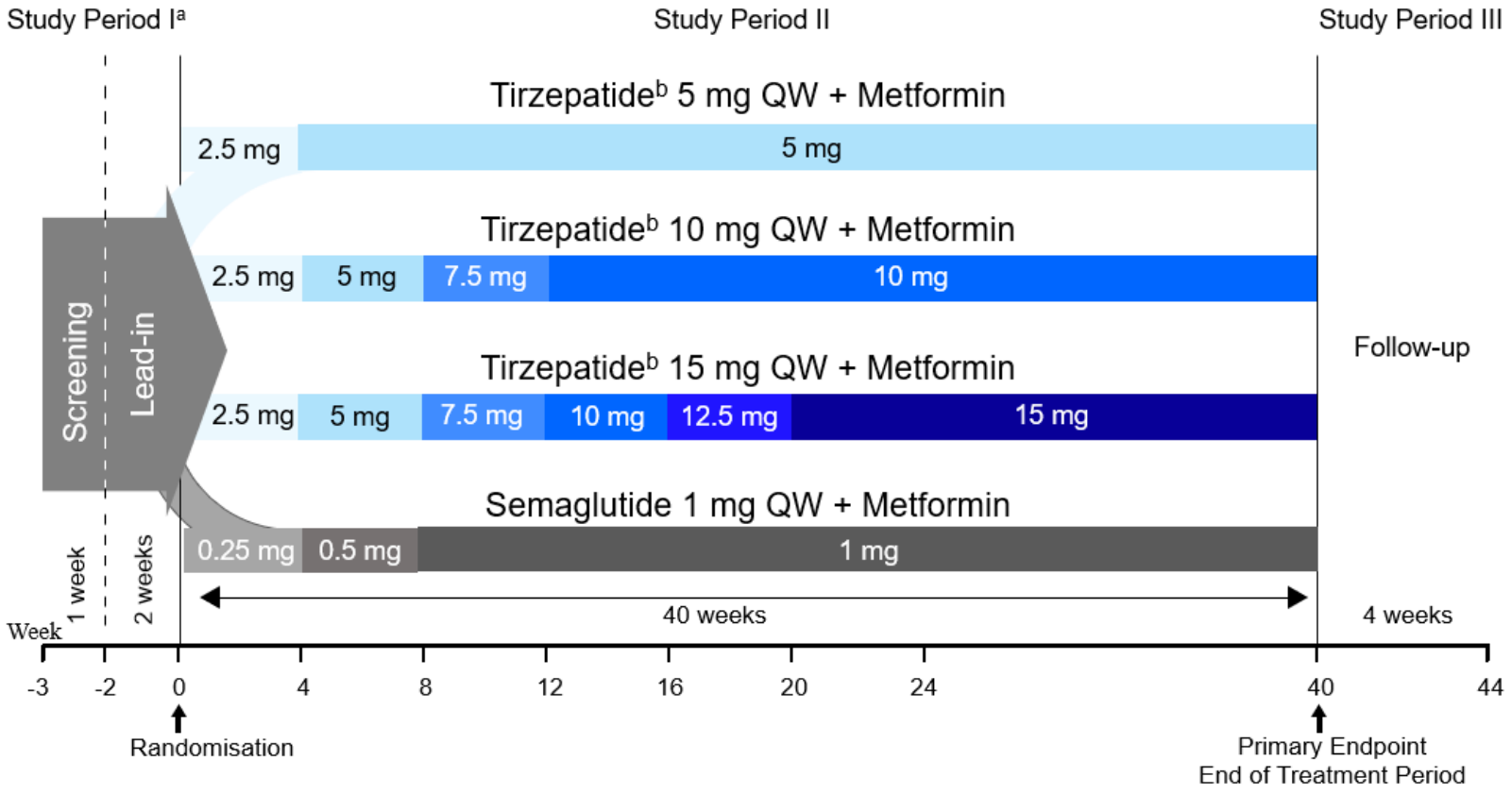
Randomised, open-label, active-controlled, parallel-group, multicentre, multinational trial

Key Inclusion Criteria

- Type 2 diabetes ≥ 18 years[c]
- HbA1c ≥7.0% to ≤10.5% at screening
- BMI ≥25 kg/m^2 with stable weight
- On stable dose of metformin ≥1500 mg/day

Key Exclusion Criteria

- Type 1 diabetes
- History of pancreatitis, nonproliferative diabetic retinopathy that warranted urgent treatment, proliferative diabetic retinopathy, or diabetic maculopathy
- eGFR <45 mL/min/1.73 m^2
- Use of any antihyperglycaemic treatment other than metformin in the 3 months prior to screening



[a]Stable doses of metformin ≥1500 mg/day for at least 3 months prior to Visit 1 and during the screening/lead-in period. [b]All tirzepatide doses will be double-blinded. [c]Inadequately controlled with metformin at a dose of at least 1500 mg per day.

BMI=Body Mass Index; eGFR=Estimated Glomerular Filtration Rate; HbA1c=Glycated Haemoglobin; QW=Once-Weekly; T1D=Type 1 Diabetes; T2D=Type 2 Diabetes.

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Baseline Demographics and Clinical Characteristics

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- Baseline demographics and clinical characteristics were well-balanced across the treatment groups

Parameters	Tirzepatide 5 mg N=470	Tirzepatide 10 mg N=469	Tirzepatide 15 mg N=470	Semaglutide 1 mg N=469	Total N=1878
Age (y)	56.3 ± 10.0	57.2 ± 10.5	55.9 ± 10.4	56.9 ± 10.8	56.6 ± 10.4
Female, n (%)	265 (56.4)	231 (49.3)	256 (54.5)	244 (52.0)	996 (53.0)
Duration of Diabetes (y)	9.1 ± 7.16	8.4 ± 5.90	8.7 ± 6.85	8.3 ± 5.80	8.6 ± 6.46
HbA1c (%)	8.32 ± 1.08	8.30 ± 1.02	8.26 ± 1.00	8.25 ± 1.01	8.28 ± 1.03
FSG (mg/dL)	173.8 ± 51.87	174.2 ± 49.79	172.4 ± 54.37	171.4 ± 49.77	172.9 ± 51.46
Weight (kg)	92.5 ± 21.76	94.8 ± 22.71	93.8 ± 21.83	93.7 ± 21.12	93.7 ± 21.86
BMI (kg/m^2)	33.8 ± 6.85	34.3 ± 6.60	34.5 ± 7.11	34.2 ± 7.15	34.2 ± 6.93
Waist circumference (cm)	108.06±14.81	110.55±16.05	109.55±15.60	109.04±14.90	109.30±15.36
Metformin use, yes [n (%)]	470 (100.0)	469 (100.0)	470 (100.0)	469 (100.0)	1878 (100.0)

Note: Data are mean ± SD, unless otherwise specified; mITT population.
BMI=Body Mass Index; FSG=Fasting Serum Glucose; HbA1c=Glycated Haemoglobin; mITT=Modified Intention-to-Treat; SD=Standard Deviation.
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Baseline Demographics and Clinical Characteristics

Race and Ethnicity, SURPASS-2

- Baseline demographics and clinical characteristics were well-balanced across the treatment groups

Parameters	Tirzepatide 5 mg N=470	Tirzepatide 10 mg N=469	Tirzepatide 15 mg N=470	Semaglutide 1 mg N=469	Total N=1878
Race [n (%)][a]					
American Indian or Alaska Native	53 (11.3)	53 (11.3)	57 (12.1)	45 (9.6)	208 (11.1)
Asian	6 (1.3)	11 (2.3)	5 (1.1)	3 (0.6)	25 (1.3)
Black	28 (6.0)	21 (4.5)	15 (3.2)	15 (3.2)	79 (4.2)
White	382 (81.3)	376 (80.2)	392 (83.4)	401 (85.5)	1551 (82.6)
Ethnicity [n (%)][a]					
Hispanic	325 (69.1)	322 (68.7)	334 (71.1)	336 (71.6)	1317 (70.1)
Non-Hispanic	145 (30.9)	147 (31.3)	136 (28.9)	133 (28.4)	561 (29.9)

[a]Race or ethnic group was reported by the patients.
Note: mITT population.
mITT=Modified Intention-to-Treat.
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Baseline Demographics and Clinical Characteristics

Kidney, SURPASS-2

- Baseline demographics and clinical characteristics were well-balanced across the treatment groups

Parameters	Tirzepatide 5 mg N=470	Tirzepatide 10 mg N=469	Tirzepatide 15 mg N=470	Semaglutide 1 mg N=469	Total N=1878
eGFR (CKD-EPI calculation; ml/min/1.73 m^2)	96.6 ±17.51	95.5 ±16.62	96.3 ±16.92	95.6 ±17.25	96.0 ±17.07
<60 ml/min/1.73 m^2 [n (%)]	19 (4.0)	15 (3.2)	11 (2.3)	19 (4.1)	64 (3.4)
≥60 ml/min/1.73 m^2 [n (%)]	451 (96.0)	454 (96.8)	459 (97.7)	450 (95.9)	1814 (96.6)
Urine Albumin/Creatinine Ratio (g/kg)					
<30 [n (%)]	340 (72.3)	353 (75.3)	357 (76.0)	364 (77.6)	1414 (75.3)
≥30 to ≤300 [n (%)]	111 (23.6)	87 (18.6)	85 (18.1)	90 (19.2)	373 (19.9)
>300 [n (%)]	18 (3.8)	29 (6.2)	27 (5.7)	15 (3.2)	89 (4.7)

Note: Data are mean ± SD, unless otherwise specified; mITT population. Participants with a baseline eGFR <45 mL/min/1.73 m2 were excluded from the study.
CKD-EPI=Chronic Kidney Disease-Epidemiology; eGFR=Estimated Glomerular Filtration Rate; mITT=Modified Intention-to-Treat; SD=Standard Deviation.
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Baseline Demographics and Clinical Characteristics

Cardiovascular, SURPASS-2

- Baseline demographics and clinical characteristics were well-balanced across the treatment groups

Parameters	Tirzepatide 5 mg N=470	Tirzepatide 10 mg N=469	Tirzepatide 15 mg N=470	Semaglutide 1 mg N=469	Total N=1878
Systolic blood pressure (mm Hg)	130.53 ± 14.11	131.47 ± 13.77	130.45 ± 14.32	129.96 ± 12.99	130.60 ± 13.81
Diastolic blood pressure (mm Hg)	78.61 ± 8.89	80.03 ± 9.59	78.97 ± 8.97	79.33 ± 8.61	79.23 ± 9.03
Pulse rate (bpm)	74.88 ± 9.37	74.55 ± 10.75	74.46 ± 9.86	75.10 ± 10.25	74.75 ± 10.07

Note: Data are mean ± SD, unless otherwise specified; mITT population.
BPM=Beats Per Minute; mITT=Modified Intention-to-Treat; SD=Standard Deviation.
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Patient Disposition

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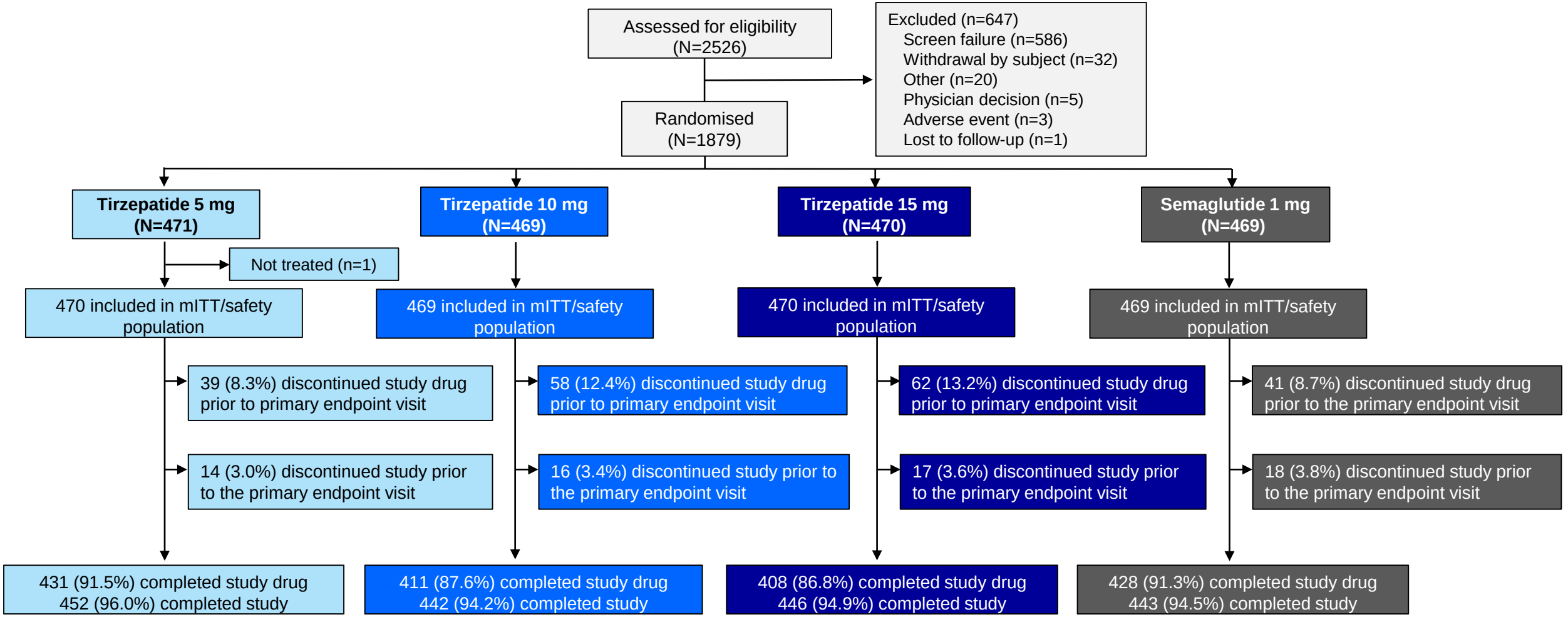

Note: Two participants (Tirzepatide 15 mg and Semaglutide) discontinued study drug due to inadvertent enrolment and were excluded from efficacy analyses. To see reasons for study drug discontinuation, see slide no. 9.
mITT population=Modified Intent-to-Treat Population (all randomly assigned participants who took at least 1 dose of study drug); n=Number of Patients in the Specified Category; N (Screened Population)=All Participants Who Signed Informed Consent; N (Randomized Population)=All Participants Who Were Randomly Assigned to a Treatment Arm; N (mITT Population)=All Randomly Assigned Participants Who Took at least 1 Dose of Study Drug.
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Reasons for Study Drug Discontinuation

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Parameter	Tirzepatide 5 mg N=470	Tirzepatide 10 mg N=469	Tirzepatide 15 mg N=470	Semaglutide 1 mg N=469
Permanent Discontinuation from Study Drug, n (%)	39 (8.3)	58 (12.4)	62 (13.2)	41 (8.7)
Adverse event	24 (5.1)	36 (7.7)	37 (7.9)	18 (3.8)
Death	4 (0.8)	4 (0.9)	3 (0.6)	1 (0.2)
Failure to meet randomisation criteria	0	0	1 (0.2)	1 (0.2)
Lost to follow-up	4 (0.8)	4 (0.9)	8 (1.7)	9 (1.9)
Physician decision	0	3 (0.6)	0	2 (0.4)
Protocol deviation	0	1 (0.2)	0	1 (0.2)
Withdrawal by subject	6 (1.3)	7 (1.5)	7 (1.5)	7 (1.5)
Pregnancy	1 (0.2)	0	1 (0.2)	1 (0.2)
Other	0	3 (0.6)	5 (1.1)	1 (0.2)

Note: Data are n (%); All Randomised Population.

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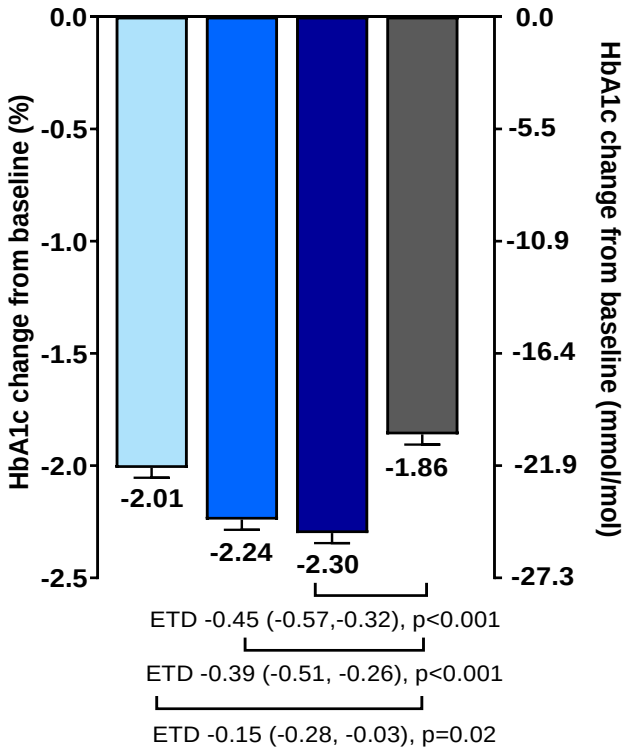
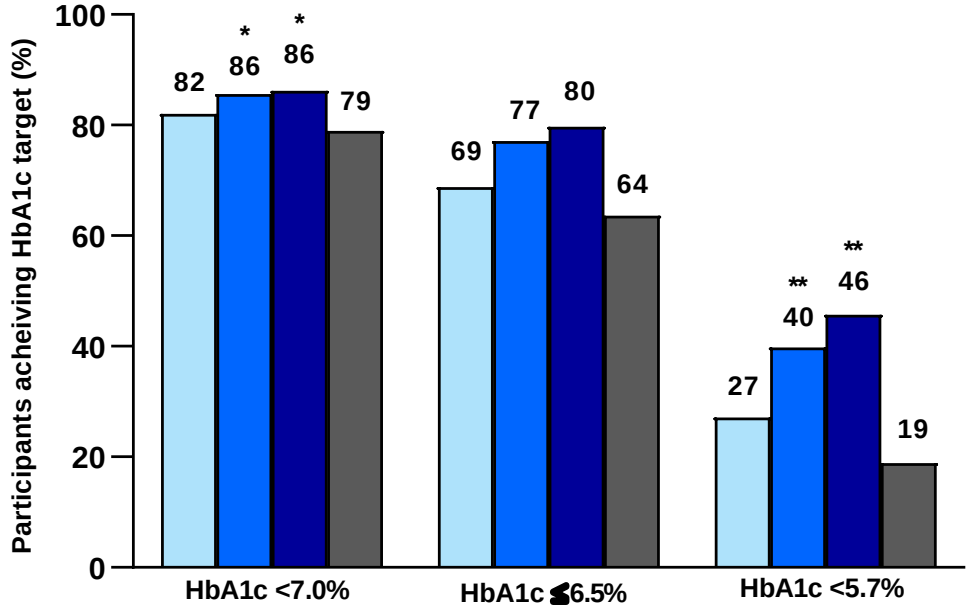
HbA1c: Treatment-Regimen Estimand

SURPASS-2

A. Change from Baseline in HbA1c at 40 Weeks (Treatment-Regimen Estimand)



B. % of Participants Reaching HbA1c Goals at 40 Weeks (Treatment-Regimen Estimand)



Tirzepatide 5 mg
Tirzepatide 10 mg
Tirzepatide 15 mg
Semaglutide 1 mg

*p<0.05 and **p<0.001 vs. Semaglutide 1 mg at 40 weeks.

Note: Data are LSM (SE), unless otherwise noted. Estimated treatment differences are LSM (95% confidence interval) at 40 weeks, mITT population. mITT (efficacy estimand), ANCOVA analysis (week 0), and MMRM analysis (week 40). (A) Change from baseline in HbA1c at 40 weeks from ANCOVA with multiple imputation by treatment for missing HbA1c at 40 weeks (treatment-regimen estimand). (B) Proportion of participants achieving HbA1c targets <7.0%, ≤6.5% and <5.7% at 40 weeks (treatment-regimen estimand). Proportion was obtained by dividing the number of participants reaching respective goals at Week 40 by the number of participants with baseline value and at least one non-missing postbaseline value. HbA1c ≤6.5% and <5.7% (tirzepatide 5 mg only) were not controlled for type 1 error, thus p-values were not presented. Estimated treatment difference (95% CI) of Tirzepatide vs Semaglutide was: i) 5 mg -0.23** (-0.36, -0.10), ii) 10 mg -0.51** (-0.64, -0.38), and iii) 15 mg -0.60** (-0.73, -0.47). *p<0.05 and **p<0.001 vs. Semaglutide 1 mg at 40 weeks.

ANCOVA=Analysis of Covariance; ETD=Estimated Treatment Difference; HbA1c=Glycated Haemoglobin; LSM=Least Squares Mean; mITT=Modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; SE=Standard Error.

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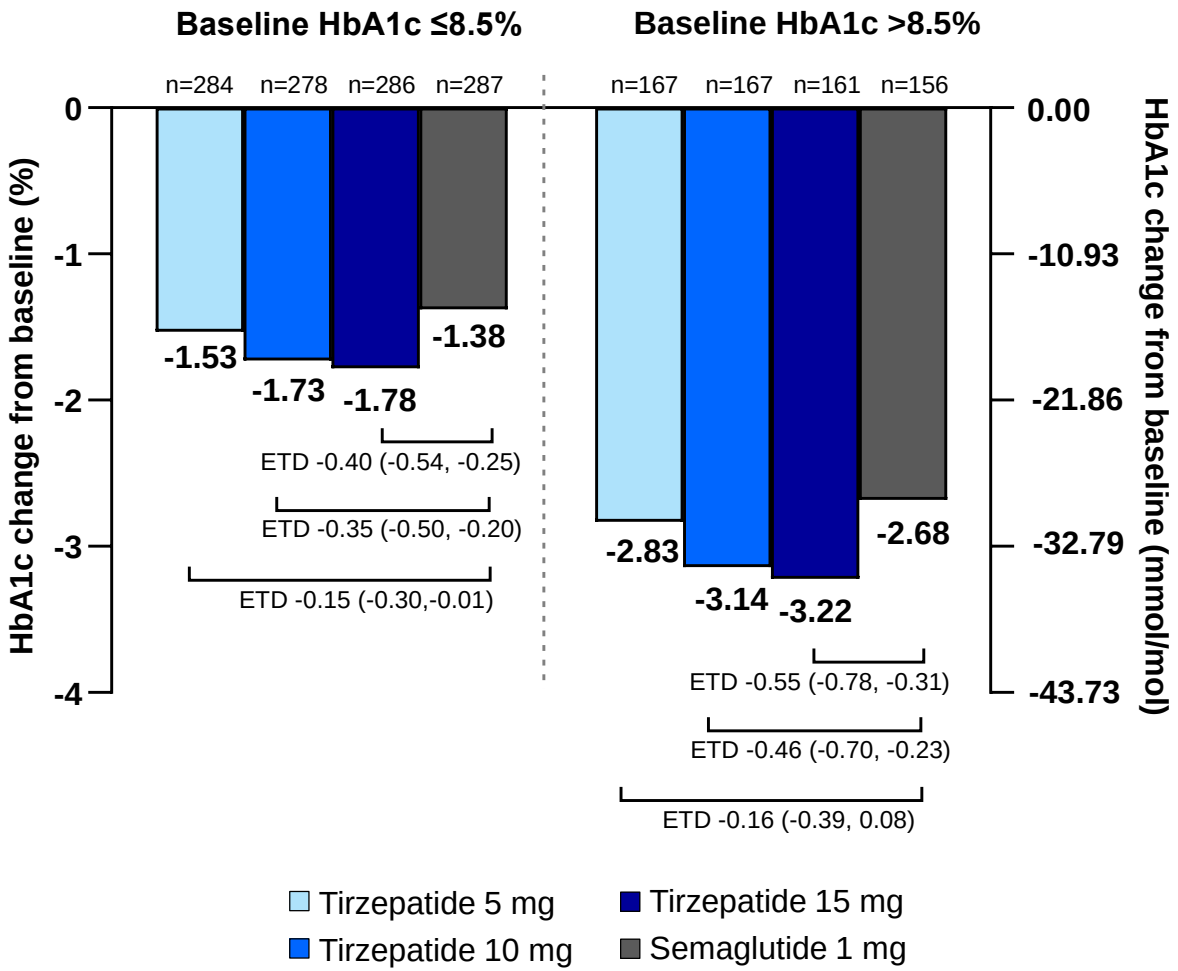
Change from Baseline in HbA1c at 40 Weeks by Baseline HbA1c (HbA1c ≤8.5% and >8.5%)

SURPASS-2



Note: Data are LSM at 40 weeks by baseline HbA1c (≤8.5%, >8.5%). Estimated treatment difference are LSM (95% confidence interval) at 40 weeks. ANCOVA with imputation method: retrieved dropout imputation, mITT population (treatment-regimen estimand). The widths of confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects.

ANCOVA=Analysis of Covariance; ETD=Estimated Treatment Difference; HbA1c=Glycated Haemoglobin; LSM=Least Squares Mean; mITT=Modified Intent-to-Treat.

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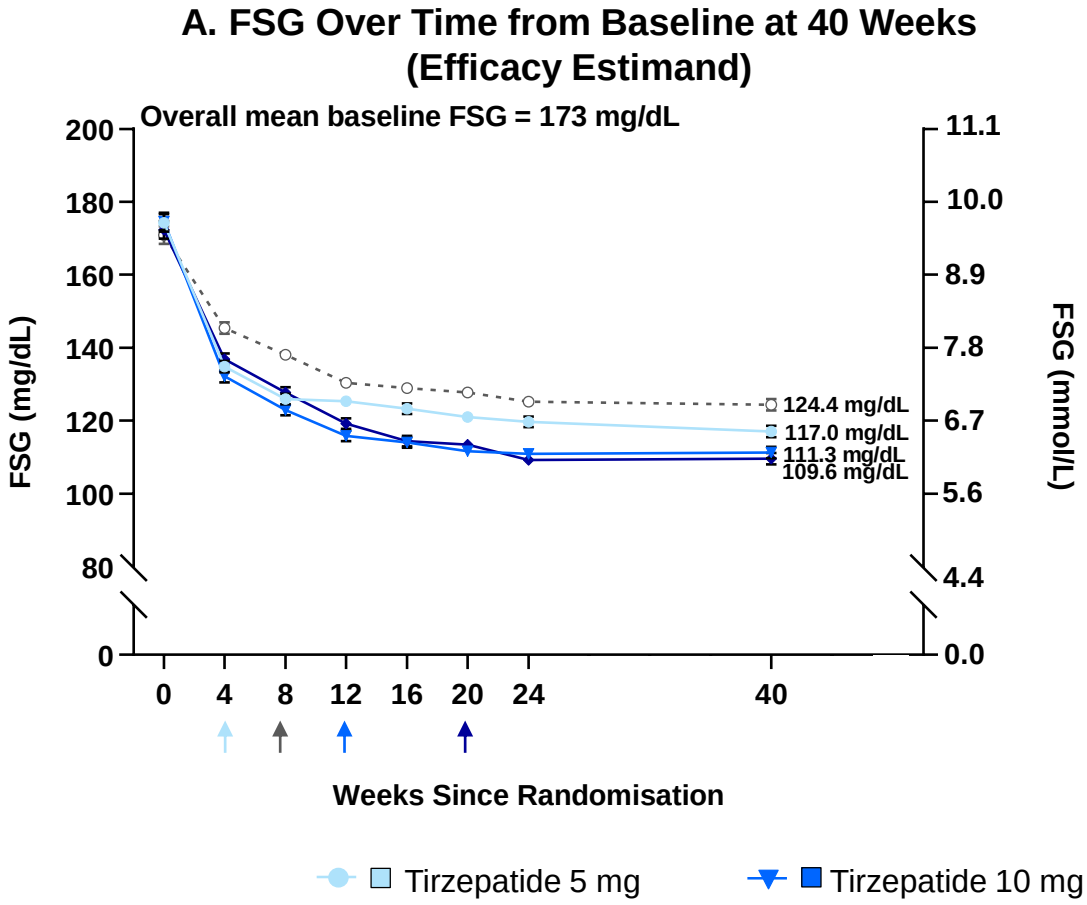
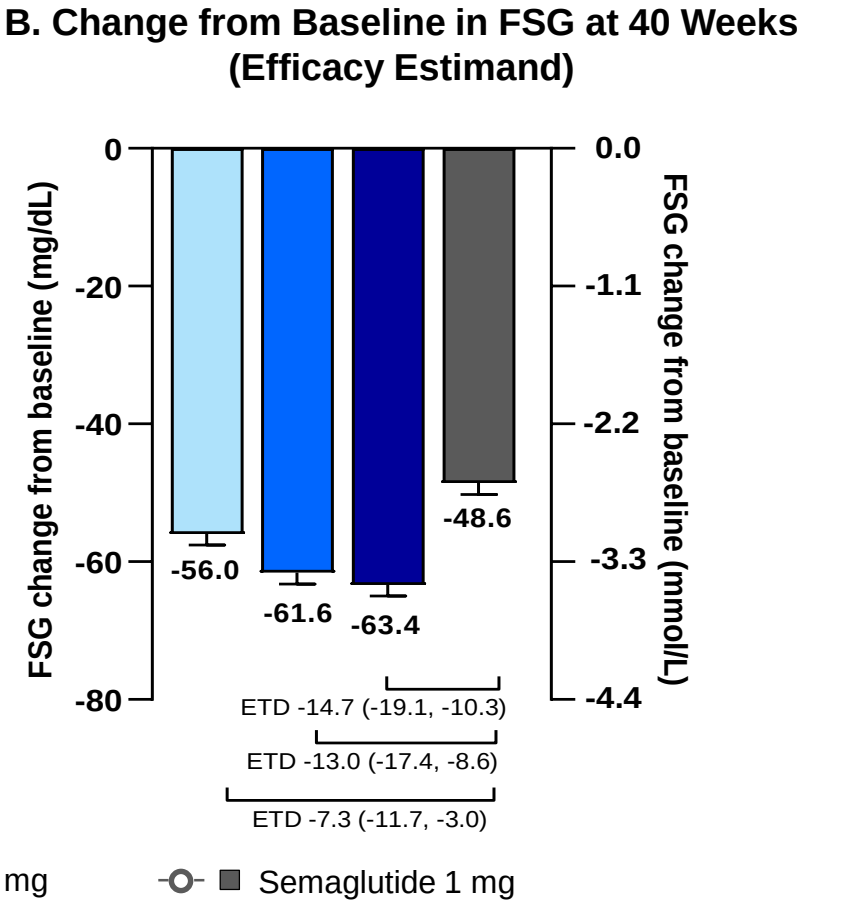
Additional Glycaemic Efficacy Results: FSG

SURPASS-2





Tirzepatide 5 mg | Tirzepatide 10 mg | Tirzepatide 15 mg | Semaglutide 1 mg

Note: Data are LSM (SE), unless otherwise noted. Estimated treatment differences are LSM (95% confidence interval) at 40 weeks, mITT population. mITT (efficacy estimand), ANCOVA analysis (week 0), and MMRM analysis (week 40). Arrows indicate when the maintenance dose of Tirzepatide 5 mg, 10 mg and 15 mg and Semaglutide 1 mg are achieved. (A) FSG values over time from MMRM analysis (efficacy estimand). (B) Change from Baseline in FSG at 40 Weeks from MMRM analysis (Efficacy Estimand). Estimated treatment differences (95% CI) of Tirzepatide vs Semaglutide was: i) 5 mg -7.3* (-11.7, -3.0), ii) 10 mg -13.0** (-17.4, -8.6), and iii) 15 mg -14.7** (-19.1, -10.3). *p<0.05 and **p<0.001 vs. Semaglutide 1 mg at 40 weeks.

ANCOVA=Analysis of Covariance; ETD=Estimated Treatment Difference; FSG=Fasting Serum Glucose; LSM=Least Squares Mean; mITT=Modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; SE=Standard Error.

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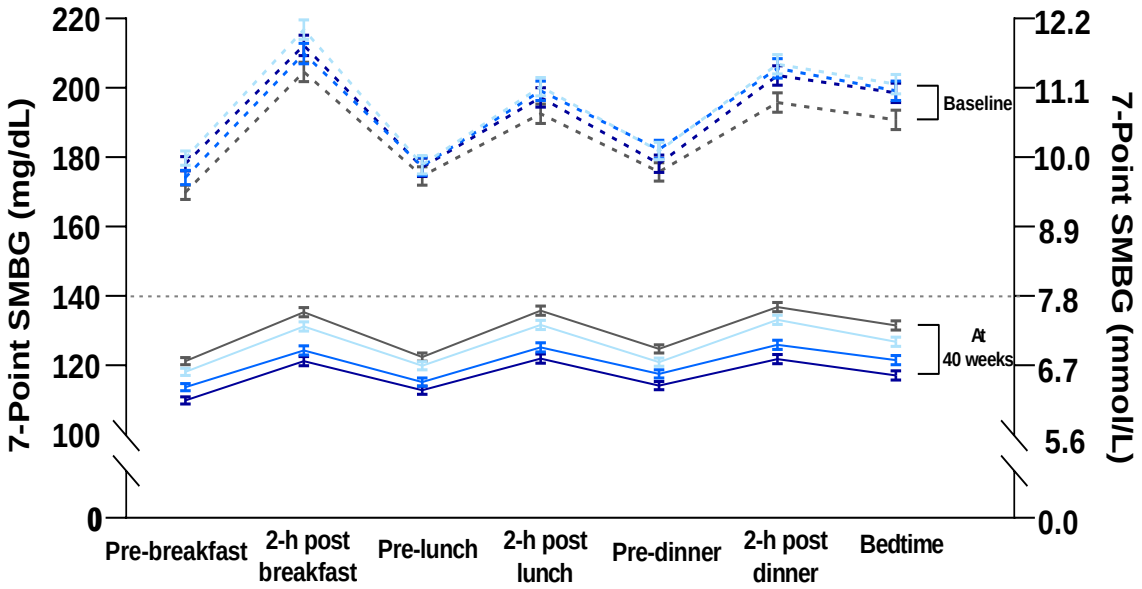
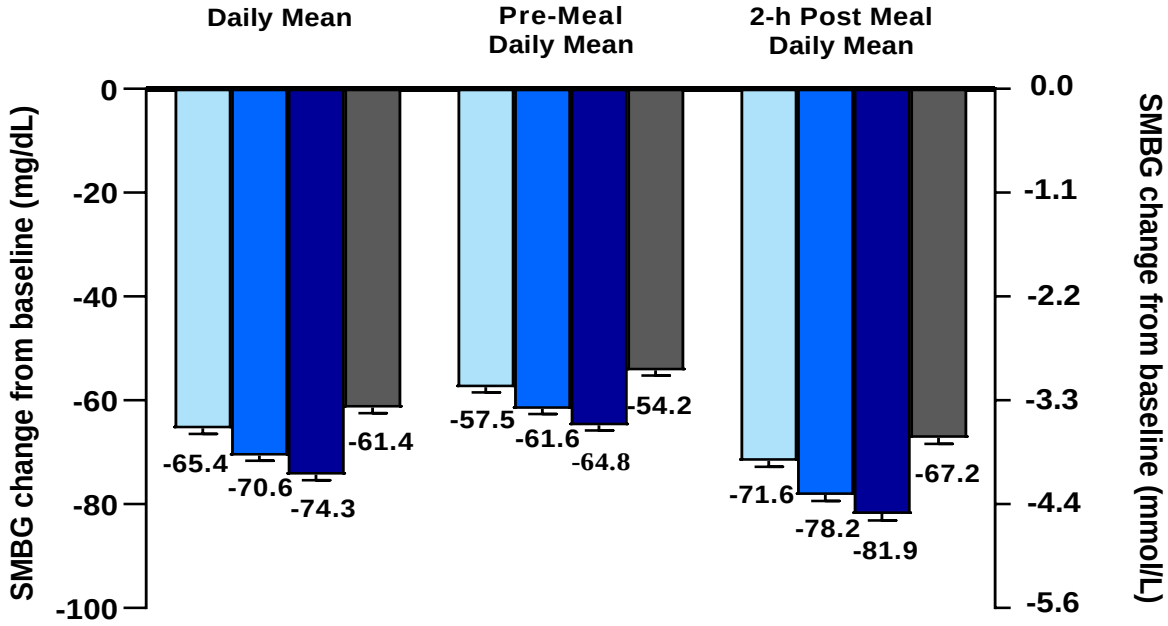
7-Point SMBG at Baseline and 40 Weeks

SURPASS-2

A. 7-point SMBG Profile at Baseline and at 40 Weeks



B. SMBG Change from Baseline at 40 Weeks



Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg Semaglutide 1 mg

Note: Data are LSM (SE); MMRM analysis (40 weeks). mITT population (efficacy analysis set). (A) 7-Point SMBG at baseline and 40 weeks. Dotted lines represent baseline values. ANOVA analysis (baseline) and MMRM analysis (40 weeks). (B). Daily mean, pre-meal daily mean and 2-h post meal daily mean SMBG change from baseline at 40 weeks.

ANOVA=Analysis of Variance; LSM=Least Squares Mean; mITT=Modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; SE=Standard Error; SMBG=Self-Monitoring of Blood Glucose.

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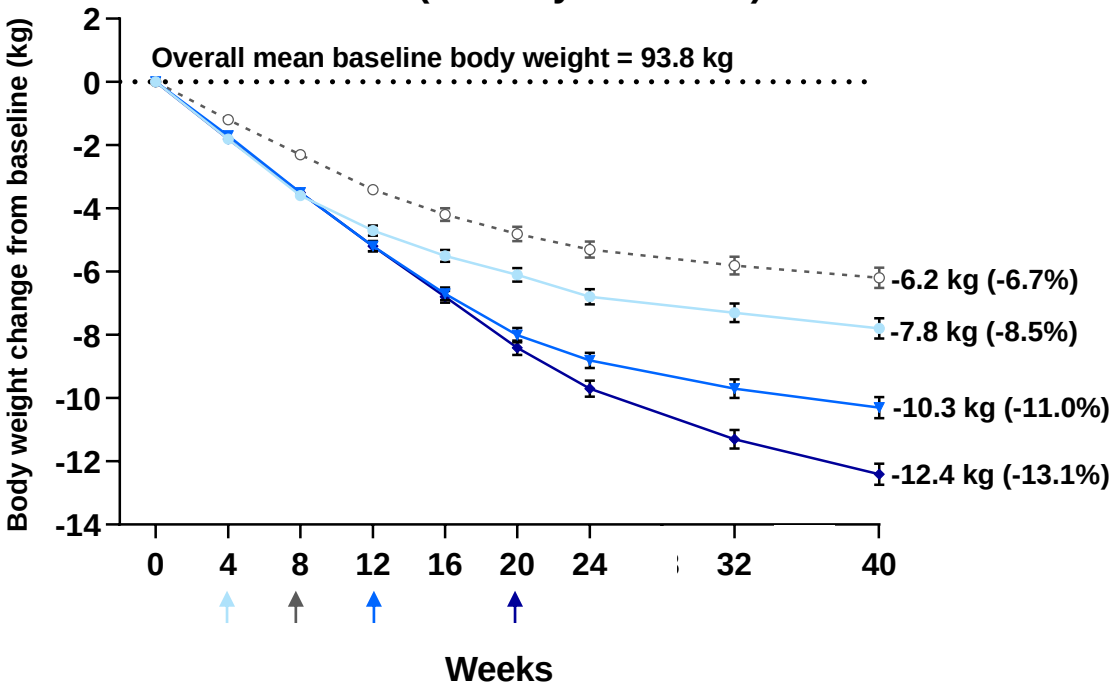
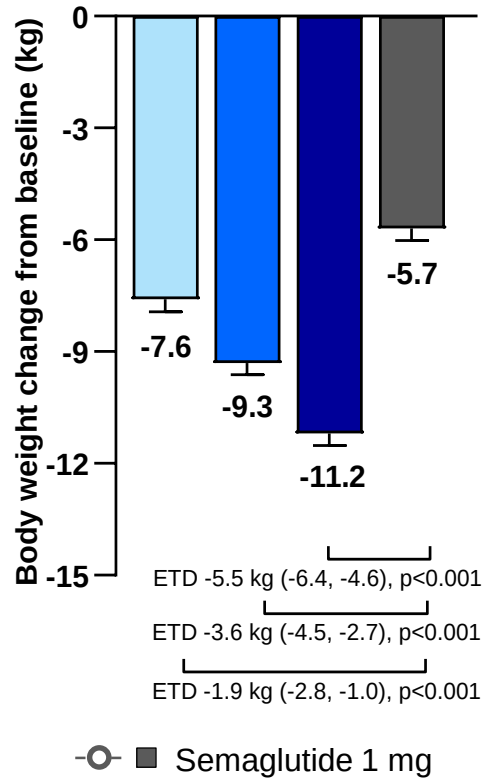
Change in Body Weight at 40 Weeks

SURPASS-2

A. Change from Baseline in Body Weight Over Time at 40 Weeks (Efficacy Estimand)



B. Change from baseline in body weight at 40 weeks (Treatment-Regimen Estimand)



Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg Semaglutide 1 mg

Note: Data are LSM (SE), unless otherwise noted. Estimated treatment differences are LSM (95% confidence interval) at 40 weeks, mITT population. mITT (efficacy estimand) ANCOVA analysis (week 0) and MMRM analysis (week 40). Arrows indicate when the maintenance dose of Tirzepatide 5 mg, 10 mg and 15 mg and Semaglutide 1 mg are achieved. (A) Change from baseline in body weight over time from MMRM analysis (efficacy estimand). Percent change from baseline values at 40 weeks are in parentheses. (B) Change from baseline in body weight at 40 weeks from ANCOVA with multiple imputation by treatment for missing weight at 40 weeks (treatment-regimen estimand). Estimated treatment difference (95% CI) of Tirzepatide vs Semaglutide was: i) 5 mg -1.7** (-2.6, -0.7), ii) 10 mg -4.1** (-5.0, -3.2), and iii) 15 mg -6.2** (-7.1, -5.3). *p<0.05 and **p<0.001 vs. Semaglutide 1 mg at 40 weeks
ANCOVA=Analysis of Covariance; LSM=Least Squares Mean; mITT=Modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; SE=Standard Error.

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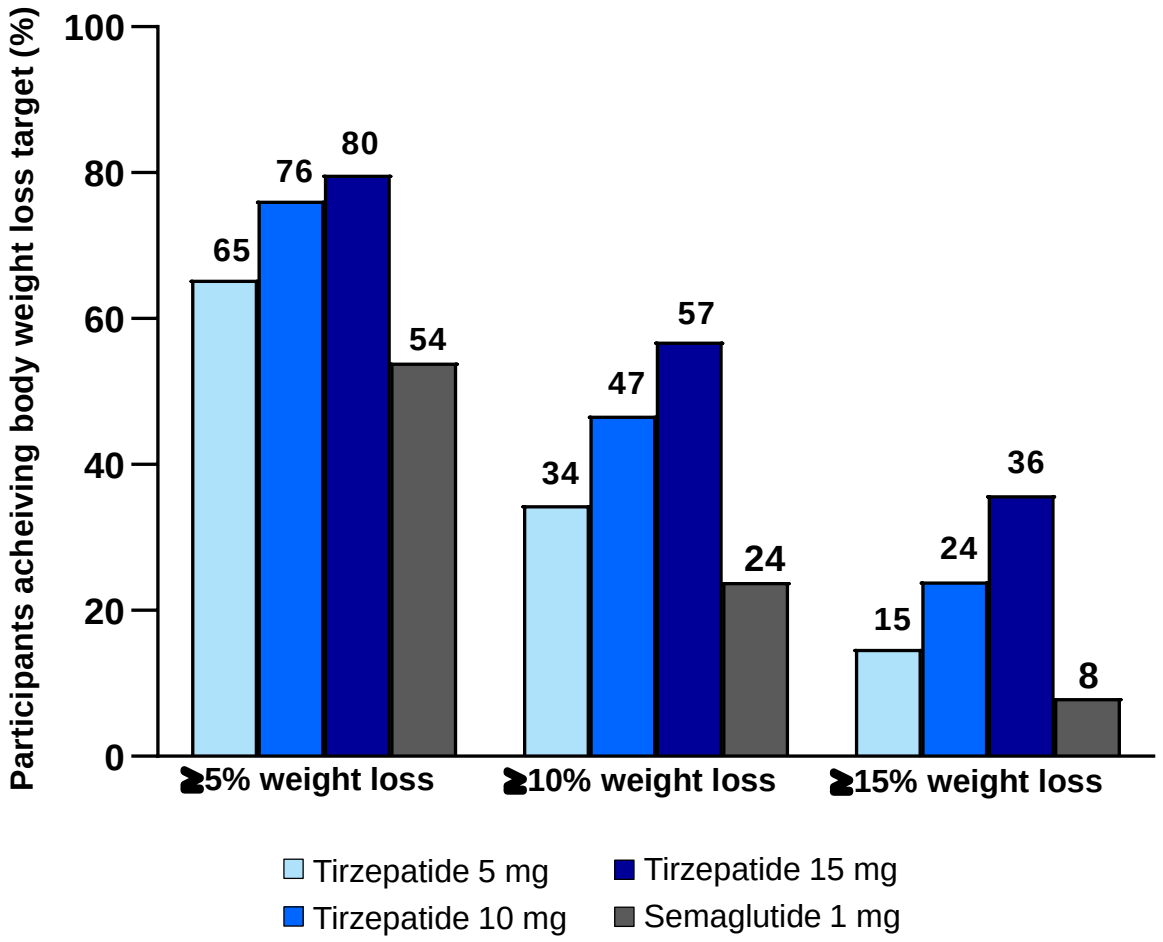
Proportion of Participants Achieving Weight Loss ≥5%, ≥10%, ≥15%: Treatment-Regimen Estimand

SURPASS-2



Note: mITT population. Proportion of participants achieving weight loss ≤5%, ≤10% and ≤15% (treatment-regimen estimand). Proportion was obtained by dividing the number of participants reaching respective goals at Week 40 by the number of participants with baseline value and at least one non-missing postbaseline value. Missing value at Week 40 was predicted from MMRM analysis.

mITT=Modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures.

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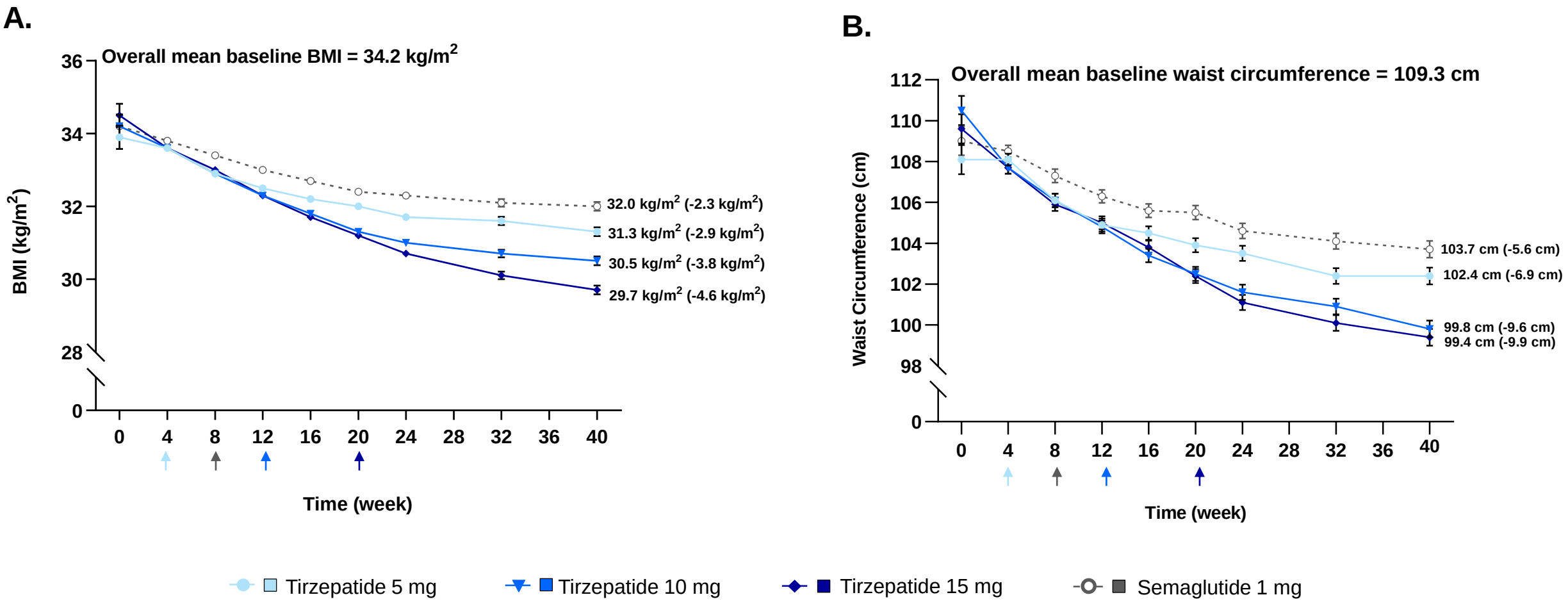
Mean BMI and Mean Waist Circumference Over Time

SURPASS-2



Note: Data are LSM (SE), mITT population (efficacy analysis set). Arrows indicate when the maintenance dose of tirzepatide 5 mg, 10 mg and 15 mg are and semaglutide 1 mg achieved. (A) Mean BMI over time. Change from baseline in mean BMI at 40 weeks are in parentheses. (B) Mean waist circumference over time. Change from baseline in mean waist circumference at 40 weeks are in parentheses.

BMI=Body Mass Index; LSM=Least Squares Mean; mITT=Modified Intent-to-Treat; SE=Standard Error.

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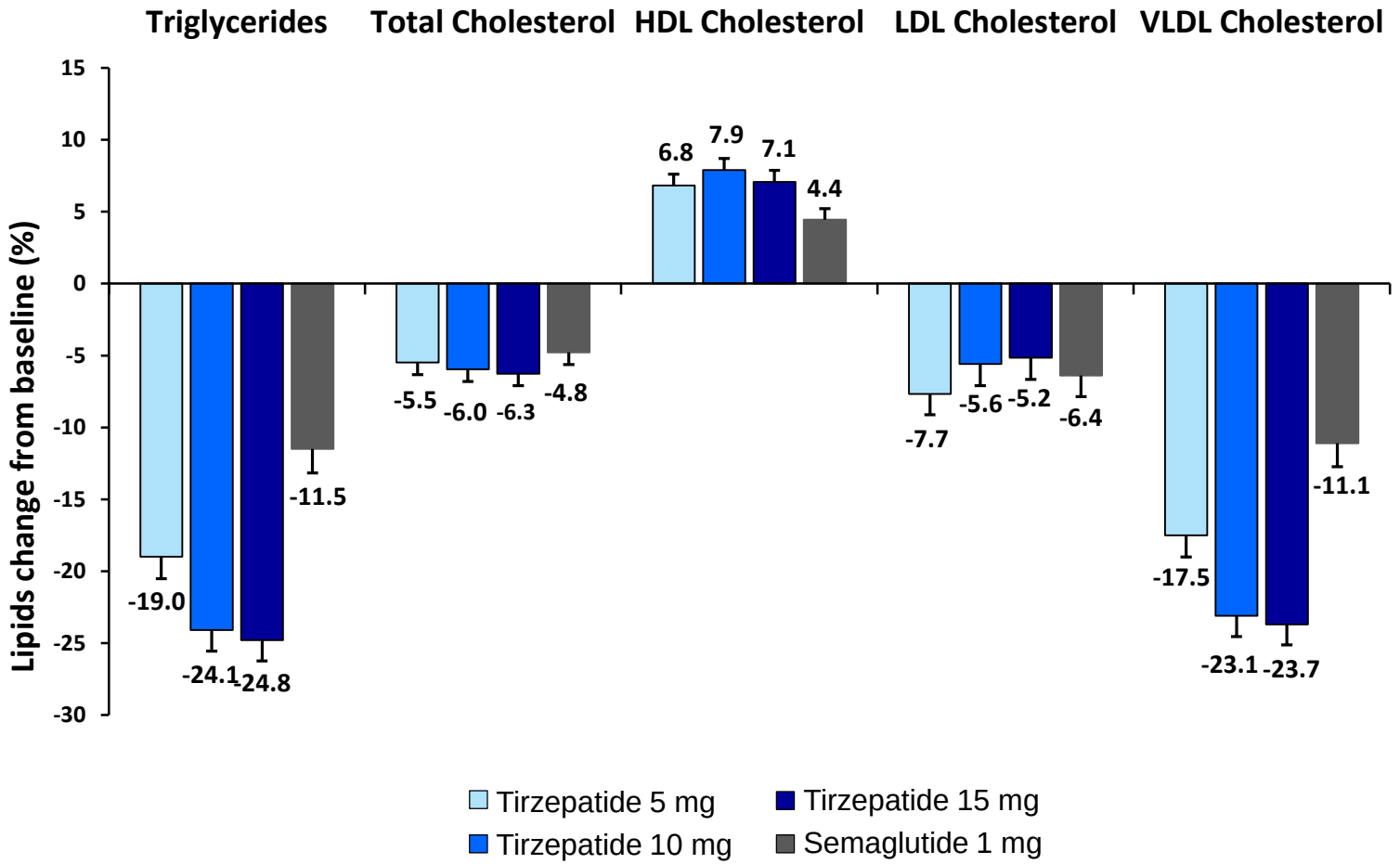
Percent Change from Baseline in Lipids at 40 Weeks

SURPASS-2



Note: MMRM analysis, mITT population (efficacy analysis set). Data estimated percent means (SE) using log transformation.

BMI=Body Mass Index; HDL=High-Density Lipoprotein; LDL=Low-Density Lipoprotein; LSM=Least Squares Mean; mITT=Modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; SE=Standard Error; VLDL=Very Low-Density Lipoprotein.

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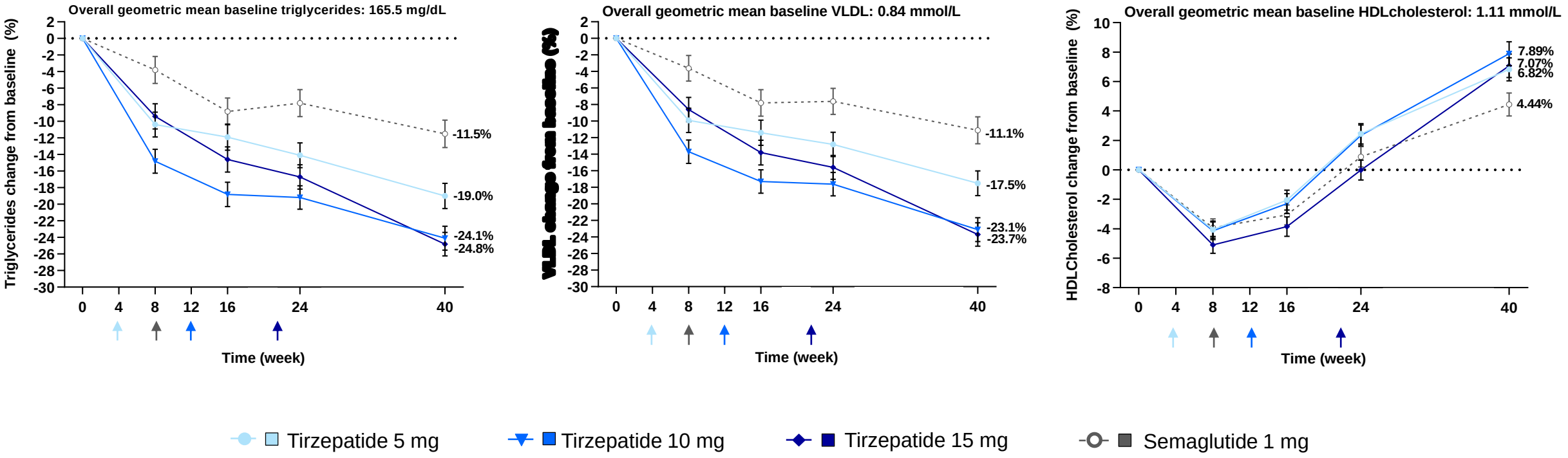
Percent Change from Baseline in Triglycerides, VLDL and HDL Cholesterol Over Time

SURPASS-2



Note: Data are estimate (SE) from MMRM analysis using log transformation, mITT (efficacy analysis set). Arrows indicate when the maintenance dose of tirzepatide 5 mg, 10 mg and 15 mg and semaglutide 1 mg are achieved.
HDL=High-Density Lipoprotein; mITT=Modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; SE=Standard Error; VLDL=Very Low-Density Lipoprotein.
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Overview of Adverse Events

SURPASS-2

Parameters	Tirzepatide 5 mg N=470	Tirzepatide 10 mg N=469	Tirzepatide 15 mg N=470	Semaglutide 1 mg N=469	Total N=1878
Participants with ≥1 TEAE	299 (63.6)	322 (68.7)	324 (68.9)	301 (64.2)	1246 (66.3)
Participants with ≥1 SAEs	33 (7.0)	25 (5.3)	27 (5.7)	13 (2.8)	98 (5.2)
Deaths[a]	4 (0.9)	4 (0.9)	4 (0.9)	1 (0.2)	13 (0.7)
AEs leading to discontinuation of tirzepatide or semaglutide	28 (6.0)	40 (8.5)	40 (8.5)	19 (4.1)	127 (6.8)
AEs occurring in ≥5% of patients in any treatment group					
Nausea	82 (17.4)	90 (19.2)	104 (22.1)	84 (17.9)	360 (19.2)
Diarrhoea	62 (13.2)	77 (16.4)	65 (13.8)	54 (11.5)	258 (13.7)
Vomiting	27 (5.7)	40 (8.5)	46 (9.8)	39 (8.3)	152 (8.1)
Dyspepsia	34 (7.2)	29 (6.2)	43 (9.1)	31 (6.6)	137 (7.3)
Decreased appetite	35 (7.4)	34 (7.2)	42 (8.9)	25 (5.3)	136 (7.2)
Constipation	32 (6.8)	21 (4.5)	21 (4.5)	27 (5.8)	101 (5.4)
Abdominal pain	14 (3.0)	21 (4.5)	24 (5.1)	24 (5.1)	83 (4.4)
All gastrointestinal AEs	188 (40.0)	216 (46.1)	211 (44.9)	193 (41.2)	808 (43.0)

[a]Deaths are also included as SAEs and discontinuations due to AE.

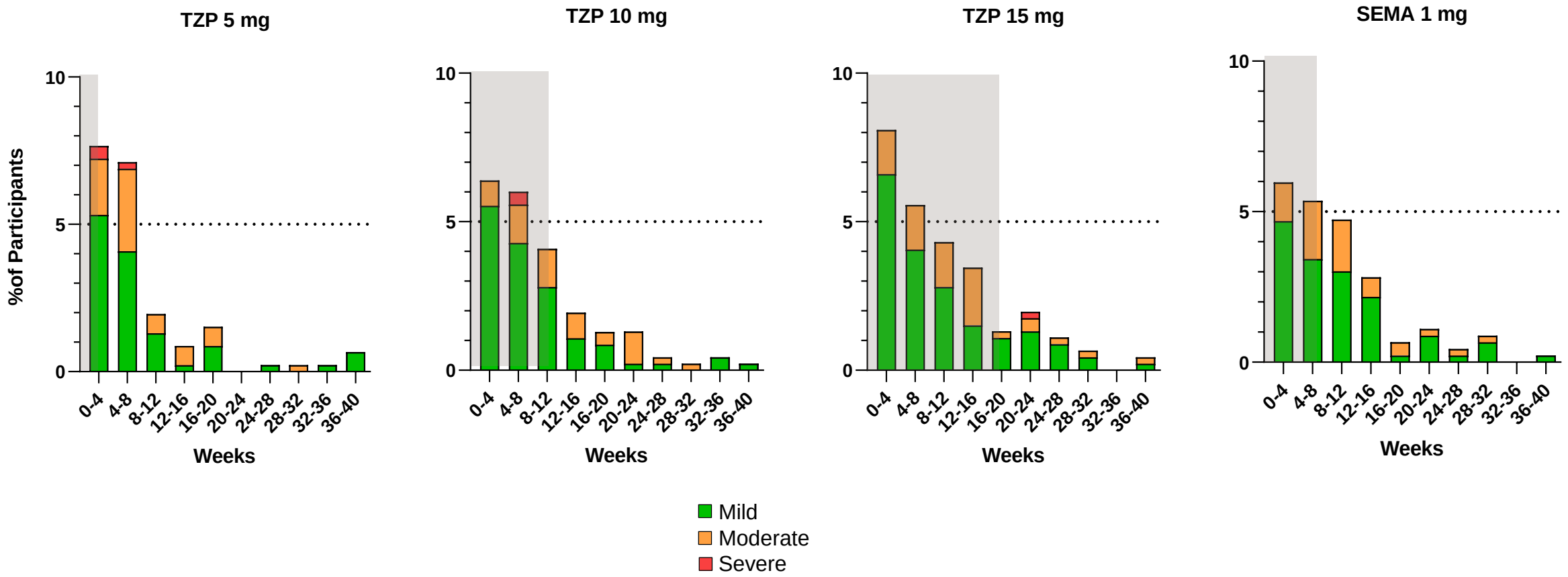
Note: Data are n (%); mITT population (safety analysis set). Patients may be counted in more than 1 category.

AE=Adverse Event; SAEs=Serious Adverse Events; TEAE=Treatment-Emergent Adverse Event.

Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.

Incidence of Nausea

SURPASS-2



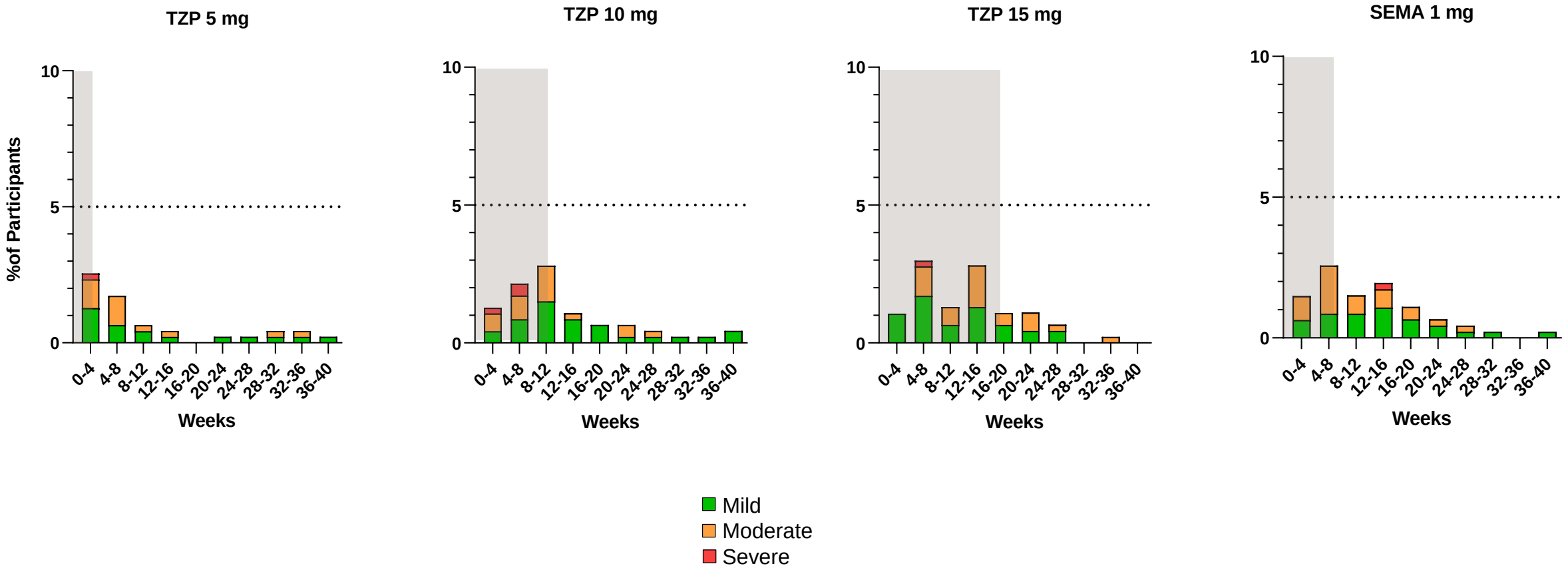
Note: Data are percent of participants who reported a new event relative to participants at risk during a time interval; mITT population (safety analysis set). Incidence refers to the proportion of participants who have a new event during a time interval. Shaded areas indicate the period of time before reaching the maintenance dose of the study treatments.

SEMA=Semaglutide; TZP=Tirzepatide.

Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.

Incidence of Vomiting

SURPASS-2



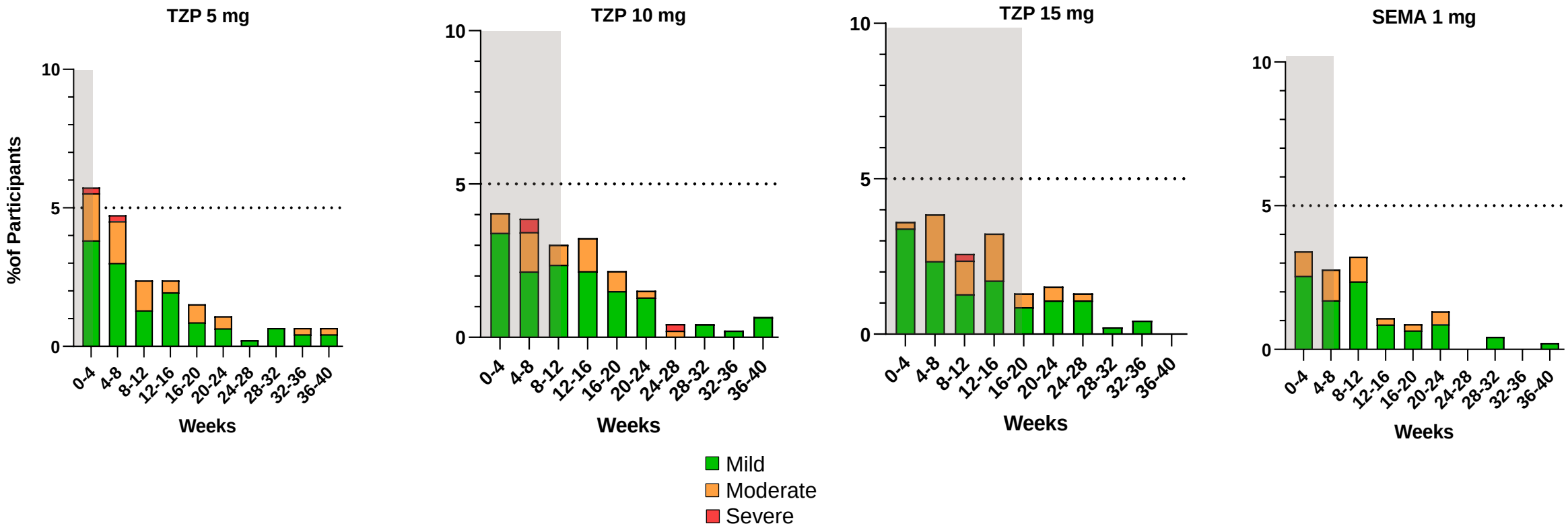
Note: Data are percent of participants who reported a new event relative to participants at risk during a time interval; mITT population (safety analysis set). Incidence refers to the proportion of participants who have a new event during a time interval. Shaded areas indicate the period of time before reaching the maintenance dose of the study treatments.

SEMA=Semaglutide; TZP=Tirzepatide.

Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.

Incidence of Diarrhoea

SURPASS-2



Note: Data are percent of participants who reported a new event relative to participants at risk during a time interval; mITT population (safety analysis set). Incidence refers to the proportion of participants who have a new event during a time interval. Shaded areas indicate the period of time before reaching the maintenance dose of the study treatments.
SEMA=Semaglutide; TZP=Tirzepatide.
Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.

Hypoglycaemia and Other TEAEs of Interest

SURPASS-2

Parameters	Tirzepatide 5 mg N=470	Tirzepatide 10 mg N=469	Tirzepatide 15 mg N=470	Semaglutide 1 mg N=469	Total N=1878
Hypoglycaemia (blood glucose <54 mg/dL)	3 (0.6)	1 (0.2)	8 (1.7)	2 (0.4)	14 (0.7)
Severe hypoglycaemia	1 (0.2)	0	1 (0.2)[a]	0	2 (0.1)
Adverse events of special interest					
Injection site reaction	9 (1.9)	13 (2.8)	21 (4.5)	1 (0.2)	44 (2.3)
Hypersensitivity[b]	9 (1.9)	13 (2.8)	8 (1.7)	11 (2.3)	41 (2.2)
Adjudicated pancreatitis	0	2 (0.4)	2 (0.4)	3 (0.6)	7 (0.4)
Cholelithiasis	4 (0.9)	4 (0.9)	4 (0.9)	2 (0.4)	14 (0.7)
Cholecystitis acute	1 (0.2)	2 (0.4)	2 (0.4)	0	5 (0.3)
Diabetic retinopathy[c]	0	2 (0.4)	0	0	2 (0.1)

[a]One participant randomised to tirzepatide 15 mg had an event of hypoglycaemia that was not considered severe by the investigator but was reported as an SAE. [b]Include immediate (<24 hours after study drug administration) and non-immediate (>24 hours after study drug administration) hypersensitivity events. One immediate event was reported in the tirzepatide 15 mg group. [c]Confirmed by fundoscopic examination.

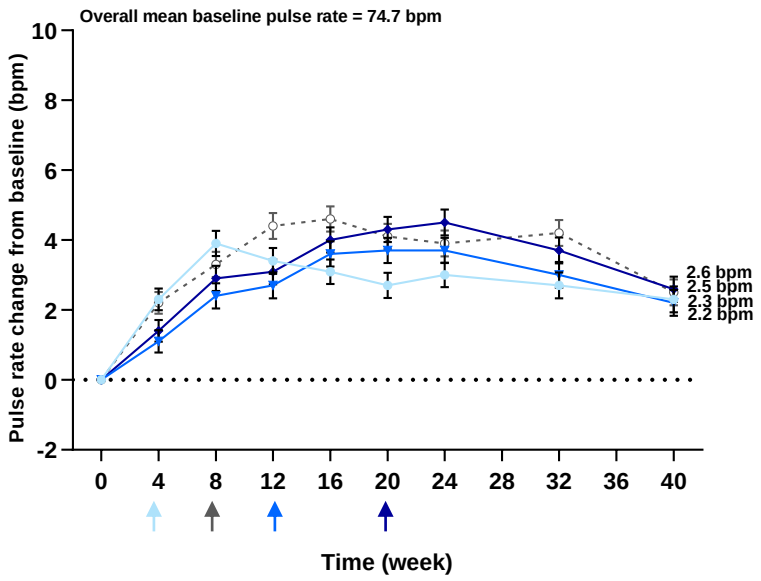
Note: Data are n (%), unless otherwise specified; mITT population. No clinically relevant changes in mean calcitonin levels were observed and no cases of medullary thyroid cancer were reported.

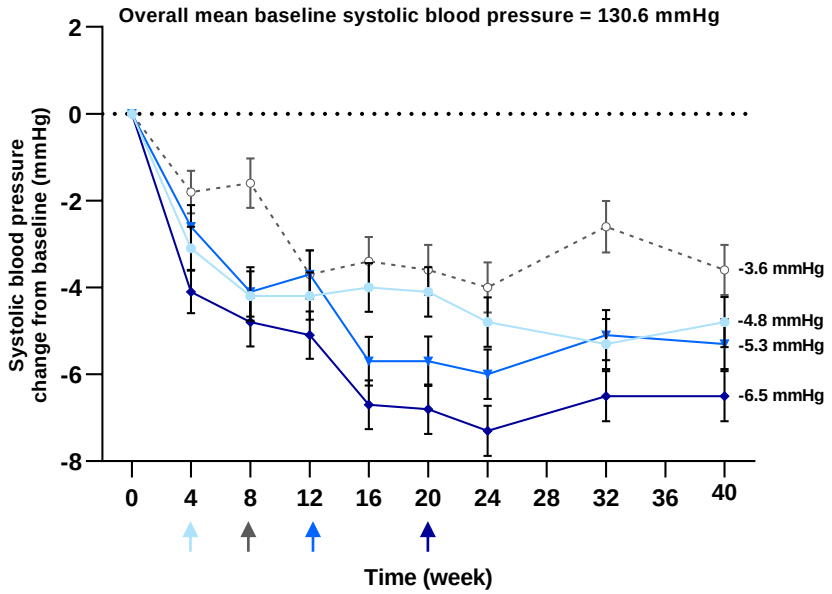
mITT=Modified Intention-to-Treat; SAE=Serious Adverse Event; TEAE=Treatment-Emergent Adverse Event.

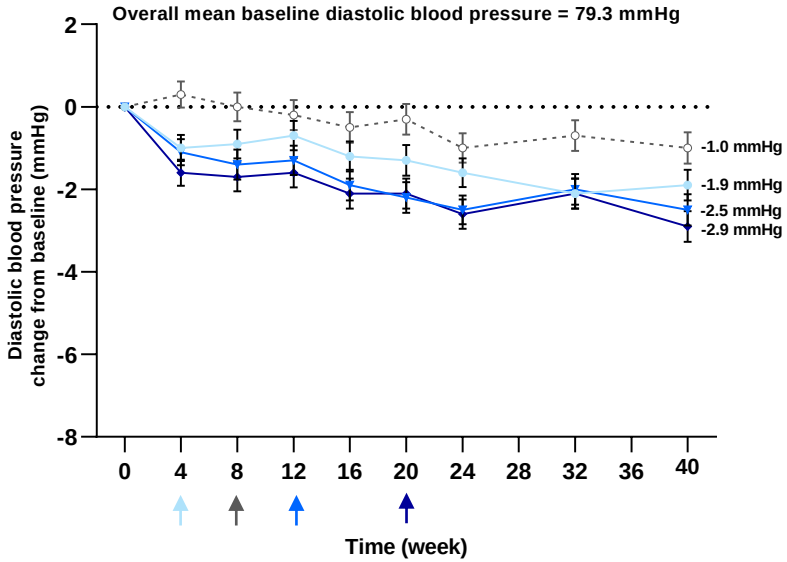
Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.

Change from Baseline in Pulse Rate and Blood Pressure Over Time

SURPASS-2







Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg Semaglutide 1 mg

Note: Data are LSM (SE); mITT population (safety analysis set). Arrows indicate when the maintenance dose of tirzepatide 5 mg, 10 mg and 15 mg and semaglutide 1 mg are achieved.
LSM=Least Squares Mean; mITT=Modified Intent-to-Treat; SE=Standard Error.
Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.

Conclusion

SURPASS-2

- In people with T2D inadequately controlled on metformin monotherapy, once weekly tirzepatide, a dual GIP/GLP-1 receptor agonist, demonstrated:
  - superior and clinically meaningful improvements in glycaemic control
  - significant reduction in body weight
  - achievements of HbA1c reflecting normoglycaemia (<5.7%) in up to 51% of participants
  - low risk of hypoglycaemia (blood glucose <54 mg/dL or severe)

GIP=Glucose-Dependent Insulinotropic Polypeptide; GLP=Glucagon-Like Peptide; HbA1c=Glycated Haemoglobin; T2D=Type 2 Diabetes.

Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.

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Back-Up

Number of Participants Enroled Per Country

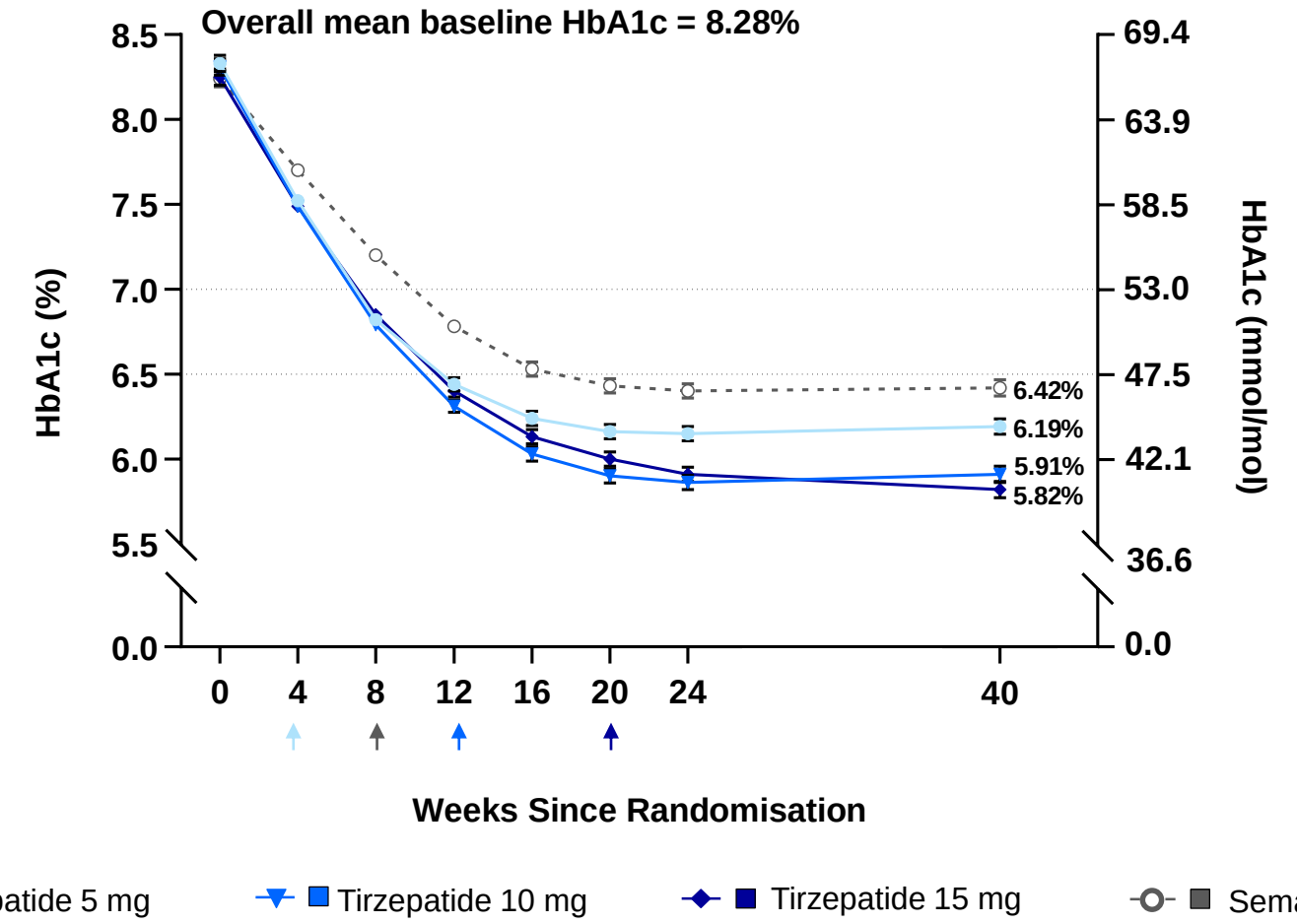
SURPASS-2

Country	Enrolled (%)
Argentina	641 (34.1)
Australia	46 (2.4)
Brazil	147 (7.8)
Canada	59 (3.1)
Israel	87 (4.6)
Mexico	352 (18.7)
United Kingdom	72 (3.8)
United States	475 (25.3)

Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.

HbA1c Over Time: Efficacy Estimand

SURPASS-2



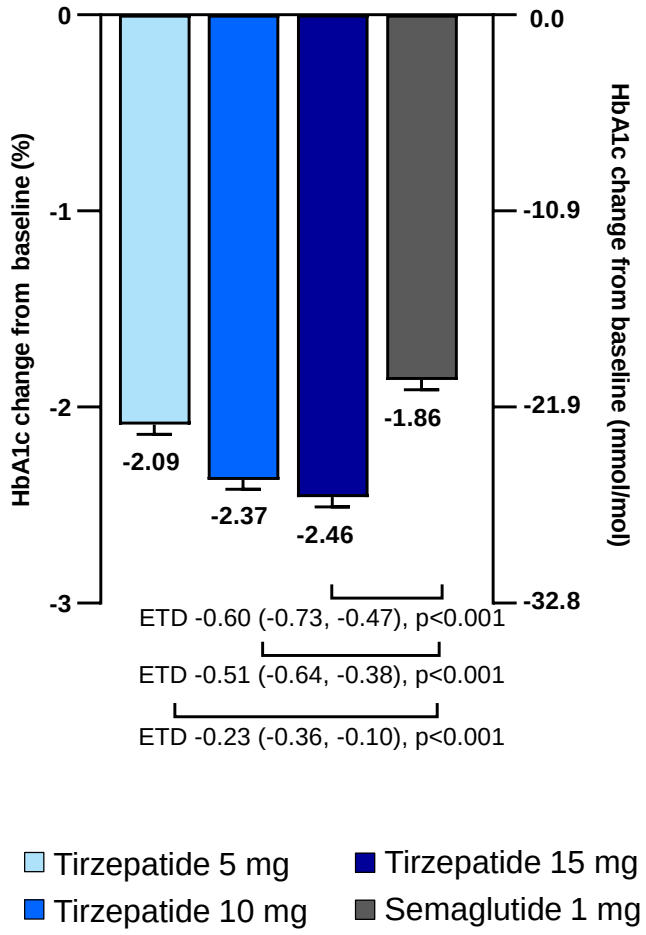
Note: Data are LSM (SE); mITT (efficacy estimand) ANCOVA analysis (week 0) and MMRM analysis (week 40). HbA1c values over time from MMRM analysis (efficacy estimand). Arrows indicate when the maintenance dose of tirzepatide 5 mg, 10 mg and 15 mg and semaglutide 1 mg are achieved. Estimated treatment difference (95% CI) of Tirzepatide vs Semaglutide was: i) 5 mg -0.23** (-0.36, -0.10), ii) 10 mg -0.51** (-0.64, -0.38), and iii) 15 mg -0.60** (-0.73, -0.47). *p<0.05 and **p<0.001 vs. Semaglutide 1 mg at 40 weeks.

ANCOVA=Analysis of Covariance; HbA1c=Glycated Haemoglobin; LSM=Least Squares Mean; mITT=Modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; SE=Standard Error.

Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.

Change in HbA1c at 40 Weeks: Efficacy Estimand

SURPASS-2



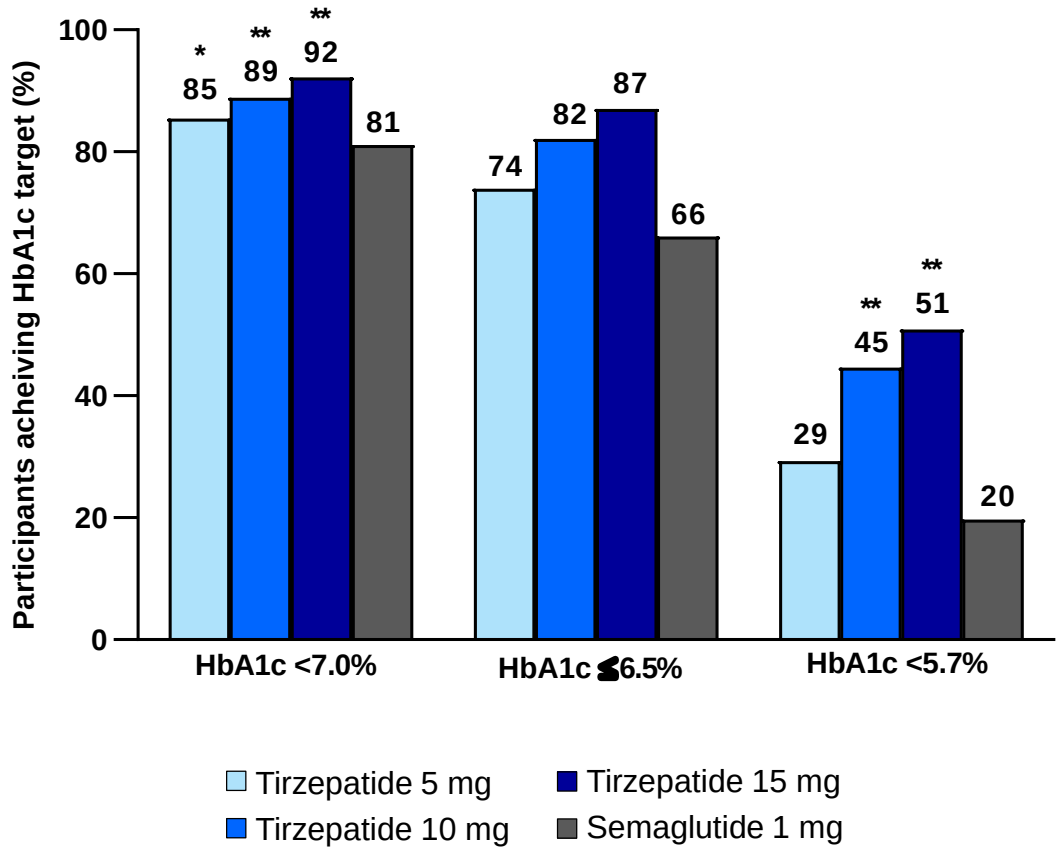
Note: Data are LSM (SE), unless otherwise noted. Estimated treatment differences are LSM (95% confidence interval) at 40 weeks, mITT population (efficacy analysis set). MMRM analysis. ***P*<0.001 versus Semaglutide 1 mg at 40 weeks.

ETD: Estimated Treatment Difference; HbA1c=Glycated Haemoglobin; LSM=Least Squares Mean; mITT=Modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; SE=Standard Error.

Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.

Proportion of Participants Achieving HbA1c Targets <7.0%, ≤6.5% and <5.7%: Efficacy Estimand

SURPASS-2



*p<0.05 and **p<0.001 versus semaglutide 1 mg at 40 weeks.

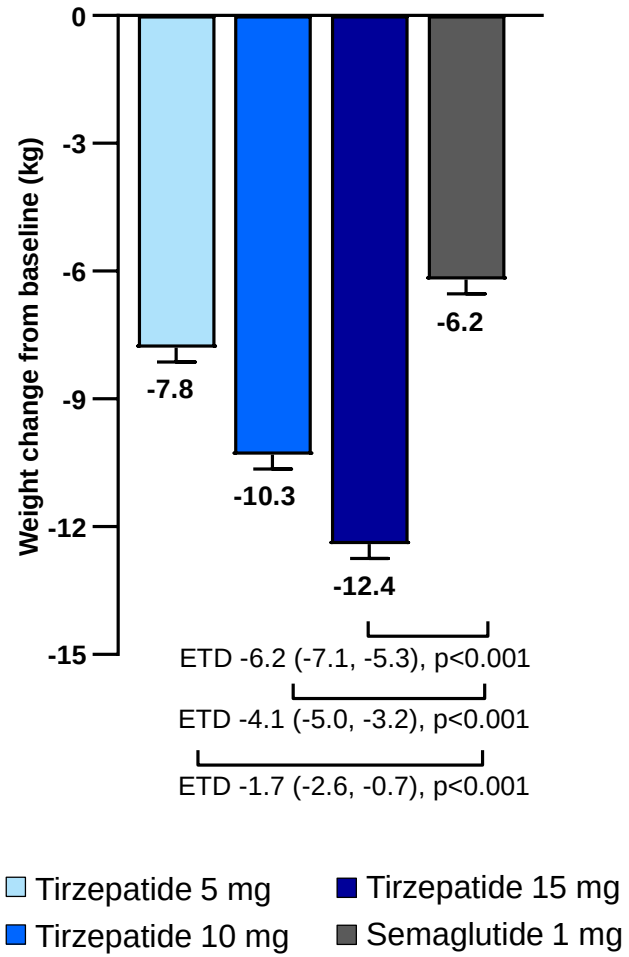
Note: mITT population (efficacy analysis set). Proportion of participants achieving HbA1c targets <7.0%, ≤6.5% and <5.7% was obtained by dividing the number of participants reaching respective goals at Week 40 by the number of participants with baseline value and at least one non-missing postbaseline value. Missing value at Week 40 was predicted from MMRM analysis. HbA1c ≤6.5% and 5.7% (tirzepatide 5 mg only) were not controlled for type 1 error, thus p-values were not presented.

HbA1c=Glycated Haemoglobin; mITT=Modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; SE=Standard Error.

Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.

Change in Body Weight at 40 Weeks: Efficacy Estimand

SURPASS-2



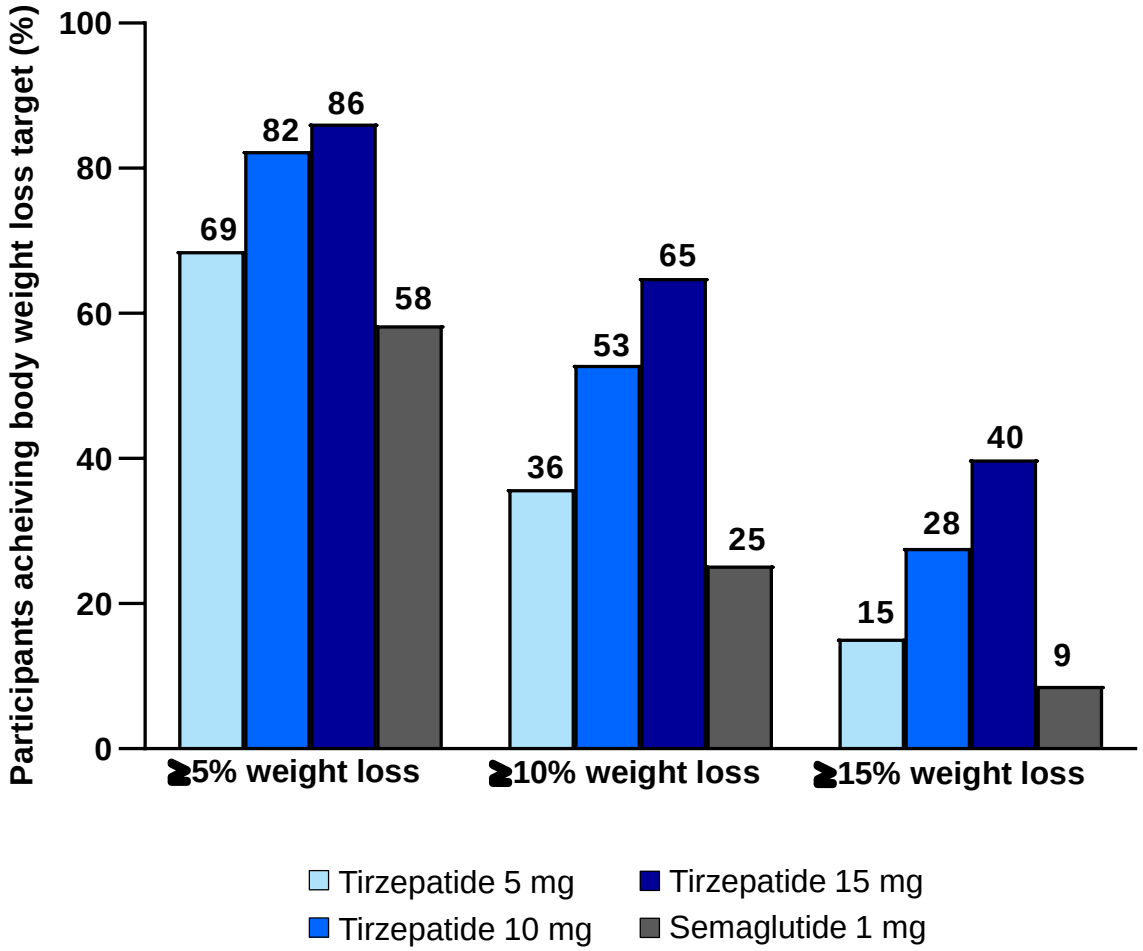
Note: Data are LSM (SE), unless otherwise noted. Estimated treatment differences are LSM (95% confidence interval) at 40 weeks, mITT population (efficacy analysis set). MMRM analysis. ***P*<0.001 versus Semaglutide 1 mg at 40 weeks.

ETD=Estimated Treated Difference; LSM-Least Squares Mean; mITT=Modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; SE=Standard Error.

Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.

Proportion of Participants Achieving Weight Loss ≥5%, ≥10%, ≥15%: Efficacy Estimand

SURPASS-2



Note: mITT population (efficacy analysis set). Proportion of participants achieving weight loss ≤5%, ≤10% and ≤15% was obtained by dividing the number of participants reaching respective goals at Week 40 by the number of participants with baseline value and at least one non-missing postbaseline value. Missing value at Week 40 was predicted from MMRM analysis.

mITT=Modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; SE=Standard Error.

Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.

AEs Occurring in at least 0.2% of the Overall Population

SURPASS-2

Parameters	Tirzepatide 5 mg N=470 n (%)	Tirzepatide 10 mg N=469 n (%)	Tirzepatide 15 mg N=470 n (%)	Semaglutide 1 mg N=469 n (%)	Total N=1878 n (%)
AEs occurring in at least 0.2% of the overall population (i.e., 3 participants) leading to study treatment discontinuation					
Nausea	6 (1.3)	7 (1.5)	4 (0.9)	4 (0.9)	21 (1.1)
Vomiting	1 (0.2)	4 (0.9)	4 (0.9)	3 (0.6)	12 (0.6)
Diarrhoea	1 (0.2)	3 (0.6)	6 (1.3)	1 (0.2)	11 (0.6)
Abdominal pain	2 (0.4)	1 (0.2)	2 (0.4)	4 (0.9)	9 (0.5)
Dyspepsia	2 (0.4)	1 (0.2)	2 (0.4)	0	5 (0.3)
Decreased appetite	1 (0.2)	2 (0.4)	2 (0.4)	0	5 (0.3)
Fatigue	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	4 (0.2)
Blood calcitonin increased	1 (0.2)	1 (0.2)	1 (0.2)	0	3 (0.2)
Constipation	0	2 (0.4)	0	1 (0.2)	3 (0.2)
COVID-19 pneumonia	1 (0.2)	1 (0.2)	0	1 (0.2)	3 (0.2)
Injection site reaction	0	2 (0.4)	1 (0.2)	0	3 (0.2)

Note: Data are n (%); mITT population (safety analysis set). Patients may be counted in more than 1 category.
AE=Adverse Event; COVID-19. Coronavirus 19; mITT=Modified Intention-to-Treat.
Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.

Reported Deaths During the Study (1 of 2)

SURPASS-2

Patient (age, sex)	Treatment Group	Baseline BMI (kg/m^2)	CV Risk Factors (apart from T2D)	Description	Days from Randomisation	Days since Last Dose of Study Drug	Adjudication Cause of Death[a]
59 y, male	Tirzepatide 5 mg	32.4	HTN, HLD, prior MI, CABG, HF, former tobacco user	Cardiac arrest and respiratory arrest	23	23	CV
53 y, female	Tirzepatide 5 mg	39.2	HLD, CAD, prior MI, CABG, former tobacco user	Death (natural causes- CAD)	85	7	Undetermined
59 y, female	Tirzepatide 5 mg	35.8	HTN	COVID-19 pneumonia	241	31	Infection
53 y, male	Tirzepatide 5 mg	49.5	HTN, HLD	Pyelonephritis and nephrolithiasis leading to septic shock	35	14	Infection
75 y, female	Tirzepatide 10 mg	39.2	HTN, Afib, HF, former tobacco user	End stage renal failure, nephrotic syndrome, minimal change disease, portal vein thrombosis and potential renal carcinoma	174	76	Malignancy
58 y, male	Tirzepatide 10 mg	28.0	Current tobacco user	Sudden death (natural causes- cardiogenic shock)	271	54	CV

[a]All deaths were adjudicated by an external committee of physicians with cardiology expertise.

Afib=Atrial Fibrillation; BMI=Body Mass Index; CABG=Coronary Artery Bypass Grafting; CAD=Coronary Artery Disease; COVID-19=Coronavirus 2019; CV=Cardiovascular; HLD=Hyperlipidaemia; HF=Heart Failure; HTN=Hypertension; MI=Myocardial Infarction; T2D=Type 2 Diabetes; y=Years.

Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.

Reported Deaths During the Study (2 of 2)

SURPASS-2

Patient (age, sex)	Treatment Group	Baseline BMI (kg/m^2)	CV Risk Factors (apart from T2D)	Description	Days from Randomisation	Days since Last Dose of Study Drug	Adjudication Cause of Death[b]
43 y, female	Tirzepatide 10 mg	37.9	HTN	COVID-19 pneumonia	248	10	Infection
55 y, female	Tirzepatide 10 mg	34.9	HTN	COVID-19	235	67	Undetermined
65 y, male	Tirzepatide 15 mg	30.7	HTN, HLD, prior MI, CAD, brain aneurysm, former tobacco user	Acute myocardial infarction	120	15	CV
69 y, male	Tirzepatide 15 mg	25.9	HTN, HLD, prior stroke	Suspected COVID-19 (family exposure to COVID-19 developed symptoms and died within two hours of arriving to the hospital without COVID-19 testing)	240	211[a]	CV
60 y, female	Tirzepatide 15 mg	39.5	HTN, prior stroke	COVID-19 pneumonia	268	15	Infection
65 y, male	Tirzepatide 15 mg	27.0	None	Cerebrovascular accident	74	4	CV
63 y, female	Semaglutide 1 mg	44.7	HLD	COVID-19 bilateral pneumonia	194	26	Pulmonary

[a]The patient who died from suspected COVID-19 discontinued the study drug prior to the event. [b]All deaths were adjudicated by an external committee of physicians with cardiology expertise.

Afib=Atrial Fibrillation; BMI=Body Mass Index; CABG=Coronary Artery Bypass Grafting; CAD=Coronary Artery Disease; COVID-19=Coronavirus 2019; CV=Cardiovascular; HLD=Hyperlipidaemia; HF=Heart Failure; HTN=Hypertension; MI=Myocardial Infarction; T2D=Type 2 Diabetes; y=Years.

Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.

Serious Adverse Events

SURPASS-2

Parameters	Tirzepatide 5 mg N=470	Tirzepatide 10 mg N=469	Tirzepatide 15 mg N=470	Semaglutide 1 mg N=469	Total N=1878
Serious AEs reported in ≥2 participants	13 (2.8)	11 (2.3)	15 (3.2)	7 (1.5)	46 (2.4)
COVID-19 pneumonia	2 (0.4)	2 (0.4)	2 (0.4)	4 (0.9)	10 (0.5)
Cholecystitis acute	1 (0.2)	2 (0.4)	2 (0.4)	0	5 (0.3)
Acute myocardial infarction	2 (0.4)	0	2 (0.4)	0	4 (0.2)
Pneumonia	1 (0.2)	0	1 (0.2)	1 (0.2)	3 (0.2)
Abdominal pain upper	1 (0.2)	0	1 (0.2)	0	2 (0.1)
Atrial fibrillation	2 (0.4)	0	0	0	2 (0.1)
Bacteraemia	0	1 (0.2)	0	1 (0.2)	2 (0.1)
COVID-19	0	1 (0.2)	0	1 (0.2)	2 (0.1)
Cardio-respiratory arrest	1 (0.2)	0	1 (0.2)	0	2 (0.1)
Cerebrovascular accident	0	0	2 (0.4)	0	2 (0.1)
Chest pain	0	1 (0.2)	1 (0.2)	0	2 (0.1)
Hypoglycaemia	1 (0.2)	0	1 (0.2)	0	2 (0.1)
Nephrolithiasis	1 (0.2)	1 (0.2)	0	0	2 (0.1)
Pleural effusion	1 (0.2)	0	1 (0.2)	0	2 (0.1)
Syncope	0	1 (0.2)	1 (0.2)	0	2 (0.1)
Urinary tract infection	0	2 (0.4)	0	0	2 (0.1)

Note: Data are n (%); mITT population (safety analysis set).
AE=Adverse Event; COVID-19=Coronavirus 19; mITT=Modified Intention-to-Treat.
Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.

Gastrointestinal Adverse Events by Maximum Severity

SURPASS-2

Adverse Event Maximum Severity	Tirzepatide 5 mg N=470	Tirzepatide 10 mg N=469	Tirzepatide 15 mg N=470	Semaglutide 1 mg N=469	Total N=1878
Diarrhoea					
Mild	18 (3.8)	16 (3.4)	16 (3.4)	12 (2.6)	62 (3.3)
Moderate	8 (1.7)	3 (0.6)	1 (0.2)	4 (0.9)	16 (0.9)
Severe	1 (0.2)	0	0	0	1 (0.1)
Nausea					
Mild	25 (5.3)	26 (5.5)	31 (6.6)	22 (4.7)	104 (5.5)
Moderate	9 (1.9)	4 (0.9)	7 (1.5)	6 (1.3)	26 (1.4)
Severe	2 (0.4)	0	0	0	2 (0.1)
Vomiting					
Mild	6 (1.3)	2 (0.4)	5 (1.1)	3 (0.6)	16 (0.9)
Moderate	5 (1.1)	3 (0.6)	0	4 (0.9)	12 (0.6)
Severe	1 (0.2)	1 (0.2)	0	0	2 (0.1)

Note: Data are n (%); mITT population (safety analysis set).
AE=Adverse Event; mITT=Modified Intention-to-Treat.
Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.

Treatment-Emergent Diabetic Retinopathy Complications

SURPASS-2

Event Category Preferred Term	Tirzepatide 5 mg N=470	Tirzepatide 10 mg N=469	Tirzepatide 15 mg N=470	Semaglutide 1 mg N=469
Participants with ≥1 TEAE of diabetic retinopathy complications	5 (1.1)	3 (0.6)	2 (0.4)	2 (0.4)
Macular oedema	3 (0.6)	2 (0.4)	0	0
Vision blurred	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Diabetic retinopathy	0	2 (0.4)	0	0
Diabetic hypertensive	1 (0.2)	0	1 (0.2)	0
Maculopathy	0	0	0	1 (0.2)
Retinal vein occlusion	1 (0.2)	0	0	0

Note: Data are n (%); mITT population (safety analysis set).
mITT=Modified Intention-to-Treat; N=Number of Participants in the Population; TEAE=Treatment-Emergent Adverse Events.
Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.

Additional Laboratory Measures at Baseline and 40 Weeks (1 of 3)

SURPASS-2

Parameters	Tirzepatide 5 mg N=470	Tirzepatide 10 mg N=469	Tirzepatide 15 mg N=470	Semaglutide 1 mg N=469
ALT[a]				
Baseline (IU/L)	24.6	25.8	24.0	25.1
Change from baseline (IU/L)	-5.6	-7.3	-7.5	-5.4
Percent change from baseline (%)	-22.4	-29.2	-30.0	-21.6
Semaglutide-adjusted percent change (%) (95% CI)	-1.0 (-6.5, 4.8)	-9.7 (-14.8, -4.4)	-10.7 (-15.7, -5.4)	N/A
AST[a]				
Baseline (IU/L)	20.2	21.3	20.2	20.6
Change from baseline (IU/L)	-1.8	-2.8	-2.9	-1.9
Percent change from baseline (%)	-8.72	-13.73	-14.10	-9.20
Semaglutide-adjusted percent change (%) (95% CI)	0.52 (-3.42, 4.63)	-4.99 (-8.73, -1.10)	-5.4 (-9.11, -1.54)	N/A

[a]Analysis with log-transformation.

Note: mITT population (safety analysis set). The widths of confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects.

ALT=Alanine Transaminase; AST=Aspartate Aminotransferase; CI=Confidence Interval; mITT=Modified Intention-to-Treat.

Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.

Additional Laboratory Measures at Baseline and 40 Weeks (2 of 3)

SURPASS-2

Parameters	Tirzepatide 5 mg N=470	Tirzepatide 10 mg N=469	Tirzepatide 15 mg N=470	Semaglutide 1 mg N=469
eGFR CKD-EPI Calculation				
Baseline (mL/min/1.73m^2)	96.7	95.5	96.4	95.8
Change from baseline (mL/min/1.73m^2)	-4.6	-4.8	-5.0	-4.5
Semaglutide-adjusted change (LSM treatment difference [95% CI]; mL/min/1.73m^2)	-0.2 (-1.5, 1.2)	-0.3 (-1.6, 1.0)	-0.6 (-1.9, 0.8)	N/A
Urine Albumin/Creatinine Ratio[a]				
Baseline (g/kg)	14.0	13.1	13.5	12.4
Change from baseline (g/kg)	-1.1	-0.2	-1.7	-0.6
Percent change from baseline (%)	-8.5	-1.4	-12.8	-4.3
Semaglutide-adjusted percent change (%) (95% CI)	-4.4 (-15.0, 7.5)	3.0 (-8.5, 15.9)	-8.9 (-19.1, 2.5)	N/A

[a]Analysis with log-transformation.

Note: mITT population (safety analysis set). The widths of confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects.

CI=Confidence Interval; CKD-EPI=Chronic Kidney Disease-Epidemiology; eGFR=Estimated Glomerular Filtration Rate; LSM=Least Squares Mean; mITT=Modified Intention-to-Treat.

Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.

Additional Laboratory Measures at Baseline and 40 Weeks (3 of 3)

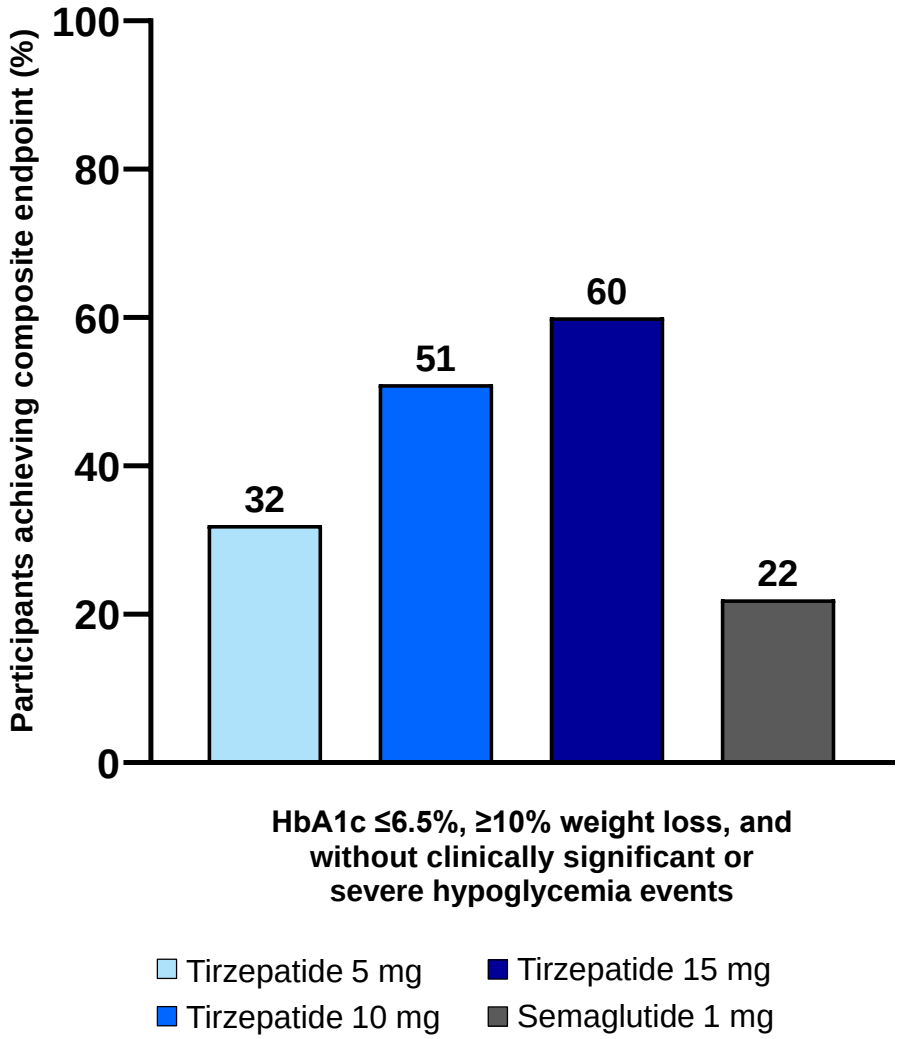
SURPASS-2

Parameters	Tirzepatide 5 mg N=470	Tirzepatide 10 mg N=469	Tirzepatide 15 mg N=470	Semaglutide 1 mg N=469
HOMA2-IR (computed with fasting insulin)[a]				
Baseline	1.94	2.08	2.01	1.95
Change from baseline	-0.31	-0.39	-0.48	-0.10
Percent change from baseline (%)	-15.5	-19.5	-24.0	-5.1
Semaglutide-adjusted percent change (%) (95% CI)	-11.0 (-17.5, -4.0)	-15.2 (-21.4, -8.5)	-19.9 (-25.8, -13.6)	N/A
Fasting glucagon (adjusted for fasting serum glucose), pmol/L*mmol/L[a]				
Baseline	100.6	104.3	99.3	102.0
Change from baseline	-49.5	-53.8	-56.1	-48.5
Percent change from baseline (%)	-48.7	-53.0	-55.3	-47.7
Semaglutide-adjusted percent change (%) (95% CI)	-1.9 (-10.9, 8.0)	-10.0 (-18.3, -0.9)	-14.5 (-22.4, -5.8)	N/A

Note: mITT population (efficacy analysis set). The widths of confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects.
CI=Confidence Interval; HOMA2-IR=Homeostatic Model Assessment for Insulin Resistance; mITT=Modified Intention-to-Treat.
Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.

Composite Endpoint

HbA1c ≤6.5%, ≥10% weight loss, and without clinically significant (blood glucose <54 mg/dL) or severe hypoglycaemia events, SURPASS-2



Note: mITT population (efficacy estimand).
HbA1c=Glycated Haemoglobin; mITT=Modified Intention-to-Treat.
Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.