

Tirzepatide Versus Insulin Glargine in Type 2 Diabetes and Increased Cardiovascular Risk (SURPASS-4): A Randomised, Open-label, Parallel-Group, Multicentre, Phase 3 Trial

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Objectives

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Primary Objective:

- To demonstrate that once-weekly tirzepatide 10 mg and/or 15 mg is noninferior to titrated insulin glargine for change from baseline in HbA1c at 52 weeks

Key Secondary Objectives (Controlled for Type 1 Error):

To demonstrate that:

- TZP 5 mg is noninferior to titrated insulin glargine for mean CFB in HbA1c at 52 weeks
- TZP 5 mg, 10 mg, and/or 15 mg are superior to titrated insulin glargine for mean CFB at 52 weeks for:
 - HbA1c
 - Body weight
- TZP 5 mg, 10 mg and/or 15 mg are superior to titrated insulin glargine for the proportion of patients with HbA1c target values of <7.0% (<53 mmol/mol) at 52 weeks

Secondary Safety Objectives (Not Controlled for Type 1 Error):

- Includes TEAEs, AEs, hypoglycaemia, blood pressure, pulse rate, adjudicated MACE-4 (CV death, myocardial infarction, stroke, hospitalisation for unstable angina)

Key Inclusion and Exclusion Criteria

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Key Inclusion Criteria

- Adults with type 2 diabetes
- HbA1c $\geq 7.5\%$ to $\leq 10.5\%$
- BMI ≥ 25 kg/m² and stable weight ($\leq 5\%$ fluctuation in either direction)) prior 3 months
- Increased CV risk
 - Known coronary, peripheral arterial or cerebrovascular disease, OR
 - Age ≥ 50 years with either history of
 - Chronic kidney disease and eGFR < 60 mL/min/1.73m² OR
 - History of congestive heart failure
- Use of 1 to 3 OAMs:
 - metformin,
 - SGLT-2i
 - sulfonylurea



Key Exclusion Criteria

- Type 1 diabetes
- History of pancreatitis

Study Design

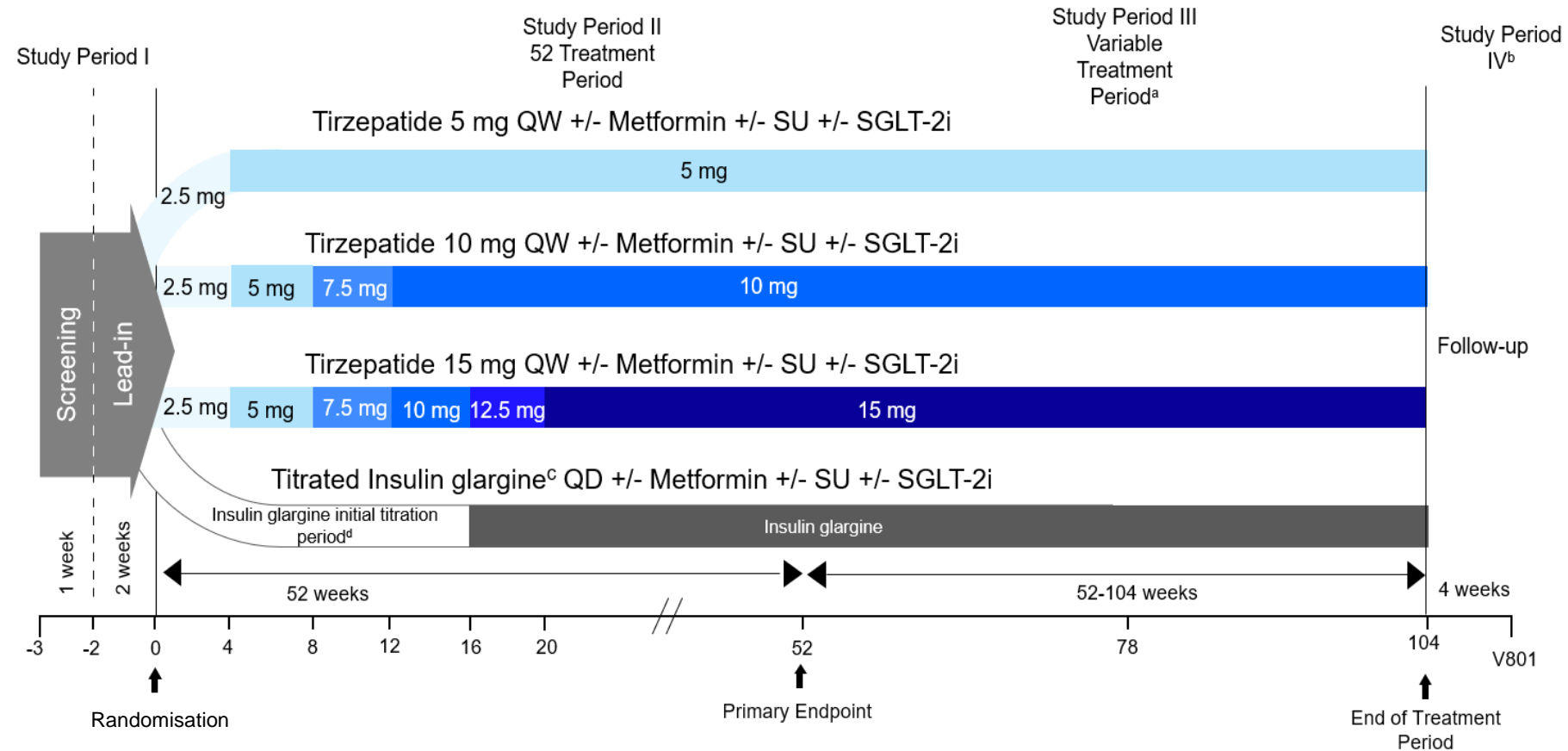
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Randomisation scheme

- 1:1:1:3

Study End Criteria

- All participants reach 52 weeks
- ≥ 300 participants reach 78 weeks
- ~ 110 participants ≥ 1 MACE-4 endpoint



^aParticipants were on study medication for at least 12 months and received no more than 24 months of treatment. ^bFour weeks after their last treatment visit, all participants performed a Visit 801, an off-medication safety follow-up visit.

^cThe starting dose of insulin glargine was 10 IU/day at bedtime, titrated to a FBG < 100 mg/dL, following a treat-to-target algorithm. ^dParticipants titrated the insulin glargine dose in a weekly manner and made the dose decision with the investigator for the first eight weeks (phone or clinic visit). From Week 8 to Week 16, participants continued the titration by a phone consultation or clinic visit every other week, with three weeks between Visits 13 and 14.

FBG=Fasting Blood Glucose; MACE=Major Adverse Cardiovascular Events; QD=Once-Daily; QW=Once-Weekly; SGLT2i=Sodium-Glucose Cotransporter-2 Inhibitors; SU=Sulfonylureas.

Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

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=329	Tirzepatide 10 mg N=328	Tirzepatide 15 mg N=338	Insulin Glargine N=1000	Total N=1995
Age (years)	62.9 (8.6)	63.7 (8.7)	63.7 (8.6)	63.8 (8.5)	63.6 (8.6)
Female, n (%)	131 (40%)	119 (36%)	135 (40%)	364 (36%)	749 (38%)
Duration of Diabetes [median (IQR) ,(years)]	9.8 (6.2, 15.3)	10.6 (6.5, 16.2)	10.4 (5.5, 15.7)	10.7 (6.3, 16.5)	10.5 (6.2, 15.9)
HbA1c (%)	8.52 (0.84)	8.59 (0.91)	8.52 (0.98)	8.50 (0.85)	8.52 (0.88)
Weight (kg)	90.3 (20.32)	90.6 (18.21)	90.0 (16.34)	90.2 (19.00)	90.3 (18.66)
BMI (kg/m²)	32.6 (6.06)	32.8 (5.51)	32.5 (5.02)	32.5 (5.55)	32.6 (5.54)
History of CVD, n (%)	275 (84%)	296 (90%)	293 (87%)	874 (87%)	1738 (87%)
eGFR <60, CKD-EPI mL/min per 1.73 m², n (%)	62 (19%)	56 (17%)	58 (17%)	166 (17%)	342 (17%)
Sulfonylurea use, yes, n (%)	189 (57%)	181 (55%)	179 (53%)	537 (54%)	1086 (54%)
Metformin use, yes, n (%)	306 (93%)	316 (96%)	317 (94%)	954 (95%)	1893 (95%)

Note: Data are mean (SD) or n (%) unless otherwise specified; mITT population.

BMI=Body Mass Index; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; CVD=Cardiovascular Disease; eGFR=Estimated Glomerular Filtration Rate; HbA1c=Glycated Haemoglobin; IQR=Interquartile Range;

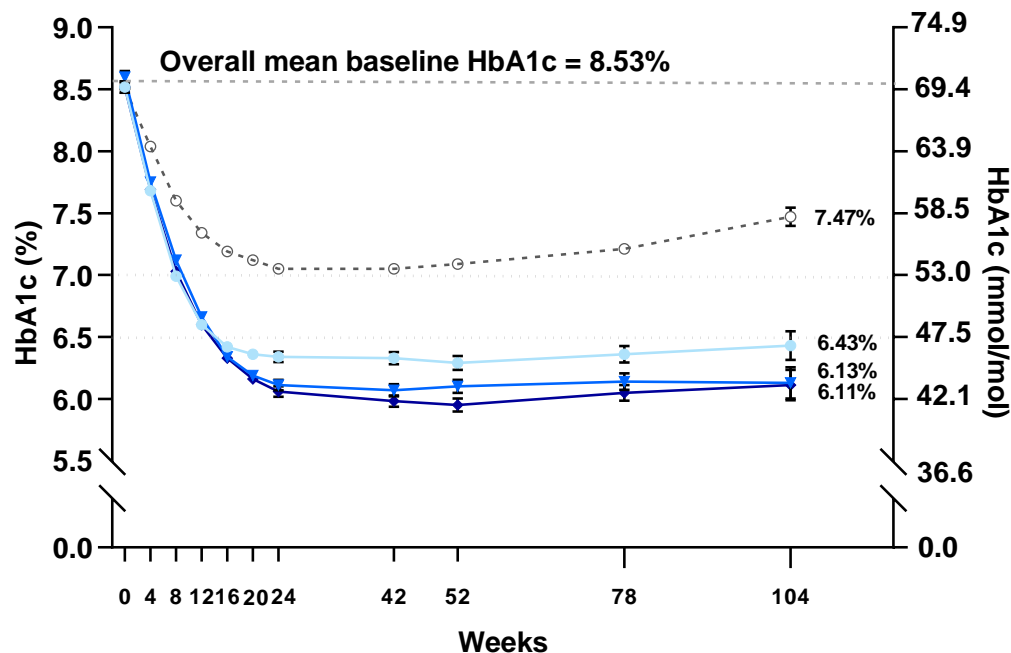
mITT=Modified Intention-to-Treat; N=All Randomly Assigned Participants Who Took at Least 1 Dose of Study Drug (mITT Population); n=Number of Patients in the Specified Category; SD=Standard Deviation.

Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

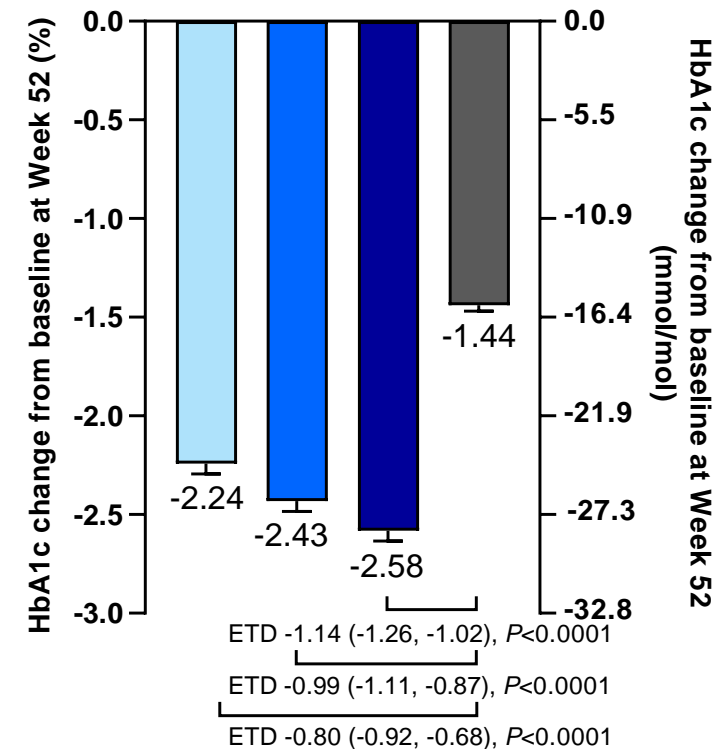
HbA1c: Change Over Time and Change from Baseline

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**HbA1c over Time from Baseline at Week 104
(Efficacy Estimand)**



**Change from Baseline in HbA1c at Week 52
(Efficacy Estimand)**



Weeks	All TZP (n)	Glargine (n)
0	981	978
52	863	887
104	577	589
104	105	94

—●— Tirzepatide 5 mg —◆— Tirzepatide 15 mg
—▼— Tirzepatide 10 mg - - - Insulin Glargine

Note: Data are LSM (SE) from a MMRM analysis; mITT population (efficacy analysis set). ETD versus insulin glargine are LSM (95% CI) at Week 52. n indicates the numbers of participants with baseline and postbaseline values who received tirzepatide and glargine at specific time points.

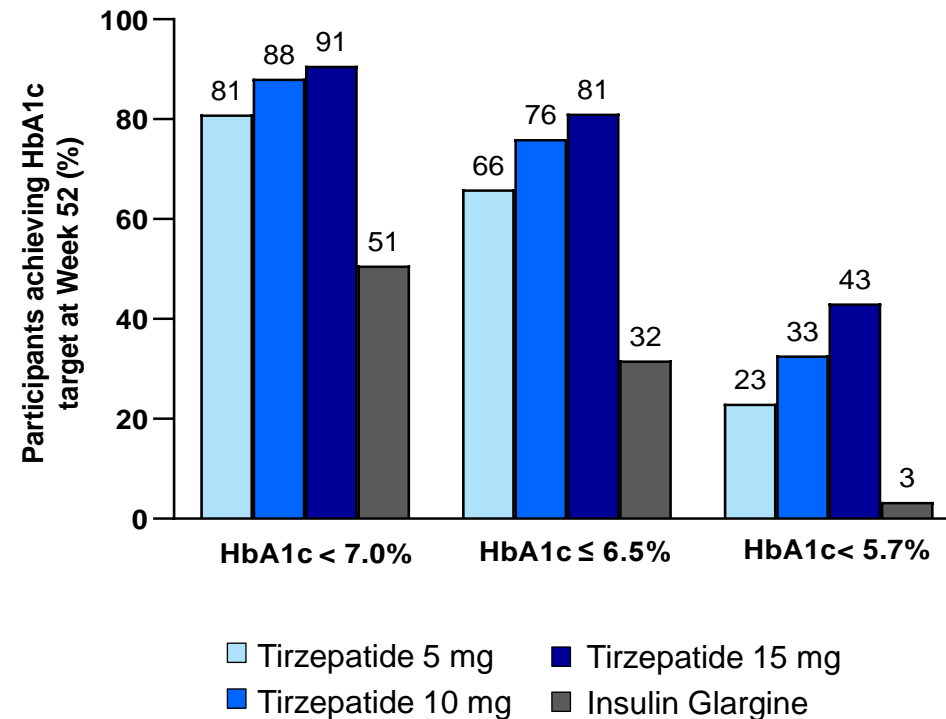
CI=Confidence Interval; ETD=Estimated Treatment Difference; HbA1c=Glycated Haemoglobin; LSM=Least Squares Mean; mITT=Modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; SE=Standard Error; TZP=Tirzepatide.

Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

HbA1c: Participants Achieving HbA1c Target

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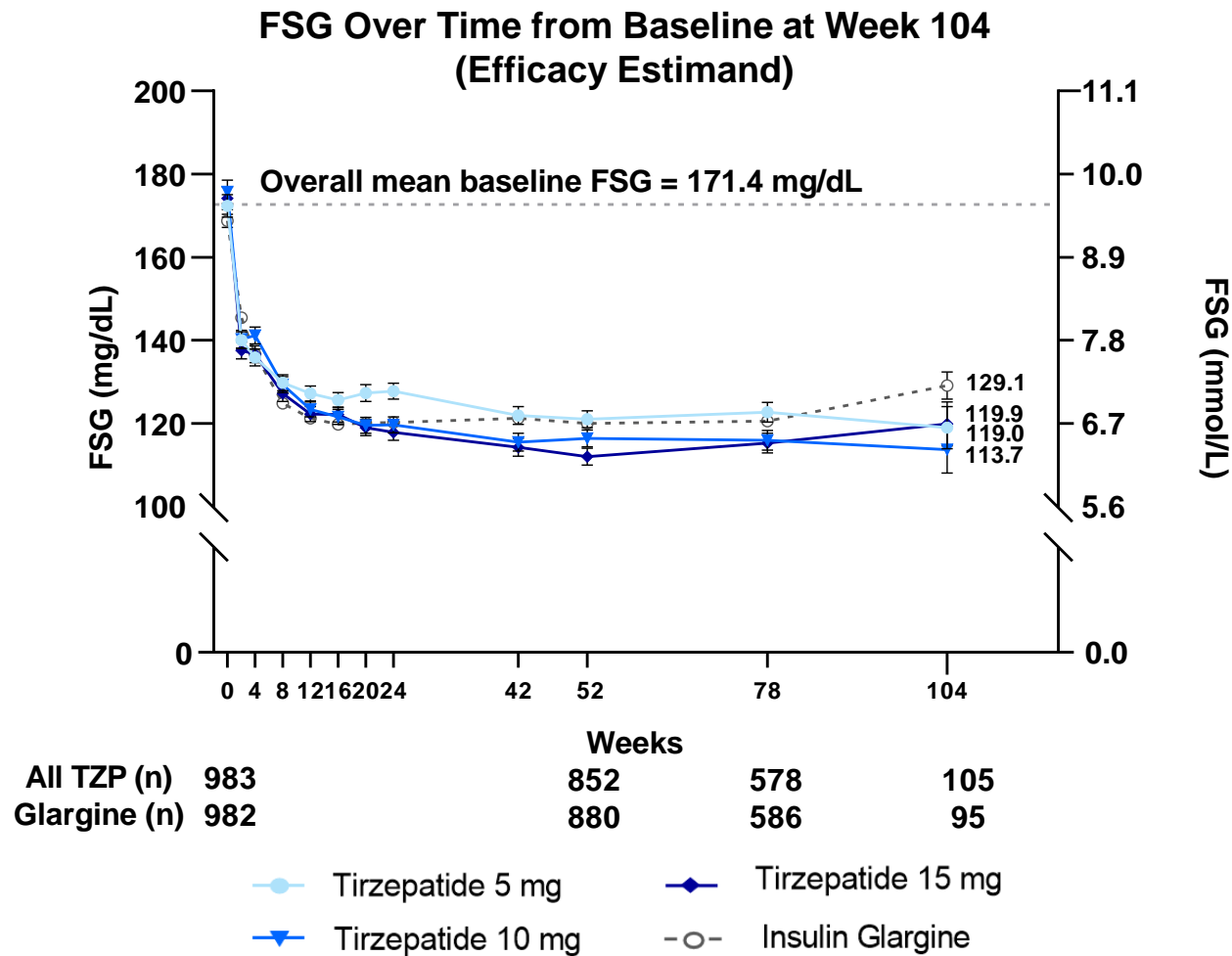
Participants Reaching HbA1c Target at Week 52
(Efficacy Estimand)



Note: mITT population (efficacy analysis set). Missing data at Week 52 were predicted from MMRM analysis.
HbA1c=Glycated Haemoglobin; mITT=Modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures.
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FSG: Change Over Time at Week 104

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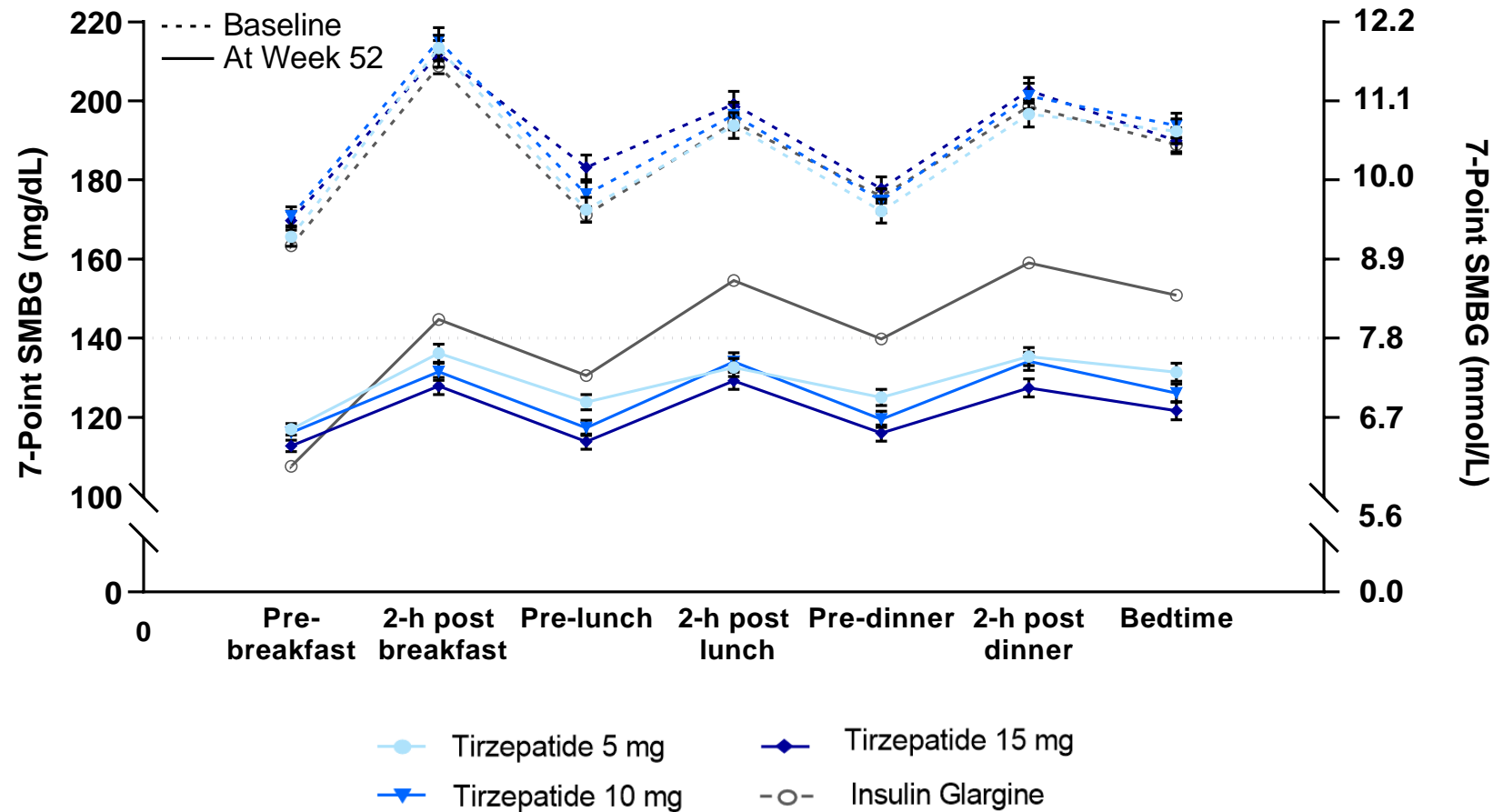
Note: Data are LSM (SE) from a MMRM analysis; mITT population (efficacy analysis set). Dashed line shows baseline values. n indicates the numbers of participants with baseline and postbaseline values who received tirzepatide and glargine at specific time points.

FSG=Fasting Serum Glucose; LSM=Least Squares Mean; mITT=Modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; SE=Standard Error; TZP=Tirzepatide.

Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

7-Point SMBG at Baseline and Week 52

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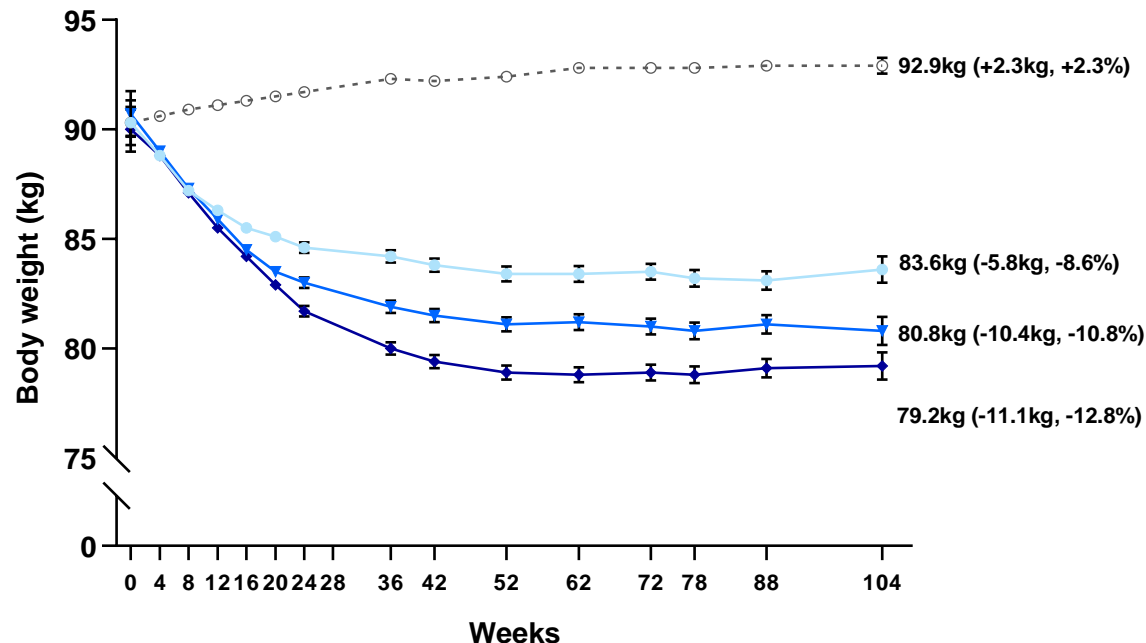


Note: Data are LSM (SE) from a MMRM analysis; mITT population (efficacy analysis set). ANOVA analysis (baseline) and MMRM analysis (52 weeks). Dotted line shows target value. LSM=Least Squares Mean; mITT=Modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; SE=Standard Error; SMBG=Self-Monitored Blood Glucose. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

Body Weight: Change Over Time and Change from Baseline

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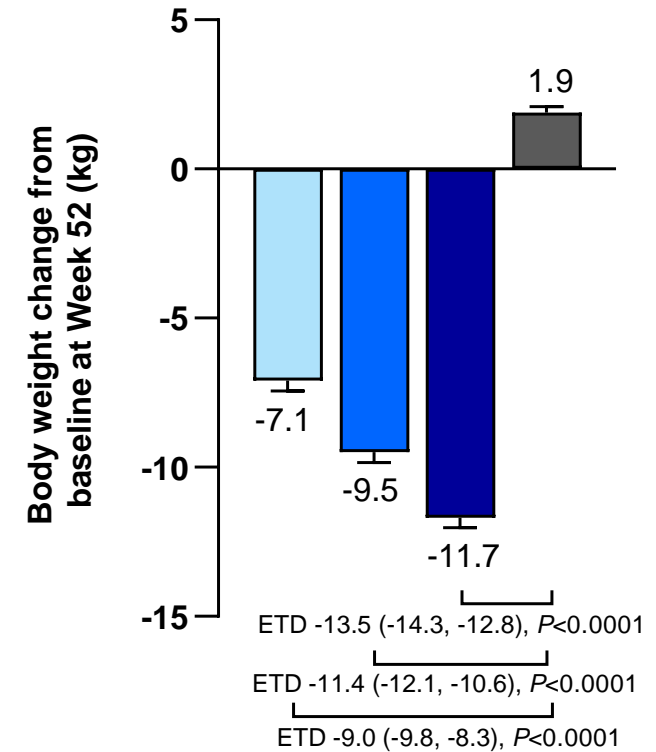
**Body Weight Over Time from Baseline at Week 104
(Efficacy Estimand)**



All TZP (n)	981	864	583	105
Glargine (n)	978	891	600	97

—●— Tirzepatide 5 mg —◆— Tirzepatide 15 mg
—▼— Tirzepatide 10 mg - - - Insulin Glargine

**Change from Baseline in Body Weight at Week 52
(Efficacy Estimand)**



Note: Data are LSM (SE) from a MMRM analysis; mITT population (efficacy analysis set). ETD versus insulin glargine are LSM (95% CI) at Week 52. Left graph shows absolute body weight at week 104 (change from baseline, % reduction)

CI=Confidence Interval; ETD=Estimated Treatment Difference; LSM=Least Squares Mean; mITT=Modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; SE=Standard Error; TZP=Tirzepatide.

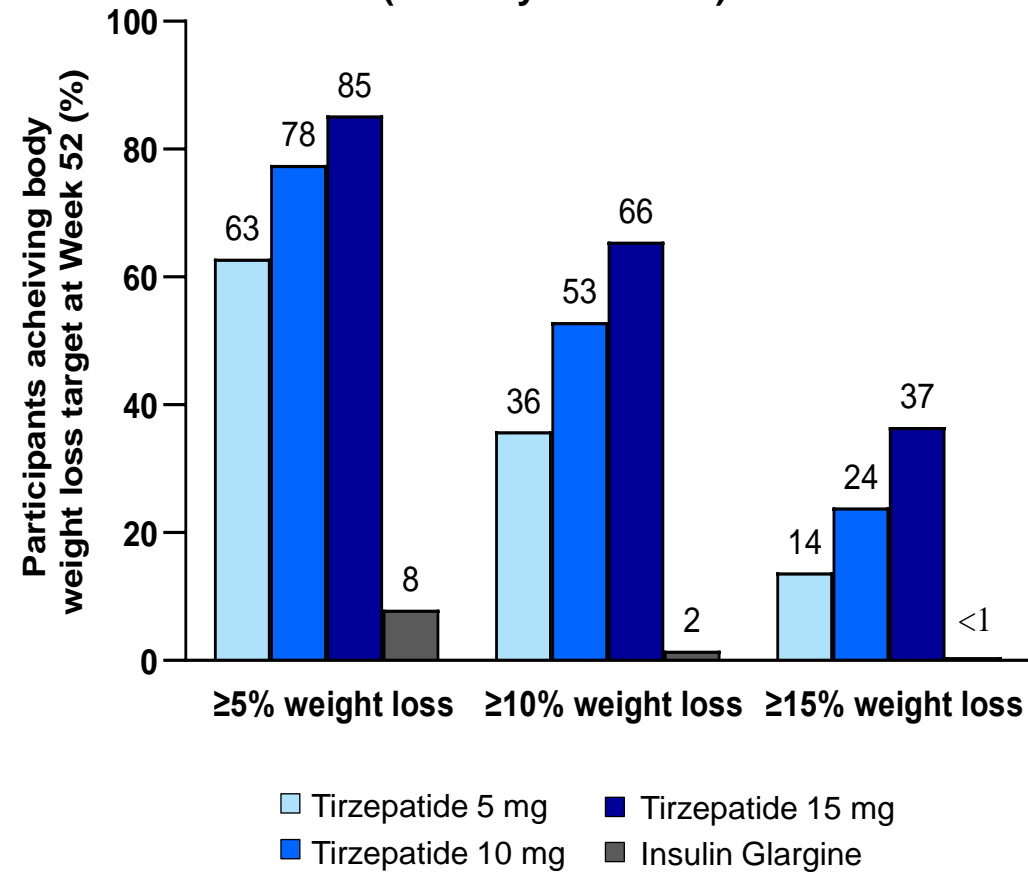
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Body Weight: Achieving Body Weight Loss Target at Week 52

Week 52

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Proportion of Participants Achieving Body Weight Loss Target at Week 52 (Efficacy Estimand)

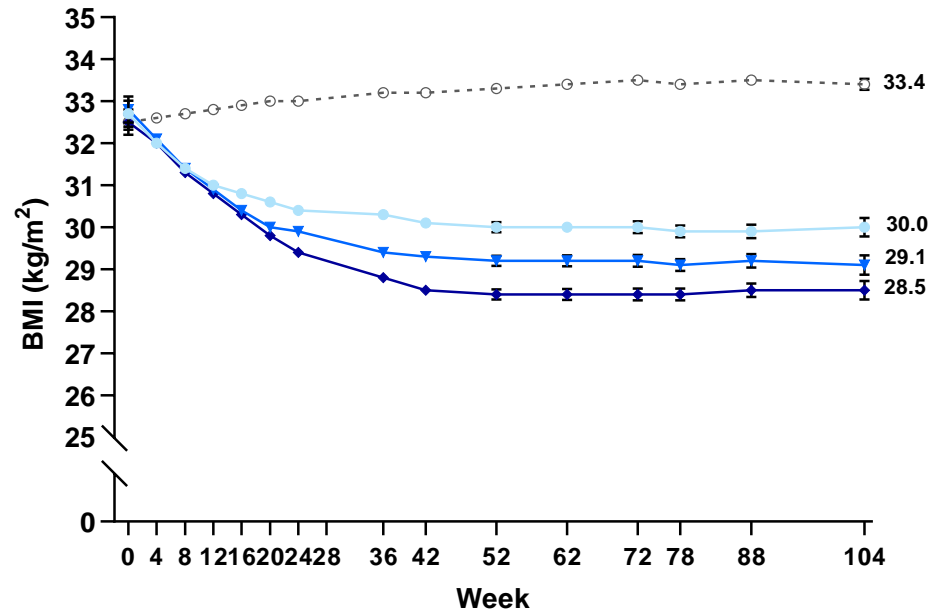


Note: mITT population (efficacy analysis set). Missing data at Week 52 were predicted from MMRM analysis.
mITT=Modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures.
Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

Mean BMI and Mean Waist Circumference Over Time at Week 104

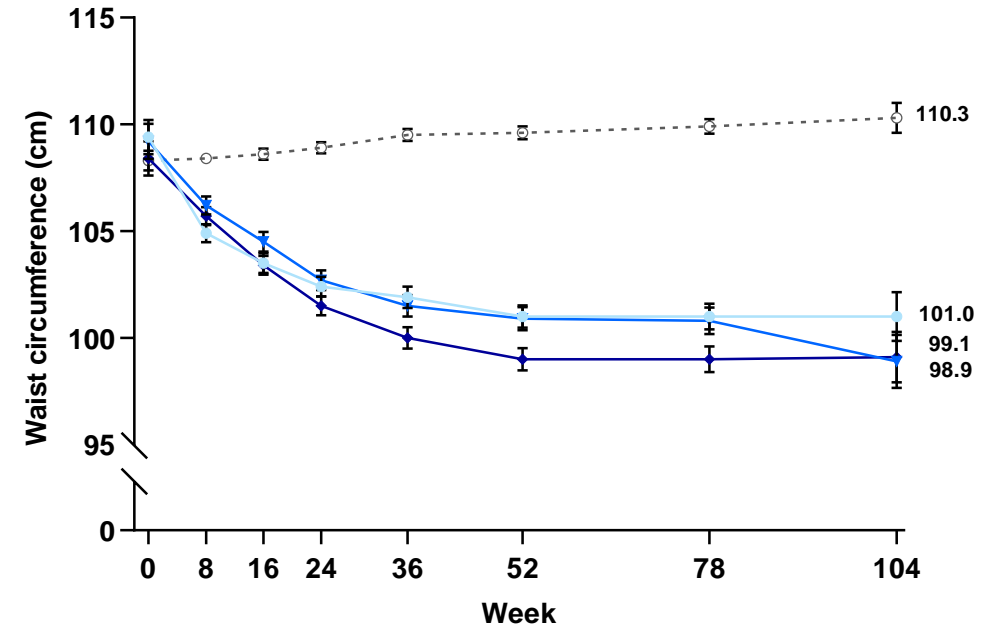
SURPASS-4

Mean BMI Over Time from Baseline at Week 104



	Week 0	Week 52	Week 78	Week 104
All TZP (n)	981	864	583	105
Glargine (n)	978	891	600	97

Mean Waist Circumference Over Time from Baseline at Week 104



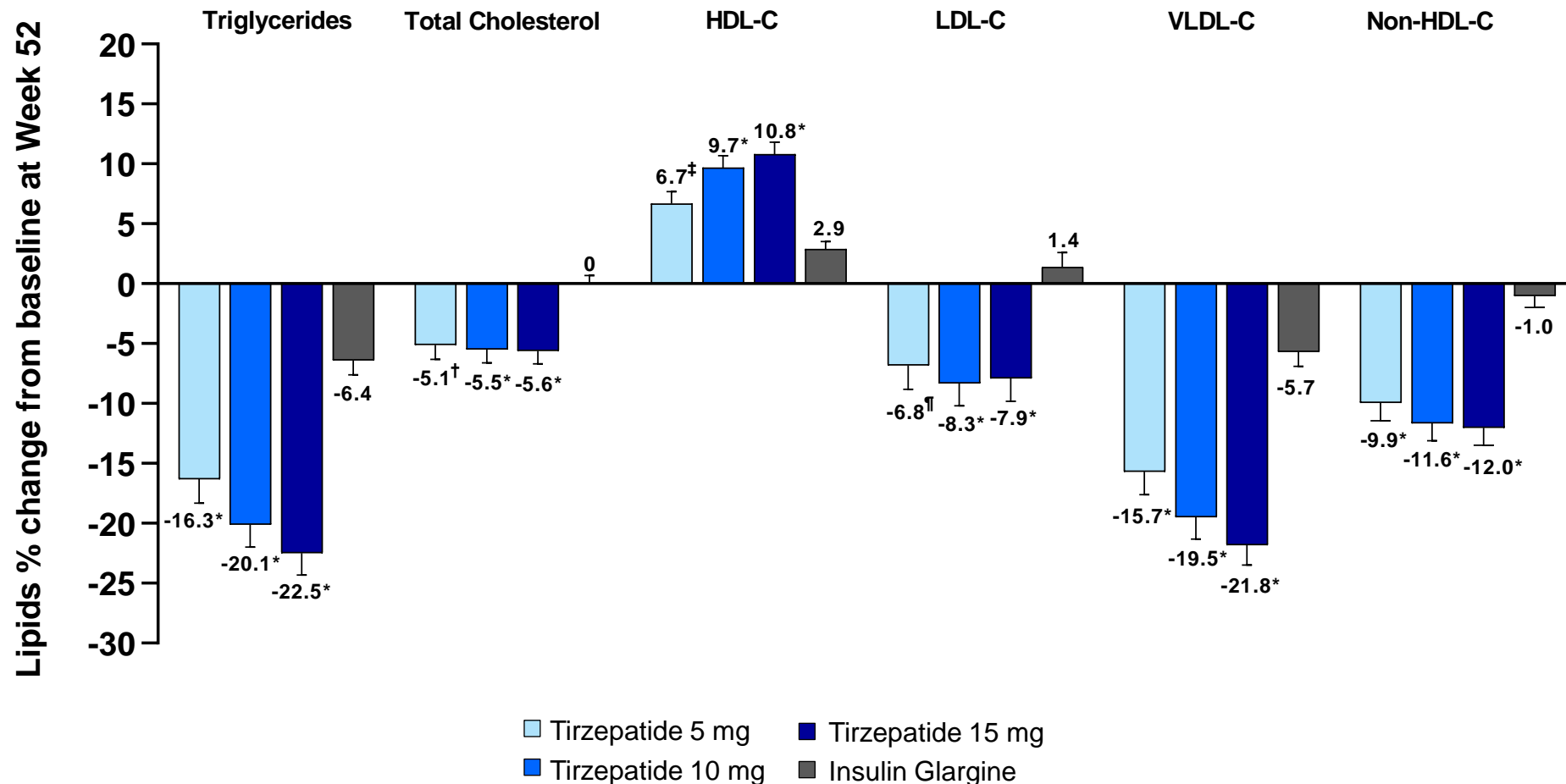
	Week 0	Week 52	Week 78	Week 104
All TZP (n)	957	860	581	104
Glargine (n)	973	889	598	97

- Tirzepatide 5 mg
- ◆ Tirzepatide 15 mg
- ▼ Tirzepatide 10 mg
- Insulin Glargine

Note: Data are LSM (SE); mITT population (efficacy analysis set). n indicates the numbers of participants with baseline and postbaseline values who received tirzepatide and glargine at specific time points. BMI=Body Mass Index; LSM=Least Squares Mean; mITT=Modified Intent-to-Treat; SE=Standard Error; TZP=Tirzepatide. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

Percent Change from Baseline in Lipids at Week 52

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* $P < 0.0001$, † $P = 0.0002$, ‡ $P = 0.0008$, ¶ $P = 0.0005$ versus insulin glargine

Note: Data are LSM (SE) from MMRM analysis using log transformation; mITT population (efficacy analysis set).

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

Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

Overview of Adverse Events Through Week 52

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Parameters	Tirzepatide 5 mg N=329	Tirzepatide 10 mg N=328	Tirzepatide 15 mg N=338	Insulin Glargine N=1000
Participants with at least one TEAEs	232 (71%)	241 (74%)	259 (77%)	679 (68%)
SAEs	48 (15%)	54 (17%)	41 (12%)	193 (19%)
Deaths^a	15 (5%)	2 (<1%)	8 (2%)	35 (4%)
Treatment Discontinuation due to AE	37 (11%)	28 (9%)	36 (11%)	54 (5%)
TEAE with ≥5% frequency in any arm				
Nausea	39 (12%)	53 (16%)	76 (23%)	23 (2%)
Diarrhoea	41 (13%)	65 (20%)	74 (22%)	44 (4%)
Decreased appetite	29 (9%)	36 (11%)	35 (10%)	5 (<1%)
Vomiting	16 (5%)	27 (8%)	29 (9%)	16 (2%)
Dyspepsia	18 (6%)	27 (8%)	26 (8%)	13 (1%)
Lipase increased	10 (3%)	13 (4%)	21 (6%)	18 (2%)
Nasopharyngitis	10 (3%)	16 (5%)	16 (5%)	65 (7%)
Constipation	17 (5%)	14 (4%)	14 (4%)	5 (<1%)
COVID-19	15 (5%)	14 (4%)	19 (6%)	59 (6%)

^aDeaths 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; mITT=Modified Intent-to-Treat; N=All Randomly Assigned Participants Who Took at Least 1 Dose of Study Drug (mITT population); SAEs=Serious Adverse Events; TEAEs=Treatment-Emergent Adverse Events.
Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

Hypoglycaemia and Other TEAEs of Interest Through Safety Follow-Up

SURPASS-4

Parameters	Tirzepatide 5 mg N=329	Tirzepatide 10 mg N=328	Tirzepatide 15 mg N=338	Insulin Glargine N=1000
Hypoglycaemia (blood glucose \leq70 mg/dL)	112 (34%)	107 (33%)	127 (38%)	641 (64%)
Hypoglycaemia (blood glucose $<$54 mg/dL)	29 (9%)	20 (6%)	27 (8%)	191 (19%)
Severe Hypoglycaemia	1 ($<$ 1%)	0 (0.00%)	3 (1%)	11 (1%)
AEs of special interest				
Injection site reaction	1 ($<$ 1%)	2 ($<$ 1%)	1 ($<$ 1%)	4 ($<$ 1%)
Cholelithiasis	3 ($<$ 1%)	1 ($<$ 1%)	1 ($<$ 1%)	4 ($<$ 1%)
Cholecystitis	0	2 ($<$ 1%)	0	6 ($<$ 1%)
Diabetic retinopathy complications	5 (2%)	5 (2%)	4 (1%)	15 (2%)
Adjudicated pancreatitis	3 ($<$ 1%)	2 ($<$ 1%)	1 ($<$ 1%)	1 ($<$ 1%)

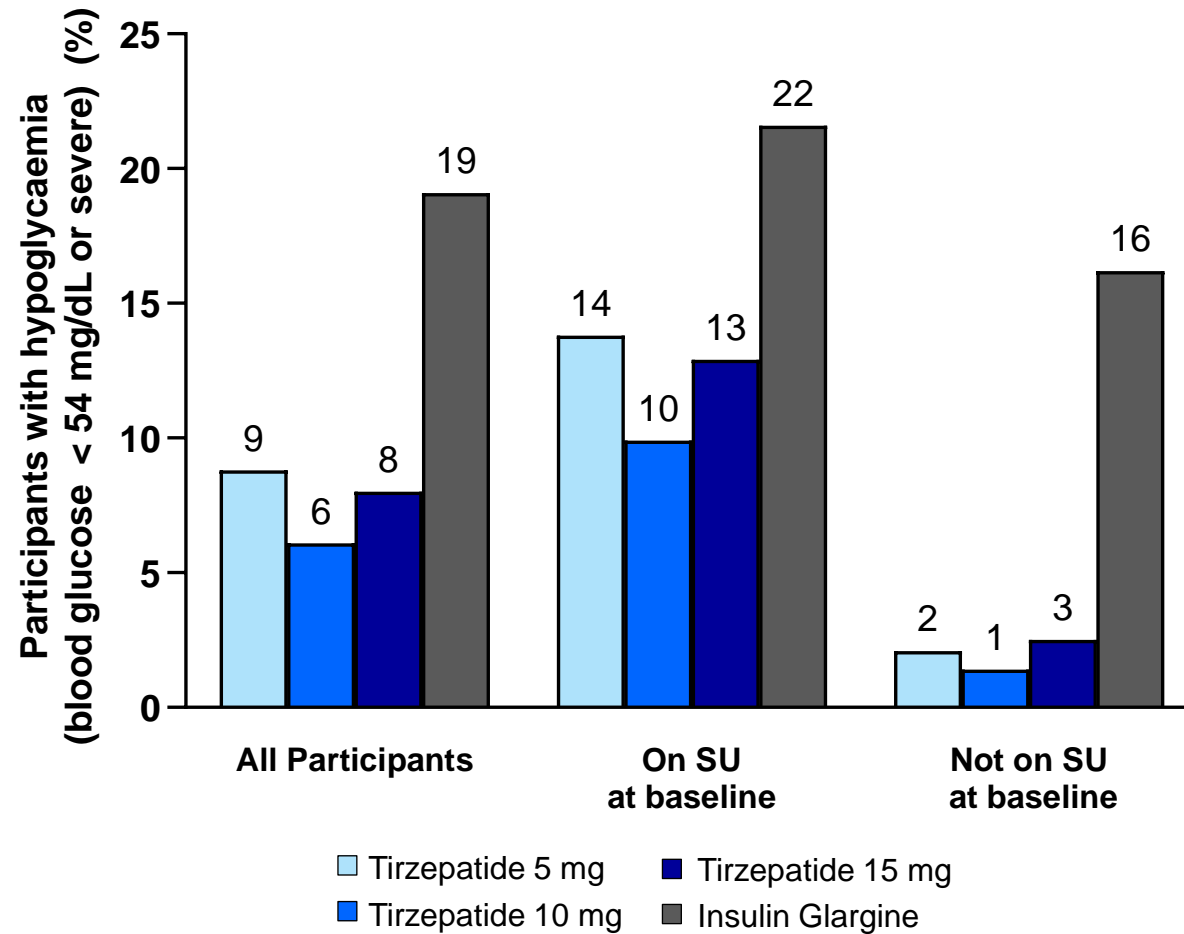
Note: Data are n (%); mITT population (safety analysis set). Patients may be counted in more than 1 category.

AE=Adverse Event; mITT=Modified Intent-to-Treat; N=All Randomly Assigned Participants Who Took at Least 1 Dose of Study Drug (mITT population); TEAEs=Treatment-Emergent Adverse Events.

Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

Incidence of Hypoglycaemia

Blood Glucose <54 mg/dL (< 3 mmol/L) or severe, SURPASS-4



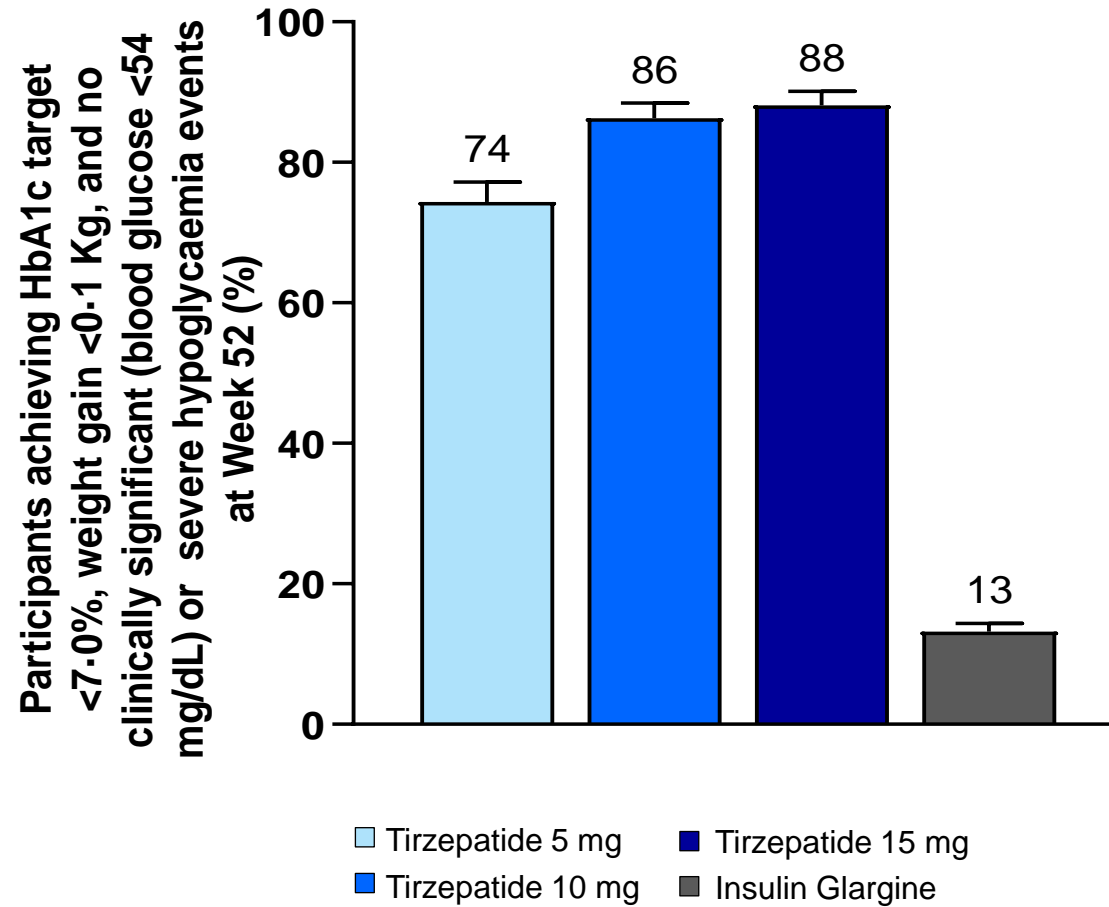
Note: mITT population (safety analysis set), excluding events occurring after initiation of a new glucose-lowering therapy.

mITT=Modified Intention-to-Treat.

Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

Composite Endpoint

Participants achieving HbA1c target <7.0%, weight gain <0.1 Kg, and no clinically significant (blood glucose <54 mg/dL) or severe hypoglycaemia events at Week 52, SURPASS-4



Note: Data are estimated from longitudinal logistic regression at 52 weeks, mITT population (efficacy analysis set).

HbA1c=Glycated Haemoglobin; mITT=Modified Intention-to-Treat.

Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

Summary of MACE and Deaths During the Study

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Event Category	TZP 5 mg (N=329)	TZP 10 mg (N=328)	TZP 15 mg (N=338)	All TZP (N=995)		Insulin Glargine (N=1000)		HR (95% CI)
	n (%)	n (%)	n (%)	n (%)	n/100 person-yr	n (%)	n/100 person-yr	
MACE-4	19 (6%)	17 (5%)	11 (3%)	47 (5%)	2.97	62 (6%)	3.99	0.74 (0.51, 1.08)*
CV death	10 (3%)	1 (<1%)	5 (2%)	16 (2%)	1.01	21 (2%)	1.35	
Myocardial infarction	7 (2%)	9 (3%)	3 (<1%)	19 (2%)	1.20	26 (3%)	1.67	
Hospitalisation for unstable angina	0 (0%)	2 (<1%)	2 (<1%)	4 (<1%)	0.25	8 (<1%)	0.51	
Stroke	5 (2%)	5 (2%)	1 (<1%)	11 (1%)	0.70	13 (1%)	0.84	
Other MACE								
Coronary interventions ^a	10 (3%)	11 (3%)	8 (2%)	29 (3%)	1.83	37 (4%)	2.38	
Transient ischemic attack	0	2 (<1%)	1 (<1%)	3 (<1%)	0.19	0 (0%)	0	
Hospitalisation for heart failure	1 (<1%)	1 (<1%)	2 (<1%)	4 (<1%)	0.25	6 (<1%)	0.39	
Death	15 (5%)	2 (<1%)	8 (2%)	25 (3%)	1.58	35 (4%)	2.25	0.70 (0.42, 1.17)*
Cardiovascular	4 (1%)	0	2 (<1%)	6 (<1%)	0.38	9 (<1%)	0.58	
Undetermined	6 (2%)	1 (<1%)	3 (<1%)	10 (1%)	0.63	12 (1%)	0.77	
Non-cardiovascular	5 (2%)	1 (<1%)	3 (<1%)	9 (<1%)	0.57	14 (1%)	0.90	

^aIncludes coronary artery bypass graft and percutaneous coronary intervention.

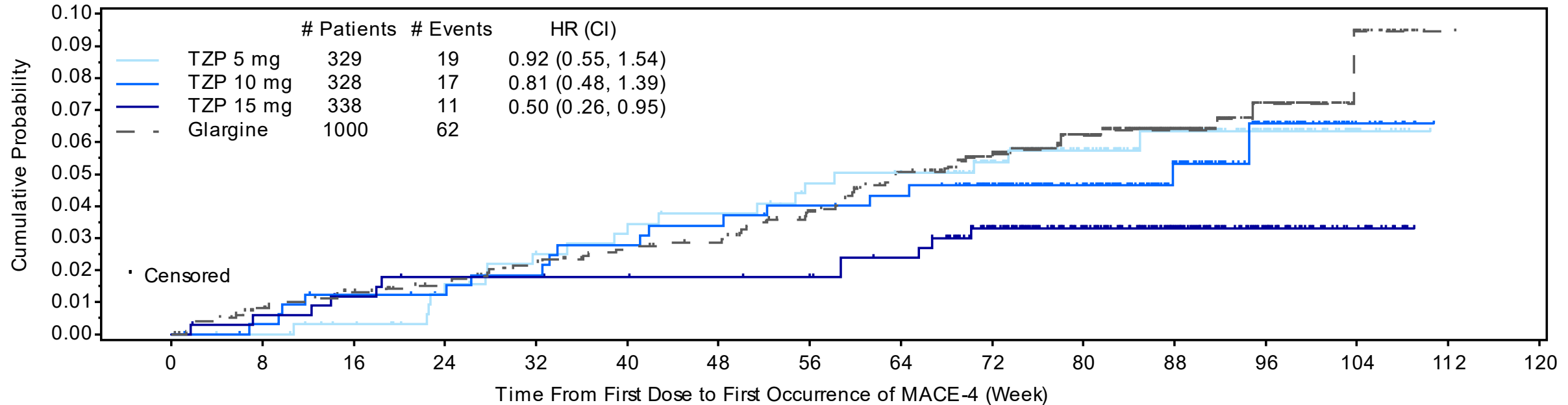
Note: Data are n (%), n/100 person-yr, or hazard ratio (95% CI). mITT population (safety analysis set). All events confirmed by the Clinical Endpoint Committee. MACE-4 is a composite endpoint of death from cardiovascular or undetermined causes, myocardial infarction, stroke, and hospitalisation for unstable angina. *Point estimate and 95% CI of hazard ratio comparing pooled tirzepatide arms versus glargine obtained from time- to- first event analysis using Cox proportional hazards model.

CI=Confidence Interval; HR=Hazard Ratio; MACE=Major Adverse Cardiovascular Events; mITT=Modified Intention-to-Treat; TZP=Tirzepatide.

Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

MACE-4 Kaplan-Meier Plot

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At Risk	0	8	16	24	32	40	48	56	64	72	80	88	96	104	112	120
TZP 5 mg	329	328	322	315	310	307	304	299	297	264	203	128	60	15	0	0
TZP 10 mg	328	325	321	319	317	314	312	307	305	280	211	137	62	12	0	0
TZP 15 mg	338	335	332	329	329	328	327	326	321	288	217	144	66	18	0	0
Glargine	1000	982	971	961	947	937	932	916	892	794	584	392	172	37	1	0

Kaplan-Meier plot of time to first occurrence of positively adjudicated MACE-4, mITT population (safety analysis set); Hazard ratios and 95% CIs unstratified are for comparison of tirzepatide treatment groups versus glargine from Cox proportional-hazards model; Deaths with an undetermined cause are included in death due to CV cause for analysis purposes. MACE-4 includes cardiovascular death, myocardial infarction, stroke, and hospitalisation for unstable angina.

CI=Confidence Interval; CV=Cardiovascular; MACE=Major Adverse Cardiovascular Events; mITT=Modified Intention-to-Treat.

Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

Conclusion

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- In patients with long duration of type 2 diabetes at high CV risk treated with up to 3 oral glucose-lowering medications, once-weekly tirzepatide demonstrated versus titrated insulin glargine::
 - robust improvements in glycaemic control sustained to 104 weeks
 - significant reduction in body weight beyond 1 year to 104 weeks
 - HbA1c reduction without weight gain attained with fewer incidence of hypoglycaemia with tirzepatide compared to titrated insulin glargine
- The improvement in cardiovascular risk profile and distribution of cardiovascular events (MACE-4) between treatment groups suggests that tirzepatide is safe from a cardiovascular perspective; further definitive studies are required to assess cardiovascular safety, as well as potential cardiovascular protection
- Treatment with tirzepatide does not increase the risk of hypoglycaemia unless it is combined with insulin or sulfonylurea

Note: Data are n (%); mITT population (safety analysis set). Patients may be counted in more than 1 category.
CV=Cardiovascular; HbA1c=Glycated Haemoglobin; MACE=Major Adverse Cardiovascular Events..
Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

Back-Up Supplements

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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=329	Tirzepatide 10 mg N=328	Tirzepatide 15 mg N=338	Insulin Glargine N=1000	Total N=1995
Race [n (%)]					
Asian	15 (5%)	16 (5%)	8 (2%)	31 (3%)	70 (4%)
Black or African American	13 (4%)	17 (5%)	11 (3%)	32 (3%)	73 (4%)
White	260 (79%)	259 (79%)	285 (85%)	825 (83%)	1629 (82%)
Fasting Serum Glucose (mg/dL)	172.3 (49.11)	175.5 (51.93)	174.1 (53.84)	168.4 (49.72)	171.2 (50.75)
SGLT-2i use, yes, n (%)	78 (24%)	81 (25%)	86 (25%)	256 (26%)	501 (25%)
Microalbuminuria (UACR 30- 300 mg/g) [n (%)]	76 (24%)	97 (30%)	103 (31%)	270 (28%)	546 (28%)
Macroalbuminuria (UACR >300 mg/g) [n (%)]	25 (8%)	33 (10%)	24 (7%)	79 (8%)	161 (8%)

Note: Data are mean (SD) or n (%) unless otherwise specified; mITT population.

mITT=Modified Intention-to-Treat; N=All Randomly Assigned Participants Who Took at Least 1 Dose of Study Drug (mITT Population); n=Number of Patients in the Specified Category; SGLT-2i=Sodium-Glucose Cotransporter-2 Inhibitor; SD=Standard Deviation; UACR=Urinary Albumin-to-Creatinine Ratio.

Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

Baseline Demographics and Clinical Characteristics

SURPASS-4

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

Parameters	Tirzepatide 5 mg N=329	Tirzepatide 10 mg N=328	Tirzepatide 15 mg N=338	Insulin Glargine N=1000	Overall population N=1995
History of CVD [n (%)]	275 (84%)	296 (90%)	293 (87%)	874 (87%)	1738 (87%)
Documented coronary artery disease	133 (40%)	146 (44%)	146 (43%)	455 (45%)	880 (44%)
Myocardial infarction	109 (33%)	87 (26%)	106 (31%)	344 (34%)	646 (32%)
Coronary revascularisation procedure	109 (33%)	104 (32%)	102 (30%)	329 (33%)	644 (32%)
Hospitalisation for unstable angina	21 (6%)	30 (9%)	22 (7%)	91 (9%)	164 (8%)
Hospitalisation for heart failure	22 (7%)	31 (9%)	19 (6%)	68 (7%)	140 (7%)
Stroke	37 (11%)	36 (11%)	43 (13%)	125 (12%)	241 (12%)
Transient ischemic attack	16 (5%)	12 (4%)	17 (5%)	53 (5%)	98 (5%)
Peripheral artery disease	89 (27%)	109 (33%)	106 (31%)	302 (30%)	606 (30%)

Note: Note: Data are mean (SD) or n (%) unless otherwise specified; mITT population.

CVD=Cardiovascular Disease; mITT=Modified Intention-to-Treat; N=All Randomly Assigned Participants Who Took at Least 1 Dose of Study Drug (mITT Population); n=Number of Patients in the Specified Category.

Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

Baseline Demographics and Clinical Characteristics

SURPASS-4

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

Parameters	Tirzepatide 5 mg N=329	Tirzepatide 10 mg N=328	Tirzepatide 15 mg N=338	Insulin Glargine N=1000	Overall population N=1995
Blood Pressure (mmHg)					
Systolic	133.3 (14.18)	135.1 (16.11)	134.3 (15.02)	134.6 (15.67)	134.4 (15.40)
Diastolic	78.4 (8.75)	78.6 (9.50)	78.2 (9.16)	78.4 (9.62)	78.4 (9.38)
Pulse Rate (beats/min)					
	72.4 (10.82)	73.2 (10.61)	72.7 (10.53)	72.8 (10.34)	72.8 (10.49)
Lipids [Geometric mean (CV (%))^a					
Serum triglycerides (mg/dL)	167.7 (54.64)	161.7 (49.44)	161.2 (54.43)	158.4 (54.58)	160.9 (53.74)
Serum total cholesterol (mg/dL)	158.5 (26.32)	152.0 (26.59)	155.1 (27.05)	154.7 (27.43)	154.9 (27.06)
Serum non-HDL cholesterol (mg/dL)	114.4 (35.18)	109.7 (35.03)	111.8 (34.42)	111.2 (36.96)	111.6 (35.94)
Concomitant medications					
Blood pressure lowering	303 (92%)	307 (94%)	315 (93%)	930 (93%)	1855 (93%)
Lipid lowering	262 (80%)	274 (84%)	284 (84%)	818 (82%)	1638 (82%)
Anti-platelet	228 (69%)	218 (67%)	239 (71%)	704 (70%)	1389 (70%)

^aOnly participants with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis.

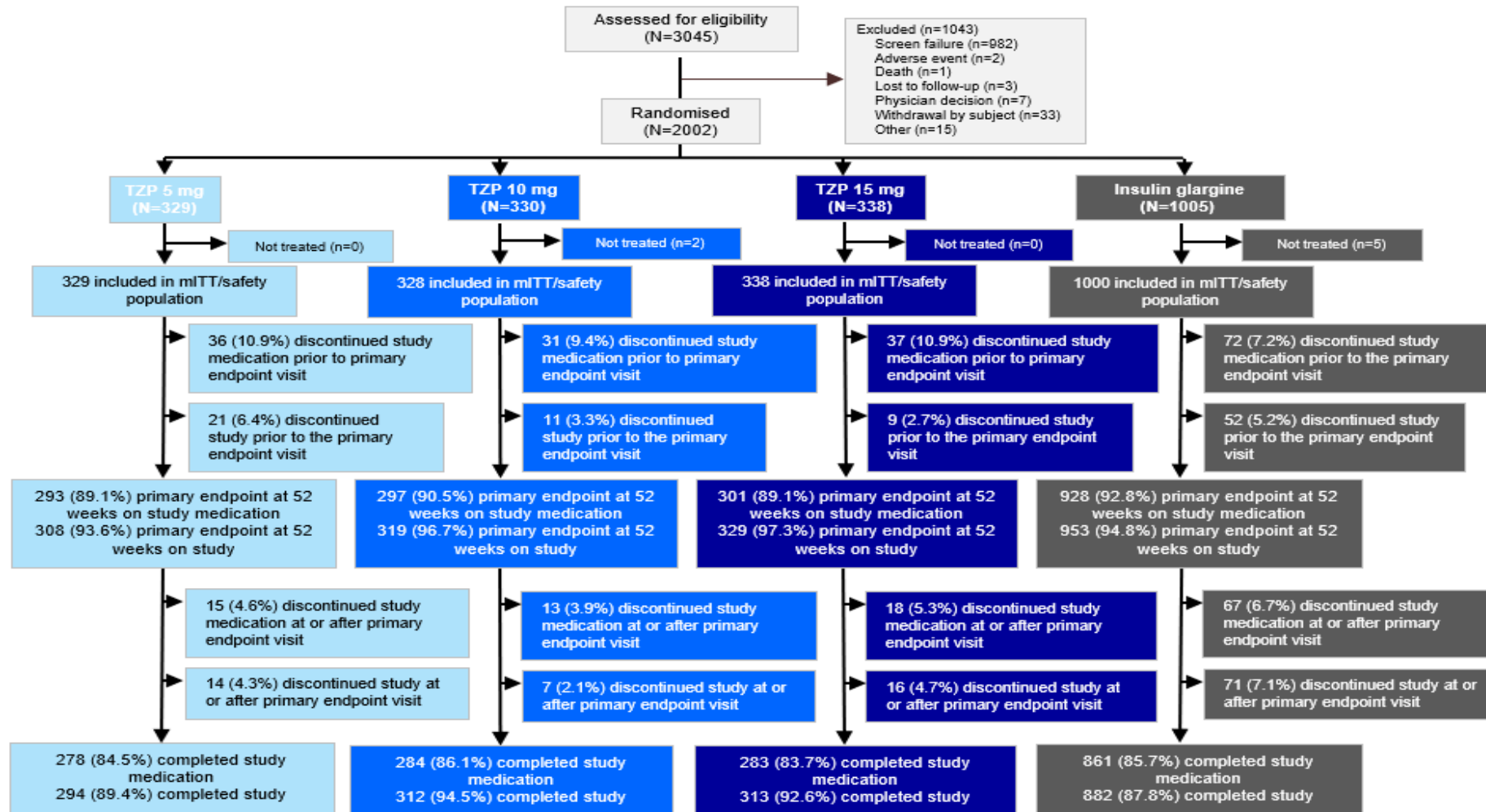
Note: Note: Data are mean (SD) or n (%) unless otherwise specified; mITT population.

CV=Coefficient of Variation; mITT=Modified Intention-to-Treat; N=All Randomly Assigned Participants Who Took at Least 1 Dose of Study Drug (mITT Population); SD=Standard Deviation.

Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

Patient Disposition

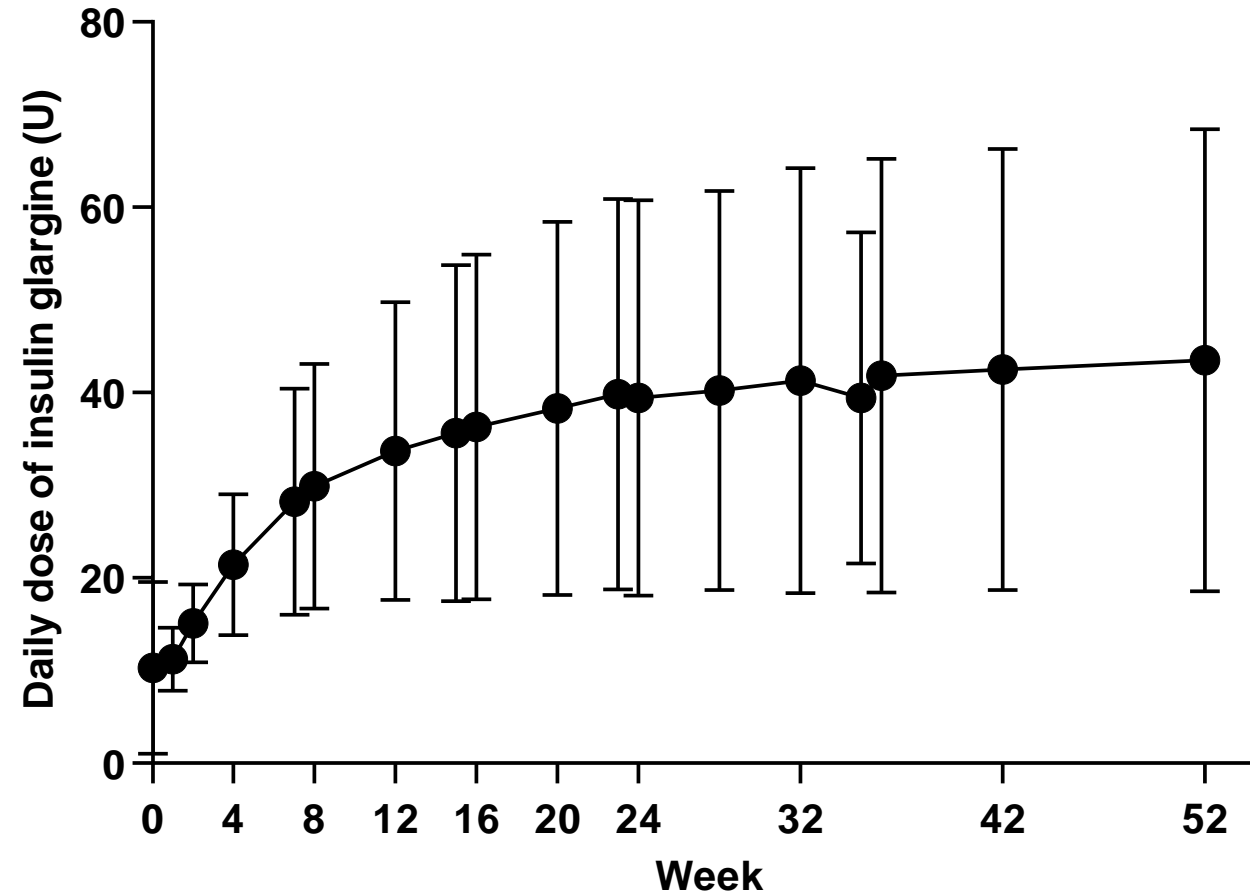
SURPASS-4



Note: Six participants (one each on tirzepatide 5 mg and 15 mg, two each on tirzepatide 10 mg and glargine) discontinued study medication due to inadvertent enrolment and were excluded from efficacy analyses. 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 (Randomised 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; TZP=Tirzepatide. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

Mean Daily Dose of Insulin Glargine Over Time

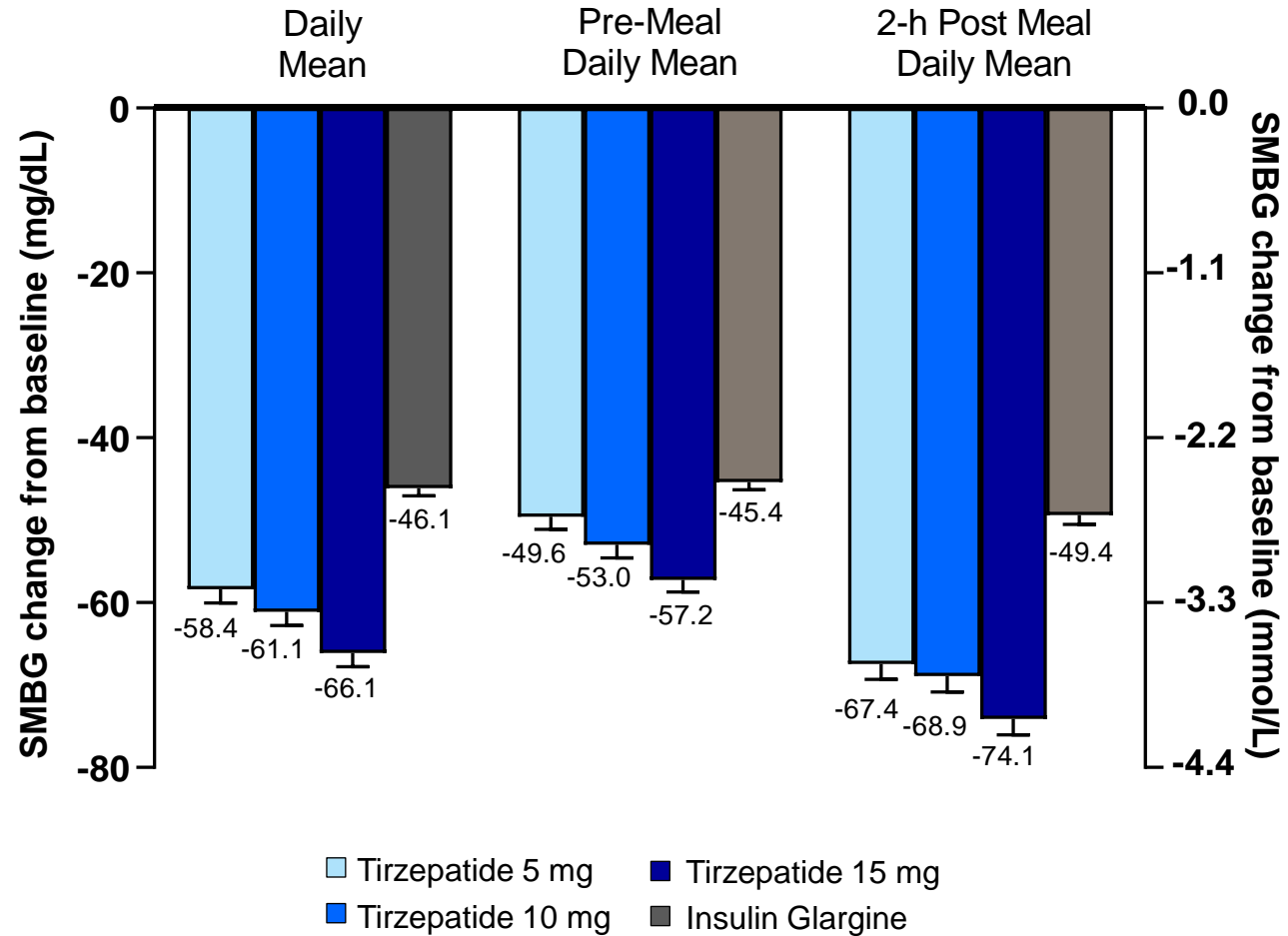
SURPASS-4



Note: Data are Mean (SD), mITT population (safety analysis set).
mITT=Modified Intention-to-Treat; SD=Standard Deviation.
Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

SMBG Change from Baseline at Week 52

SURPASS-4



Note: Data are LSM (SE) from MMRM analysis, mITT population (efficacy analysis set).

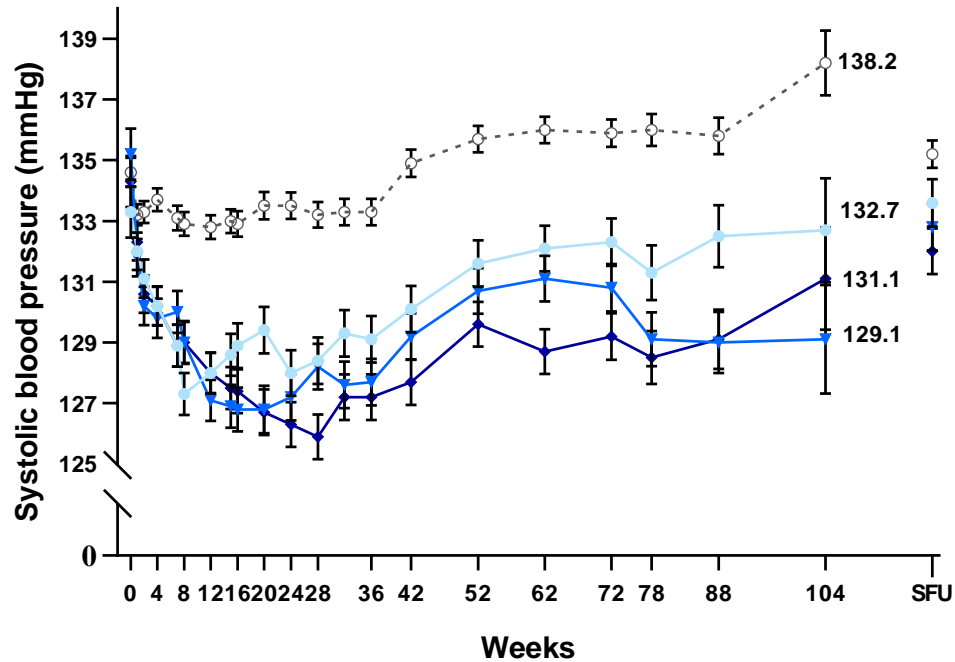
LSM=Least Squares Mean; mITT=Modified Intention-to-Treat; MMRM=Mixed Model Repeated Measures; SE=Standard Error; SMBG=Self-Monitored Blood Glucose.

Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

Change from Baseline in Blood Pressure Over Time to Week 104

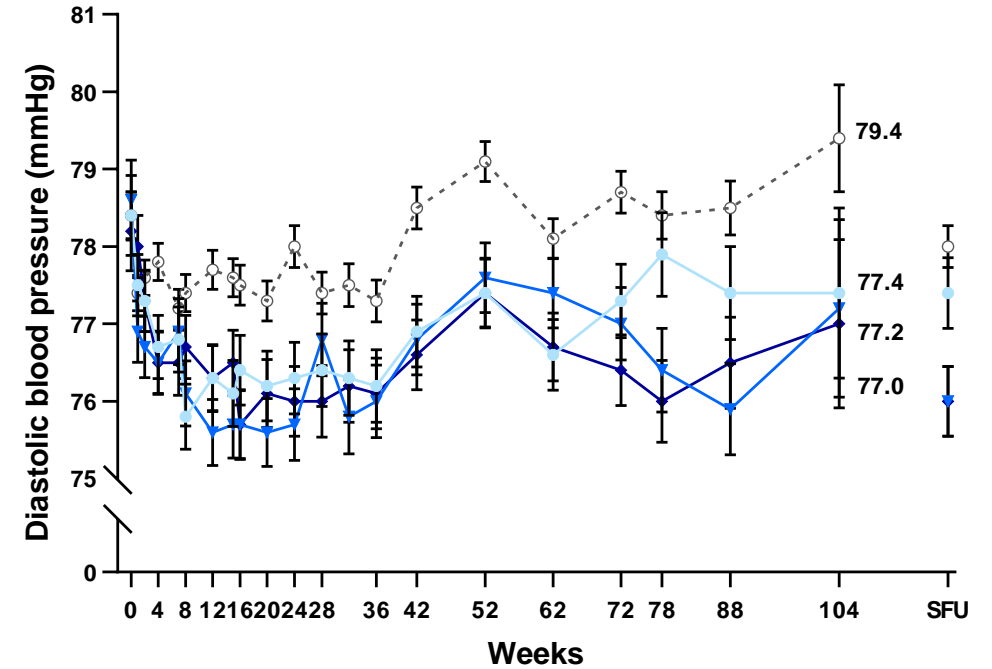
SURPASS-4

Systolic Blood Pressure



	Weeks	Weeks	Weeks
All TZP (n)	994	934	642
Glargine (n)	995	917	618
			120
			104

Diastolic Blood Pressure



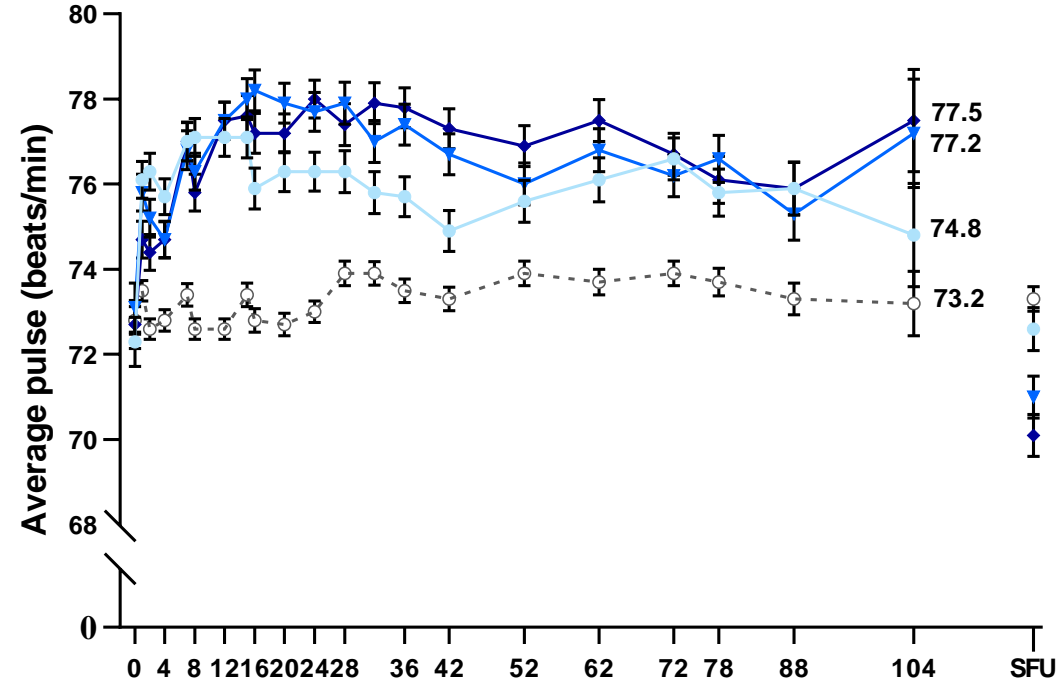
	Weeks	Weeks	Weeks
All TZP (n)	994	934	642
Glargine (n)	995	917	618
			120
			104

- Tirzepatide 5 mg
- Tirzepatide 15 mg
- ▼ Tirzepatide 10 mg
- Insulin Glargine

Note: Data are LSM (SE) from MMRM analysis, mITT population (safety analysis set). n indicates the numbers of participants with baseline and postbaseline values who received tirzepatide and glargine at specific time points. LSM=Least Squares Mean; mITT=Modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; SE=Standard Error; TZP=Tirzepatide.
 Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

Change from Baseline in Pulse Rate Over Time to Week 104

SURPASS-4



	Weeks	Weeks	Weeks
All TZP (n)	994	934	642
Glargine (n)	995	917	618
			120
			104

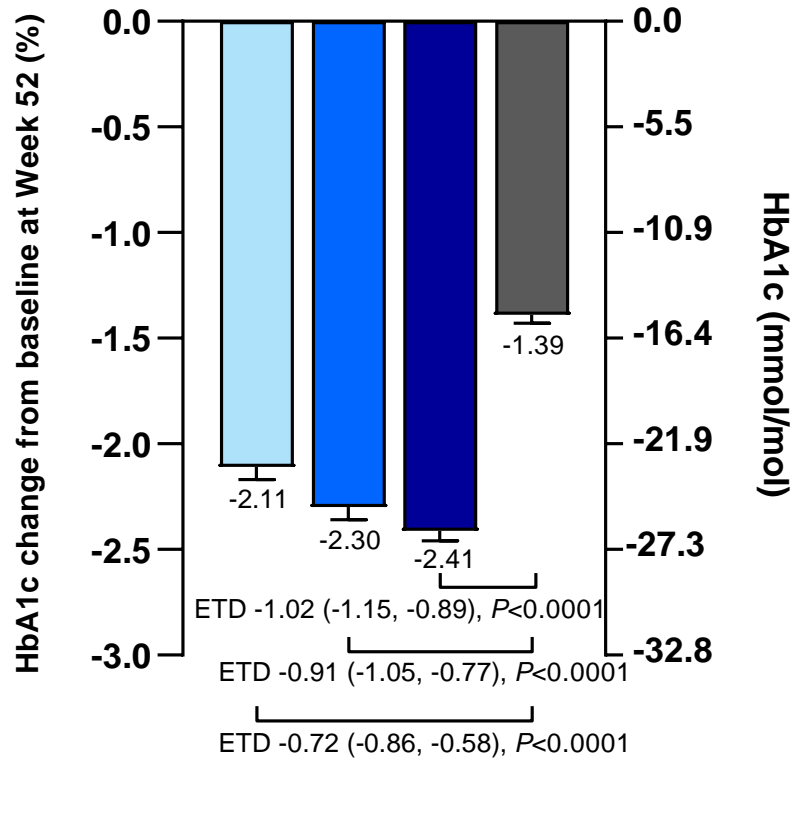
- Tirzepatide 5 mg
- ▼ Tirzepatide 10 mg
- ◆ Tirzepatide 15 mg
- Insulin Glargine

Note: Data are LSM (SE) from MMRM analysis, mITT population (safety analysis set). n indicates the numbers of participants with baseline and postbaseline values who received tirzepatide and glargine at specific time points. LSM=Least Squares Mean; mITT=Modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; SE=Standard Error; TZP=Tirzepatide. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

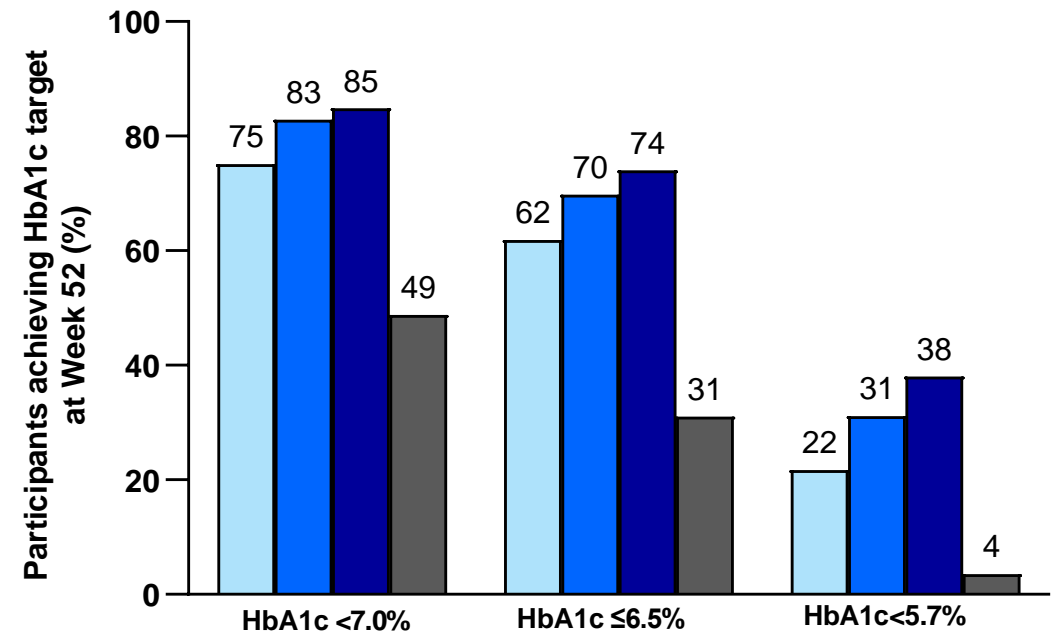
HbA1c: Treatment-Regimen Estimand

SURPASS-4

Change from Baseline in HbA1c at Week 52
(Treatment-Regimen Estimand)



% of Participants Reaching HbA1c Goals at Week 52
(Treatment-Regimen Estimand)



Note: Data are LSM (SE); mITT population (full analysis set). ETD versus insulin glargine are LSM (95% CI) at Week 52. Change from baseline in HbA1c from ANCOVA analysis with multiple imputation according to treatment for the missing HbA1c at 52 weeks. Proportion of people achieving HbA1c targets <7.0%, ≤6.5% and <5.7% at Week 52 are based on imputed data and calculated by combining proportion of participants achieving target in imputed datasets using Rubin's rule.

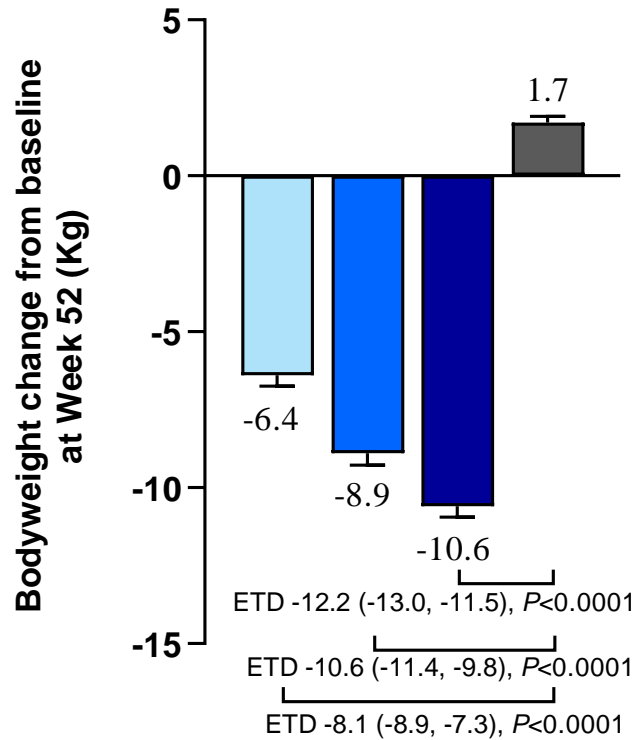
ANCOVA=Analysis of Covariance; CI=Confidence Interval; ETD=Estimated Treatment Difference; HbA1c=Glycated Haemoglobin; LSM=Least Squares Mean; mITT=Modified Intent-to-Treat; SE=Standard Error.

Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

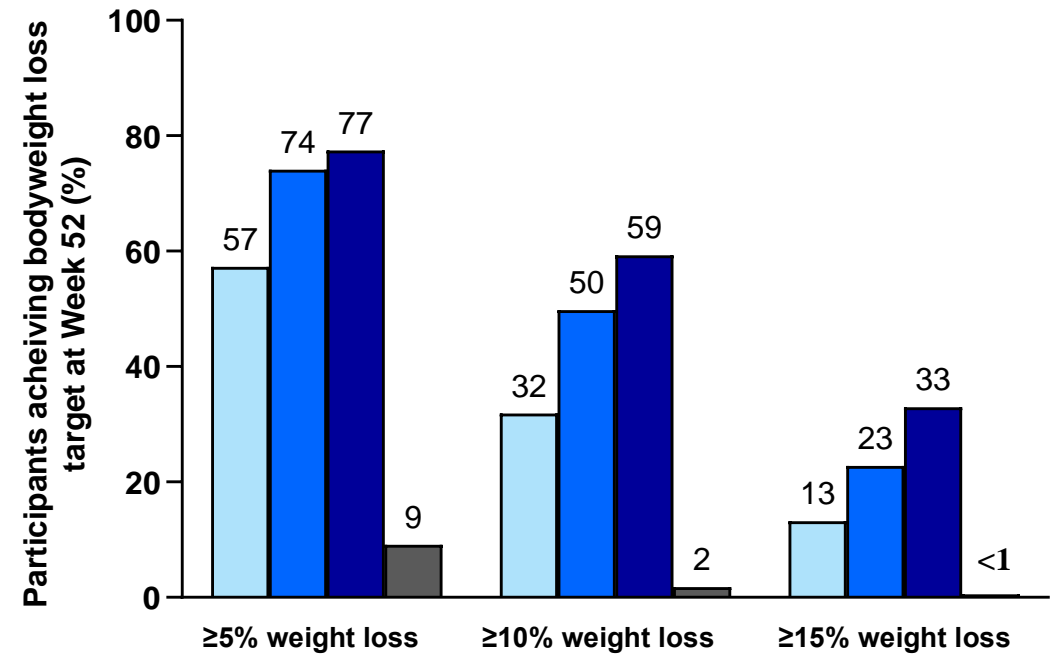
Body Weight: Treatment-Regimen Estimand

SURPASS-4

Change from Baseline in Body Weight at Week 52
(Treatment-Regimen Estimand)



% of Participants Achieving Weight Loss Goals at Week 52
(Treatment-Regimen Estimand)



■ Tirzepatide 5 mg ■ Tirzepatide 15 mg
■ Tirzepatide 10 mg ■ Insulin Glargine

Note: Data are LSM (SE); mITT population (full analysis set). ETD versus insulin glargine are LSM (95% CI) at Week 52. Change from baseline in body weight from ANCOVA analysis with multiple imputation according to treatment for the missing HbA1c at 52 weeks. Proportion of people achieving HbA1c targets <7.0%, ≤6.5% and <5.7% at Week 52 are based on imputed data and calculated by combining proportion of participants achieving target in imputed datasets using Rubin's rule.

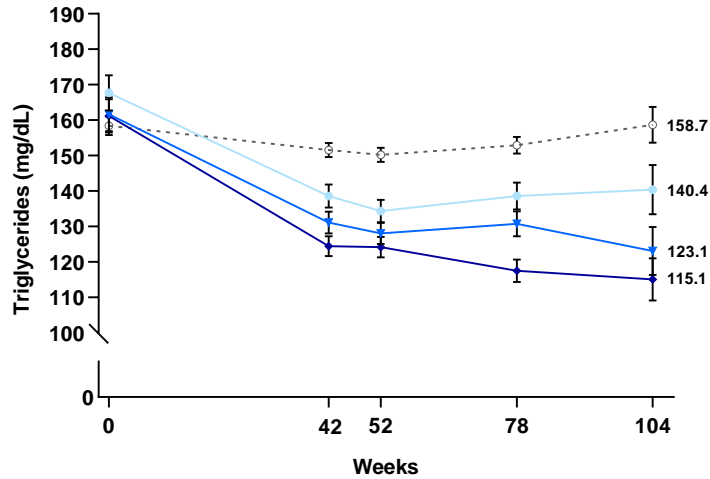
ANCOVA=Analysis of Covariance; CI=Confidence Interval; ETD=Estimated Treatment Difference; LSM=Least Squares Mean; mITT=Modified Intent-to-Treat; SE=Standard Error.

Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.

Change from Baseline in Lipids Over Time to Week 104

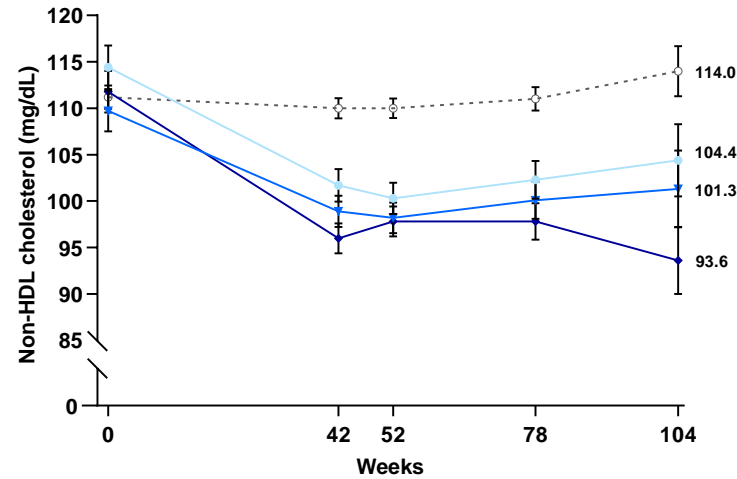
SURPASS-4

Triglycerides



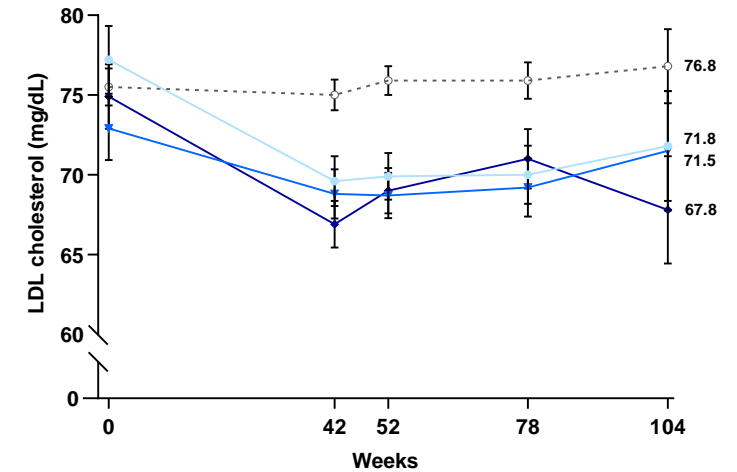
Weeks	0	42	52	78	104
All TZP (n)	877	858 846	574	574	104
Glargine (n)	907	855 871	579	579	93

Non-HDL Cholesterol



Weeks	0	42	52	78	104
All TZP (n)	876	857 845	575	575	104
Glargine (n)	907	854 871	580	580	93

LDL Cholesterol



Weeks	0	42	52	78	104
All TZP (n)	877	858 846	574	574	104
Glargine (n)	907	854 871	579	579	93

● Tirzepatide 5 mg ◆ Tirzepatide 15 mg
▼ Tirzepatide 10 mg ○ Insulin Glargine

Note: Data are Estimate (SE) from MMRM analysis using log transformation, mITT population (efficacy analysis set). n indicates the numbers of participants with baseline and postbaseline values who received tirzepatide and glargine at specific time points.

HDL-C=High-Density Lipoprotein-Cholesterol; LDL-C=Low-Density Lipoprotein-Cholesterol; mITT=Modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; SE=Standard Error; TZP=Tirzepatide..

Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824.