Efficacy and Safety of Tirzepatide, a Dual GIP/GLP-1 Receptor Agonist, Compared to Insulin Degludec in Patients with Type 2 Diabetes (SURPASS-3)

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Presenter Disclosure

Dr. Bernhard Ludvik

Consultancy: Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, MSD, Novo Nordisk, and Sanofi

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Objectives

Primary Objective:

- To demonstrate that TZP 10 mg and/or 15 mg once weekly are noninferior to insulin degludec 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 insulin degludec for change from baseline in HbA1c at 52 weeks
- TZP 5 mg, 10 mg, and/or 15 mg are superior to insulin degludec for change from baseline in
  - body weight at 52 weeks
  - HbA1c at 52 weeks
- TZP 5 mg, 10 mg, and/or 15 mg are superior to insulin degludec for the proportion of participants with HbA1c target value of <7.0% (<53 mmol/mol) at 52 weeks

Abbreviations: HbA1c = hemoglobin A1c; TZP = tirzepatide.

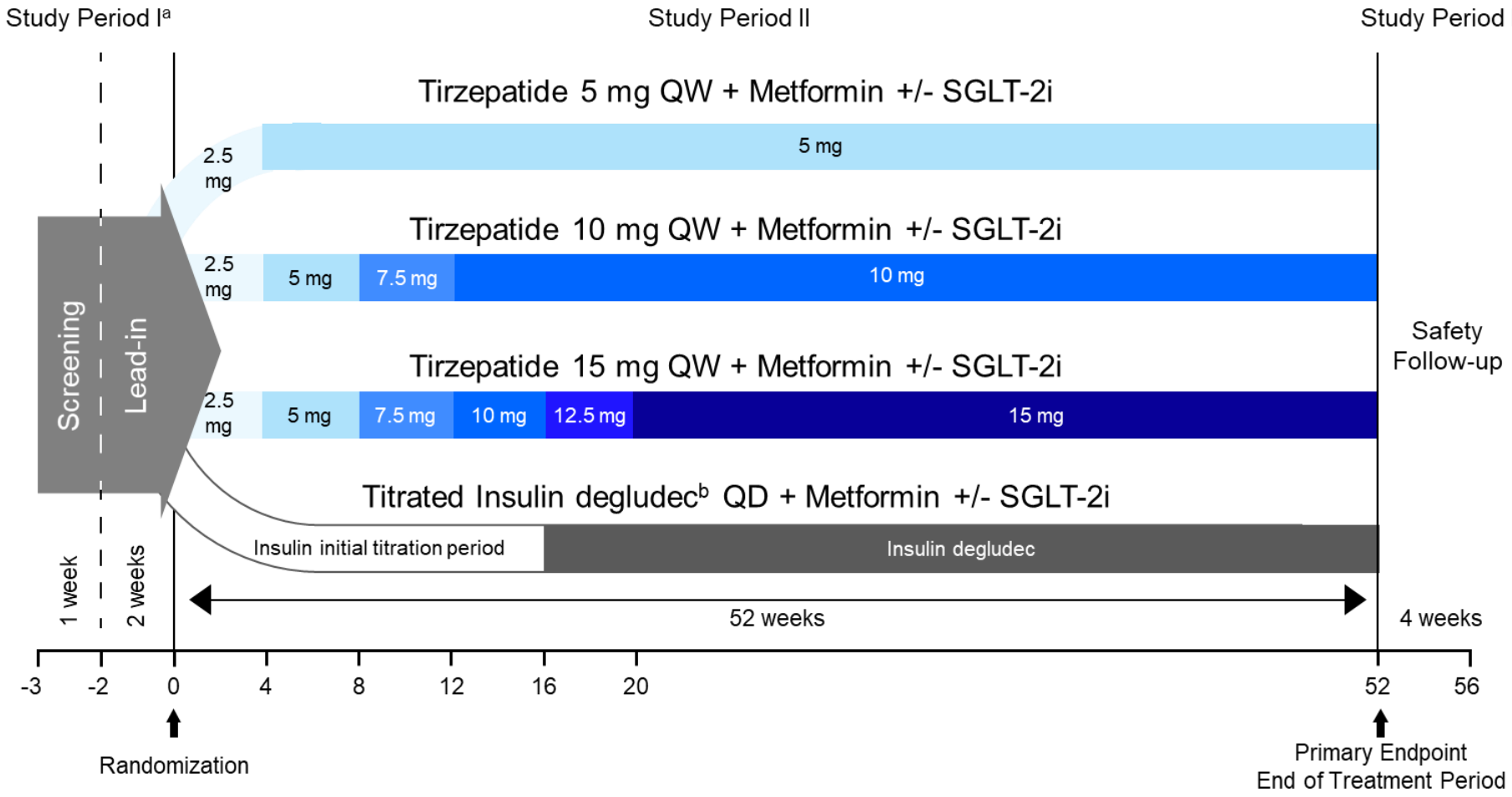
Study Design

Key Inclusion Criteria

- Type 2 diabetes
- HbA1c ≥7.0% to ≤10.5% at screening
- BMI ≥25 kg/m^2 with stable weight
- Naïve to insulin therapy (except short-term use or treatment of gestational diabetes)
- On stable dose of metformin, with or without SGLT-2i

Key Exclusion Criteria

- Type 1 diabetes
- History of pancreatitis
- eGFR <45 mL/min/1.73 m^2



Participating Countries: Argentina, Austria, Greece, Hungary, Italy, Poland, Puerto Rico, Romania, South Korea, Spain, Taiwan, Ukraine, and the USA.

[a]Stable doses of metformin (≥1500 mg/day) ± SGLT-2i for ≥3 months prior to Visit 1 and during the screening/lead-in period.

[b]The starting dose of insulin degludec was 10 U/day ideally at bedtime, titrated to a FBG <90 mg/dL, following a treat-to-target algorithm.

Abbreviations: BMI = body mass index; eGFR = estimated glomerular filtration rate; FBG = fasting blood glucose; HbA1c = hemoglobin A1c; QD = once daily; QW = once weekly; SGLT-2i = sodium-glucose cotransporter-2 inhibitor.

Baseline Demographics and Clinical Characteristics

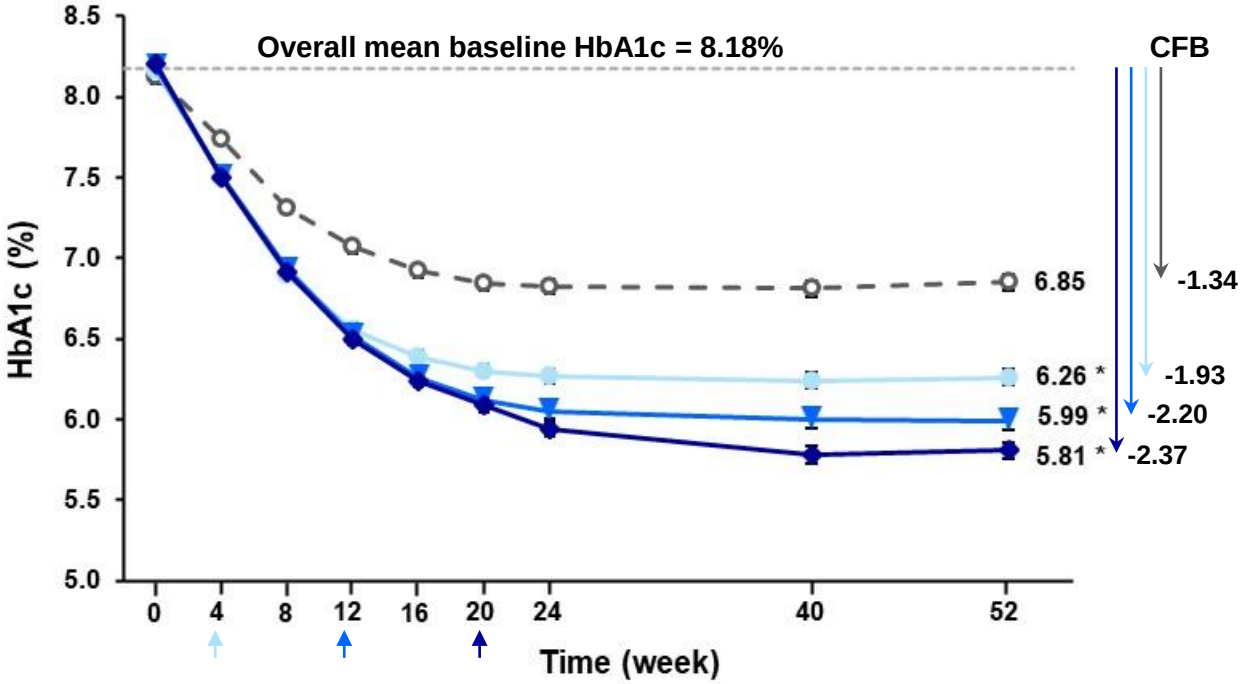
Baseline demographics and clinical characteristics were well balanced across the treatment groups

Parameter (mean ± SD, unless otherwise specified)	Tirzepatide 5 mg N=358	Tirzepatide 10 mg N=360	Tirzepatide 15 mg N=359	Insulin Degludec N=360	Total N=1437
Age (years)	57.2 ± 10.1	57.4 ± 9.7	57.5 ± 10.2	57.5 ± 10.1	57.4 ± 10.0
Female, n (%)	158 (44.1)	165 (45.8)	165 (46.0)	147 (40.8)	635 (44.2)
Race, n (%)					
Asian	20 (5.6)	19 (5.3)	20 (5.6)	17 (4.7)	76 (5.3)
Black or African American	13 (3.6)	12 (3.3)	8 (2.2)	11 (3.1)	44 (3.1)
White	323 (90.2)	328 (91.1)	327 (91.1)	329 (91.4)	1307 (91.0)
Duration of diabetes (years)	8.5 ± 5.83	8.4 ± 6.59	8.5 ± 6.47	8.1 ± 6.04	8.4 ± 6.24
HbA1c (%)	8.17 ± 0.89	8.18 ± 0.89	8.21 ± 0.94	8.12 ± 0.94	8.17 ± 0.91
≤8.5%, n (%)	248 (69.3)	249 (69.2)	252 (70.2)	256 (71.1)	1005 (69.9)
>8.5%, n (%)	110 (30.7)	111 (30.8)	107 (29.8)	104 (28.9)	432 (30.1)
Fasting serum glucose (mg/dL)	171.7 ± 47.86	170.4 ± 47.64	168.4 ± 45.95	166.7 ± 41.90	169.3 ± 45.89
On metformin alone, n (%)	246 (68.7)	242 (67.2)	247 (68.8)	244 (67.8)	979 (68.1)
On metformin + SGLT-2i, n (%)	112 (31.3)	118 (32.8)	112 (31.2)	116 (32.2)	458 (31.9)
Weight (kg)	94.4 ± 18.86	93.8 ± 19.81	94.9 ± 20.98	94.0 ± 20.59	94.3 ± 20.06
Body mass index (kg/m^2)	33.6 ± 5.87	33.4 ± 6.21	33.7 ± 6.11	33.4 ± 6.06	33.5 ± 6.06
eGFR (CKD-EPI, ml/min/1.73 m^2)	95.1 ± 17.22	93.7 ± 16.90	93.1 ± 17.25	94.6 ± 16.78	94.1 ± 17.04

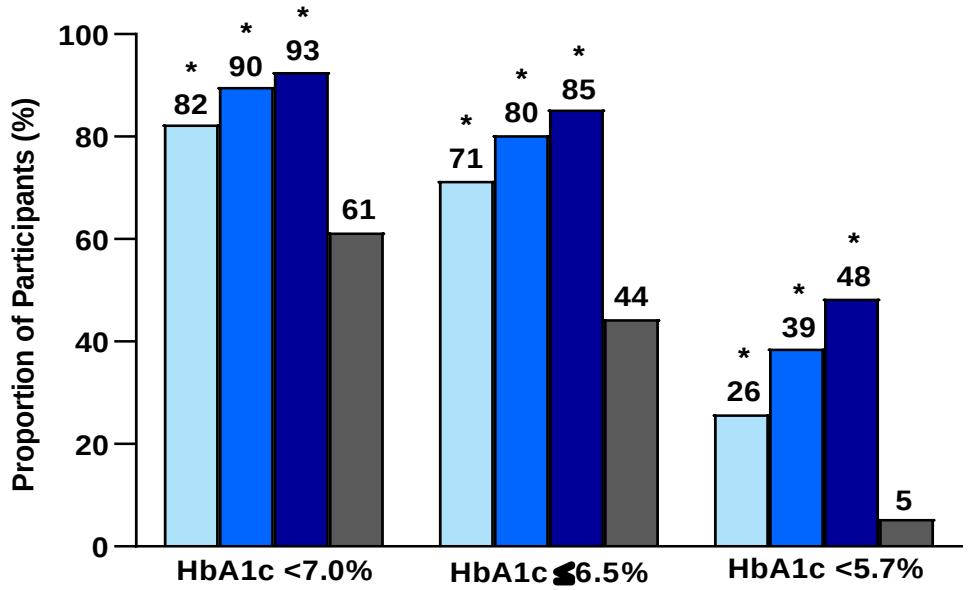
Abbreviations: CKD-EPI = Chronic Kidney Disease-Epidemiology; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; n = number of patients in the specified category; N = all randomly assigned participants who took at least 1 dose of study drug (modified Intent-to-Treat population); SD = standard deviation; SGLT-2i = sodium-glucose co-transporter-2 inhibitor.

HbA1c

HbA1c over Time and Change from Baseline at Week 52



% of Participants Achieving HbA1c Goals at Week 52



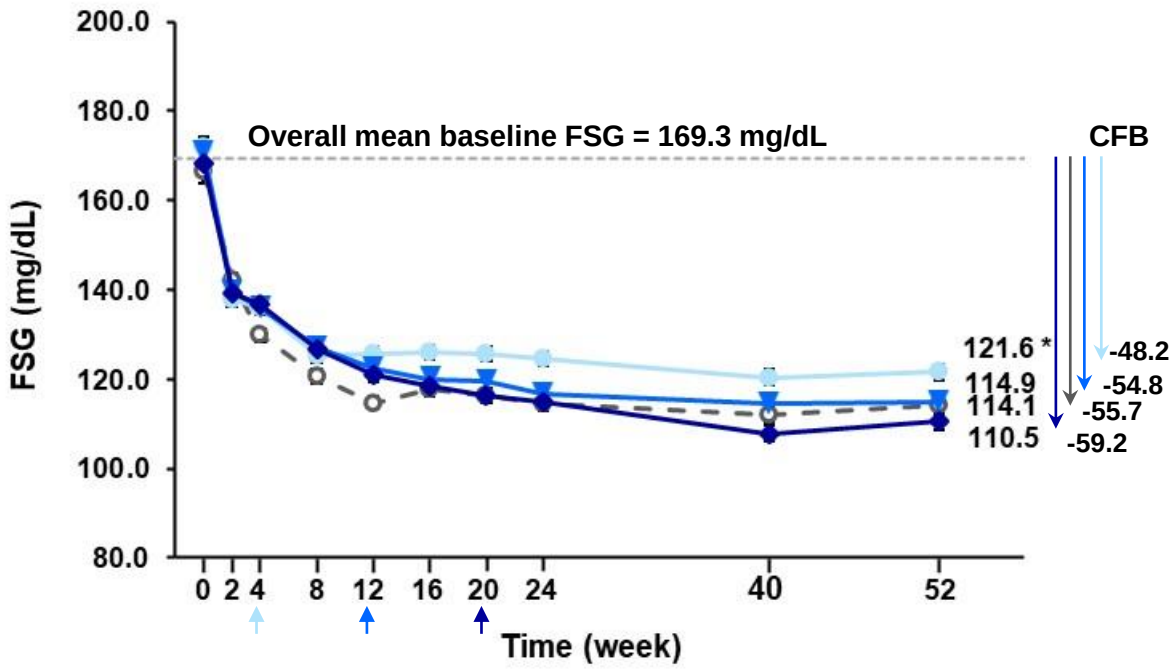
Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg Insulin Degludec

Data on left panel are LSM (SE); MMRM analysis. Data on right panel are estimated mean; Logistic regression. mITT (efficacy analysis set). Arrows on X-axis in overtime plot indicate when the maintenance dose of tirzepatide 5 mg, 10 mg, and 15 mg was initiated. Mean insulin degludec dose at Week 52 was 48.8 U/day. Estimated treatment difference (95% CI) of tirzepatide vs. insulin degludec was: i) 5 mg, -0.59%* (-0.73, -0.45); ii) 10 mg, -0.86%* (-1.00, -0.72); and iii) 15 mg, -1.04%* (-1.17, -0.90). *p<0.001 vs. insulin degludec.

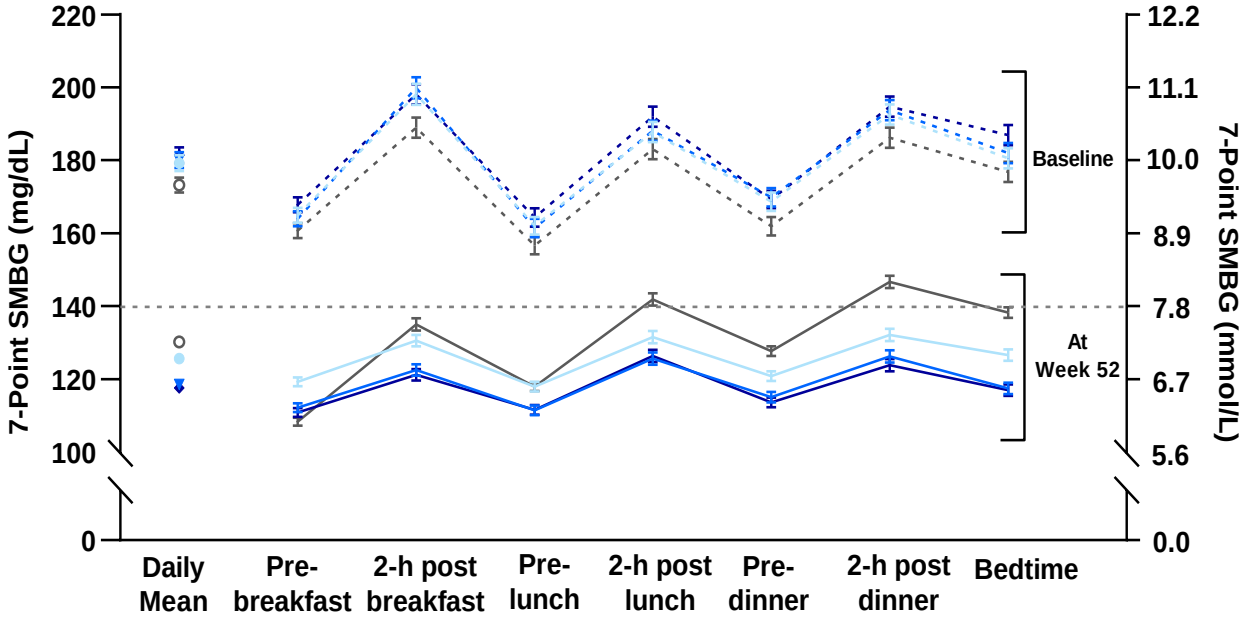
Abbreviations: CFB = change from baseline; CI = confidence interval; FSG = fasting serum glucose; HbA1c = hemoglobin A1c; LSM = least-squares mean; mITT = modified Intent-to-Treat; MMRM = mixed model repeated measures; SE = standard error.

Additional Glycemic Efficacy Results

FSG over Time and Change from Baseline at Week 52



7-Point SMBG Profile at Baseline and at Week 52

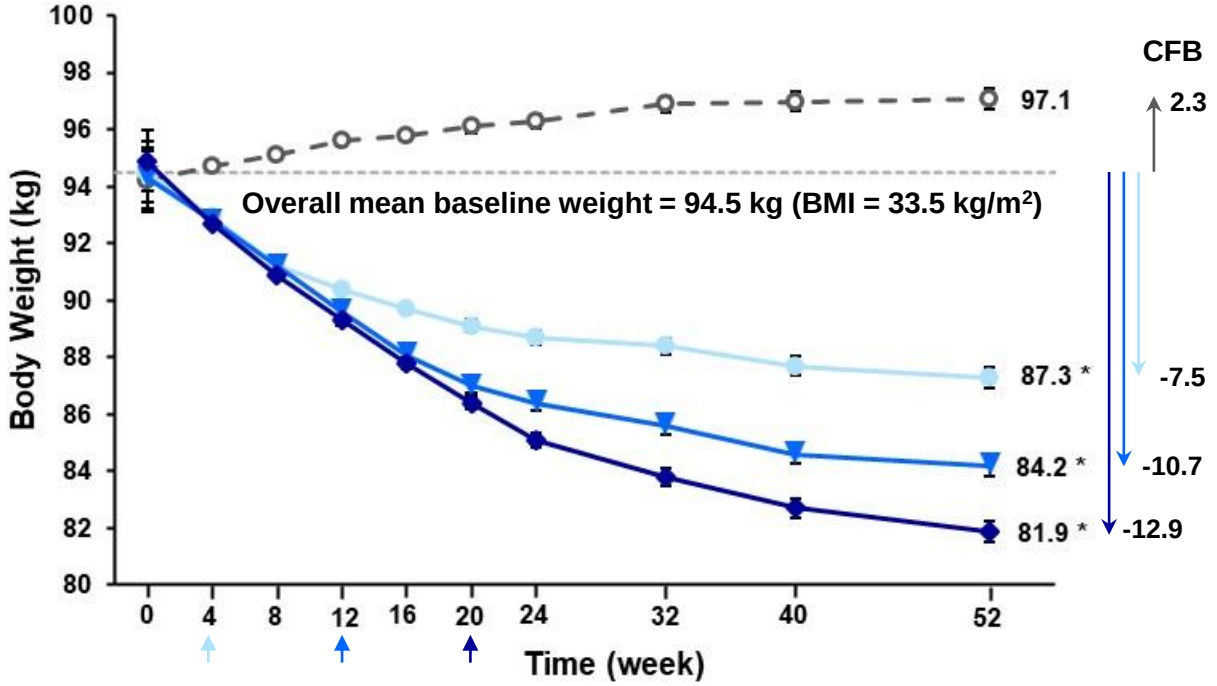


Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg Insulin Degludec

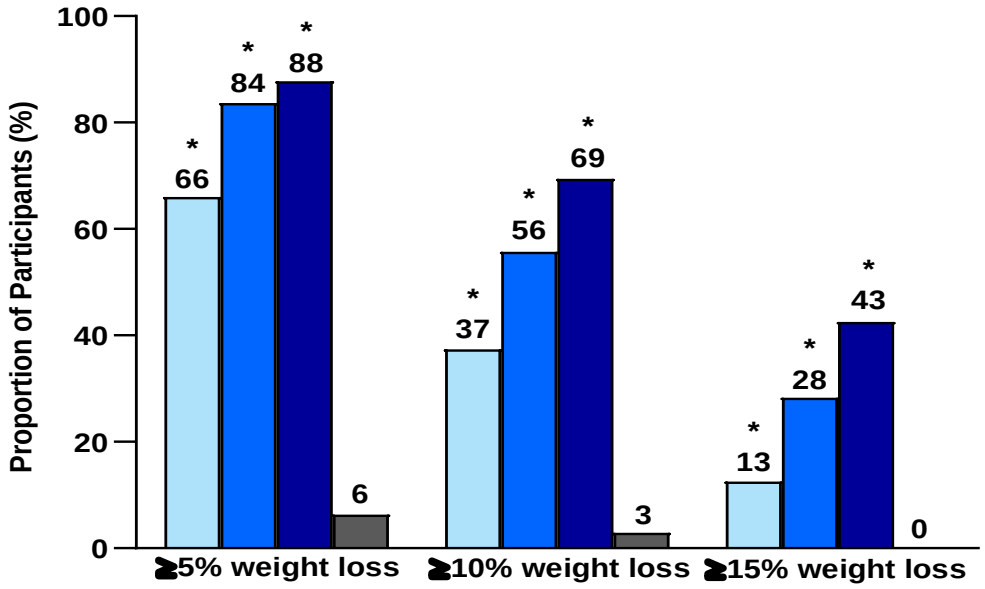
Data are LSM (SE); mITT (efficacy analysis set). MMRM analysis. Arrows on X-axis in overtime plot indicate when the maintenance dose of tirzepatide 5 mg, 10 mg, and 15 mg was initiated. Estimated treatment difference (95% CI) of tirzepatide vs. insulin degludec was: i) 5 mg, 7.5 mg/dL* (2.4, 12.5); ii) 10 mg, 0.8 mg/dL (-4.3, 5.9); and iii) 15 mg, -3.6 mg/dL (-8.7, 1.5). *p=0.004 vs. insulin degludec. Abbreviations: CFB = change from baseline; CI = confidence interval; FSG = fasting serum glucose; LSM = least-squares mean; mITT = modified Intent-to-Treat; MMRM = mixed model repeated measures; SE = standard error; SMBG = self-monitored blood glucose.

Body Weight

Body Weight over Time and Change from Baseline at Week 52



Proportion of Participants with Body Weight Loss Goals at Week 52



Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg Insulin Degludec

Data on left panel are LSM (SE); MMRM analysis. Data on right panel are estimated mean; Logistic regression. mITT (efficacy analysis set). Arrows on X-axis in overtime plot indicate when the maintenance dose of tirzepatide 5 mg, 10 mg, and 15 mg was initiated. Estimated treatment difference (95% CI) of tirzepatide vs. insulin degludec was: i) 5 mg, -9.8 kg* (-10.8, -8.8); ii) 10 mg, -13.0 kg* (-14.0, -11.9); and iii) 15 mg, -15.2 kg* (-16.2, -14.2). *p<0.001 vs. insulin degludec.

Abbreviations: BMI = body mass index; CFB = change from baseline; CI = confidence interval; LSM = least-squares mean; mITT = modified Intent-to-Treat; MMRM = mixed model repeated measures; SE = standard error.

Overview of Adverse Events through 52 Weeks

Parameter	TZP 5 mg N=358	TZP 10 mg N=360	TZP 15 mg N=359	Insulin Degludec N=360
TEAEs	219 (61.2)	248 (68.9)	263 (73.3)	193 (53.6)
SAEs	29 (8.1)	20 (5.6)[a]	26 (7.2)	22 (6.1)
Deaths[b]	1 (0.3)	2 (0.6)	1 (0.3)	1 (0.3)
Study discontinuation due to AE	6 (1.7)	9 (2.5)	4 (1.1)	2 (0.6)
Treatment discontinuation due to AE	25 (7.0)	37 (10.3)	39 (10.9)	5 (1.4)
TEAEs with ≥5% frequency in any arm				
Nausea	41 (11.5)	81 (22.5)	85 (23.7)	6 (1.7)
Diarrhea	55 (15.4)	60 (16.7)	56 (15.6)	14 (3.9)
Decreased appetite	22 (6.1)	37 (10.3)	43 (12.0)	2 (0.6)
Vomiting	21 (5.9)	34 (9.4)	36 (10.0)	4 (1.1)
Dyspepsia	15 (4.2)	32 (8.9)	18 (5.0)	0
Lipase increased	21 (5.9)	16 (4.4)	20 (5.6)	7 (1.9)
Nasopharyngitis	11 (3.1)	14 (3.9)	15 (4.2)	22 (6.1)
Abdominal pain	7 (2.0)	17 (4.7)	23 (6.4)	4 (1.1)
Hypertension	11 (3.1)	7 (1.9)	11 (3.1)	21 (5.8)

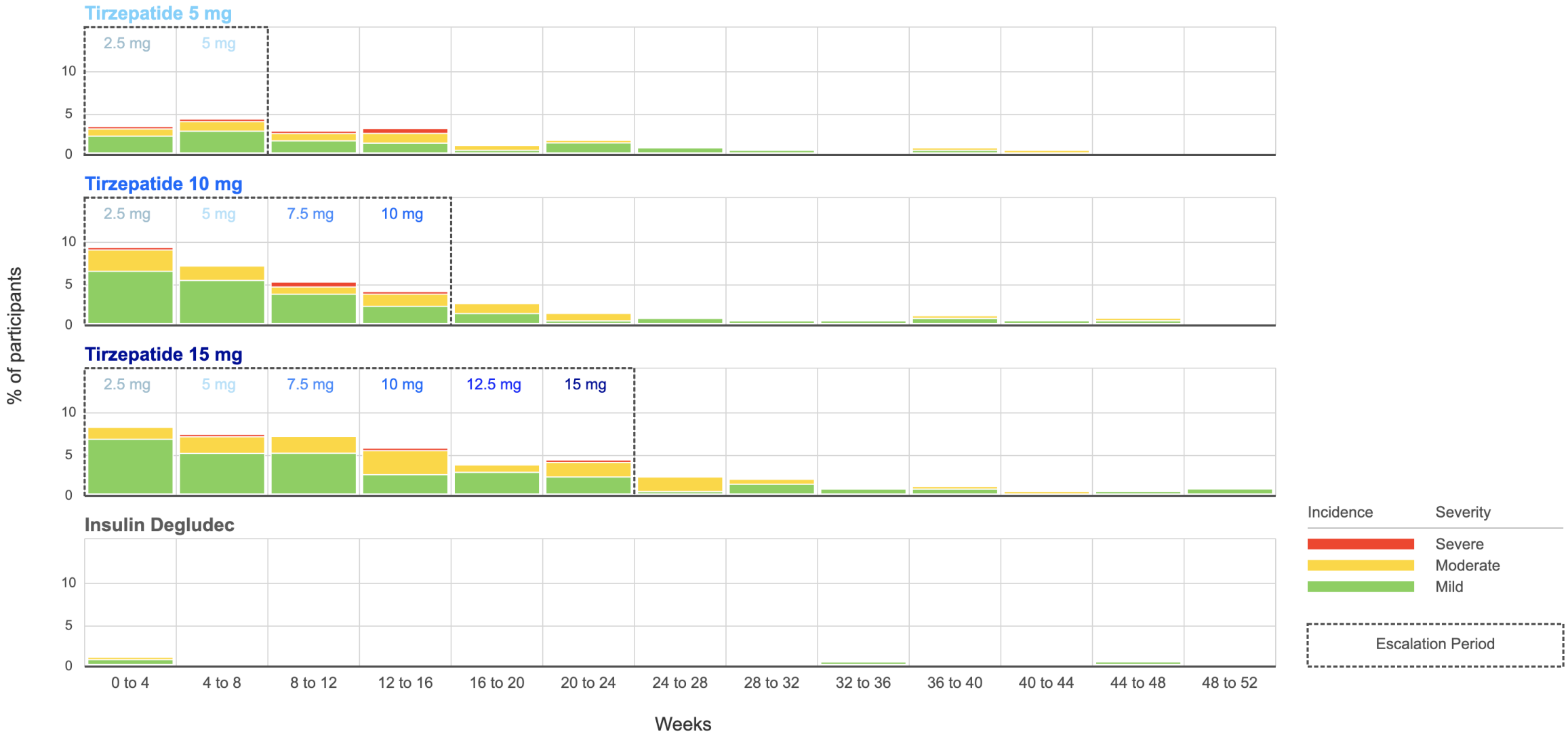
Data are n (%); mITT population (safety analysis set). Note: Patients may be counted in more than 1 category.

[a] One SAE is nonvalid because it occurred before randomization

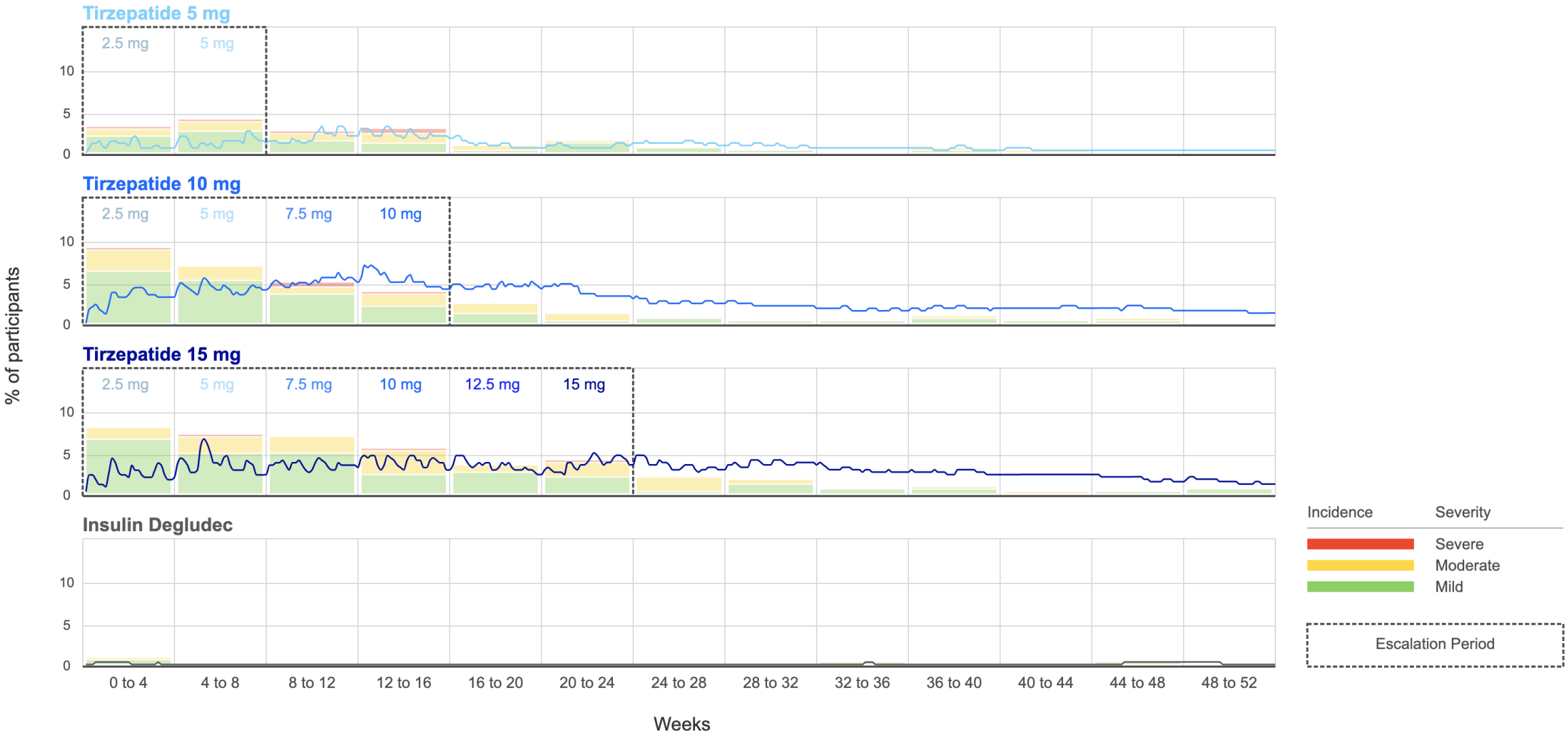
[b] Deaths are also included as SAEs and discontinuations due to AE.

Abbreviations: AE = adverse event; mITT = modified Intent-to-Treat; n = number of patients in the specified category; 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; TZP = tirzepatide.

Incidence of Nausea



Incidence and Prevalence of Nausea



Other TEAEs of Interest through Safety Follow-up

Parameter	TZP 5 mg N=358	TZP 10 mg N=360	TZP 15 mg N=359	Insulin Degludec N=360
Hypoglycemia (blood glucose <54 mg/dL or severe)[a]	5 (1.4)	4 (1.1)	8 (2.2)	26 (7.3)
Severe hypoglycemia[a]	0	0	1 (0.3)[b]	0
Injection site reaction	1 (0.3)	6 (1.7)	8 (2.2)	6 (1.7)
Cholelithiasis	2 (0.6)	1 (0.3)	1 (0.3)	0
Cholecystitis	0	0	1 (0.3)	0
Adjudicated pancreatitis	0	0	0	0
Malignant neoplasms	3 (0.8)	5 (1.4)	3 (0.8)	1 (0.3)

Data are n (%); mITT population (safety analysis set). Note: Patients may be counted in more than 1 category.
[a]Data after initiation of new glucose-lowering therapy not included.
[b]One episode of severe hypoglycemia was reported during the study for a patient assigned to the tirzepatide 15 mg group during the escalation period (Day 28).

Abbreviations: mITT = modified Intent-to-Treat; n = number of patients in the specified category; N = all randomly assigned participants who took at least 1 dose of study drug (mITT population); TEAEs = treatment-emergent adverse events; TZP = tirzepatide.

Conclusion

In patients with type 2 diabetes treated with metformin with or without SGLT-2i, once-weekly tirzepatide, a dual GIP/GLP-1 receptor agonist, demonstrated vs. insulin degludec:

- robust improvements in glycemic control
- significant reduction in body weight
- low risk of hypoglycemia (blood glucose <54 mg/dL or severe)
- greater incidence of GI AEs, consistent with the GLP-1 receptor agonist class

Abbreviations: AEs = adverse events; GI = gastrointestinal; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; SGLT-2i = sodium-glucose cotransporter-2 inhibitors.

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