BARI-STEP: A Double-blinded, Randomised, Placebo-controlled Trial of Semaglutide 2.4mg in Patients With a Sub-Optimal Clinical Response Following Metabolic/Bariatric Surgery

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NHS Homerton University Hospital NHS Foundation Trust
NIHR | University College London Hospitals Biomedical Research Centre
The Sir Jules Thorn CHARITABLE TRUST
University College London Hospitals NHS Foundation Trust

Disclosures

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JM disclosures

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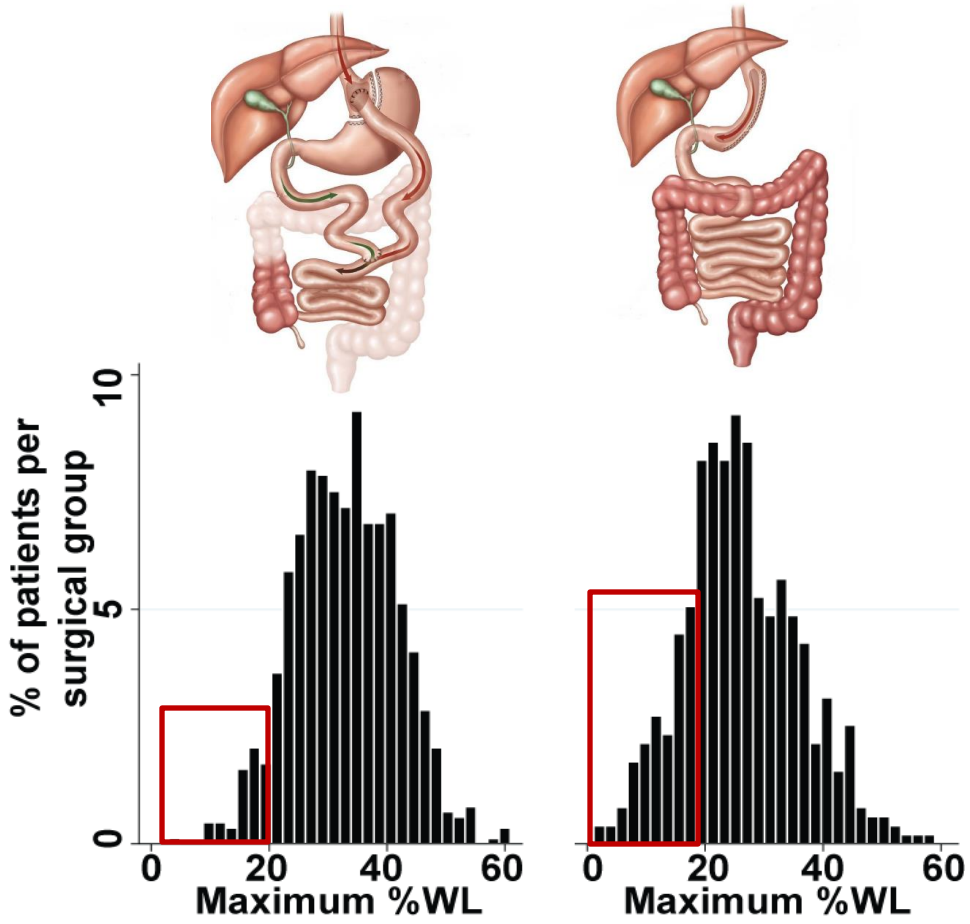
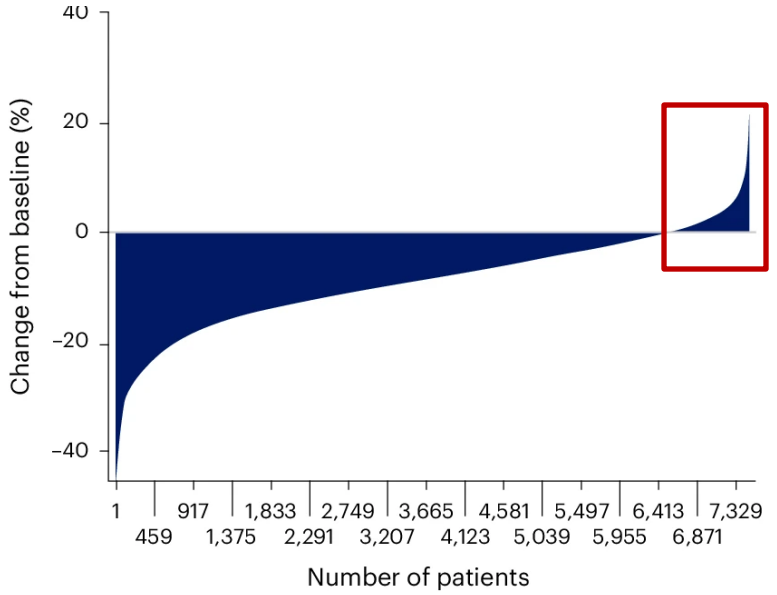
Background: Variation in Response



Manning, *et al. Surg Endosc*. 2015;29:1484–91

Semaglutide 2.4mg (SELECT)

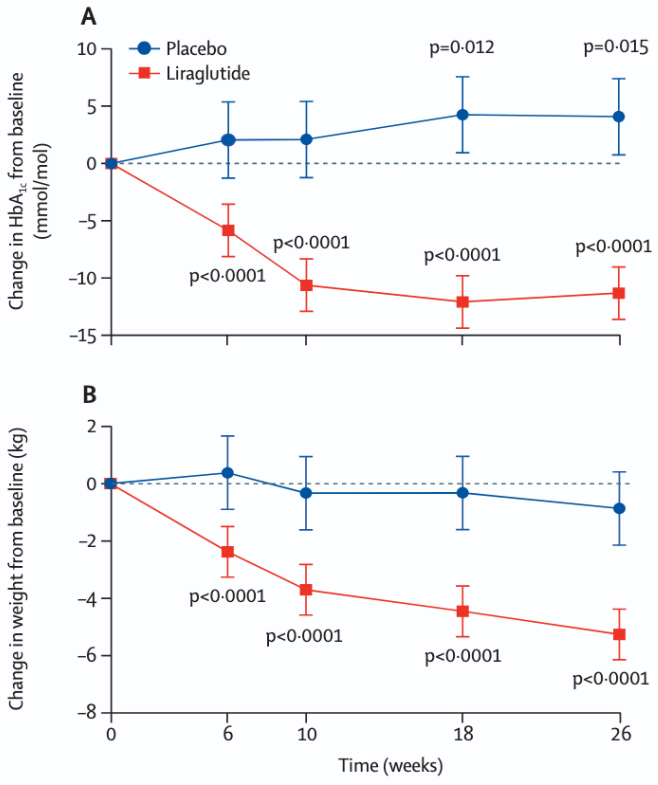


Ryan *et al. Nat Med* **30**, 2049–2057 (2024).

Once-daily liraglutide following primary MBS

Adjunctive liraglutide treatment in patients with persistent or recurrent type 2 diabetes after metabolic surgery (GRAVITAS): a randomised, double-blind, placebo-controlled trial

Alexander Dimitri Miras*, Belén Pérez-Pevida*, Madhawi Aldhwayan, Anna Kamocka, Emma Rose McGlone, Werd Al-Najim, Harvinder Chahal, Rachel L Batterham, Barbara McGowan, Omar Khan, Veronica Greener, Ahmed R Ahmed, Aviva Petrie, Samantha Scholtz, Stephen R Bloom, Tricia M Tan

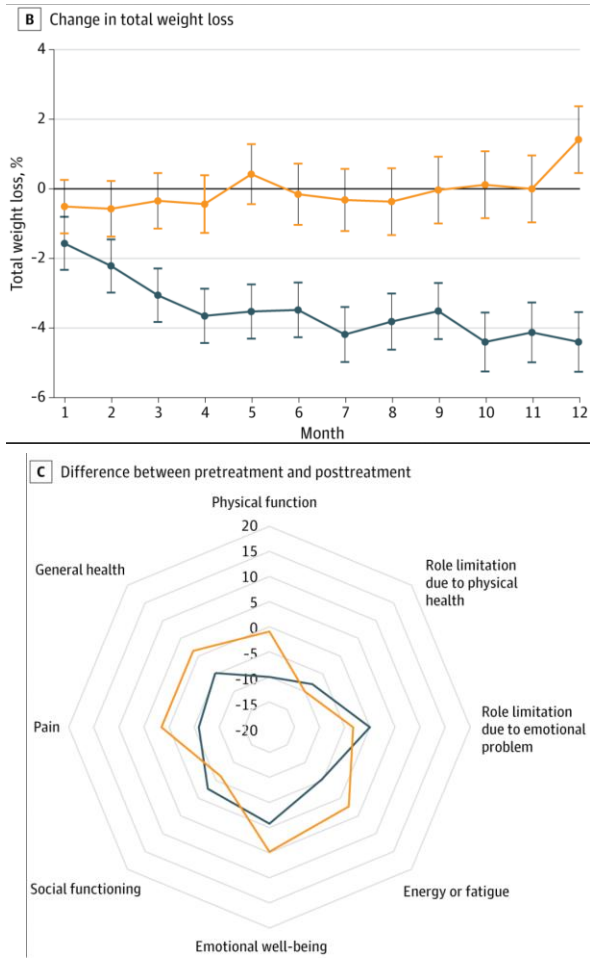


Original Investigation | Surgery

Liraglutide and Weight Loss Among Suboptimal Responders to Metabolic Bariatric Surgery

A Randomized Clinical Trial

Wendy A. Brown, PhD[1,2]; Paul R. Burton, PhD[1,2]; Cheryl Laurie, BhHSc[1]; et al

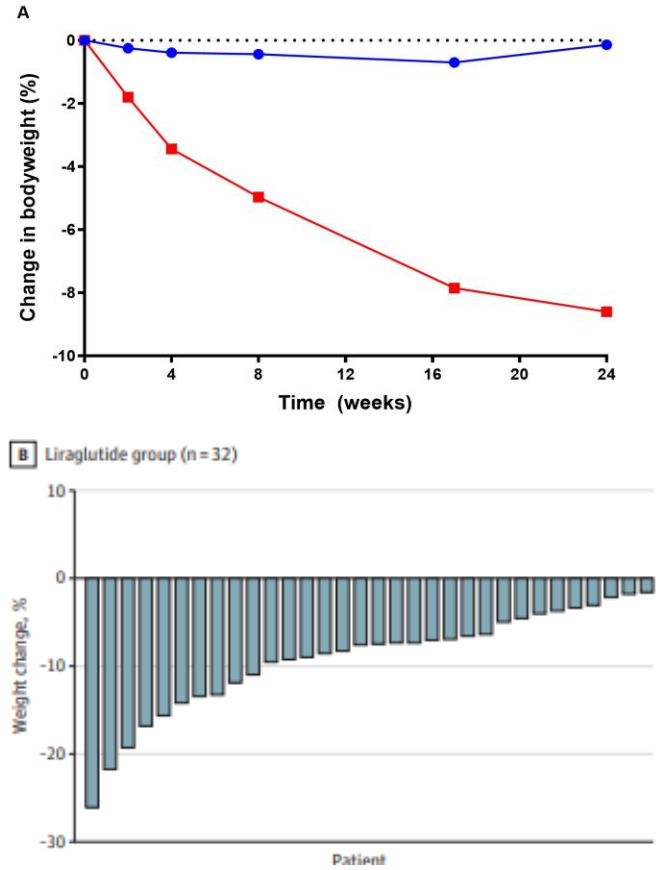


JAMA Surgery | Original Investigation

Safety and Efficacy of Liraglutide, 3.0 mg, Once Daily vs Placebo in Patients With Poor Weight Loss Following Metabolic Surgery

The BARI-OPTIMISE Randomized Clinical Trial

Jessica Mok, BMBS, MPhil; Mariam O. Adeleke, PhD; Adrian Brown, PhD; Cormac G. Magee, MBBChir, MA; Chloe Firman, MRes; Christwishes Makahamadze, MRes; Friedrich C. Jassil, PhD; Parastou Marvasti, PhD; Alisia Carnemolla, PhD; Kalpana Devalia, MBBS, MS; Naim Fakih, MD; Mohamed Elkalaawy, MRCSEd, MS, MD; Andrea Pucci, MD, PhD; Andrew Jenkinson, MBBS, MS; Marco Adamo, MD; Rumana Z. Omar, PhD; Rachel L. Batterham, MBBS, PhD; Janine Makaronidis, MBChB, PhD

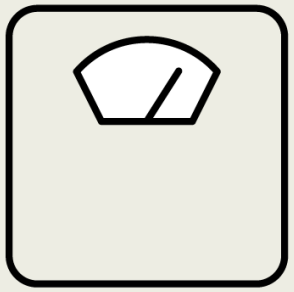


Background: BARI-OPTIMISE RCT

RCT: Safety and Efficacy of Liraglutide, 3.0 mg, Once Daily vs Placebo in Patients With Poor Weight Loss Following Metabolic Surgery

POPULATION

18 Men,
52 Women



Adults ≥1 y after metabolic surgery with poor weight loss (≤20%) and a suboptimal GLP-1 response

Mean age, 47.6 y

INTERVENTION

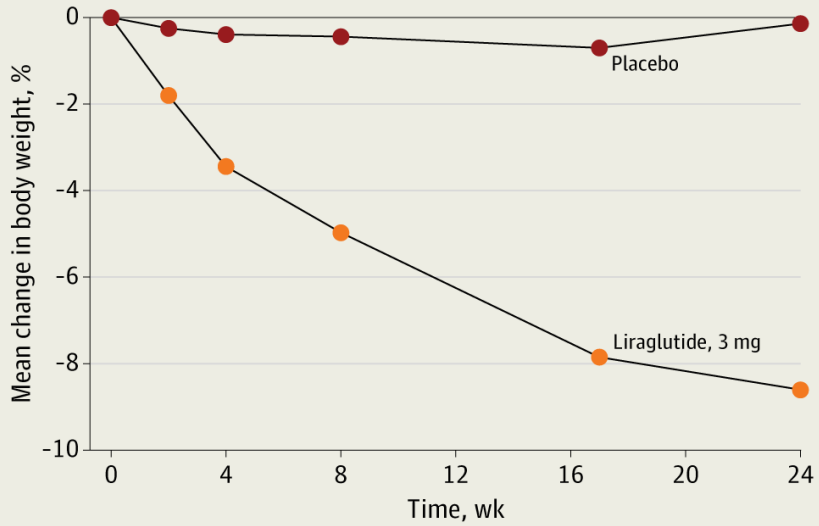
70 Patients randomized,
57 Analyzed

31 Liraglutide, 3.0 mg
Self-administration once daily of a subcutaneous injection of liraglutide, 3.0 mg, for 24 wk

26 Placebo
Self-administration once daily of placebo saline solution for the same period

FINDINGS

Liraglutide, 3.0 mg once daily, resulted in a significantly greater reduction in body weight from baseline to week 24 compared with placebo



Mean difference: -8.0%; 95% CI, -10.4 to -5.7; *P* <.001

SETTINGS / LOCATIONS

2 Hospitals in London, United Kingdom

PRIMARY OUTCOME

Change in percentage body weight from baseline to end of 24-wk study period

Mok J, Adeleke MO, Brown A, et al. Safety and efficacy of liraglutide, 3.0 mg, once daily vs placebo in patients with poor weight loss following metabolic surgery: the BARI-OPTIMISE randomized clinical trial. *JAMA Surg*. Published online July 26, 2023. doi:10.1001/jamasurg.2023.2930

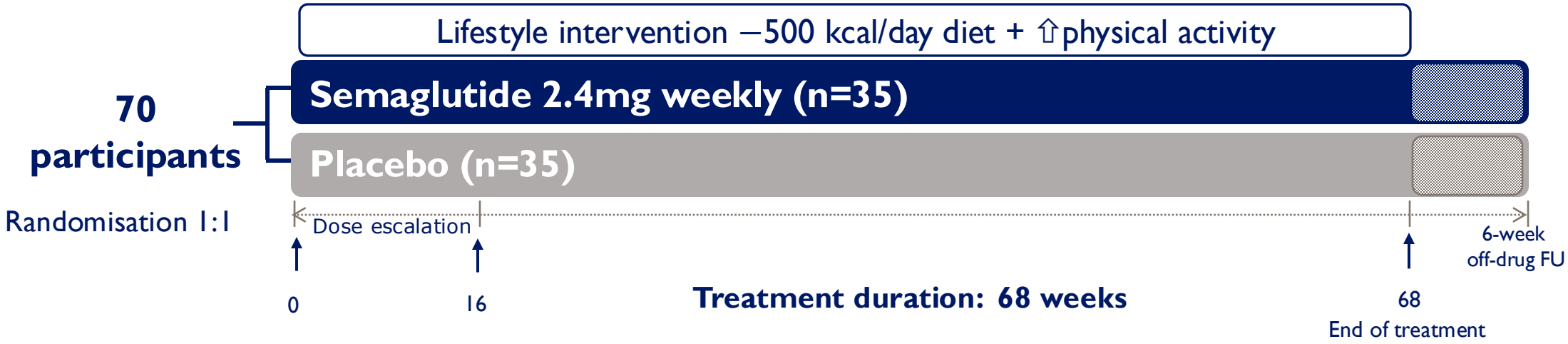
Hypothesis

Semaglutide 2.4mg weekly (or maximal tolerated dose) will lead to greater weight loss and health improvements compared to placebo in individuals with a suboptimal clinical response following Gastric Bypass or Sleeve Gastrectomy.

BARI-STEP: Trial Design

Trial objective

To confirm superiority of semaglutide 2.4mg vs. placebo, as an adjunct to a lifestyle intervention (reduced-calorie diet and physical activity), on weight loss effectiveness in individuals with recurrent weight gain or suboptimal weight loss response following primary Gastric Bypass/SG



Trial information

- November 2023 to April 2025
- Two recruitment sites in London, UK
- **Randomised, placebo-controlled, double-blind trial**

Trial Design

Inclusion Criteria

- ≥1 year after primary Gastric Bypass or SG
- <20% weight loss from day of surgery
- Weight stable
- Age 18-65 years

Key Exclusion Criteria

- Severe metabolic, renal, hepatic, psychiatric or cardiovascular disease
- Type 1 Diabetes Mellitus of Type 2 DM treated with insulin
- Concomitant use of GLP-1RA or DDP-IV inhibitors
- Chronic, recurrent or recent pancreatitis
- MEN-2, medullary thyroid carcinoma

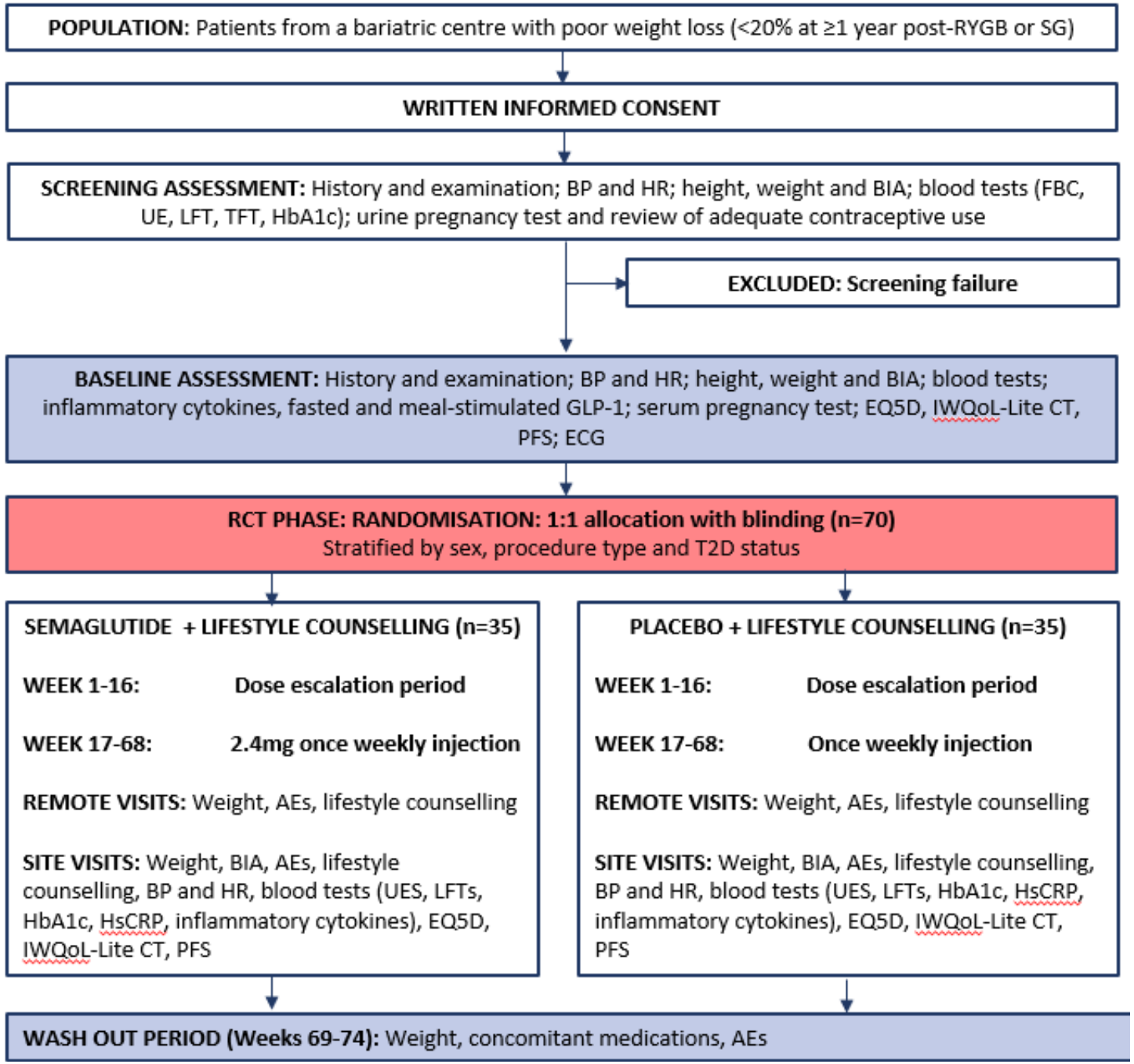
Primary Endpoint

- Change in body weight (%)

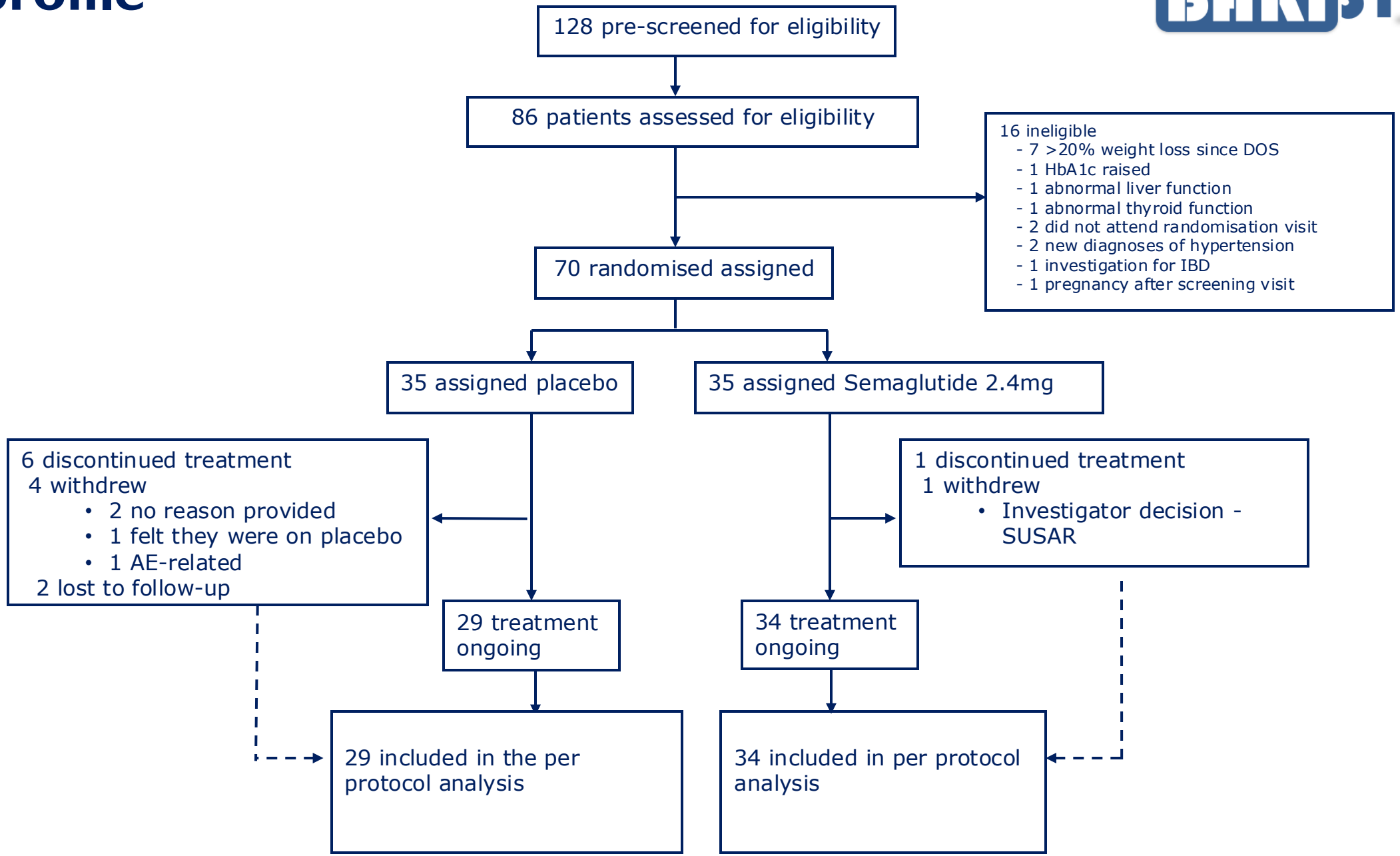
Secondary Endpoints

- % who achieve a body weight reduction ≥10%, ≥15%, ≥20%
- Body weight, body fat, lean body mass, bone density (BIA)
- HbA1c, BP, metabolic and inflammatory indices
- Relationship between GLP-1 levels at baseline and % WL
- Safety
- Health Related Quality of Life (HRQoL)

BARI-STEP: Flow Chart



Trial profile

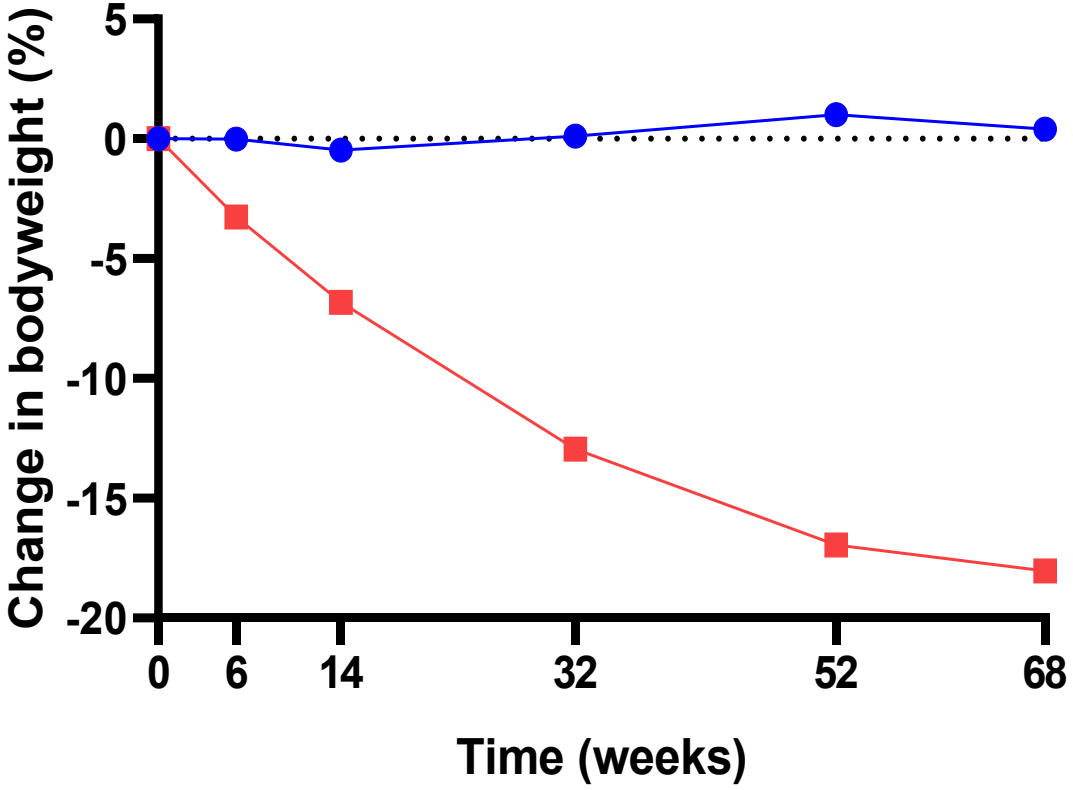


Baseline characteristics

	Placebo(n=35)	Semaglutide 2.4mg (n=35)
Sex: Female	28 (80%)	30 (85·7%)
Sex: Male	7 (20%)	5 (14·3%)
Age (years)	47.7 (10·3)	46·9 (10·4)
Ethnicity		
Asian	0 (0)	2 (5.7)
Black	10 (28.6)	6 (17.1)
White	21 (60)	26 (74.3)
Mixed/Other	4 (11.4)	1 (2.9)
Bodyweight (kg)	111·4 (19·3)	118·7 (23·3)
BMI (kg/m^2)	40·2 (6·05)	42·8 (6·8)
Procedure type		
Sleeve Gastrectomy	28 (80%)	27 (77·1%)
Gastric Bypass	7 (20%)	8 (22·9%)
Time since surgery (months)	78·6 (34·2)	88·1(50·5)
Post-surgery % Weight Loss	9·2 (6·7)	5·8 (8·2)
HbA1c (mmol/mol)	38·9 (4·2)	37·1 (5·6)
Participants with Type 2 DM (n)	4 (11·4%)	3 (8·6%)
Blood pressure (mmHg)		
Systolic	131·2 (12·1)	134·1 (11·2)
Diastolic	72·2 (9·9)	75.1 (10·5)

Results: Change in bodyweight (%)

0-68 weeks



ETD =-19.1%* (-14.8 to -23.4)

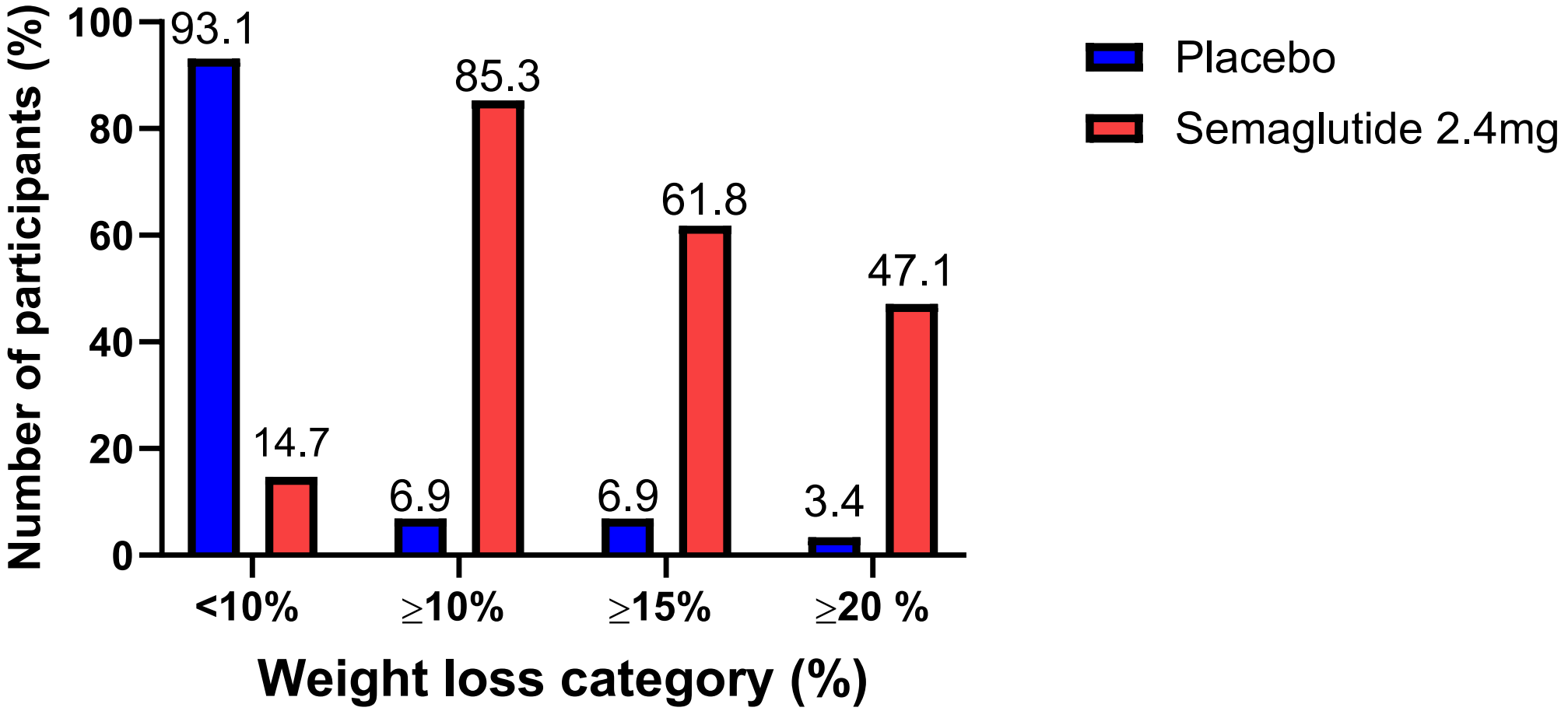
p<0.0001

Mean difference
Placebo: +0.4% (7%)
Semaglutide: -18.04% (9.2%)

*adjusting for the effects of surgery type, diabetes status, sex and baseline weight.

Categorical weight loss

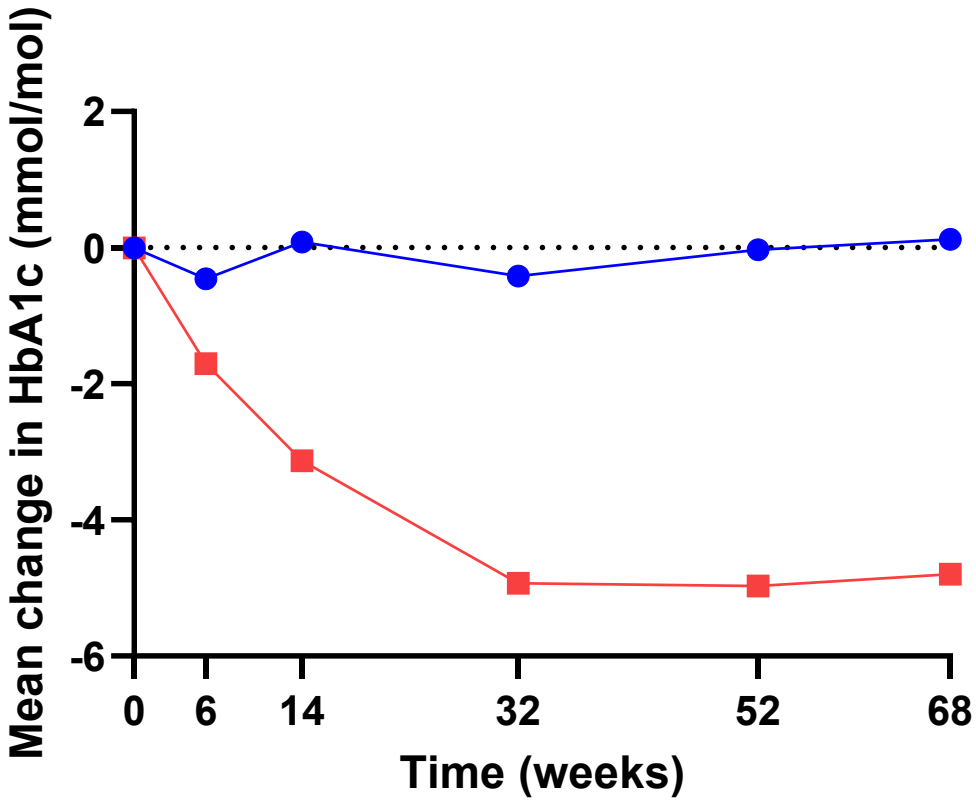
0-68 weeks



Change in cardiometabolic parameters: HbA1c

0-68 weeks

Change in HbA1c



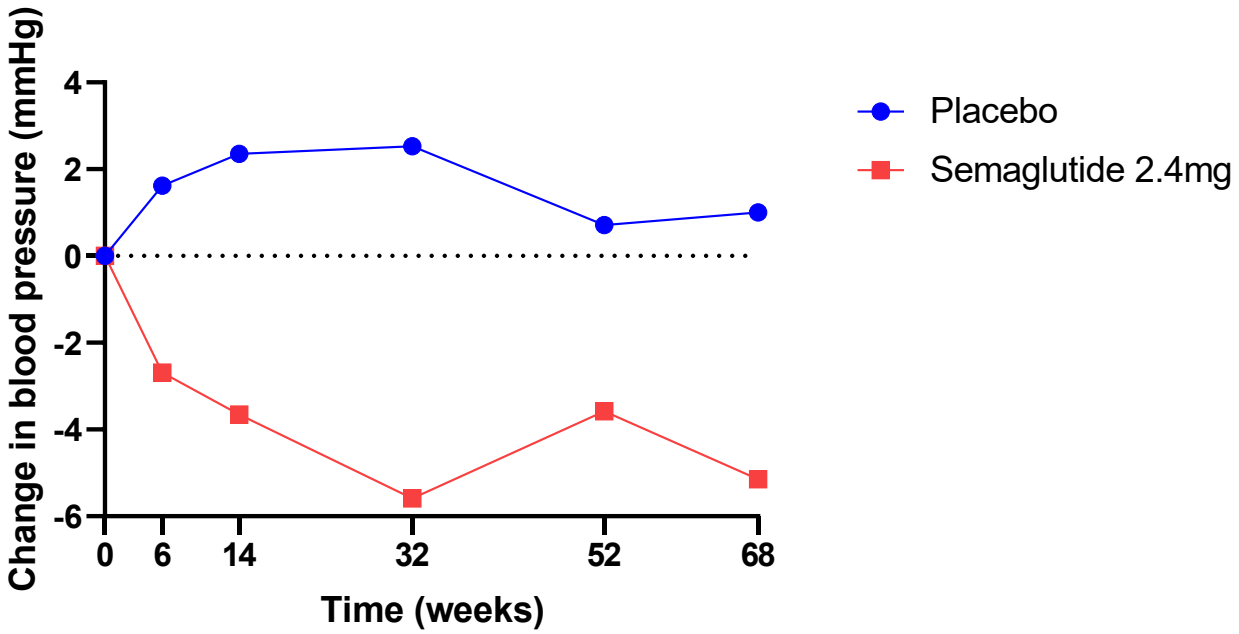
ETD = -5.3 (-6.6 to -4) (mmol/mol)

P=<0.001

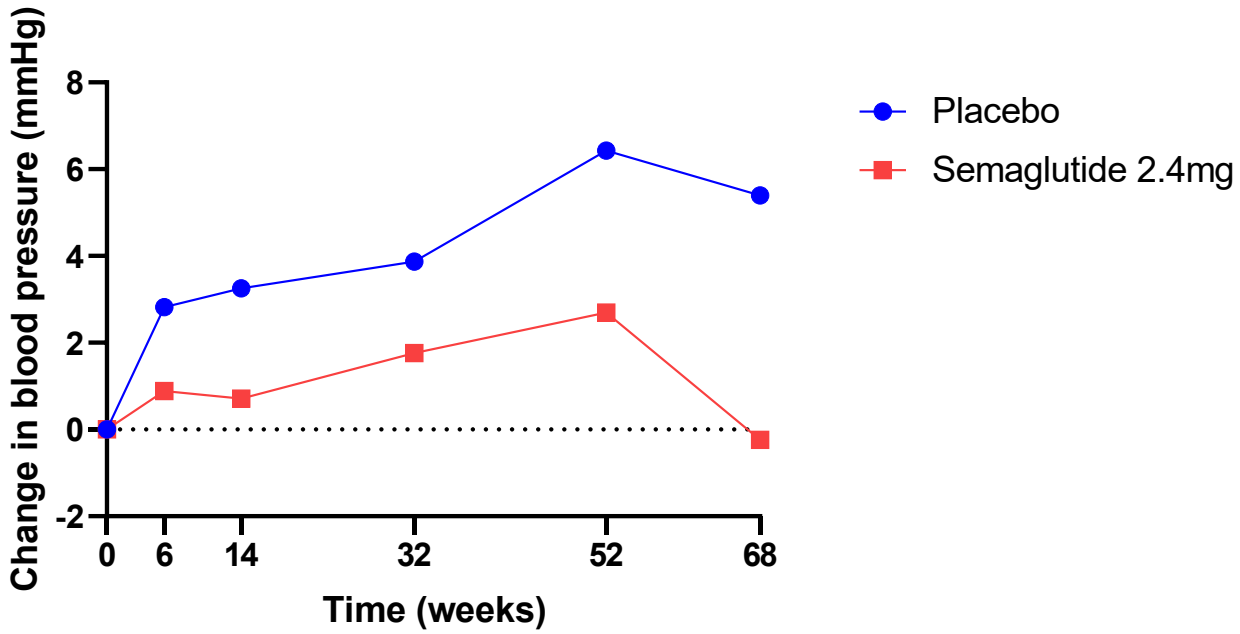
Change in cardiometabolic parameters

0-68 weeks

Systolic blood pressure



Diastolic blood pressure



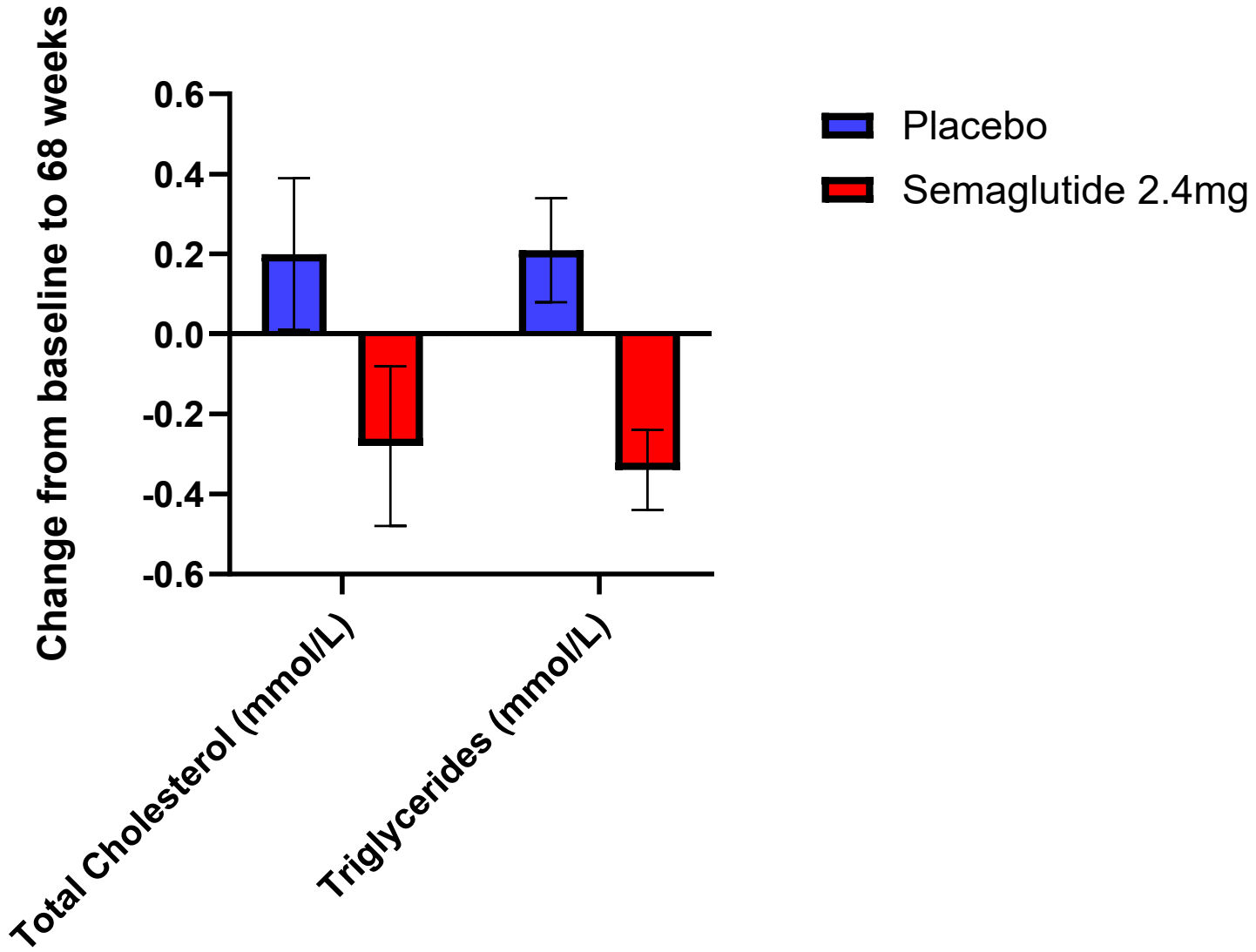
SBP ETD*: -5.99 mm/Hg (-12.0, 0.2) p=0.059

DBP ETD*: -4.2 mm/Hg (-8.8, 0.3) p=0.068

*Calculated from estimated marginal means from linear regression adjusted for Surgery, Diabetes, Sex, Baseline Weight (kg),

Change in cardiometabolic parameters

0-68 weeks: Total Cholesterol and Triglycerides



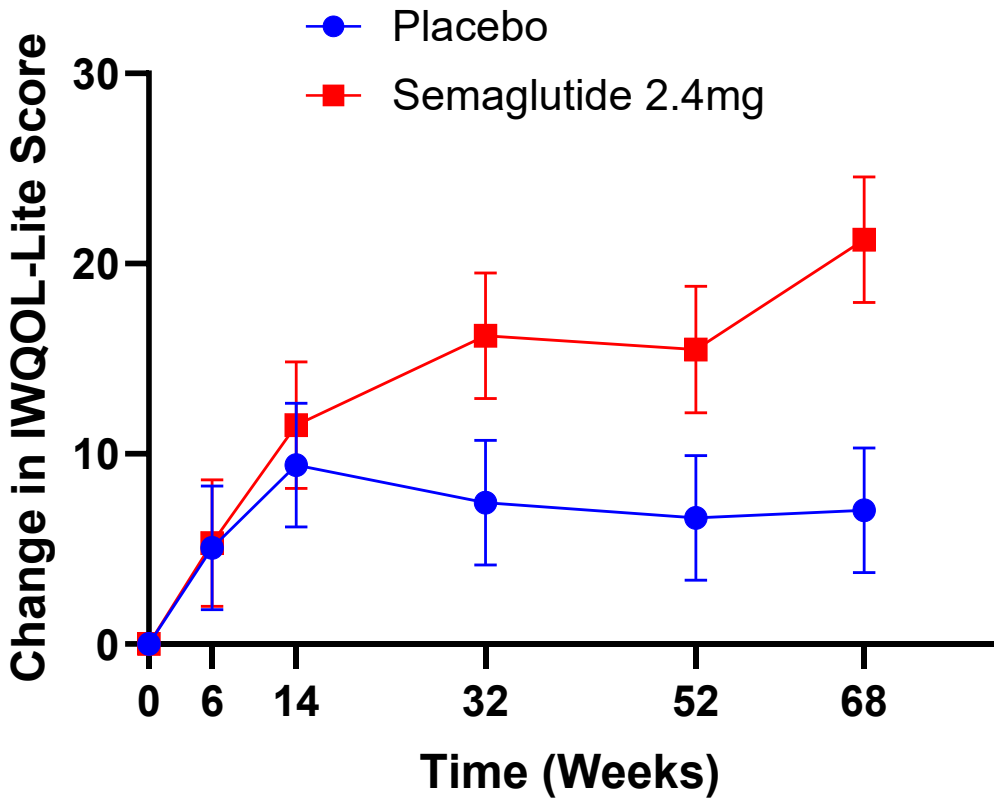
Total Cholesterol ETD* = -0.48 mmol/L (-0.9, -0.1)
p=0.014

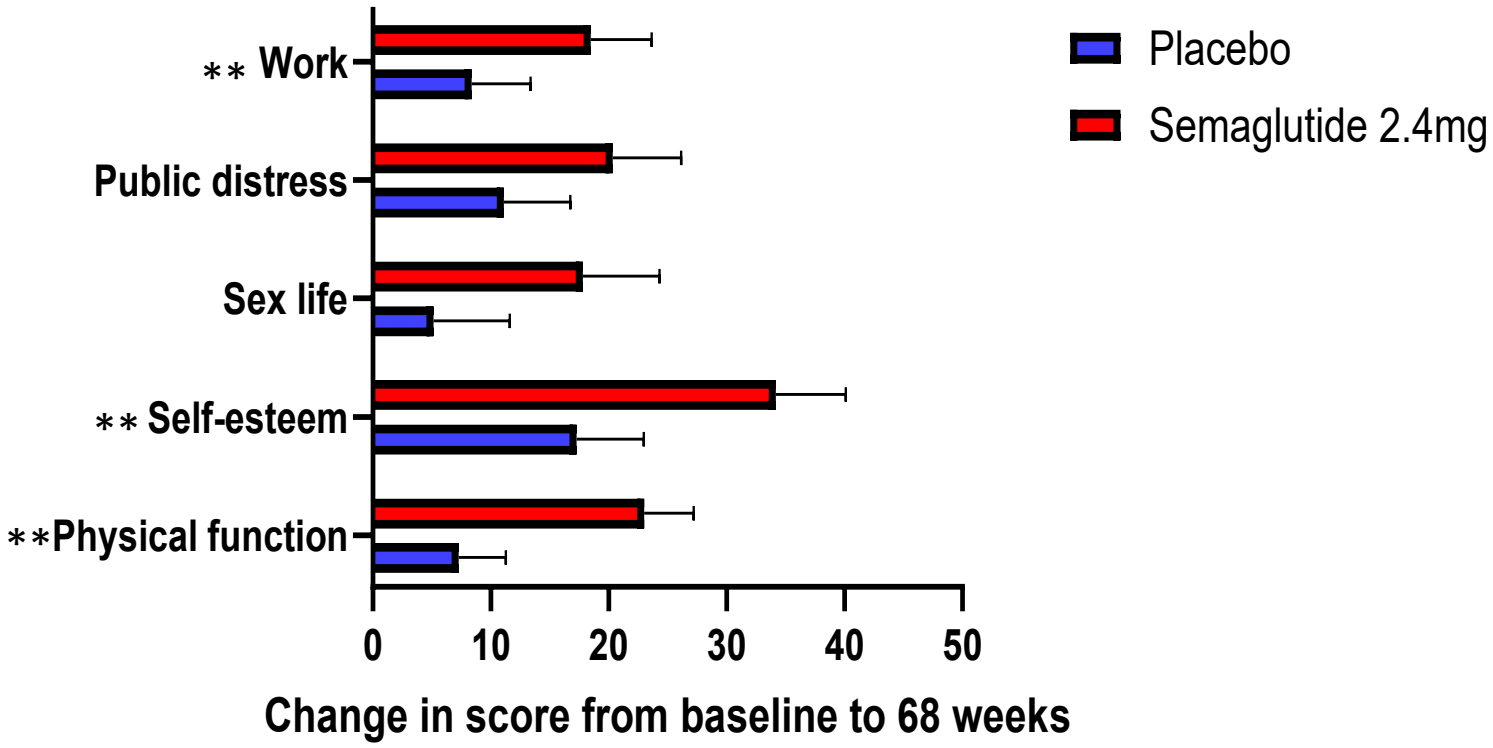
Triglycerides ETD* = -0.54 mmol/L (-0.9, -0.3)
p<0.001

*Calculated from estimated marginal means from linear regression adjusted for Surgery, Diabetes, Sex, Baseline Weight (kg)

Change in IWQOL-Lite

0-68 weeks





* Higher scores indicate better quality of life

** significant improvements in adjusted component scores

Safety profile – most common AEs

	Placebo arm (n = 35)		Semaglutide 2.4mg arm (n = 35)		Total (n = 70)	
	Number of events	Number of patients (%)	Number of events	Number of patients (%)	Number of events	Number of patients (%)
Adverse events	126	33 (94.3)	218	34 (97.1)	344	67 (97.5)
Gastrointestinal						
Diarrhoea	17	14 (40)	28	21 (60)	45	35 (50)
Nausea**	**10**	**8 (22.9)**	**27**	**24 (68.6)**	**37**	**32 (45.7)**
Decreased appetite*	**4**	**4 (11.4)**	**15**	**15 (42.9)**	**19**	**19 (27.1)**
Vomiting	7	6 (17.1)	15	10 (28.6)	22	16 (32.9)
Constipation	8	8 (22.9)	14	13 (37.1)	22	21 (30)
Abdominal pain	5	5 (14.3)	10	10 (28.6)	15	15 (21.4)
Dyspepsia	5	5 (14.3)	9	9 (25.7)	14	14 (20)
Abdominal bloating	6	6 (17.1)	4	4 (11.4)	10	10 (14.3)
Gastritis	0	0 (0)	1	1 (2.9)	1	1 (1.4)
Cardiovascular events						
Dizziness	5	5 (14.3)	11	10 (28.6)	16	15 (21.4)
Palpitations	1	1 (2.9)	3	3 (8.6)	4	4 (5.7)
Chest pain	1	1 (2.9)	1	1 (2.9)	2	2 (2.9)
Hepatobiliary						
Cholelithiasis	1	1 (2.9)	1	1 (2.9)	2	2 (2.9)
Pancreatitis	2	1 (2.9)	0	0 (0)	2	1 (1.4)
Injection site reactions	11	9 (25.7)	10	10 (28.6)	21	19 (27.1)

**Nausea = $p<0.01$, *Decreased appetite = $p<0.05$

Additional AEs reported: headaches, general AEs, Infections – Stanley at al. Nature Med, 2026

BARI-STEP: Safety Review (SAEs/SUSAR)

Serious Adverse Events (SAEs)	Number (#)	Causality	Outcome	Treatment Allocation
Gastro-oesophageal reflux disease	1	Possibly related to IMP	Recovered	Placebo
Fractured patella and ligament rupture	1	Not related to IMP	Recovered	Placebo
Gallstone Pancreatitis	1	Possibly related to IMP	Recovered	Placebo
Spontaneous bruising	1	Not related to IMP	Recovered	Semaglutide
Acute Coronary Syndrome	1	Not related to IMP	Recovered	Placebo
Abdominal wall abscess	1	Not related to IMP	Recovered	Semaglutide
Ectopic pregnancy	1	Not related to IMP	Recovered	Placebo
Bradycardia	1	Not related to IMP	Recovered	Placebo

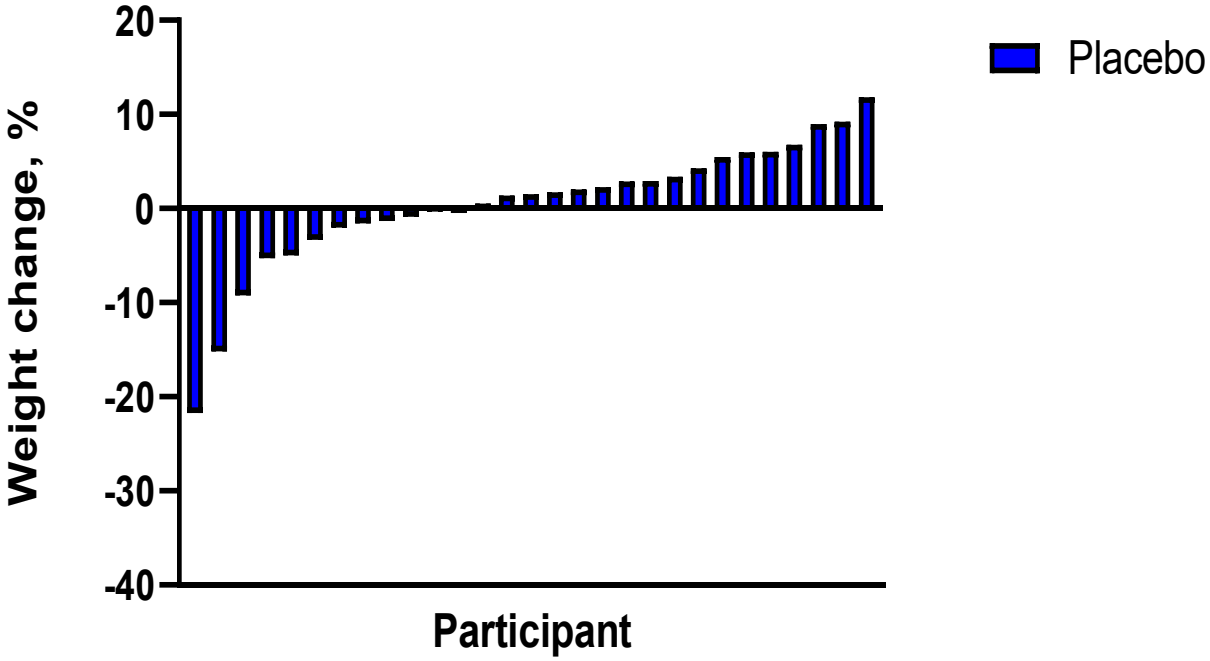
Suspected Unexpected Serious Adverse Reaction (SUSAR)

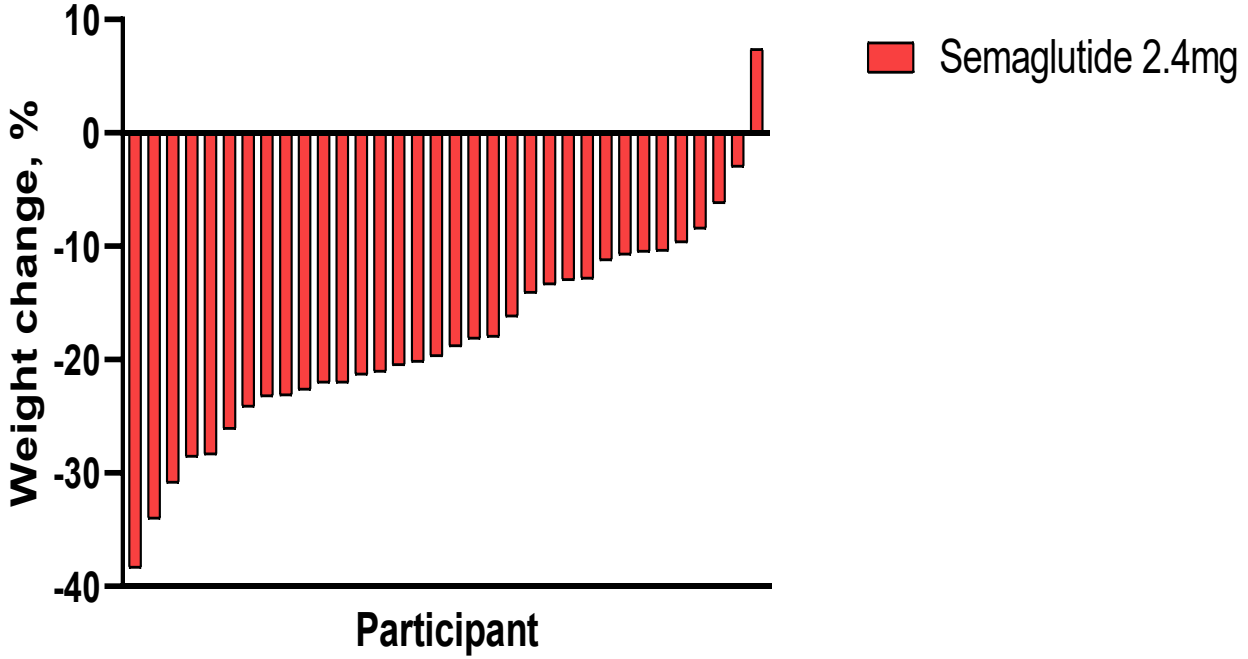
SUSAR	Number (#)	Causality	Outcome	Treatment Allocation
Eating disorder	1	Possibly related to IMP	Recovering	Semaglutide

No deaths

Variation in response: weight loss (%)

0-68 weeks





Weight loss (%) and relationship to GLP-1

0-68 weeks

Baseline endogenous meal-stimulated GLP-1 (active GLP-1)

Assessed via 30-min meal test (500kcal meal)

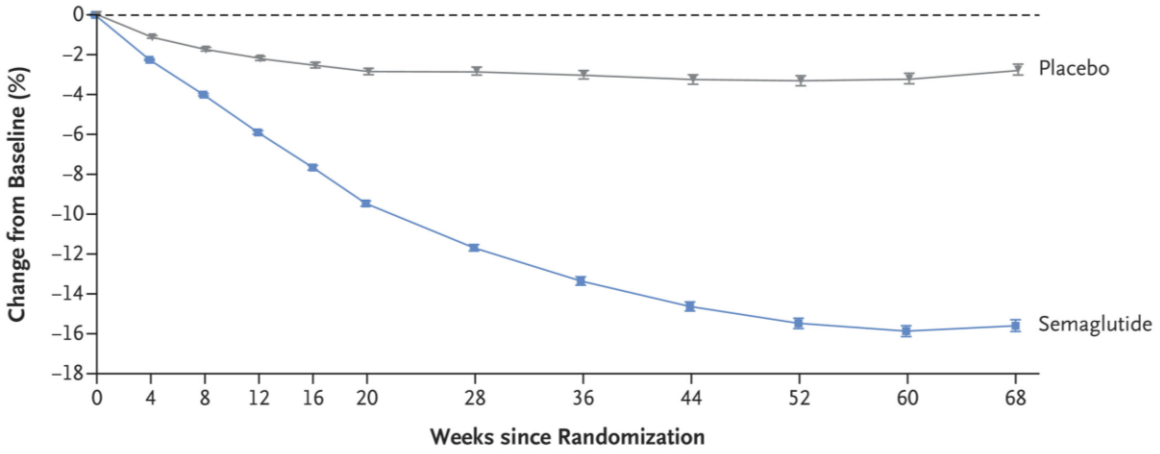
Results: Relationship to %WL

- Meal-stimulated GLP-1
- Ethnicity
- Time since surgery
- Procedure type
- Suboptimal initial response vs recurrent weight gain
- Sex
  - Menopause status

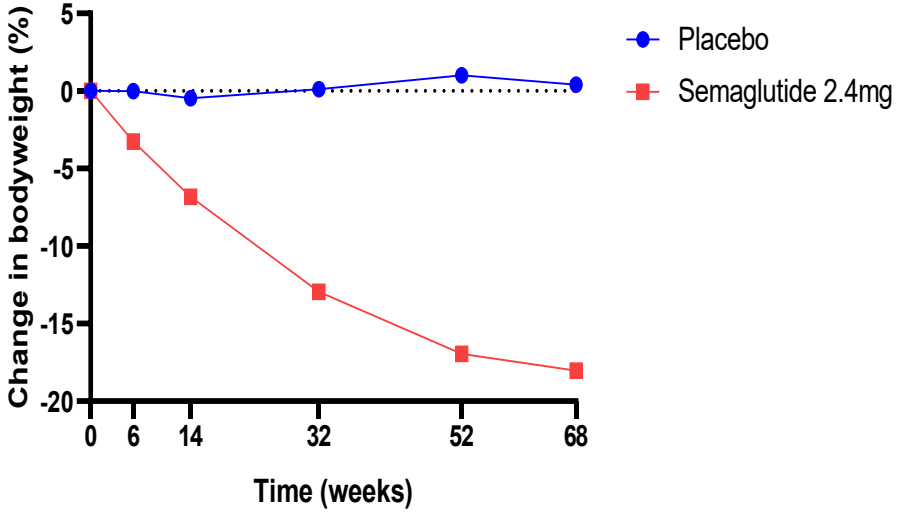
→ No relationship to % weight change

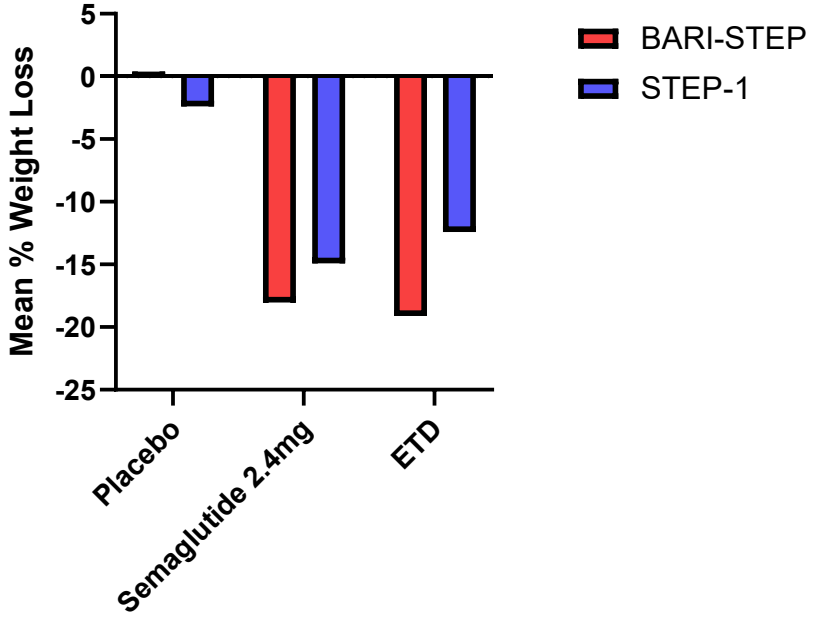
Comparison to STEP-1

Observed body weight change over time (STEP-1)



Observed body weight change over time (BARI-STEP)





Placebo: BARI-STEP [+0.4%], STEP-1 [-2.4%]

Semaglutide 2.4mg: BARI-STEP [-18.04%], STEP-1 [-14.9%]

ETD: BARI-STEP [-19.1%], STEP 1 [-12.4%]

Summary/conclusions

- Semaglutide 2.4mg weekly is safe and well tolerated in a population of patients with a suboptimal clinical response following primary MBS
- Nausea and decreased appetite were the most commonly reported adverse events
- 68 weeks of semaglutide 2.4mg or maximal tolerated dose, as an adjunct to diet and exercise, resulted in a clinically meaningful weight reduction (ETD -19.1%; -14.8 to -23.4 compared to placebo)
- Significant differences in Health Related Quality of Life (IWQOL-Lite) parameters at 68 weeks between Semaglutide 2.4mg and Placebo were observed.

Acknowledgements

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