100-OR

Efficacy and Safety of Once Weekly Tirzepatide, a dual GIP/GLP-1 Receptor Agonist Versus Placebo as Monotherapy in People with Type 2 Diabetes (SURPASS-1)

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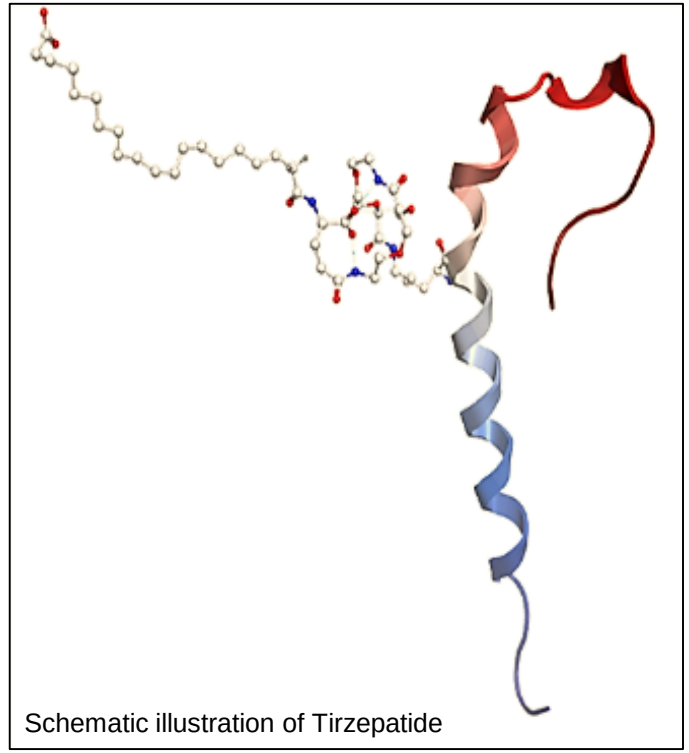
Tirzepatide: Dual GIP/GLP-1 receptor agonist

- Tirzepatide is a multi-functional peptide based on the native GIP peptide sequence, modified to bind to both GIP and GLP-1 receptors[1]
- Tirzepatide is a 39 amino acid linear peptide and includes a C20 fatty diacid moiety[1]
- *In vitro*, it has higher potency to native GIP and is less potent to native GLP-1[1]
- Tirzepatide has a mean half-life of ~5 days (116.7 h), enabling once-weekly dosing[1]
- In a Phase 2b study, Tirzepatide demonstrated significantly lower HbA1c and body weight compared with placebo or the selective GLP-1RA, Dulaglutide 1.5 mg[2]



Schematic illustration of Tirzepatide

GIP=glucose-dependent insulinotropic polypeptide; GLP-1 RAs=glucagon-like peptide-1 receptor agonists

1. Coskun et al. Mol Metab 2018;18:3-14
2. Frias et al. Lancet 2018;392(10160):2180-2193

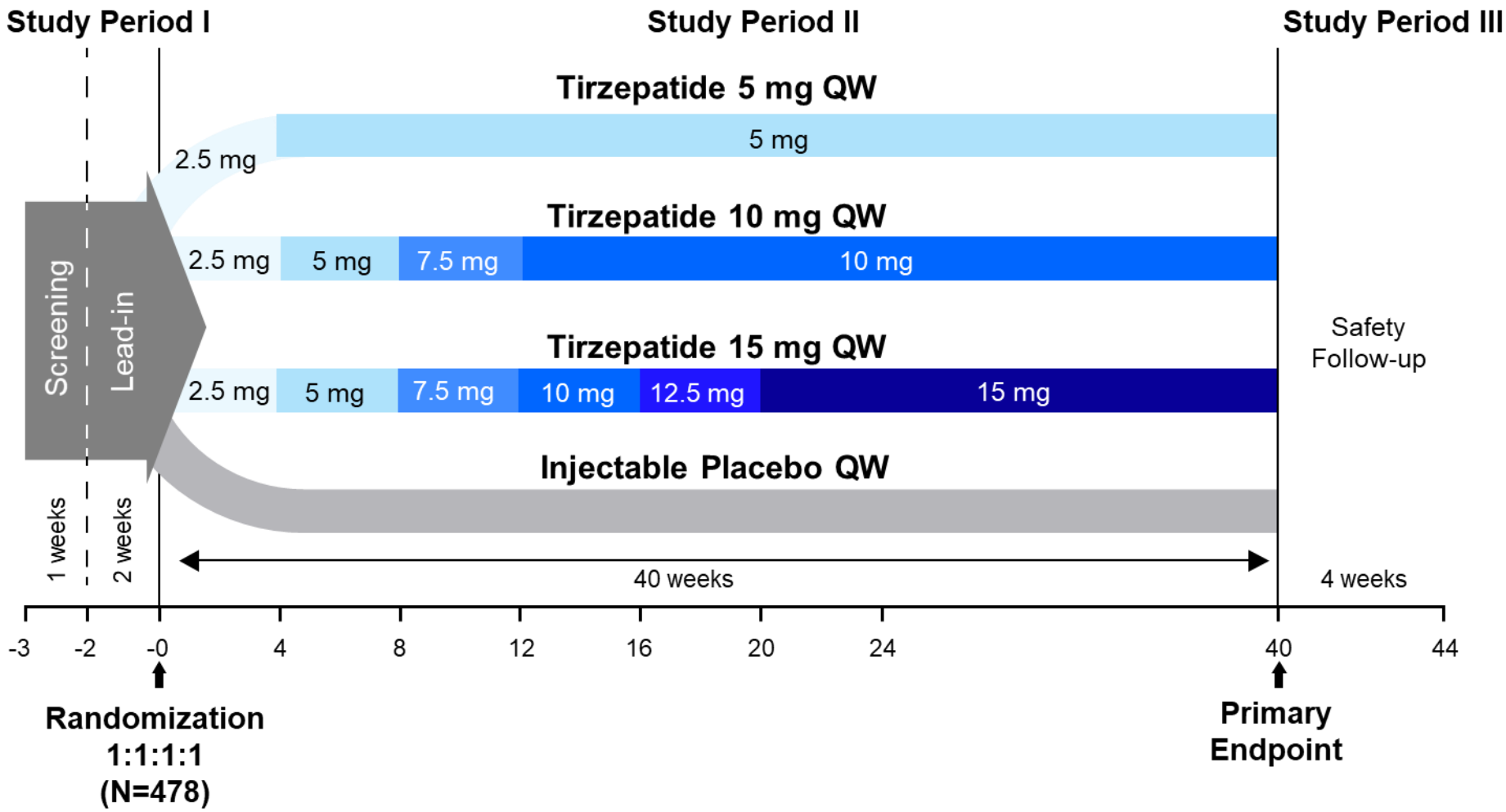
Objectives

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

Study Design

Key Inclusion Criteria

- T2D
- HbA1c ≥7.0% to ≤9.5%
- BMI ≥23 kg/m^2 Stable Weight
- Naïve to T2D Injectable therapy[a]
- Have not used any oral antihyperglycemic medication in the 3 months prior to screening



[a]Except for the use of insulin for treatment of gestational diabetes, or short-term use (≤14 days) for acute conditions such as acute illness, hospitalization, or elective surgery

Statistical Methods

Efficacy Estimand

Treatment difference in the change from baseline to Week 40 for randomized patients, had all patients completed treatment without rescue therapy

Treatment-Regimen Estimand

Treatment difference in the change from baseline to Week 40 for randomized patients *irrespective of treatment discontinuation or initiation of rescue therapy*

- Primary and key secondary efficacy analyses were performed to align with both estimands. Patients who discontinued study drug due to inadvertent enrollment were excluded from both estimands
- Safety analyses included all patients who took at least 1 dose of study drug
- Type 1 error rate controlled at the global alpha level of 0.05 for primary and key secondary endpoints within the analysis aligned to each estimand

Baseline Demographics and Clinical Characteristics

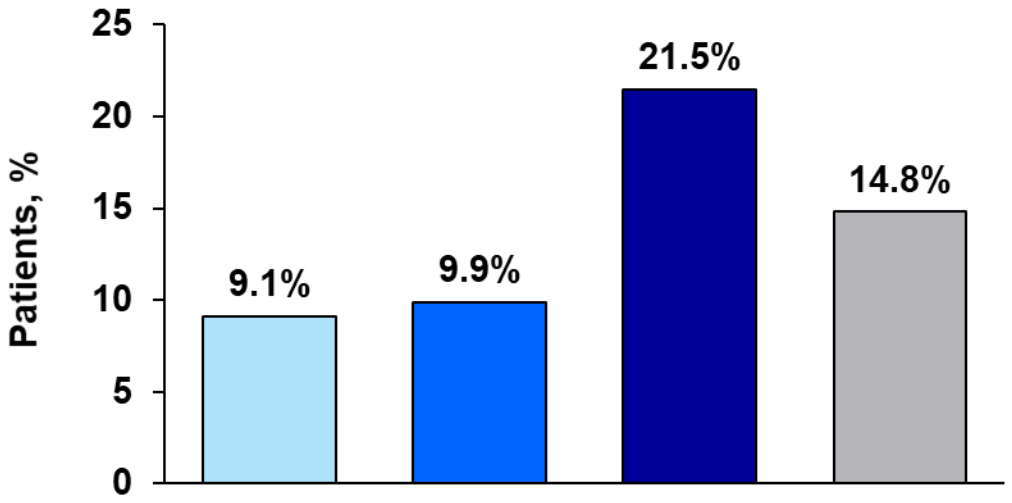
Parameter (mean ± SD, unless otherwise specified)	TZP 5 mg (N=121)	TZP 10 mg (N=121)	TZP 15 mg (N=121)	Placebo (N=115)	Total (N=478)
Age (y)	54.1 ± 11.9	55.8 ± 10.4	52.9 ± 12.3	53.6 ± 12.8	54.1 ± 11.9
Female, n (%)	65 (53.7)	49 (40.5)	58 (47.9)	59 (51.3)	231 (48.3)
Duration of Diabetes (y)	4.6 ± 5.08	4.9 ± 5.61	4.8 ± 4.99	4.5 ± 5.87	4.7 ± 5.38
Weight (kg)	87.0 ± 21.15	86.2 ± 19.50	85.4 ± 18.51	84.8 ± 20.01	85.9 ± 19.77
BMI (kg/m^2)	32.2 ± 6.98	32.2 ± 7.65	31.5 ± 5.48	31.7 ± 6.07	31.9 ± 6.59
HbA1c (%)	7.97 ± 0.84	7.90 ± 0.78	7.85 ± 1.02	8.05 ± 0.80	7.94 ± 0.87
≤8.5%, n (%)	95 (78.5)	98 (81.0)	98 (81.0)	87 (75.7)	378 (79.1)
>8.5%, n (%)	26 (21.5)	23 (19.0)	23 (19.0)	28 (24.3)	100 (20.9)
FSG (mg/dL)	153.7 ± 37.28	152.6 ± 41.72	153.3 ± 40.40	154.8 ± 40.26	153.6 ± 39.83
Prior Use of OAM, n (%)	55 (45.5)	53 (43.8)	56 (46.3)	55 (47.8)	219 (45.8)

Overall, the baseline demographics and clinical characteristics were well balanced across the treatment groups.

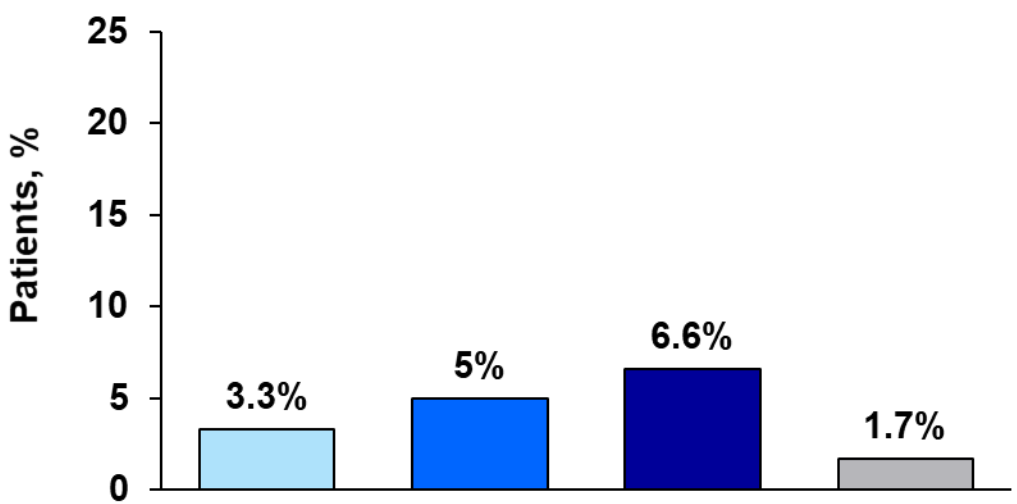
Overall Treatment Discontinuation

Tirzepatide 5 mg
Tirzepatide 10 mg
Tirzepatide 15 mg
Placebo

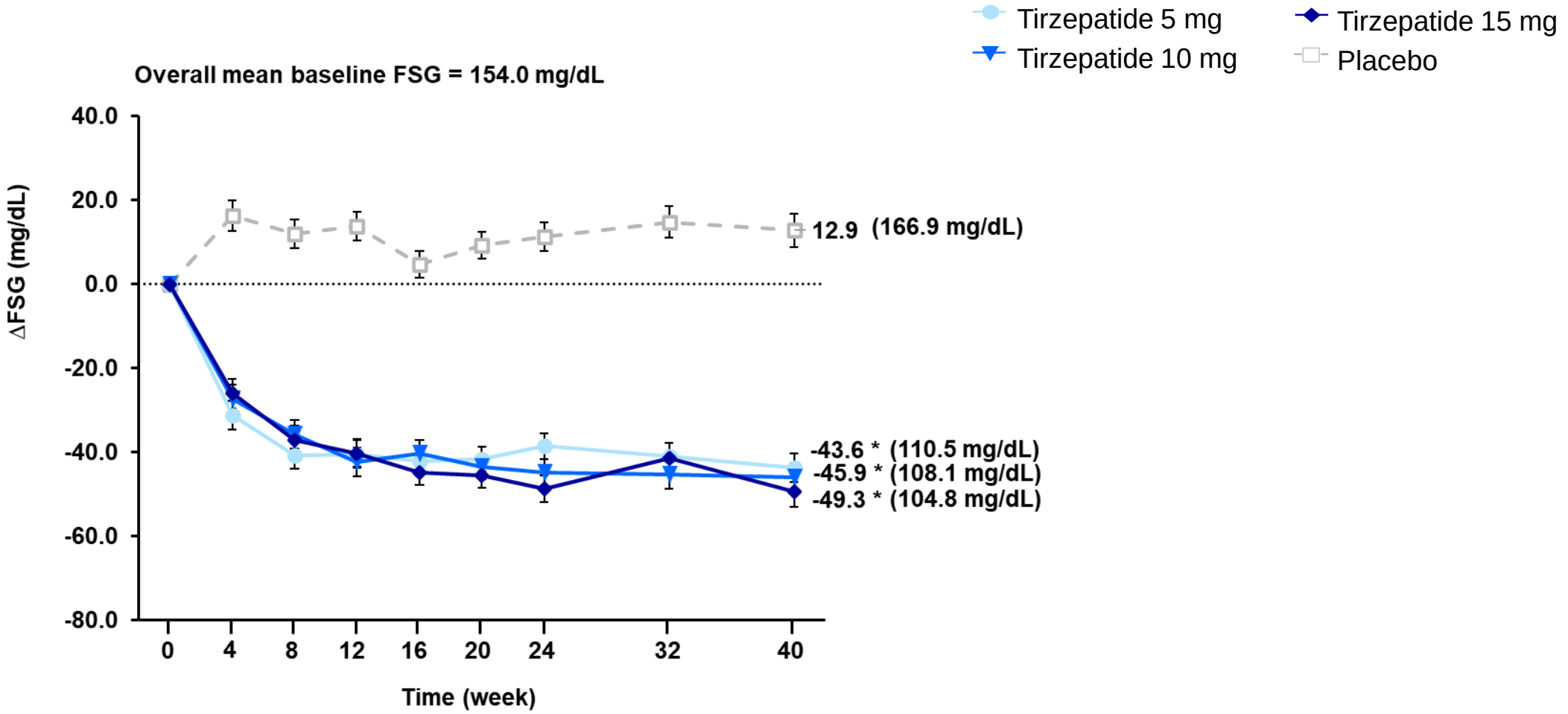
TREATMENT DISCONTINUATION



TREATMENT DISCONTINUATION DUE TO AEs

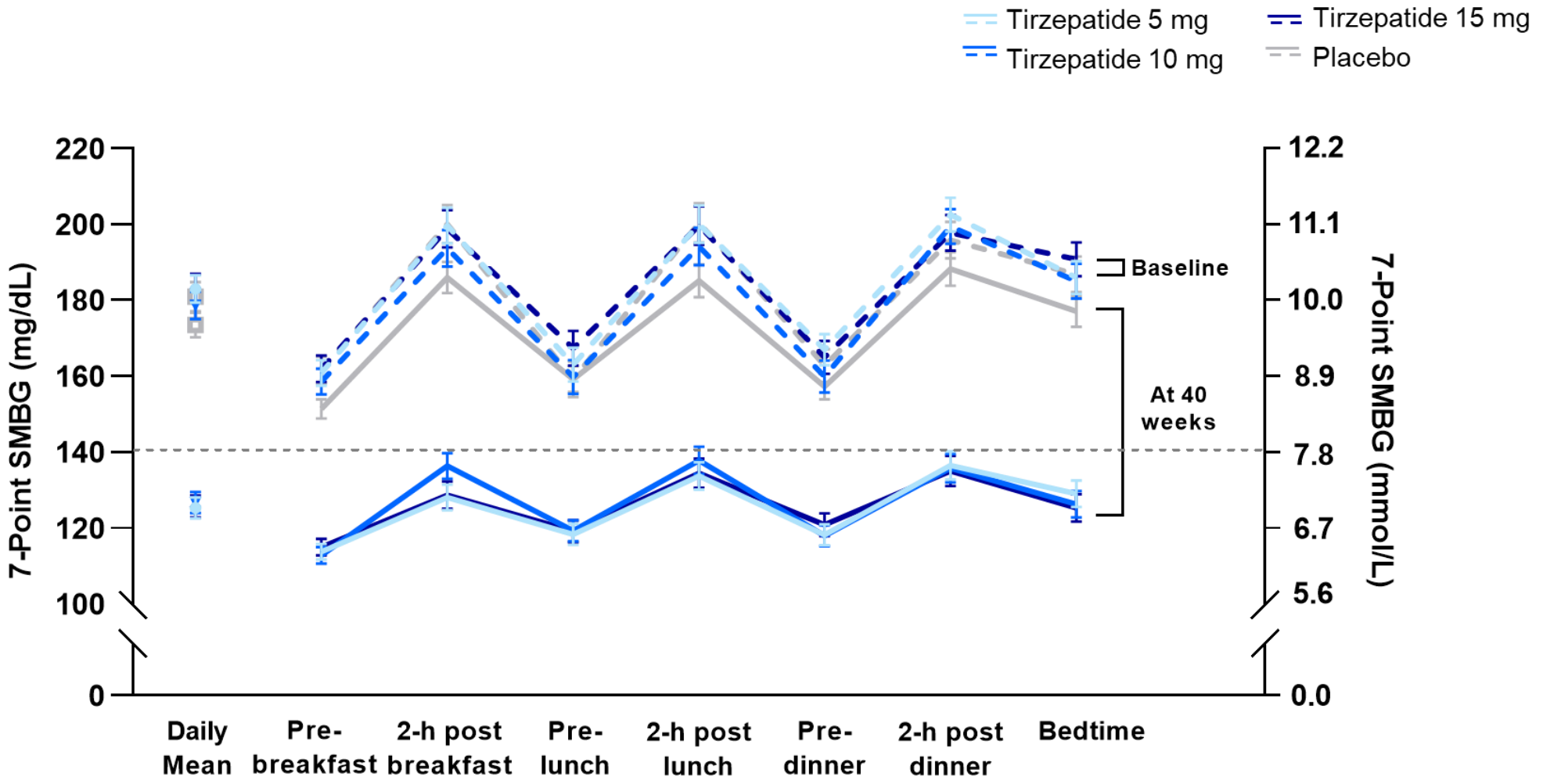


FSG Change Over Time



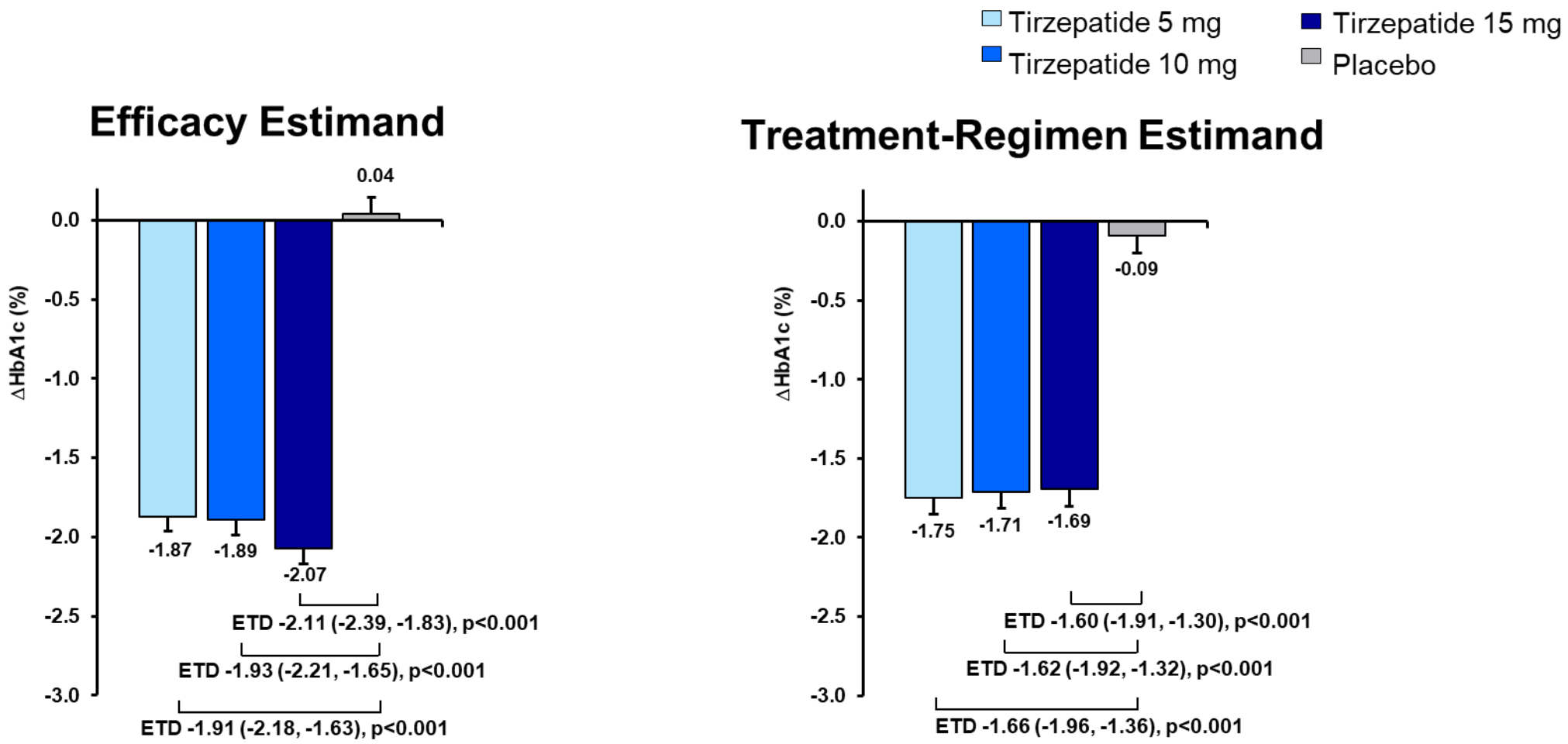
Data are LSM (SE); mITT (efficacy analysis set) ANOVA analysis (week 0) and MMRM analysis (week 40). *p<0.001 vs placebo

7-Point SMBG at Baseline and at 40 Weeks



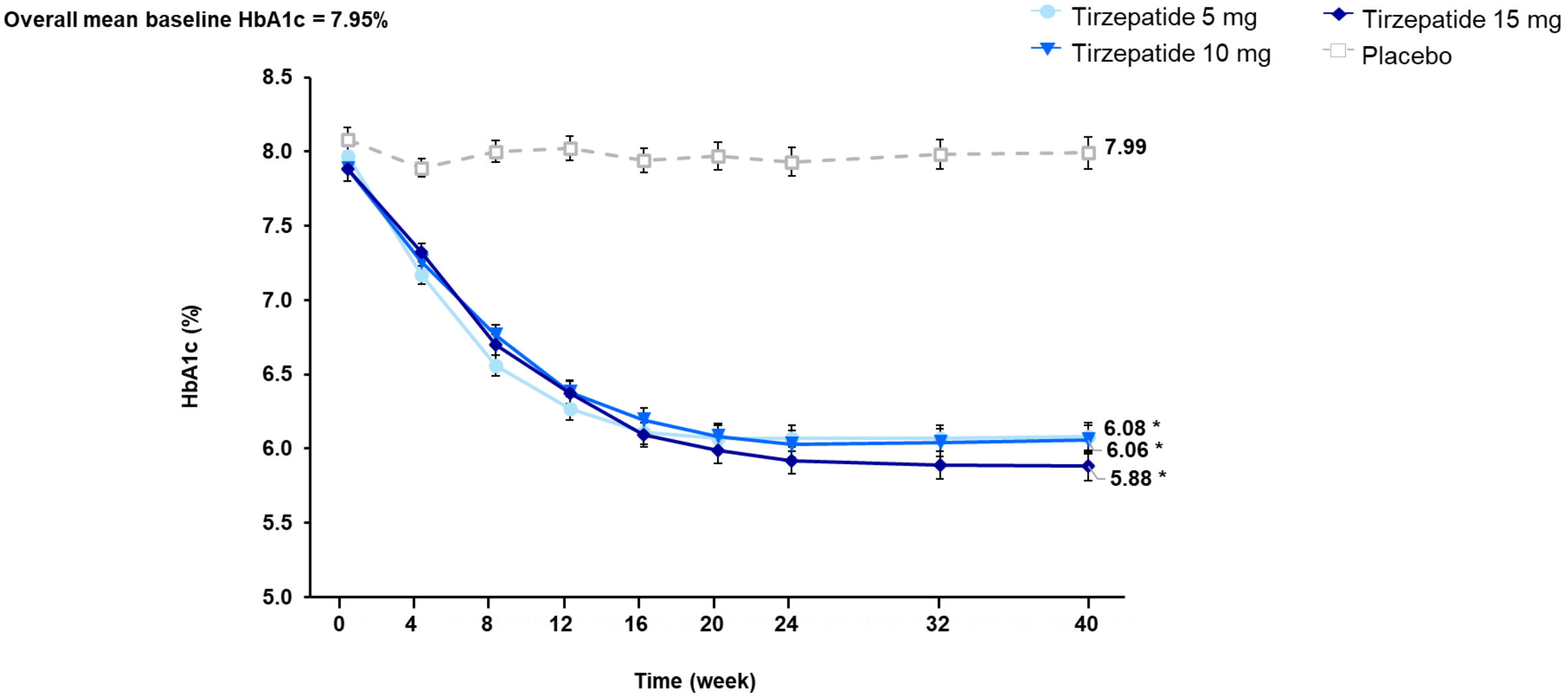
Data are LSM (SE); mITT population (efficacy analysis set) ANOVA analysis (baseline) and MMRM analysis (week 40)

HbA1c Change from Baseline at 40 Weeks



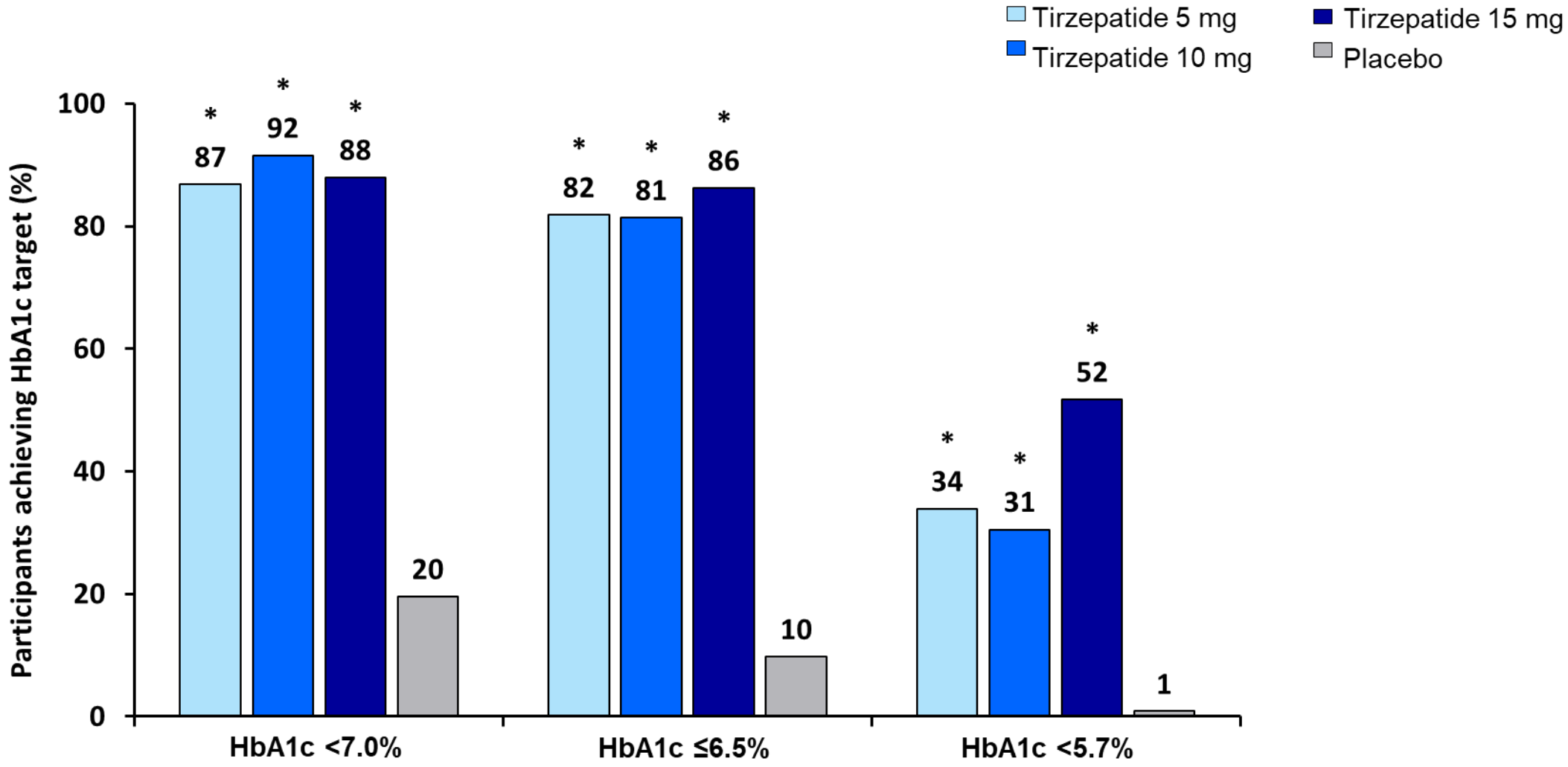
Data are LSM (SE). Efficacy Estimand: Estimated treatment differences are LSM (95% CI). MMRM analysis, mITT population (efficacy analysis set). Treatment-regimen estimand: ANCOVA analysis, mITT population (full analysis set).

HbA1c Over Time



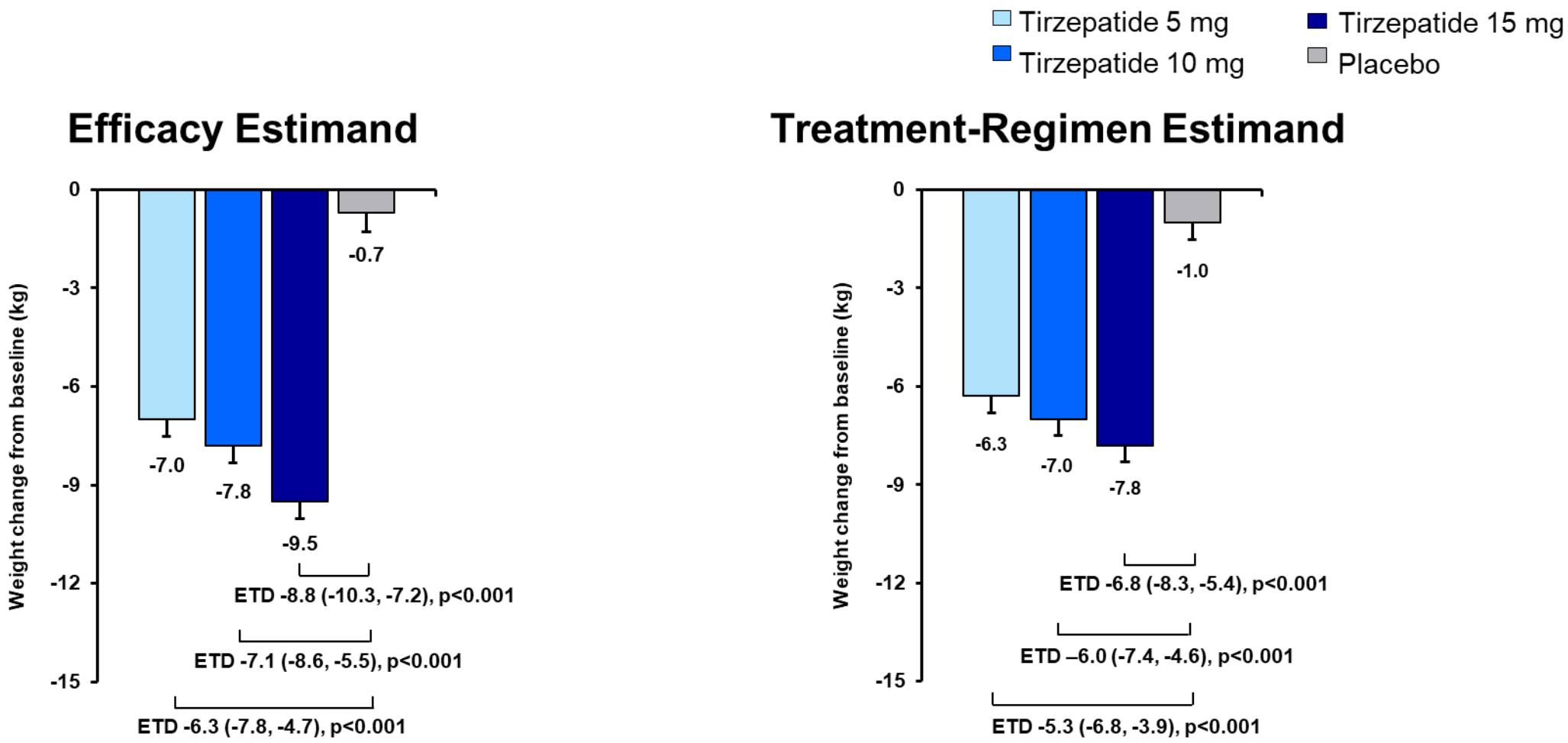
Data are LSM (SE); mITT (efficacy analysis set) ANOVA analysis (week 0) and MMRM analysis (week 40). *p<0.001 vs placebo

Proportion of Participants Achieving HbA1c Targets at 40 Weeks



Data are estimated mean; mITT (efficacy analysis set). Logistic regression. *p<0.001 vs. placebo

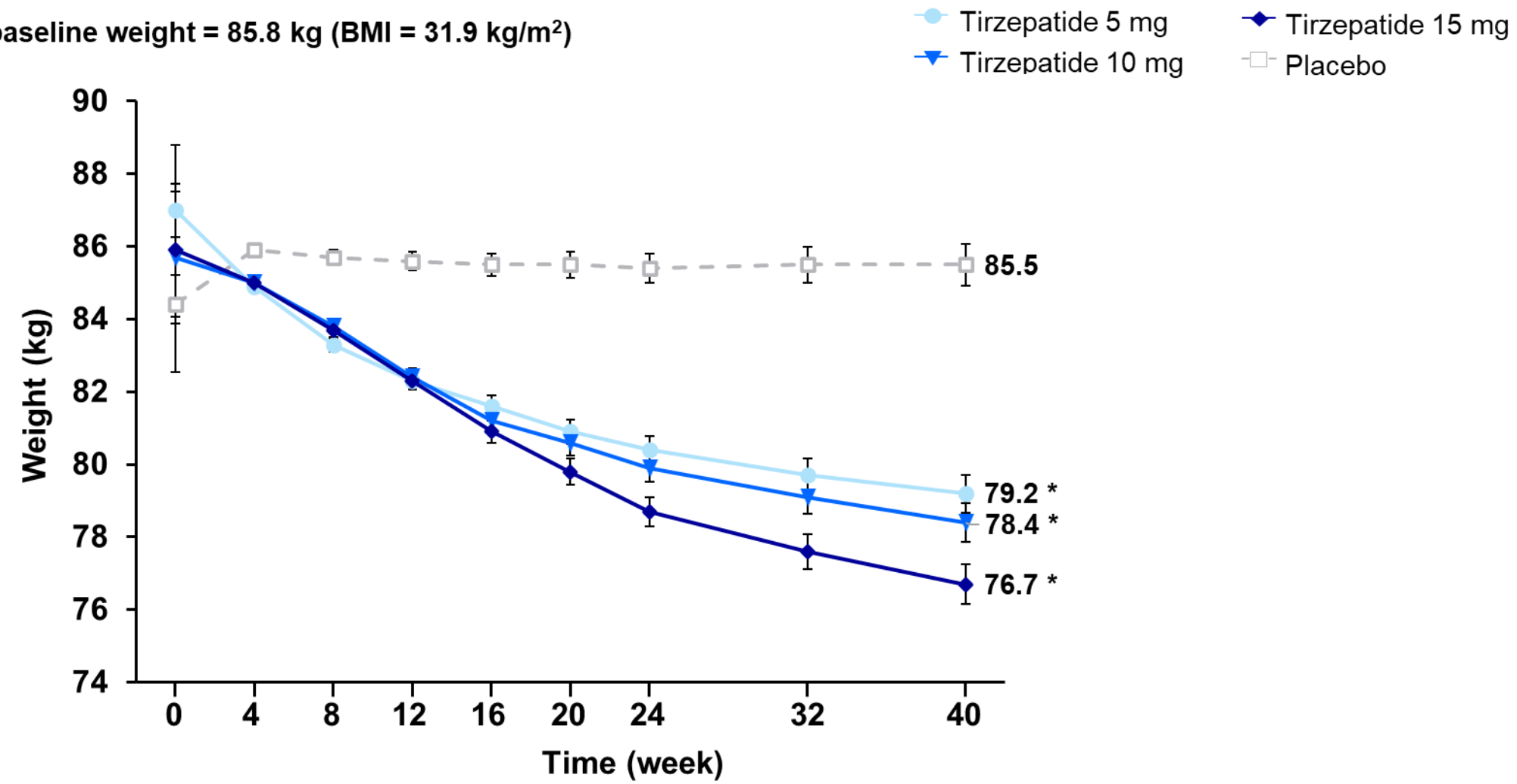
Change from Baseline in Body Weight at 40 Weeks



Data are LSM (SE). Efficacy Estimand: Estimated treatment differences are LSM (95% CI). MMRM analysis, mITT population (efficacy analysis set). Treatment-regimen estimand: ANCOVA analysis, mITT population (full analysis set).

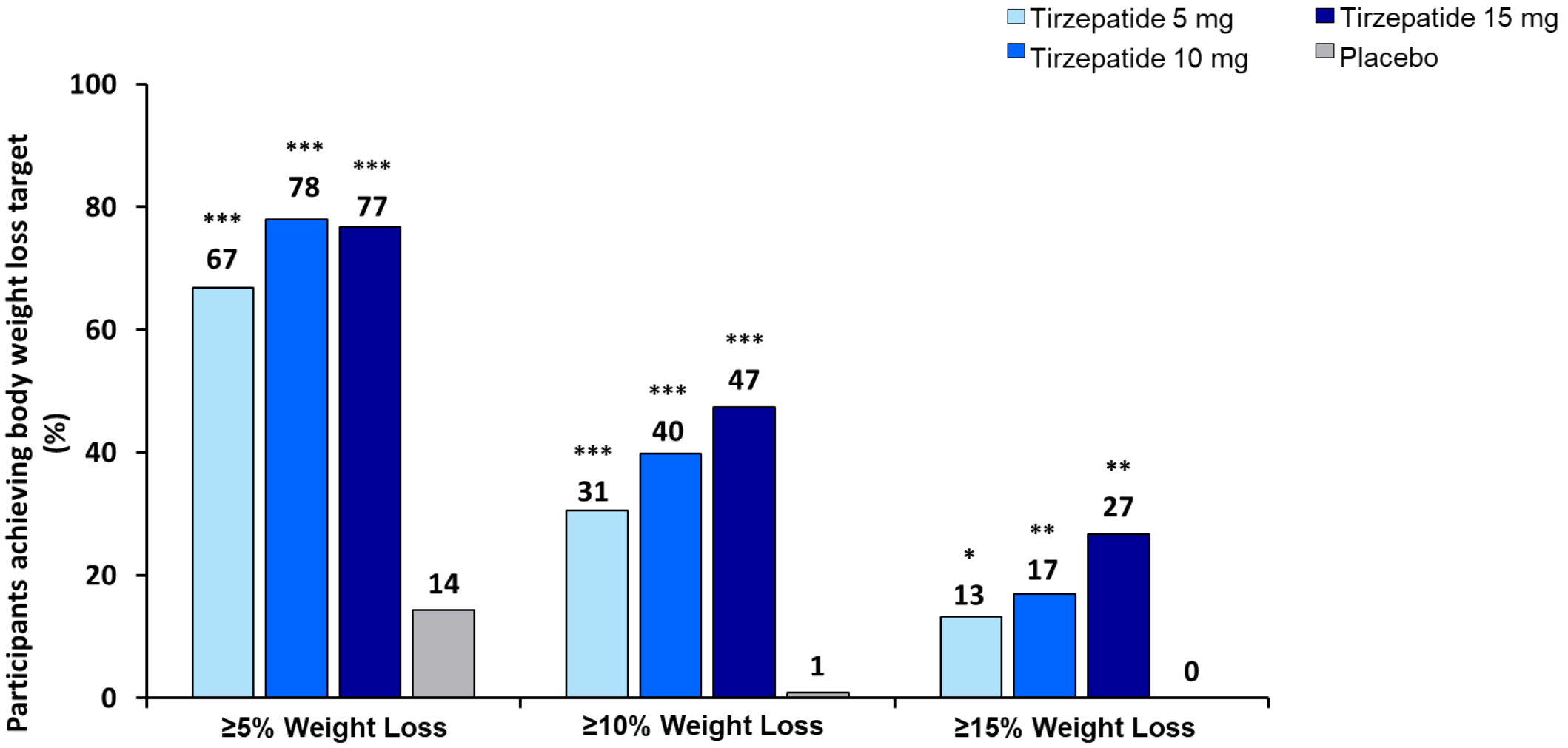
Body Weight Over Time

Overall mean baseline weight = 85.8 kg (BMI = 31.9 kg/m²)



Data are LSM (SE); mITT (efficacy analysis set) ANOVA analysis (week 0) and MMRM analysis (week 40). *p<0.001 vs placebo

Proportion of Participants Achieving Weight Loss Targets at 40 Weeks



Data are estimated mean; mITT (efficacy analysis set). Logistic regression. *p<0.05, **p<0.01 and ***p<0.001 vs. placebo

Overview of Adverse Events

Preferred Term	Tirzepatide 5 mg N=121	Tirzepatide 10 mg N=121	Tirzepatide 15 mg N=121	Placebo N=115
Serious AEs	5 (4.1)	2 (1.7)	1 (0.8)	3 (2.6)
Deaths[a]	0	0	0	1 (0.9)
TEAEs	83 (68.6)	81 (66.9)	77 (63.6)	76 (66.1)
TEAEs (≥5% of patients)				
Nausea	14 (11.6)	16 (13.2)	22 (18.2)	7 (6.1)
Diarrhea	14 (11.6)	17 (14.0)	14 (11.6)	9 (7.8)
Hyperglycemia	4 (3.3)	5 (4.1)	3 (2.5)	31 (27.0)
Nasopharyngitis	7 (5.8)	8 (6.6)	8 (6.6)	10 (8.7)
Dyspepsia	11 (9.1)	8 (6.6)	7 (5.8)	4 (3.5)
Decrease Appetite	5 (4.1)	8 (6.6)	10 (8.3)	1 (0.9)
Headache	5 (4.1)	4 (3.3)	5 (4.1)	9 (7.8)
Constipation	7 (5.8)	6 (5.0)	8 (6.6)	1 (0.9)
Vomiting	4 (3.3)	3 (2.5)	7 (5.8)	2 (1.7)
Influenza	7 (5.8)	3 (2.5)	0	2 (1.7)
Gastritis	6 (5.0)	0	3 (2.5)	0

AE=adverse event; BG=blood glucose; N=number of patients in that category; TEAE=treatment-emergent adverse event; TZP=tirzepatide

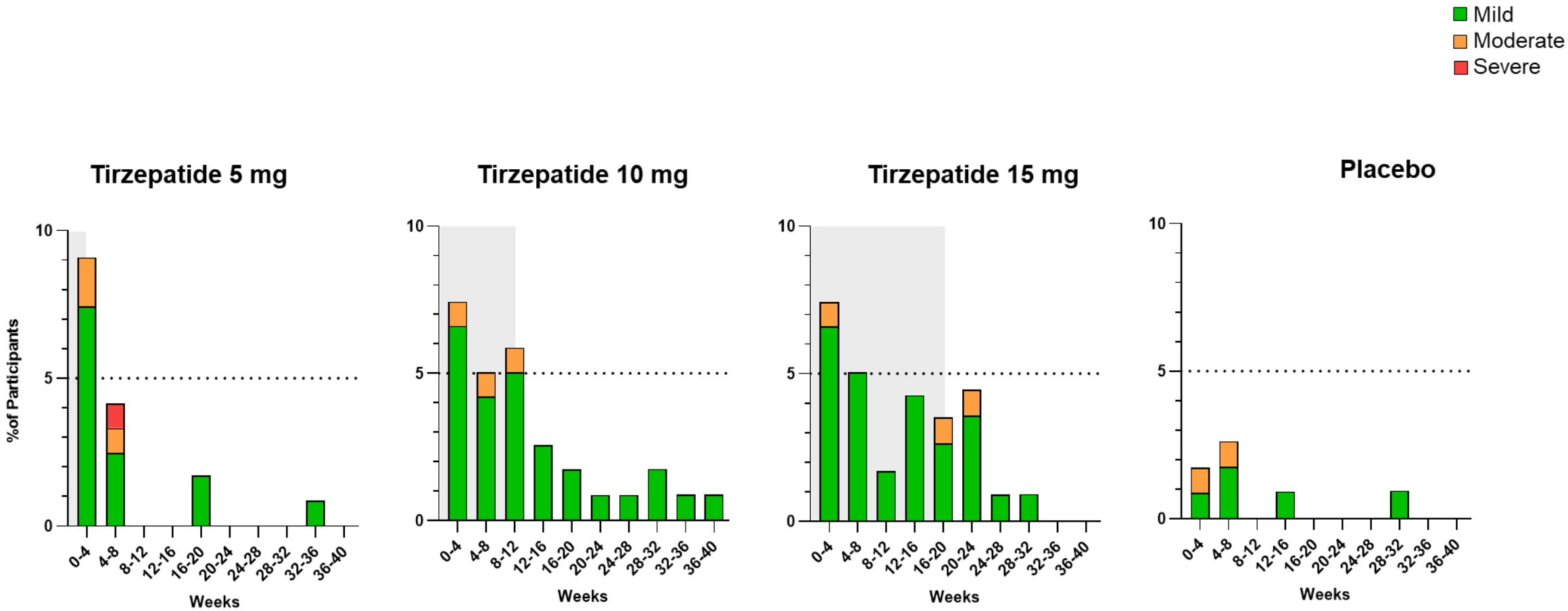
Data presented as %, unless otherwise noted. mITT population (safety analysis set). [a]Deaths are also included as SAEs and discontinuations due to AE. Note: Patients may be counted in more than 1 category.

Other Treatment-Emergent Adverse Events of Interest

Preferred Term	Tirzepatide 5 mg N=121	Tirzepatide 10 mg N=121	Tirzepatide 15 mg N=121	Placebo N=115
Other TEAEs				
Hypoglycemia (Blood Glucose ≤70 mg/dL)	7 (5.8)	10 (8.3)	10 (8.3)	1 (0.9)
Hypoglycemia (Blood Glucose <54 mg/dL)	0	0	0	1 (0.9)
Severe Hypoglycemia	0	0	0	0
Injection Site Reaction	4 (3.3)	4 (3.3)	2 (1.7)	0
Adjudicated Pancreatitis	0	0	0	0
Pancreatic Cancer	1 (0.8)	0	0	0
Cholelithiasis	1 (0.8)	0	0	0

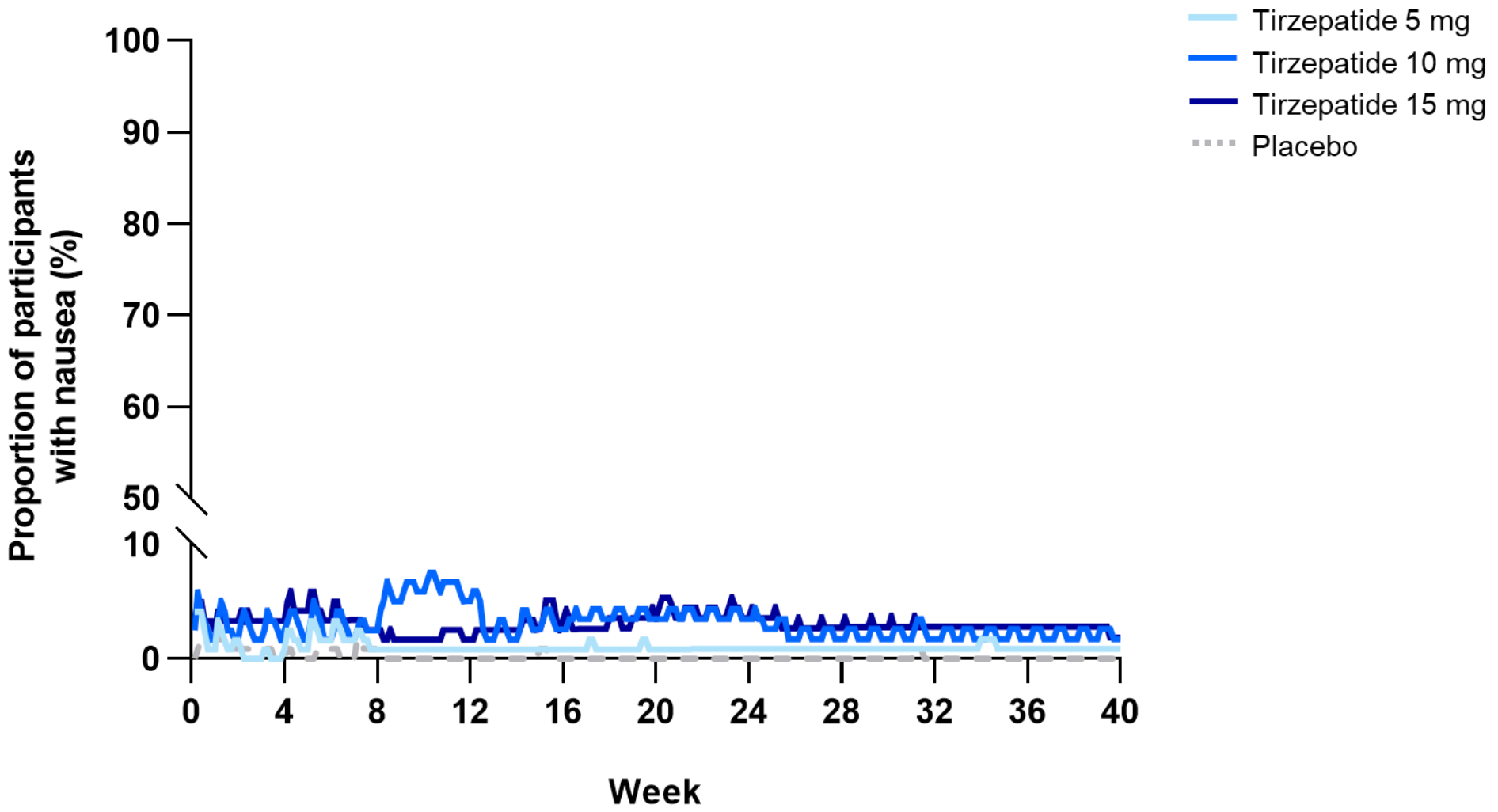
AE=adverse event; BG=blood glucose; N=number of patients in that category; TEAE=treatment-emergent adverse event; TZP=tirzepatide
Data presented as %, unless otherwise noted. mITT population (safety analysis set). Note: Patients may be counted in more than 1 category.

Incidence and Severity of Nausea Over Time Through 40 Weeks



mITT population (safety analysis set). Shaded areas indicate the period of time before reaching the maintenance dose of the study treatments.

Prevalence of Nausea Over Time Through 40 Weeks



mITT population (safety analysis set). Note: The majority of events were mild to moderate in severity.

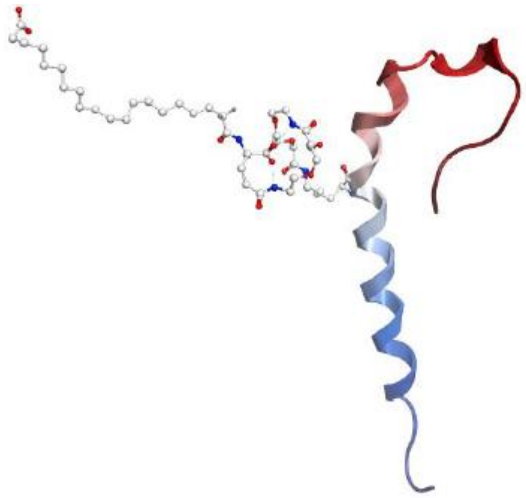
Summary

- At 40 weeks, statistically significant and clinically meaningful reductions in HbA1c, FSG and body weight were achieved with Tirzepatide 5 mg, 10 mg, and 15 mg compared with Placebo
- 87-92% of participants taking Tirzepatide achieved HbA1c <7.0%
- 31-52% of participants taking Tirzepatide achieved HbA1c <5.7% (normoglycemia)
- No severe or clinically significant hypoglycemia (BG <54 mg/dL) events occurred with Tirzepatide
- 13-27% of participants taking Tirzepatide achieved body weight loss of ≥15%
- The most common AEs with Tirzepatide were gastrointestinal in nature, which were mostly mild to moderate in severity and transient

AEs=adverse events; BG=blood glucose; FSG=fasting serum glucose; HbA1c=glycated hemoglobin A1c

Conclusion

Once weekly Tirzepatide, a dual GIP/GLP-1 receptor agonist, demonstrated robust reductions in glycemic control with at least one-third of participants achieving normoglycemia (HbA1c <5.7%), as well as significant reduction in body weight, without increased risk of hypoglycemia (severe or BG <54 mg/dL) compared with placebo



GIP=glucose-dependent insulinotropic polypeptide; GLP-1=glucagon-like peptide-1; HbA1c=glycated hemoglobin A1c; T2D=type 2 diabetes