Efficacy and Safety of Tirzepatide versus Semaglutide Once Weekly as Add-on Therapy to Metformin in People with Type 2 Diabetes (SURPASS-2)

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Presenter Disclosure

Dr. Juan P. Frias

Consultancy: Boehringer Ingelheim, Gilead, Johnson and Johnson, Eli Lilly and Company, Merck, Novo Nordisk and Sanofi

Grants: Eli Lilly and Company, AbbVie, Akcea, Allergan, AstraZeneca, Boehringer Ingelheim, BMS, Cirius, CymaBay, Enanta, Genentech, Intercept, Janssen, Johnson and Johnson, Lexicon, Ligand, Madrigal, Merck, Mylan, NGM, Novartis, Novo Nordisk, Pfizer, Sanofi and Theracos

Advisory board: Boehringer Ingelheim, Gilead, Johnson and Johnson, Eli Lilly and Company, Merck, Novo Nordisk and Sanofi

Speaker bureau: Merck and Sanofi

Objective

- **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

Study Design

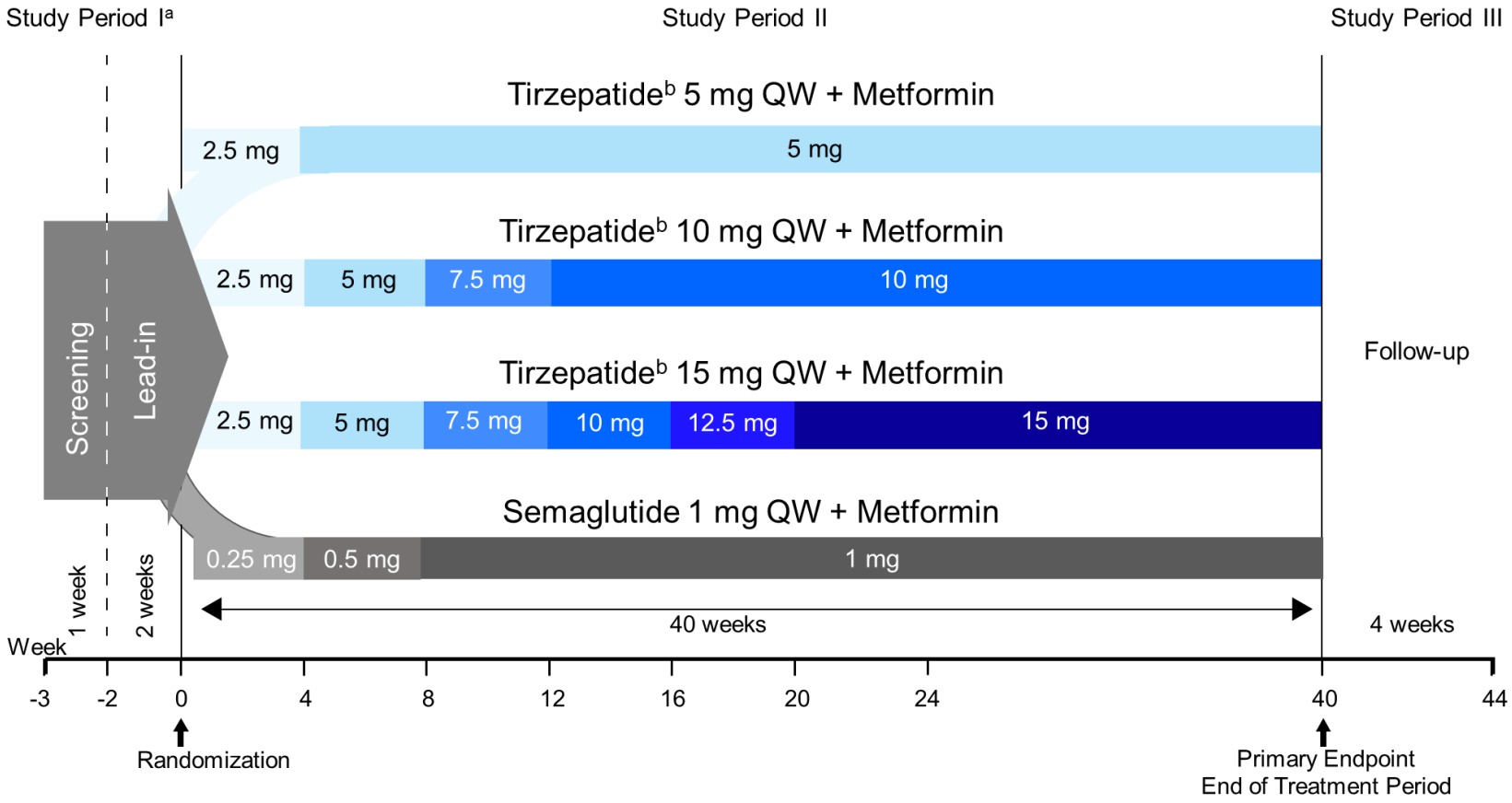
Randomized, open-label, active-controlled, parallel group, multicenter, multinational trial

Key Inclusion Criteria

- Type 2 diabetes
- 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 acute pancreatitis
- eGFR <45 mL/min/1.73 m^2
- Use of any antihyperglycemic treatment other than metformin in the 3 months prior to screening



Participating Countries: US, Argentina, Australia, Brazil, Canada, Israel, Mexico and UK.

[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 were double-blinded.

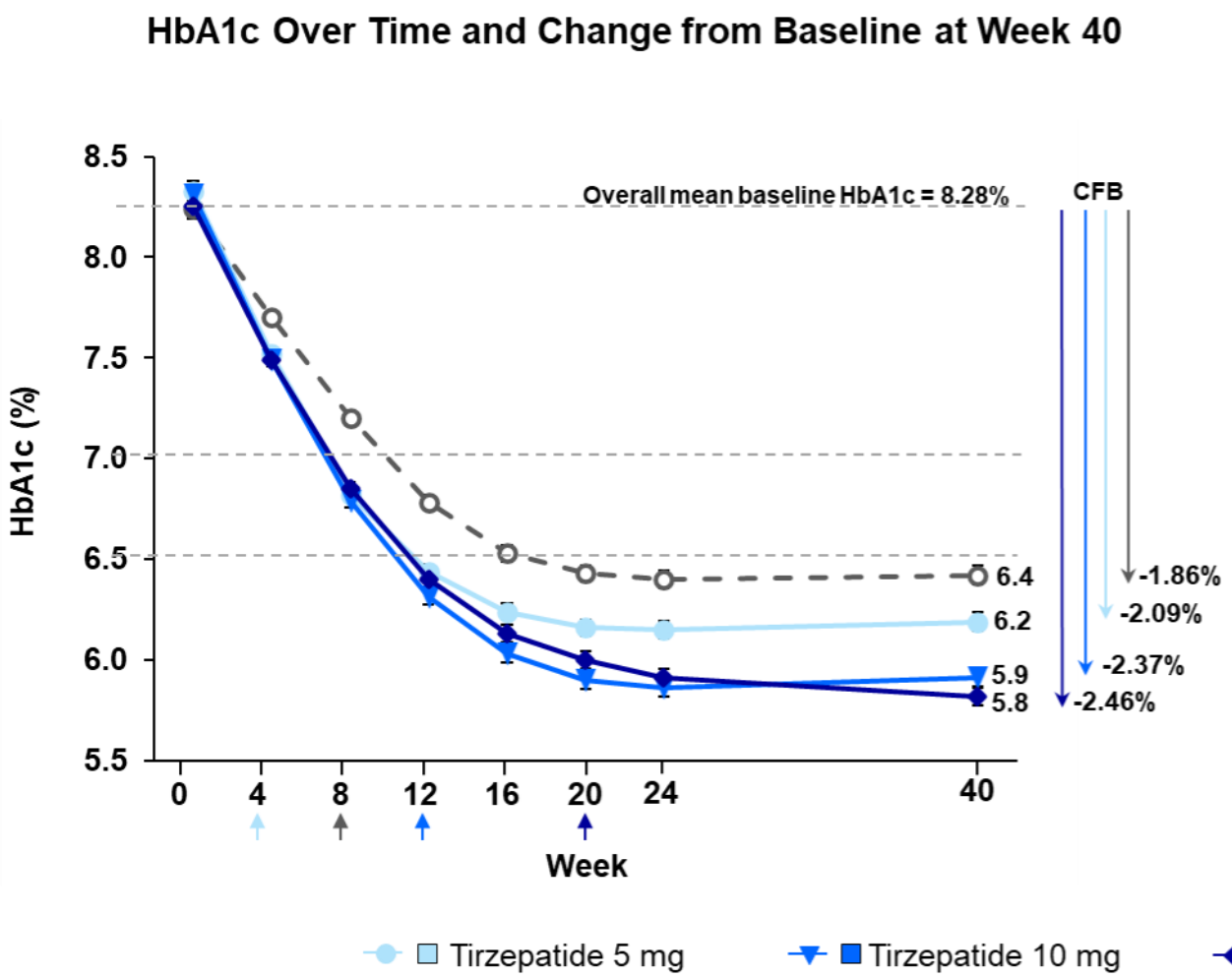
Baseline Demographics and Clinical Characteristics

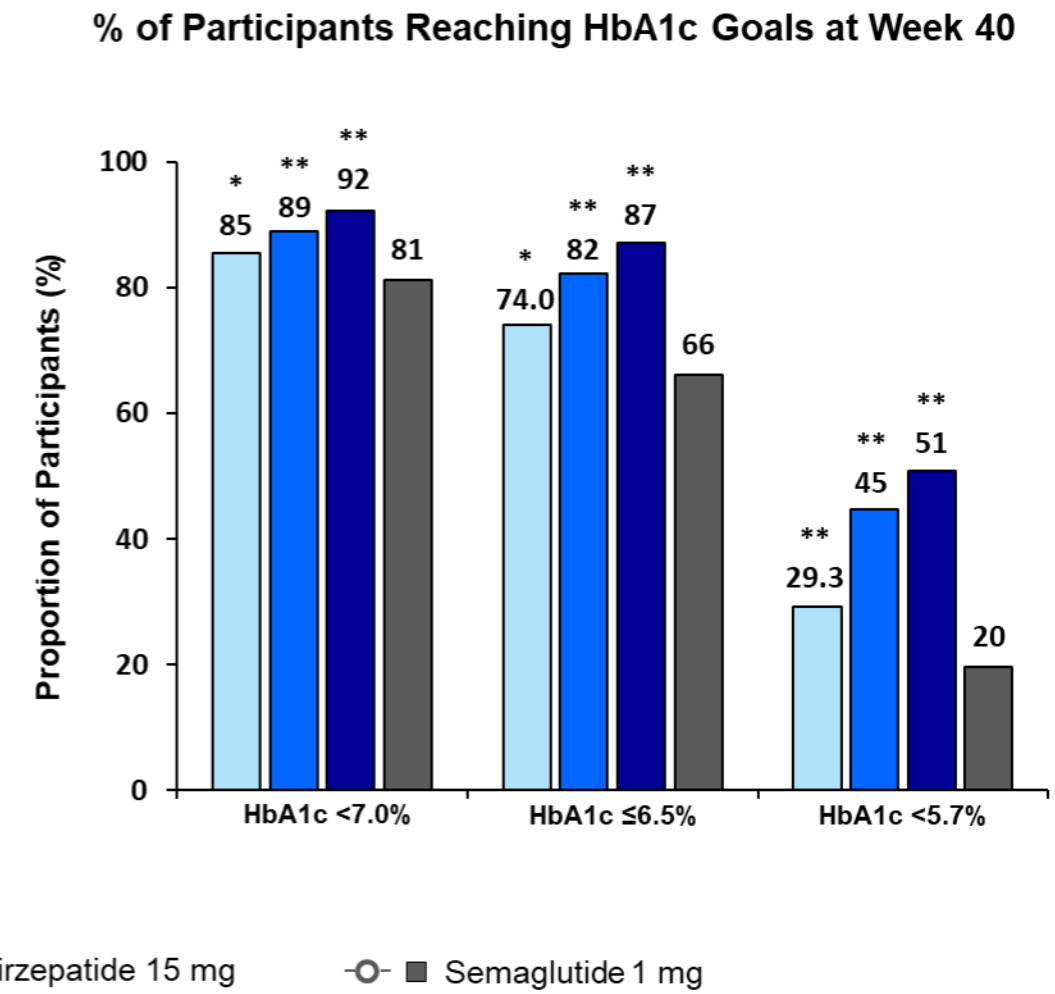
Baseline demographics and clinical characteristics were well balanced across the treatment groups.

Parameter	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

Data are mean ± SD, unless otherwise specified; mITT population

HbA1c

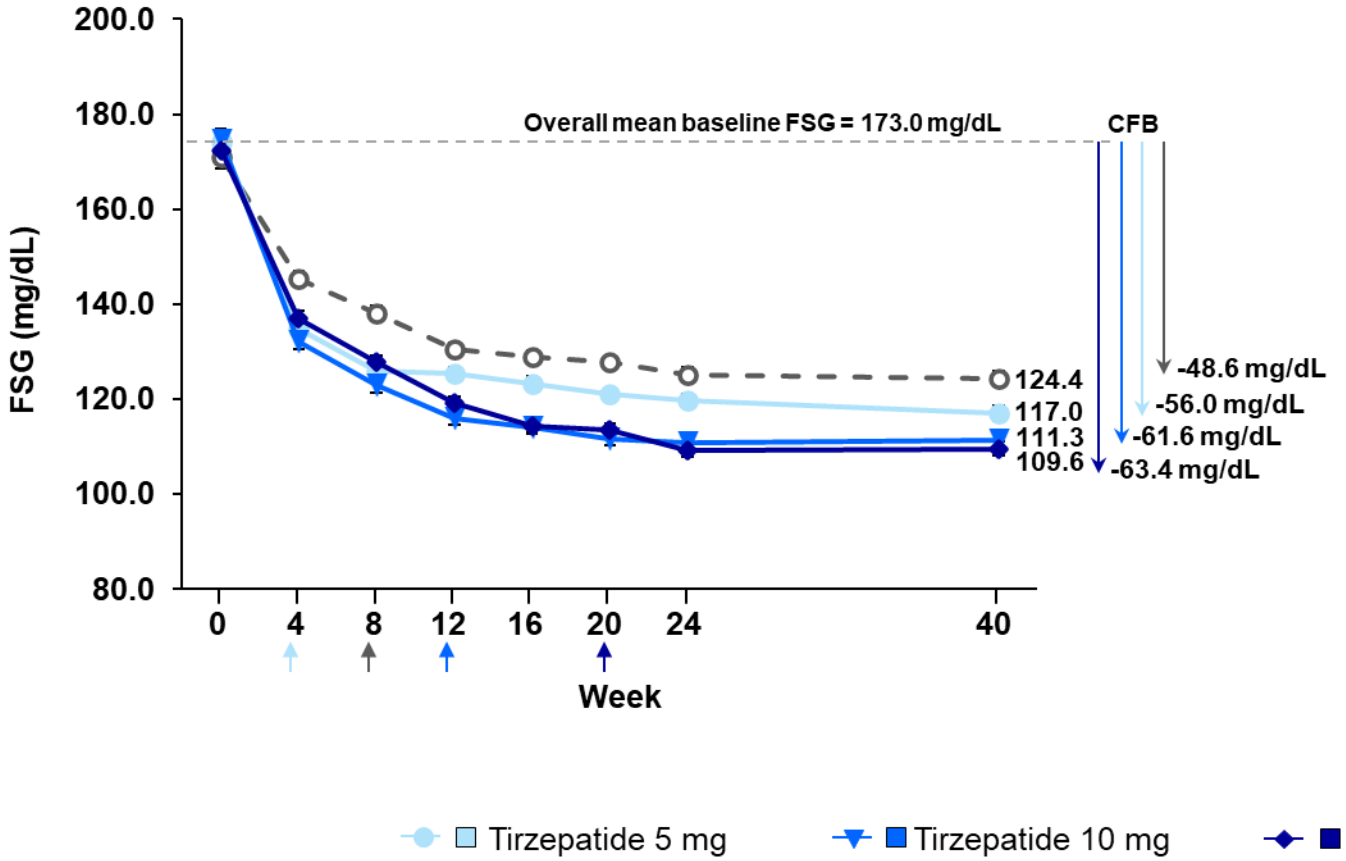




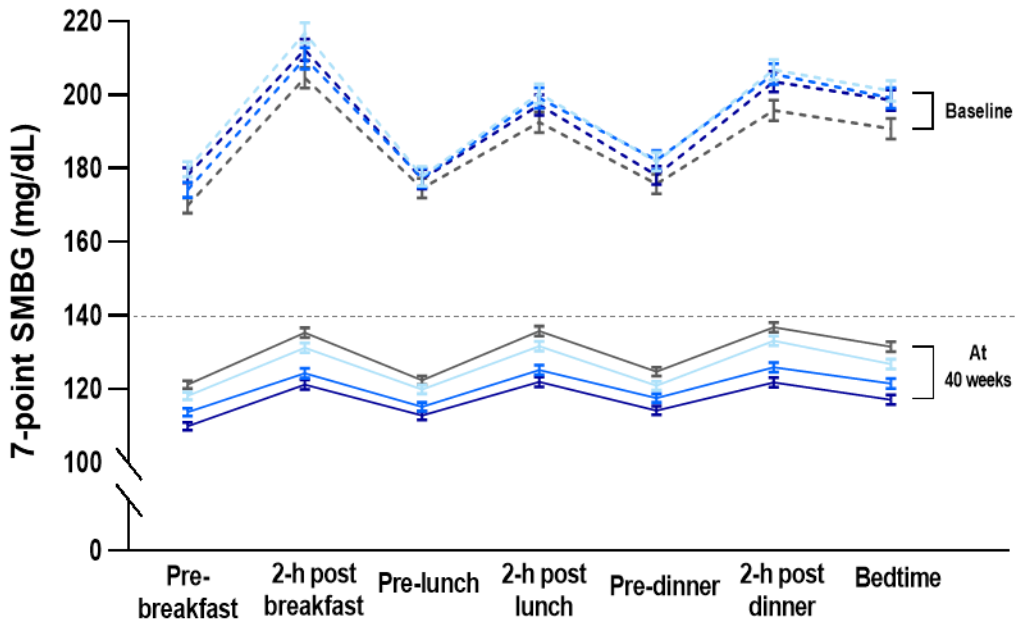
Data are LSM (SE); mITT (efficacy estimand) ANOVA analysis (week 0) and MMRM analysis (week 40). Arrows indicate when the maintenance dose of tirzepatide 5 mg, 10 mg and 15 mg and semaglutide 1 mg are achieved. Estimated treatment difference (95% CI) of tirzepatide vs semaglutide was: i) 5 mg -0.23** (-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. CFB=change from baseline

Additional Glycemic Efficacy Results

FSG Over Time and Change from Baseline at Week 40



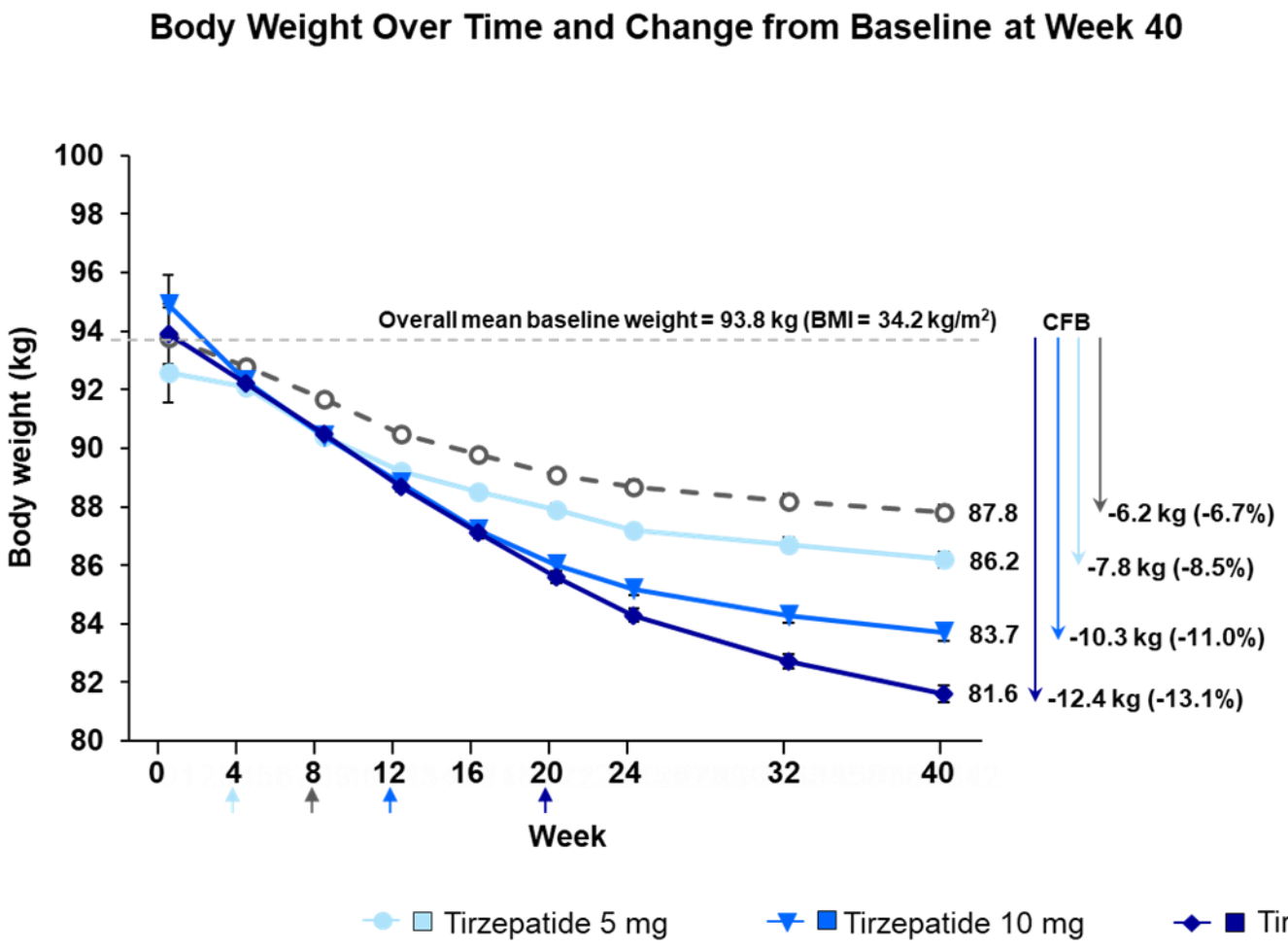
7-point SMBG Profile at Baseline and at Week 40

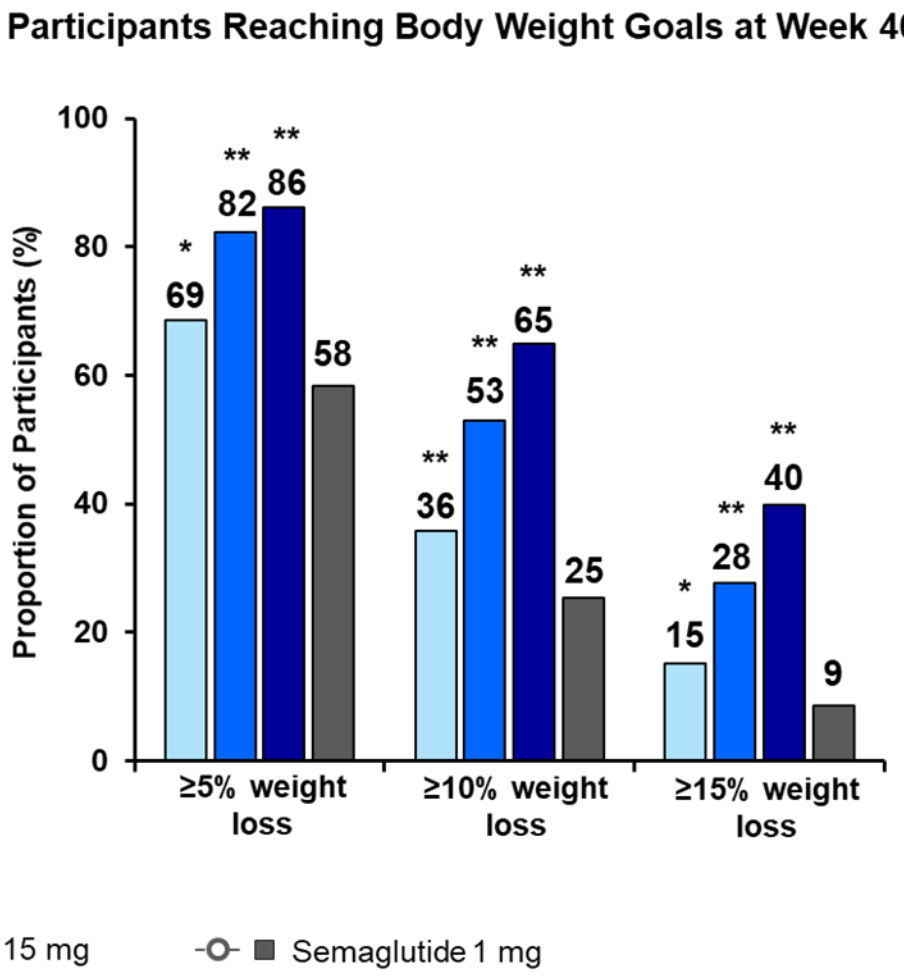


Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg Semaglutide 1 mg

Data are LSM (SE); mITT (efficacy estimand) ANOVA 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. Estimated treatment difference (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. *p<0.05 and **p<0.001 vs. semaglutide 1 mg at 40 weeks. CFB=change from baseline

Body Weight





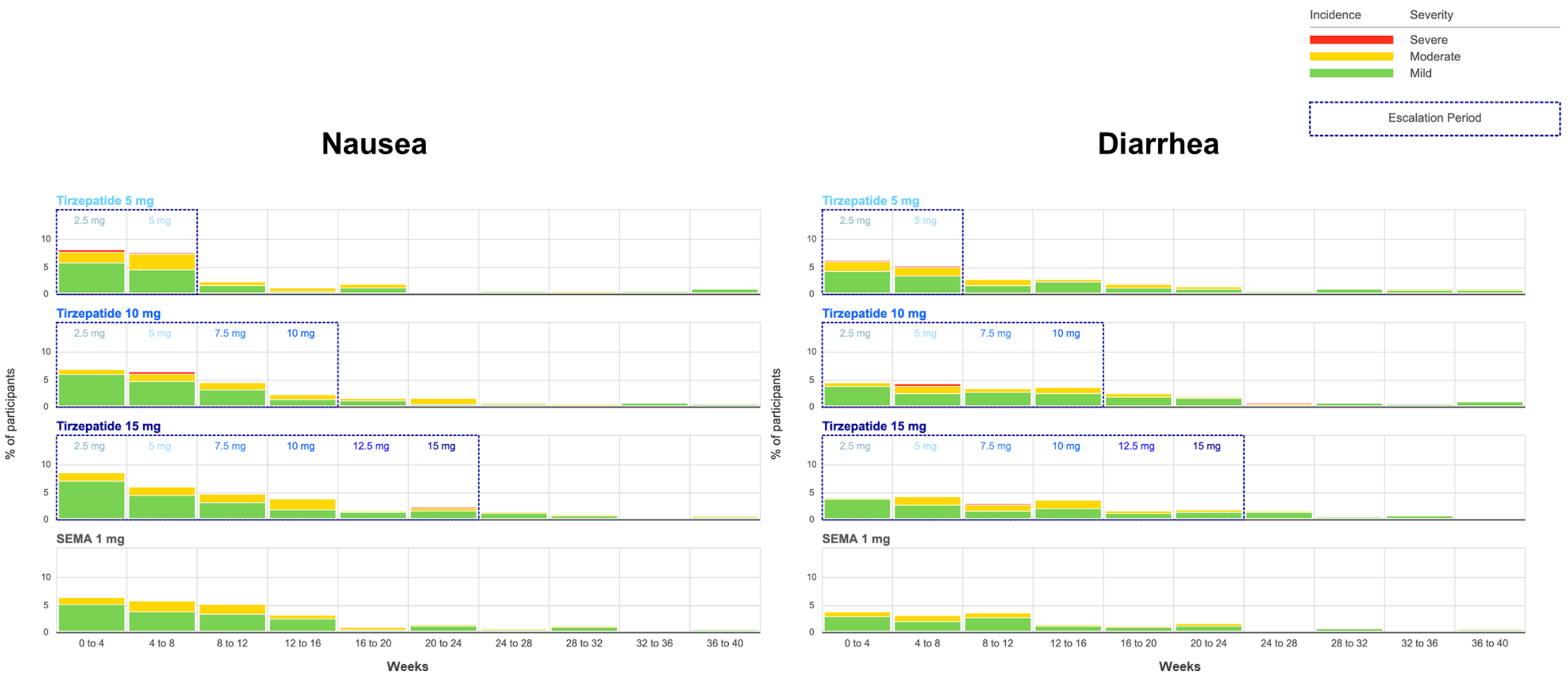
Data are LSM (SE); mITT (efficacy estimand) ANOVA analysis (week 0) and MMRM analysis (week 40). Arrows indicate when the maintenance dose of tirzepatide 5 mg, 10 mg and 15 mg and semaglutide 1 mg are achieved. Estimated treatment difference (95% CI) of tirzepatide vs semaglutide was: i) 5 mg -1.7** (-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.*p<0.05 and **p<0.001 vs. semaglutide. CFB=change from baseline

Overview of Adverse Events

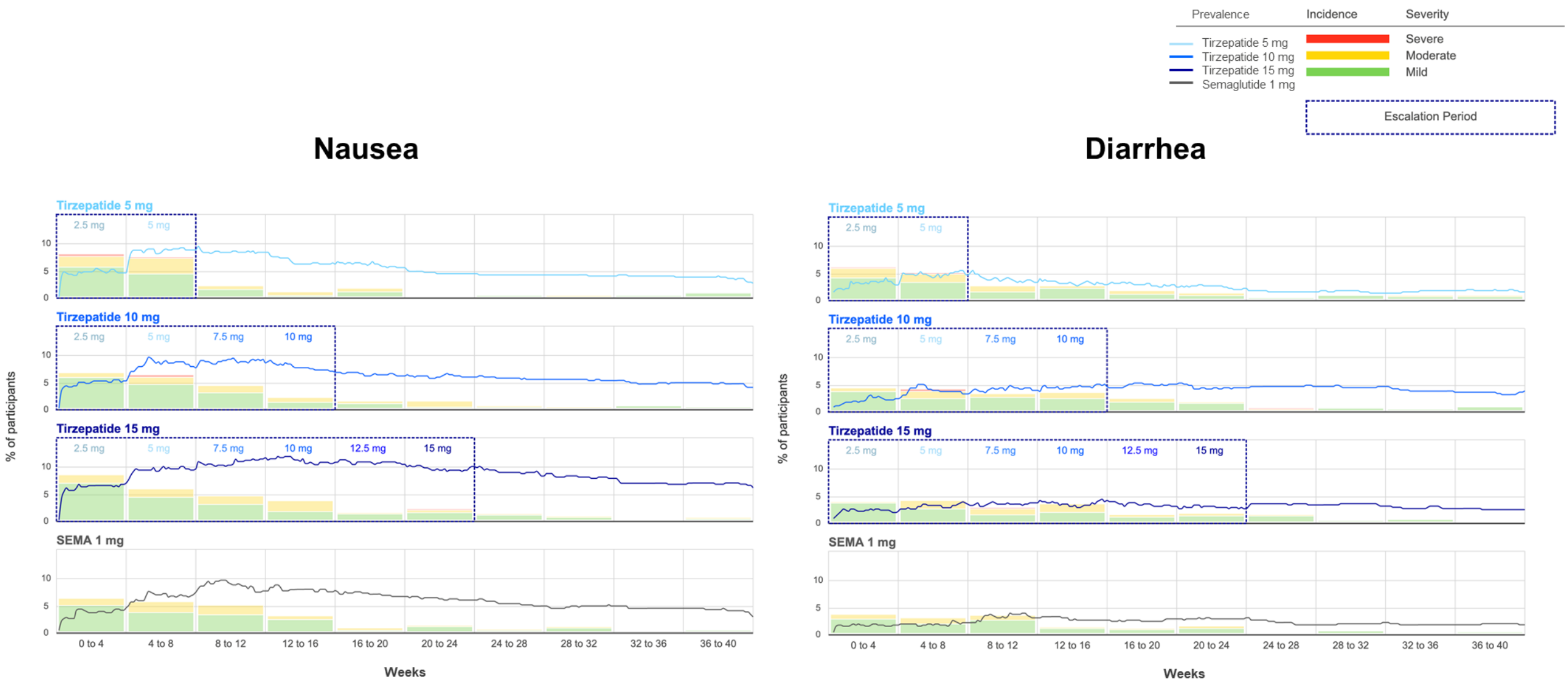
Parameter	Tirzepatide 5 mg N=470	Tirzepatide 10 mg N=469	Tirzepatide 15 mg N=470	Semaglutide 1 mg N=469
Participants with ≥1 TEAE	299 (63.6)	322 (68.7)	324 (68.9)	301 (64.2)
SAEs	33 (7.0)	25 (5.3)	27 (5.7)	13 (2.8)
Deaths[a]	4 (0.9)	4 (0.9)	4 (0.9)	1 (0.2)
Study Discontinuation due to AE	5 (1.1)	8 (1.7)	5 (1.1)	4 (0.9)
Study Drug Discontinuation due to AE	28 (6.0)	40 (8.5)	40 (8.5)	19 (4.1)
TEAE with ≥5% frequency				
Nausea	82 (17.4)	90 (19.2)	104 (22.1)	84 (17.9)
Diarrhea	62 (13.2)	77 (16.4)	65 (13.8)	54 (11.5)
Vomiting	27 (5.7)	40 (8.5)	46 (9.8)	39 (8.3)
Dyspepsia	34 (7.2)	29 (6.2)	43 (9.1)	31 (6.6)
Decreased appetite	35 (7.4)	34 (7.2)	42 (8.9)	25 (5.3)
Constipation	32 (6.8)	21 (4.5)	21 (4.5)	27 (5.8)
Abdominal pain	14 (3.0)	21 (4.5)	24 (5.1)	24 (5.1)

Data are n (%); mITT population (safety analysis set). [a]Deaths are also included as SAEs and discontinuations due to AE. Note: Patients may be counted in more than 1 category.

Incidence of Nausea and Diarrhea



Incidence and Prevalence of Nausea and Diarrhea



Hypoglycemia and Other TEAEs of Interest

Parameter	Tirzepatide 5 mg N=470	Tirzepatide 10 mg N=469	Tirzepatide 15 mg N=470	Semaglutide 1 mg N=469
Hypoglycemia (blood glucose <54 mg/dL) or severe	4 (0.9)	1 (0.2)	8 (1.7)	2 (0.4)
Severe hypoglycemia	1 (0.2)	0	0[a]	0
Adverse events of special interest				
Injection site reaction	9 (1.9)	13 (2.8)	21 (4.5)	1 (0.2)
Hypersensitivity[b]	9 (1.9)	13 (2.8)	8 (1.7)	11 (2.3)
Adjudication-confirmed pancreatitis	0	2 (0.4)	2 (0.4)	3 (0.6)
Cholelithiasis	4 (0.9)	4 (0.9)	4 (0.9)	2 (0.4)
Cholecystitis	0	0	1 (0.2)	0
Cholecystitis acute	1 (0.2)	2 (0.4)	2 (0.4)	0

Data are n (%), unless otherwise specified; mITT population. [a]One participant randomized to tirzepatide 15 mg had an event of hypoglycemia 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.

Conclusion

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 glycemic control
- significant reduction in body weight
- normoglycemia (<5.7%) in up to 51% of participants
- low risk of hypoglycemia (blood glucose <54 mg/dL or severe)

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