OP-114

Efficacy and Safety of Three Dose-Escalation Algorithms of Tirzepatide, a Novel Dual GIP and GLP-1 Receptor Agonist, in Patients with Type 2 Diabetes

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PRESENTER DISCLOSURE
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Advisory board/consulting: AstraZeneca, Boehringer Ingelheim, Menarini/Berlin-Chemie, Eli Lilly & Co., Fractyl, Genentech, GlaxoSmithKline, Merck Sharp & Dohme, Novo Nordisk

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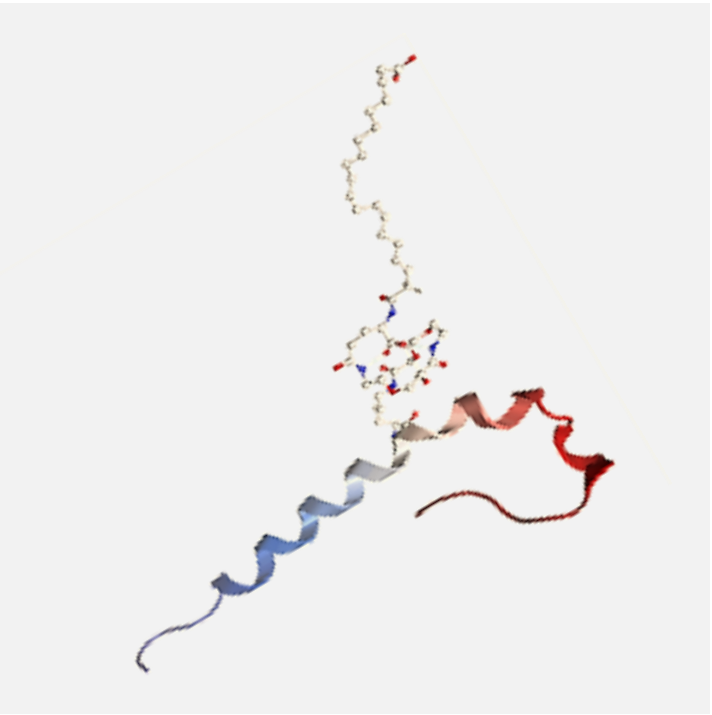
Stock: None

Travel support/cost reimbursement in connection with above-mentioned activities

Tirzepatide
Molecular Structure, Activity and PK Characteristics

- Tirzepatide (TZP; LY3298176) is a 39 amino acid synthetic peptide with agonist activity at both the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors
- Its structure is based on the GIP sequence and includes a C20 fatty diacid moiety[1]
- Mean half-life is approximately 5 days in man (116.7 h), supporting **once-weekly dosing**

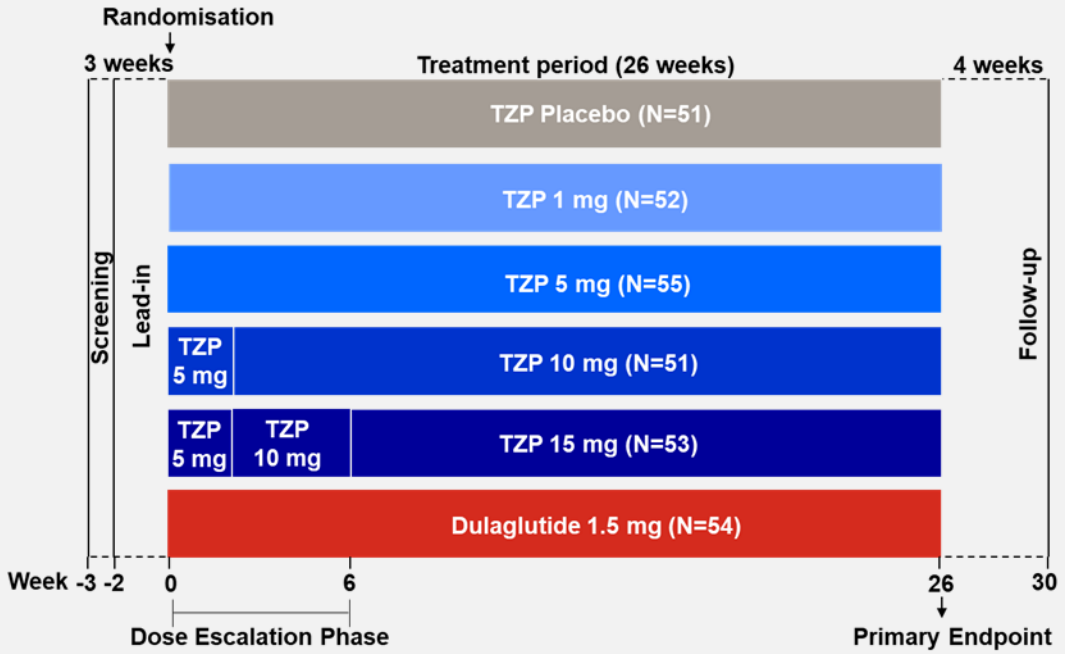


PK: pharmacokinetic

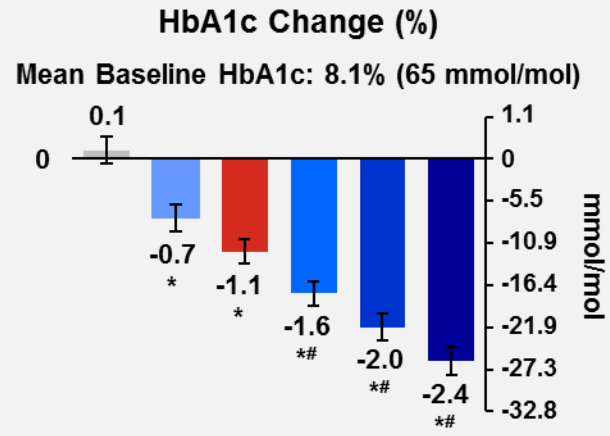
1. Coskun et al. Mol Metab. 2018;18:3-14

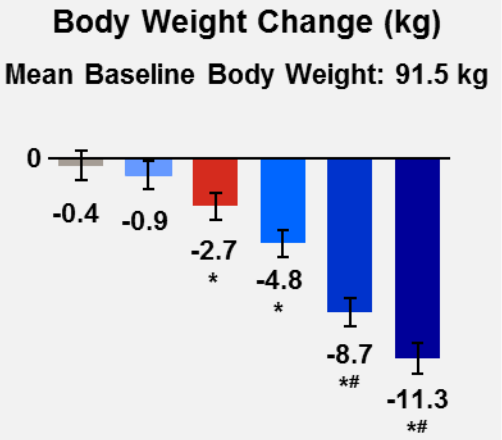
Tirzepatide: A Novel Dual GIP and GLP-1 Receptor Agonist

Phase 2b Trial Design and Key Findings



- Double-blind, placebo-controlled Phase 2b study in subjects with T2D (HbA1c 7.0-10.5% [53-91.3 mmol/mol]; diet and exercise ±metformin)[1]
- 26-week treatment period, 4-week safety follow-up





Tirzepatide showed significantly greater glucose control and weight loss compared with selective GLP-1 receptor agonist, dulaglutide, at 26 weeks[1]

TZP 1 mg TZP 5 mg TZP 10 mg TZP 15 mg Dulaglutide 1.5 mg Placebo

Data presented as LSM (SE), MMRM on treatment analysis. *p<0.05 vs PBO and #p<0.05 vs. DU 1.5 mg. DU: dulaglutide; GLP-1 RA: glucagon-like peptide-1 receptor agonist; HbA1c: glycated haemoglobin A1c; T2D: type 2 diabetes; TZP: tirzepatide

1. Frias al. Lancet 2018;392(10160):2180-2193.

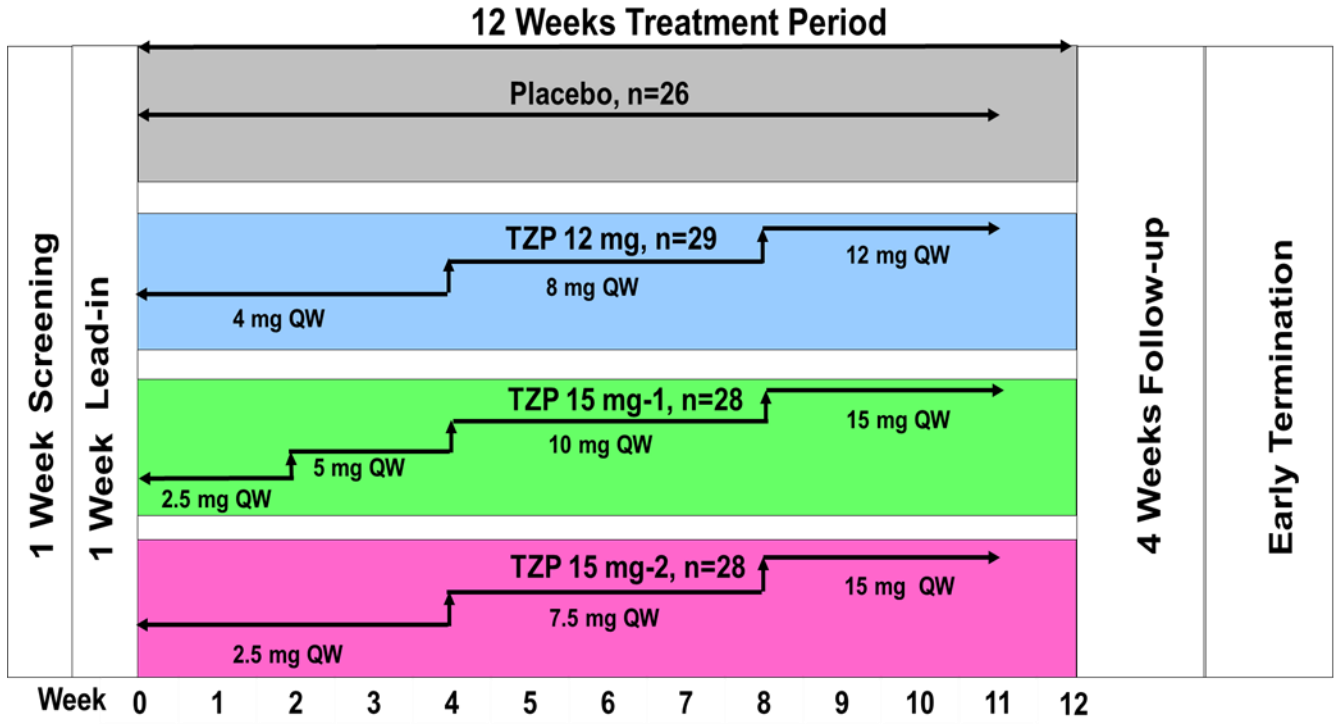
Objective and Rationale

Dose Escalation Study

- **Objective**
  - To evaluate efficacy and tolerability of 3 dose-escalation regimens of the higher tirzepatide doses (12 mg and 15 mg)

- **Rationale**
  - The 3 dose-escalation regimens used 2 different tirzepatide starting doses and different dose escalation increments to evaluate if meaningful changes in tolerability of gastrointestinal side effects occurred
  - This study provided insights to help inform a starting dose and dose-escalation regimen of tirzepatide for Phase 3 clinical trials

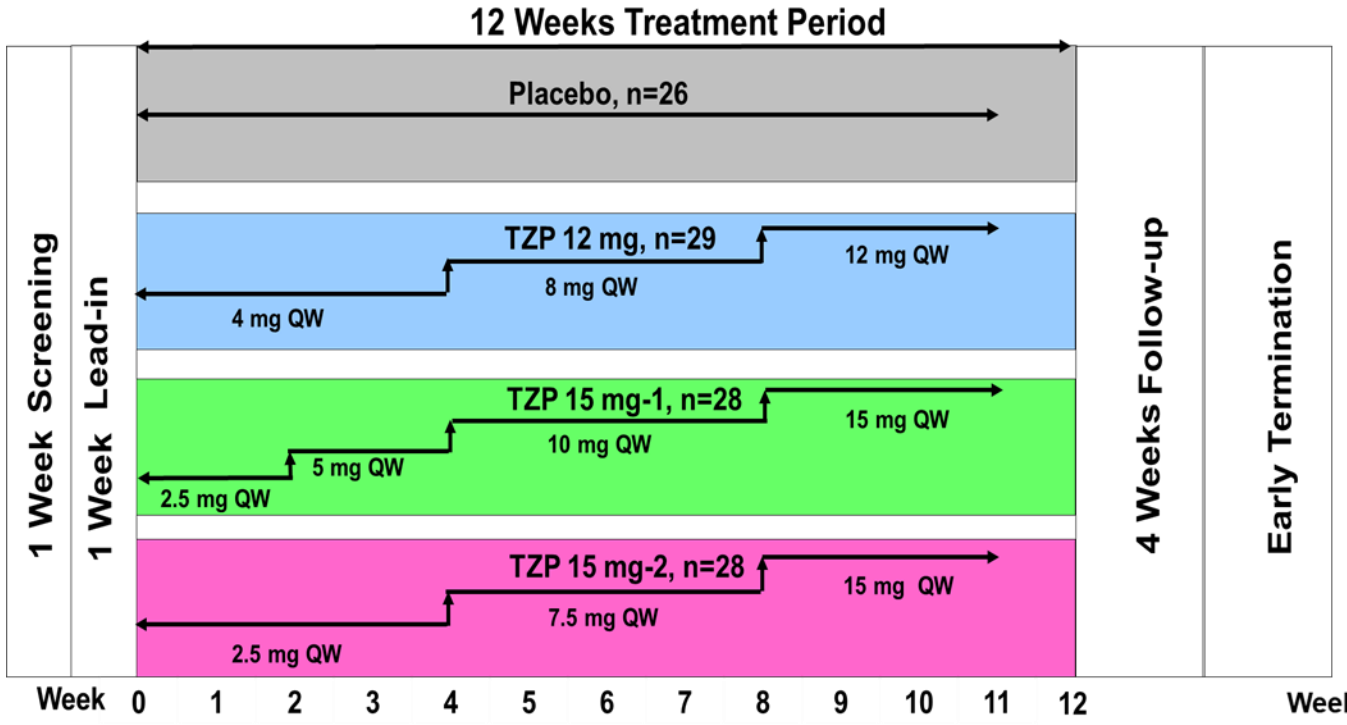
Study Design

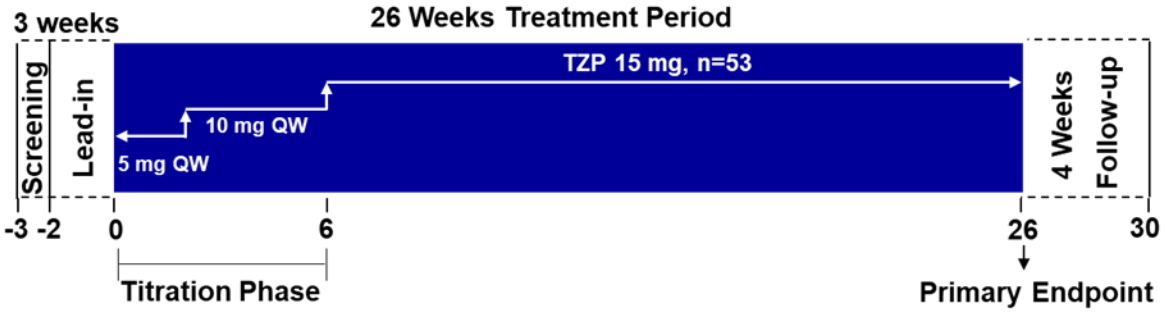


- 12-week, Phase 2, randomised, double-blind, placebo-controlled study
- Eligible patients with T2D:
  - Diet and exercise, ± metformin
  - HbA1c: 7% - 10.5%, inclusive
  - BMI: 23 - 45 kg/m^2

BMI: body mass index; HbA1c: glycated haemoglobin A1c; QW: once weekly; T2D: type 2 diabetes; TZP: tirzepatide

Study Design





BMI: body mass index; HbA1c: glycated haemoglobin A1c; QW: once weekly; T2D: type 2 diabetes; TZP: tirzepatide

Baseline Characteristics

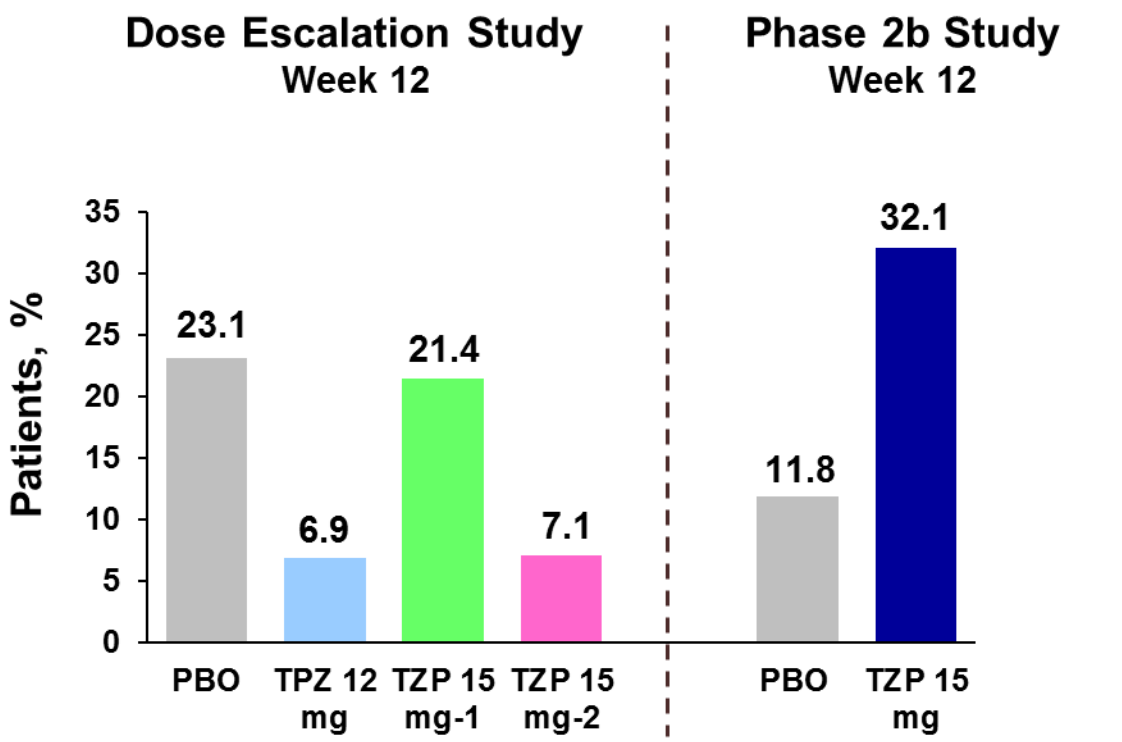
Variable	Placebo N=26	TZP 12 mg N=29	TZP 15 mg-1 N=28	TZP 15 mg-2 N=28
Age, years	56 ± 10	61 ± 8	56 ± 9	57 ± 9
Sex (male)	46%	52%	57%	82%
Diabetes duration, years	9 ± 6	11 ± 8	8 ± 5	9 ± 6
HbA1c, %	8.2 ± 1.2	8.4 ± 0.9	8.5 ± 1.2	8.4 ± 1.1
HbA1c, mmol/mol	66 ± 13	68 ± 10	69 ± 13	68 ± 12
FSG, mg/dL	169 ± 62	178 ± 55	187 ± 73	195 ± 76
FSG, mmol/L	9.7 ± 3.5	9.8 ± 3.0	10.4 ± 4.1	10.7 ± 4.2
Weight, kg	90 ± 24	88 ± 17	89 ± 18	90 ± 17
BMI, kg/m²	32.5 ± 5.7	32.0 ± 5.2	32.0 ± 5.6	31.1 ± 4.2
Metformin use [Yes]	89%	86%	89%	82%

Data presented as mean ± SD or %

BMI: body mass index; FSG: fasting serum glucose; HbA1c: glycated haemoglobin A1c; N: number of patients in that category; TZP: tirzepatide

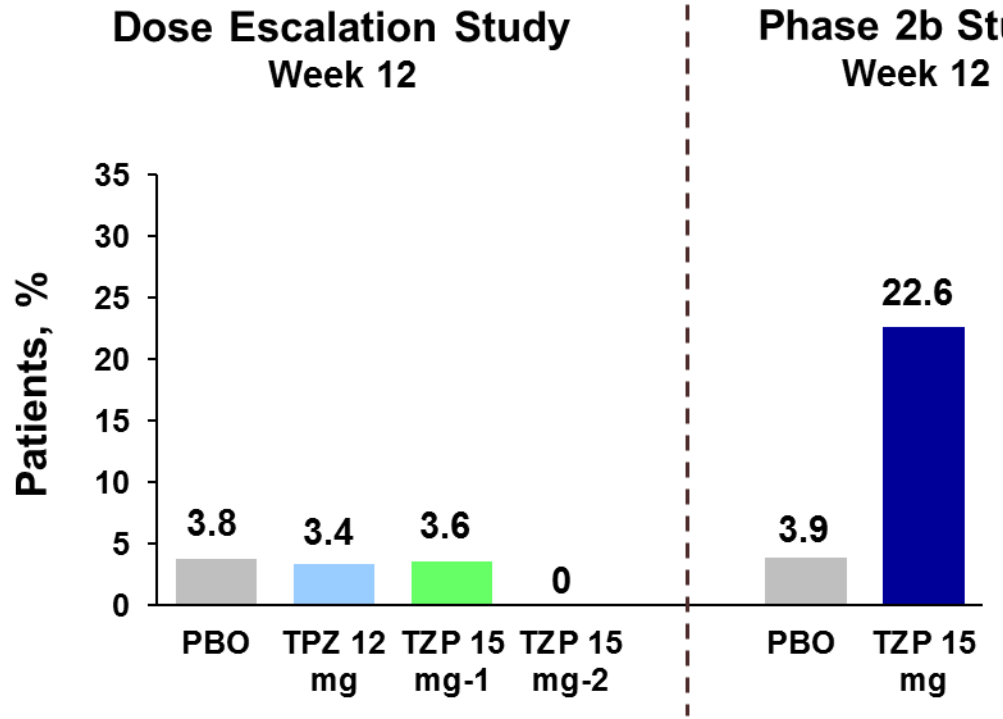
Treatment Discontinuation and Treatment Discontinuation Due to AEs Were Similar to Placebo

TREATMENT DISCONTINUATIONS



- Observed GI side effects were mild to moderate, less severe than in prior studies

TREATMENT DISCONTINUATION DUE TO AEs

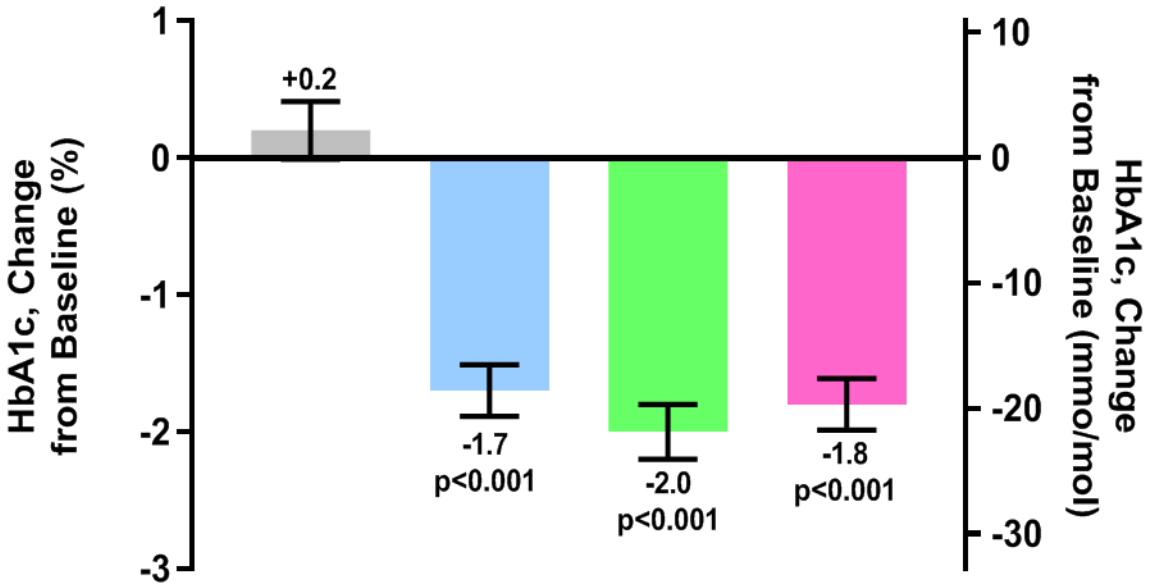


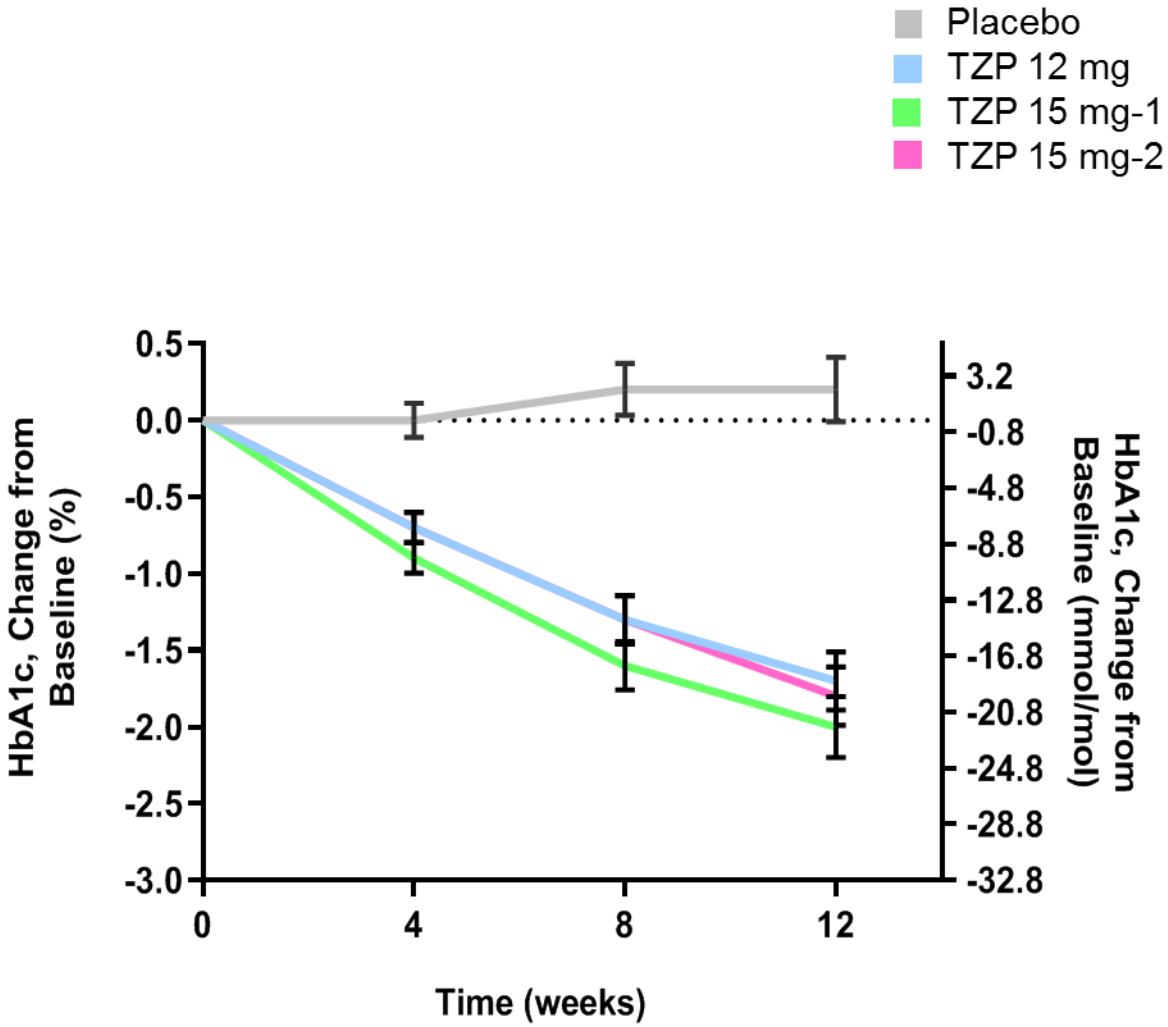
- Treatment discontinuation due to adverse events was below 4% in all three escalation schemes assessed
- No difference from placebo

AEs: adverse events; GI: gastrointestinal

Reduction in HbA1c with Tirzepatide

Change from Baseline at 12 Weeks and Over Time

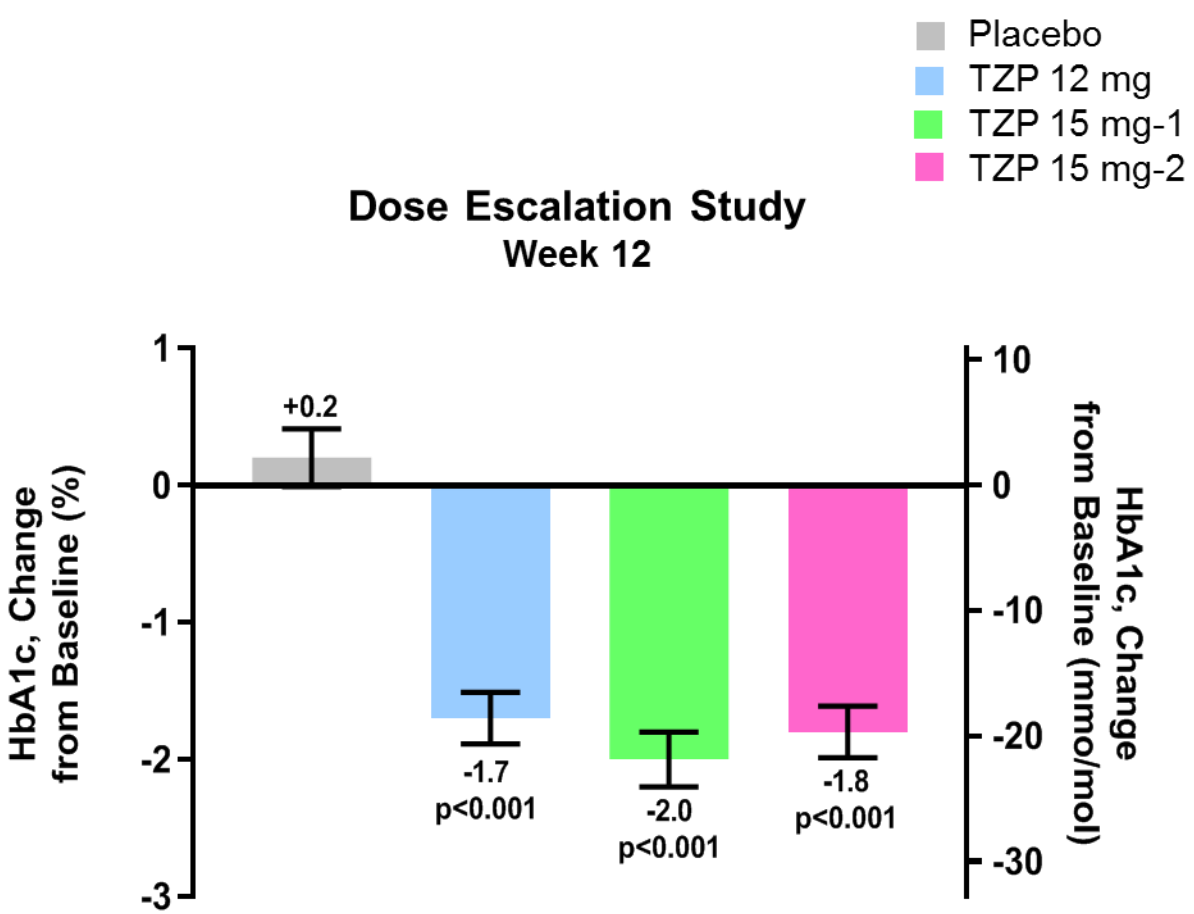


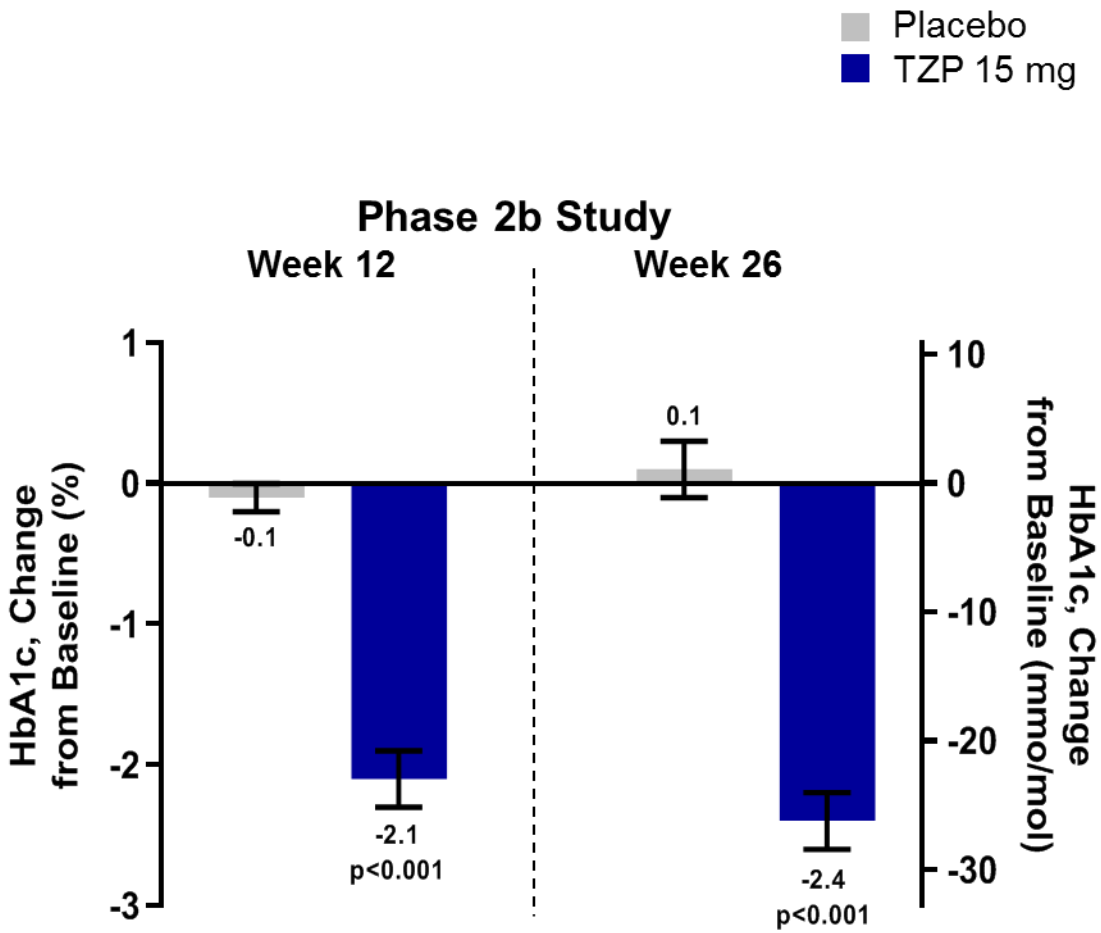


Data presented as LSM±SE at the final endpoint and overtime. P-values versus placebo

Reduction in HbA1c with Tirzepatide

Comparison with Phase 2b Study

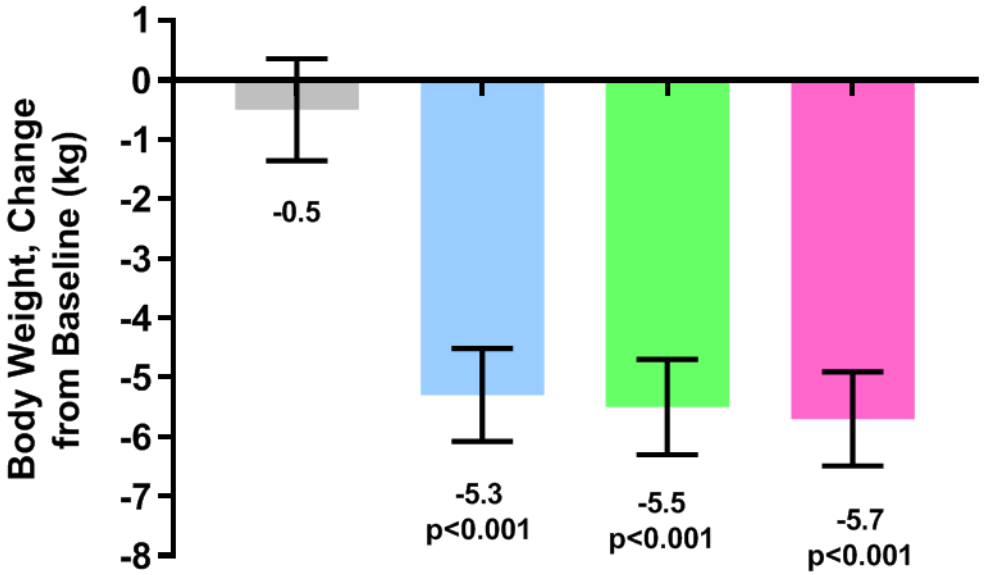


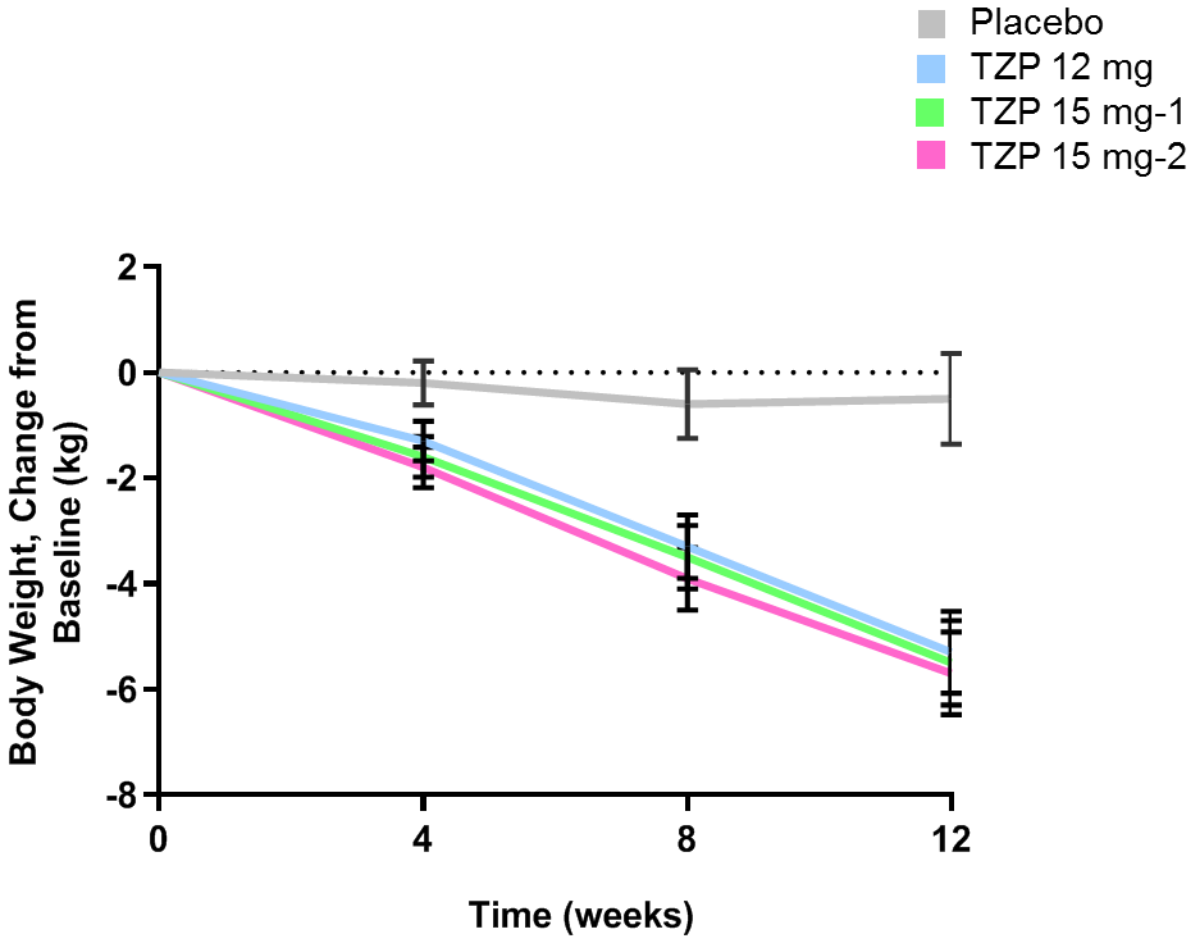


Data presented as LSM±SE at the final week endpoint. P-values versus placebo. Note: a slower titration regimen was used in the Dose Escalation Study compared to the Phase 2b Study

Reduction in Body Weight with Tirzepatide

Change from Baseline at 12 Weeks and Over Time

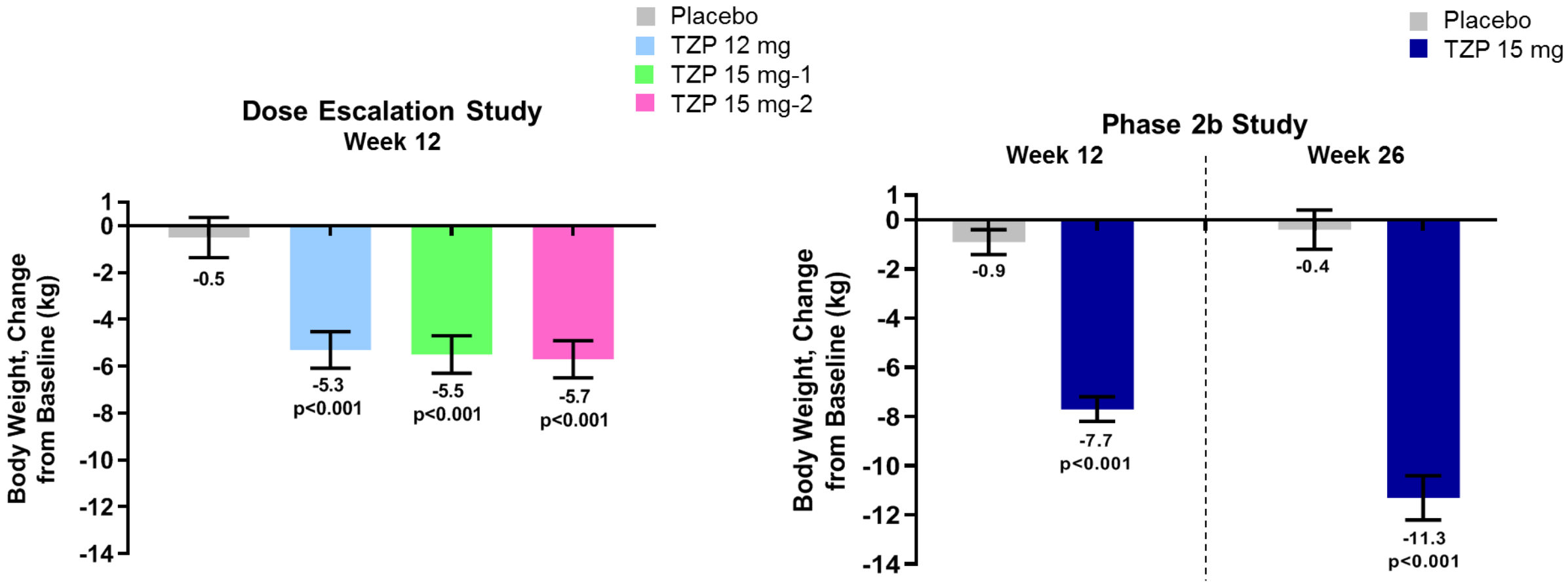




Data presented as LSM±SE at the 26 week endpoint and overtime. P-values versus placebo

Reduction in Body Weight with Tirzepatide

Comparison with Phase 2b Study



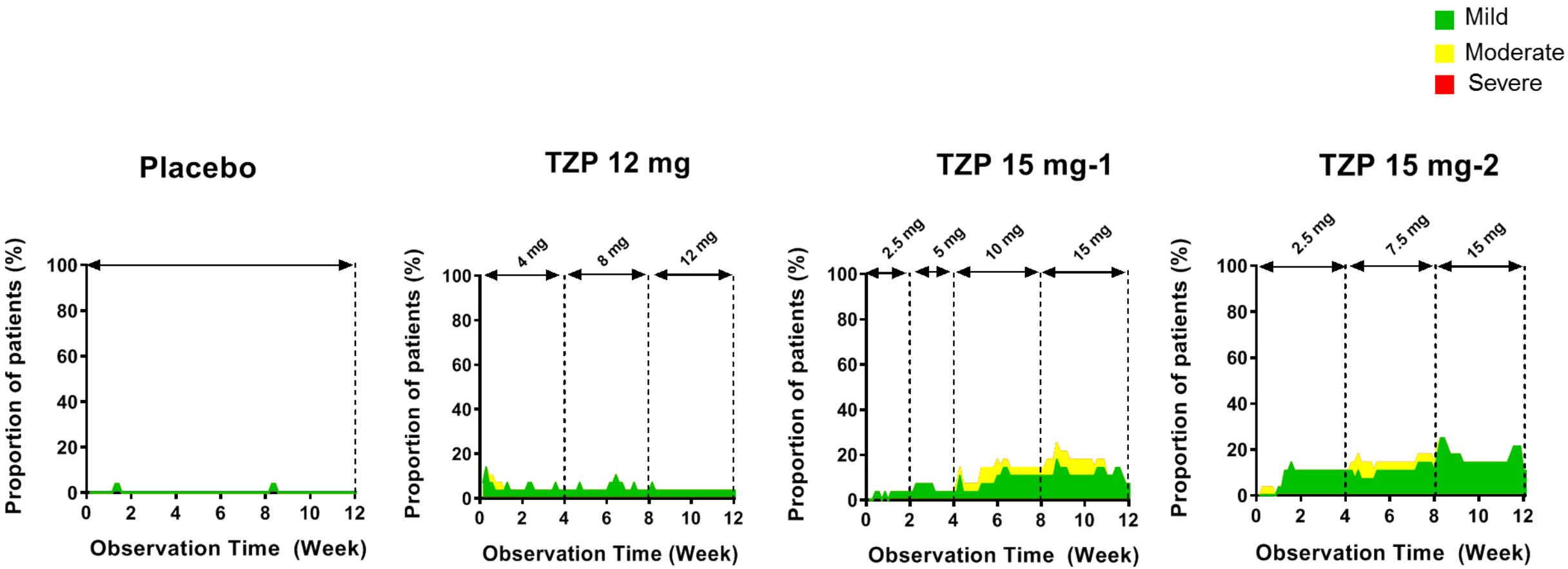
Data presented as LSM±SE at the final week endpoint. P-values versus placebo. Note: a slower titration regimen was used in the Dose Escalation Study compared to the Phase 2b Study

Treatment-Emergent Adverse Events

Preferred Term	Placebo N=26	TZP 12 mg N=29	TZP 15 mg-1 N=28	TZP 15 mg-2 N=28
Serious AEs	0	3.4	0	0
TEAEs	50.0	79.3	67.9	85.7
TEAE Severity (mild/moderate/severe), n	8/5/0	17/6/0	12/7/0	14/9/1
TEAEs (≥5% of patients)				
Nausea	7.7	24.1	39.3	35.7
Diarrhoea	7.7	31.0	35.7	32.1
Decreased appetite	0	13.8	21.4	28.6
Vomiting	3.8	17.2	17.9	17.9
Headache	7.7	6.9	21.4	17.9
Dyspepsia	0	17.2	10.7	10.7
Constipation	0	3.4	10.7	17.9
Abdominal Pain	3.8	3.4	17.9	3.6
Dizziness	7.7	0	3.6	10.7
Other TEAEs				
Total hypoglycaemia (BG ≤70 mg/dL)	0	6.9	14.3	17.9
Total hypoglycaemia (BG ≤54 mg/dL)	0	0	0	3.6
Severe hypoglycaemia	0	0	0	0
Cholecystitis	0	0	0	0
Acute pancreatitis	0	0	0	0

Data presented as %, unless otherwise noted. AE=adverse event; BG=blood glucose; N=number of patients in that category; TEAE=treatment-emergent adverse event; TZP=tirzepatide

Prevalence and Severity of Nausea by Dose Group Over Time

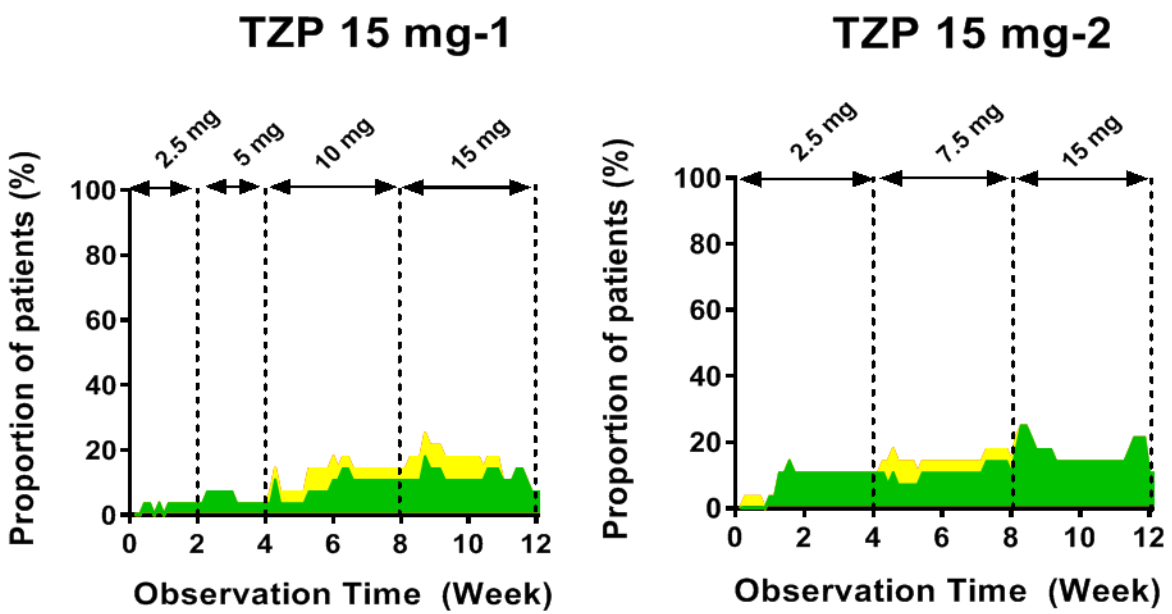


The vertical dotted lines represent dose escalations

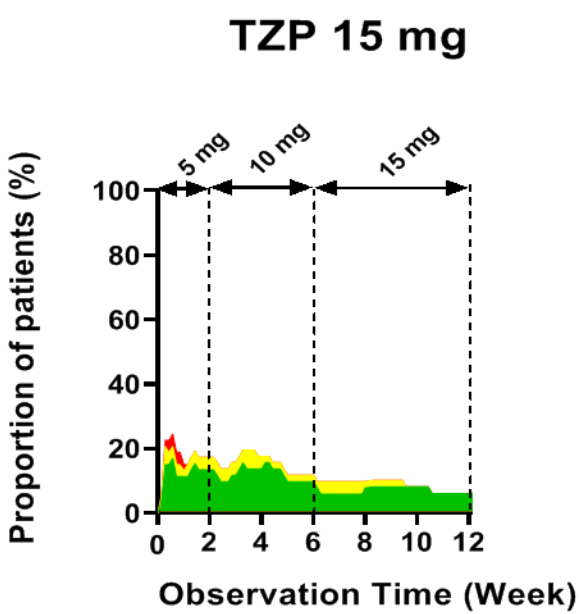
Prevalence and Severity of Nausea by Dose Group Over Time

Comparison with Phase 2b Study

Dose Escalation Study



Phase 2b Study



Mild
Moderate
Severe

The vertical dotted lines represent dose escalations

Limitations

- Although the main focus was optimising the dose regimen of tirzepatide, the study was designed with change in HbA1c as the primary objective
  - The reason for this was to have comparable results to the Phase 2b study[1] and avoid reporting bias towards GI side effects
- While this study evaluated the effect of different dose escalation regimens on GI side effects, the study was not powered to compare small differences in GI frequencies within weeks or at endpoint, so conclusions were made on numerical comparisons only
- The dose-escalation period was limited to 8 weeks; longer dose escalation may have resulted in further improvements in the incidence of nausea, vomiting, and diarrhoea

GI: gastrointestinal; HbA1c: glycated haemoglobin A1c

1. Frias et al. Lancet. 2018;392(10160):2180-2193.

Summary and Conclusion

- Tirzepatide showed consistent HbA1c reduction and consistent weight loss with the Phase 2b trial[1]
- The safety profile of tirzepatide was consistent with selective GLP-1 RAs
- The investigated dose-escalation regimen suggests improved tolerability (lower incidence GI AEs, and mostly mild severity), decreased incidence in nausea, and decreased discontinuations compared with the Phase 2b 15mg group[1]
  - Lower starting dose and smaller dose increments appeared to have resulted in fewer GI-related incidents

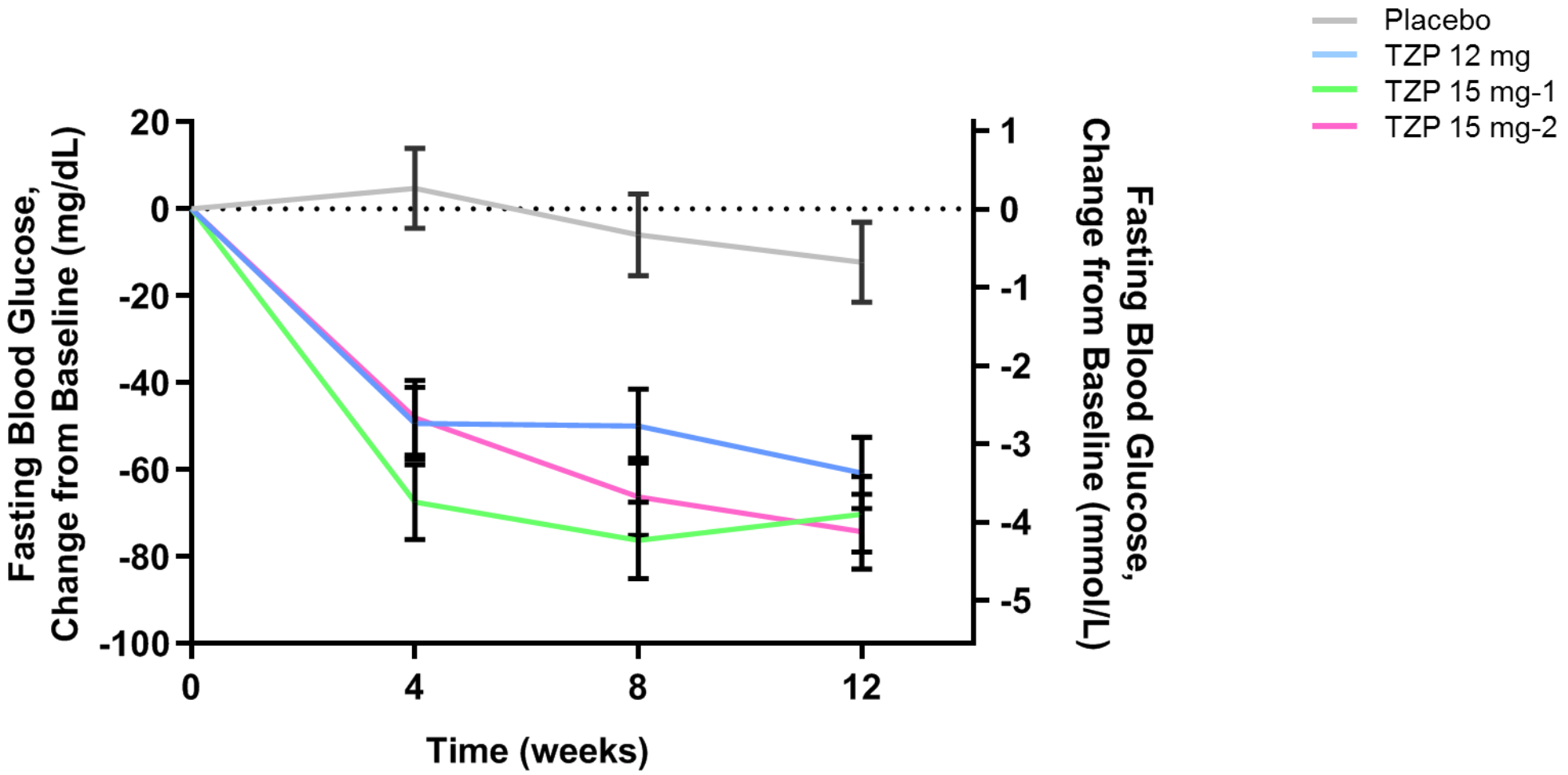
This study contributed to the starting dose and dose escalation regimen of the type 2 diabetes SURPASS Phase 3 registration program

AEs: adverse events; GI: gastrointestinal; HbA1c: glycated haemoglobin A1c

1. Frias et al. Lancet. 2018;392(10160):2180-2193.

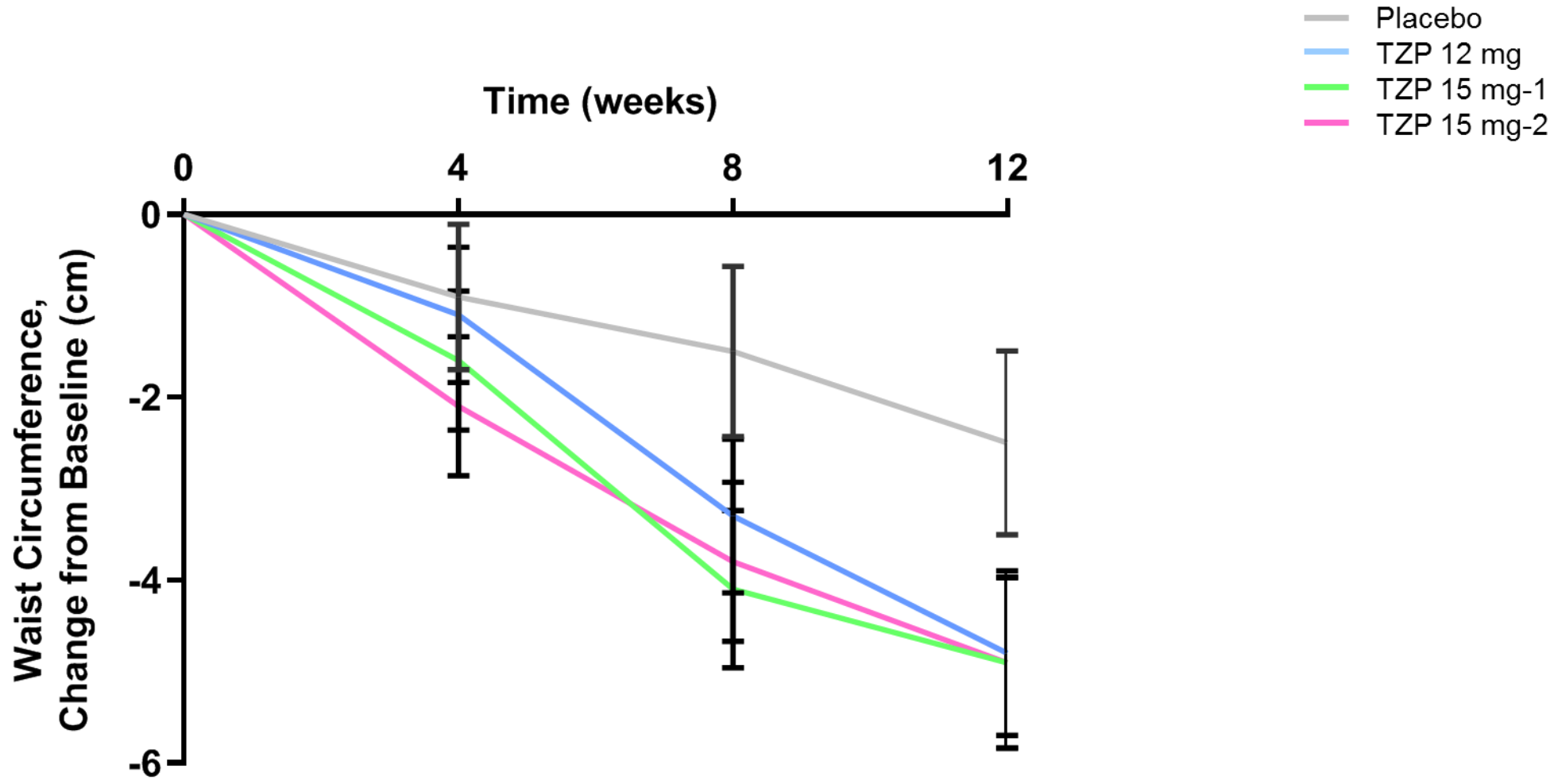
Backup

Tirzepatide Reduced Fasting Blood Glucose Over Time



Data presented as LSM±SE

Tirzepatide Reduced Waist Circumference Over Time



Data presented as LSM±SE