Cover Page

BARI-STEP: A double-blinded, randomised, placebo-controlled trial of semaglutide 2.4 mg in patients with poor weight-loss following bariatric surgery.

NCT05073835

Document: Protocol
Version: 5.0; 06.09.2024

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

TITLE PAGE

FULL/LONG TITLE OF THE TRIAL

A double-blinded, randomised, placebo-controlled trial of semaglutide 2.4 mg in patients with poor weight-loss following bariatric surgery.

SHORT TRIAL TITLE / ACRONYM

BARI-STEP

PROTOCOL VERSION NUMBER AND DATE

Version 5.0, 06-09-2024

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

RESEARCH REFERENCE NUMBERS

IRAS Number:	299128
Clinical trials.gov Number:	NCT05073835
EudraCT Number:	2021-004568-83
ISRCTN Number / Other registries: Universal Clinical Trial Number	U1111-1263-5209
SPONSOR:	University College London (UCL)
SPONSOR Number:	142522
FUNDER:	NIHR, UCLH NIHR Biomedical Research Centre and Sir Jules Thorne Charitable Trust
FUNDERS Number:	N/A

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, the UK Policy Framework for Health and Social Care Research 3rd edition 2017 (as amended), GCP guidelines, the UK Data Protection Act (2018), the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Chief Investigator: Dr Janine Makaronidis

Signature and Date: DocuSigned by: Janine Makaronidis EBAAFFBE1FF5437...

30 October 2024 | 10:44 GMT

For and on behalf of the Trial Sponsor:

Signature and Date: DocuSigned by: Rajinder Sidhu D225A0063221469...

30 October 2024 | 10:47 GMT

Name (please print):

Dr. Rajinder Sidhu

Position: Associate Director Research Governance and Ops

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

PROTOCOL VERSION HISTORY

Version Number	Date	Protocol Update Finalised By (insert name of person)	Reasons for Update
1.0	10.12.2021	Rachel Batterham	N/A
2.0	24.01.2022	Rachel Batterham	MHRA requests for approval
2.1	09.02.2022	Rachel Batterham	Drug Supplier requests – submitted as part of initial REC review
2.2	30.03.2022	Rachel Batterham	Drug Supplier requests – amendment to 'not-in-use' storage conditions and safety reporting
2.3	21.09.2022	Rachel Batterham	Update to trial team contact details. Typographical updates to Section 9: Pharmacovigilance. Removal of 15min blood test in section 7.6.
3.0	11.04.2023	Janine Makaronidis	Change in CI from Prof Rachel Batterham to Dr Janine Makaronidis Update to trial contacts.
3.1	24.10.2023	Chloe Firman	Removal of 'Roux-en-Y' and changed to 'gastric bypass' throughout the protocol as the surgical technique for gastric bypasses have evolved
4.0	20.02.2024	Andrew Tunstell	Change in Sponsor contact from Samim Patel to Andrew Tunstell.
4.1	05.06.2024	Alanna Brown	Update to trial team contact details.
5.0	06.09.2024	Chloe Firman	Update to include the use of semaglutide 3.2 mg/ml from 05 Nov 2024 when the current stock of semaglutide 3.0 mg/ml is depleted. The trial drug manufacturer has informed us that the semaglutide 3.0 mg/ml product is no longer being manufactured for release in the United Kingdom and therefore an alternative concentration will be provided. References throughout the protocol have been amended to 'semaglutide 3.0 mg/ml or 3.2 mg/ml'. Section 8.1 and 8.5 have been updated to reflect the change in dose dial.

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

			Section 8.11 updated to refer to new EudraCT reference number. Update to PL number in section 8.2. Section 7.12 has been updated to clarify the end of trial definition.

KEY TRIAL CONTACTS

Chief Investigator	Dr Janine Makaronidis Centre for Obesity Research Division of Medicine Rayne Building 5 University Street London WC1E 6JF e-mail: j.makaronidis@ucl.ac.uk
Sponsor	Andrew Tunstell Sponsor Regulatory Advisor Joint Research Office, UCL 4th Floor West, 250 Euston Road London NW1 2PG Email: CTIMPS@ucl.ac.uk
Clinical Trials Unit / Contract Research Organisation	N/A
Statistician	David Boniface RSS Chartered Statistician Honorary Senior Research Fellow Behavioural Science and Health University College London

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

	Gower Street London WC1E 6BT d.boniface@ucl.ac.uk
Trial Contacts	Dr Ritwika Mallik Clinical Research Fellow Centre for Obesity Research Division of Medicine University College London Rayne Building, 5 University Street London WC1E 6JF r.mallik@ucl.ac.uk Tapiwa Ruwona Research Nurse and Dietitian Centre for Obesity Research Division of Medicine Rayne Building, 5 University Street London WC1E 6JF t.ruwona@ucl.ac.uk Chloe Firman Research Assistant Centre for Obesity Research Division of Medicine Rayne Building, 5 University Street London WC1E 6JF chloe.firman.19@ucl.ac.uk Nausheen Hamid Dietician Centre for Obesity Research Division of Medicine Rayne Building, 5 University Street London WC1E 6JF nausheen.hamid@ucl.ac.uk Alanna Brown Trial Coordinator Centre for Obesity Research Division of Medicine Rayne Building, 5 University Street London WC1E 6JF alanna.brown@ucl.ac.uk
Laboratories and central pharmacy	Centre for Obesity Research Division of Medicine University College London

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

	Rayne Building, 5 University Street London, WC1E 6JF Email: j.makaronidis@ucl.ac.uk Tel: 02076790991 Clinical Biochemistry University College London Hospital 3rd Floor, 60 Whitfield St London, W1T 4 EU Email: debbie.mann1@nhs.net Tel: 0203 447 940 Lead Pharmacist: Chi Chung Principal R&D Pharmacist Pharmacy Department Ground Floor University College London Hospitals 235 Euston Road London, NW1 2BU Chiyee.chung@nhs.net

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

LIST of CONTENTS

TITLE PAGE		**1**
RESEARCH REFERENCE NUMBERS		**2**
SIGNATURE PAGE		**3**
PROTOCOL VERSION HISTORY		**4**
KEY TRIAL CONTACTS		**5**
i.	**LIST OF ABBREVIATIONS**	**9**
ii.	**TRIAL SUMMARY**	**111**
iii.	**ROLE OF TRIAL SPONSOR AND FUNDER**	**144**
iv.	**KEY WORDS**	**144**
1	**BACKGROUND**	**155**
2	**RATIONALE**	**166**
3	**OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS**	**2020**
4	**TRIAL DESIGN**	**24**
5	**TRIAL SETTING**	**25**
6	**PARTICIPANT ELIGIBILITY CRITERIA**	**255**
7	**TRIAL PROCEDURES**	**277**
8	**TRIAL TREATMENTS**	**355**
9	**PHARMACOVIGILANCE**	**4040**
10	**STATISTICS AND DATA ANALYSIS**	**499**
11	**DATA MANAGEMENT**	**522**
12	**OVERSIGHT COMMITTEES**	**544**
13	**MONITORING, AUDIT & INSPECTION**	**555**
14	**ETHICAL AND REGULATORY CONSIDERATIONS**	**555**
15	**DISSEMINATION POLICY**	**588**
16	**REFERENCES**	**599**

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

i. LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BDI	Beck Depression Inventory
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
BP	Blood Pressure
CI	Chief Investigator
CSRI	Client Service Receipt Inventory
eCRF	Electronic Case Report Form
DFU	Directions for use
DPA	Data Protection Act
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
DSUR	Development Safety Update Report
EMEA	European Medicines Agency
EQ-5D	EuroQol-5D
GB	Gastric Bypass
GCP	Good Clinical Practice
GLP-1	Glucagon-like peptide-1
GMP	Good Manufacturing Practice
HbA1c	Glycosylated haemoglobin
HR	Heart Rate
HRQoL	Health Related Quality of Life
IMPD	Investigational Medicinal Product Dossier
IPAQ	International Physical Activity Questionnaire
IWQOL-LITE	Impact of weight in quality of life-lite
JRO	Joint Research Office
LOCF	Last Observation Carry Forward
6MWT	6-Minute Walk Test
MHRA	Medicines and Healthcare products Regulatory Agency
NHS R&D	National Health Service Research & Development
NICE	National Institute for Health and Clinical Excellence

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

PI	Principal Investigator
PIS	Participant Information Sheet
PSS	Personal Social Services
QALY	Quality-Adjusted Life Year
RCT	Randomised Control Trial
REC	Research Ethics Committee
RYGB	Roux-en-Y Gastric Bypass
PYY	Peptide YY
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
STS	Sit-to-stand test
SG	Sleeve gastrectomy
SODA	Summary Of Drug Arrangements
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
T2D	Type 2 Diabetes Mellitus
TC	Trial Coordinator
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UCL	University College London
UCLH	University College London Hospital
UK	United Kingdom
UK GDPR	UK General Data Protection Regulation
WL	Weight Loss

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

ii. TRIAL SUMMARY

Trial Title	A double-blinded, randomised, placebo-controlled trial of semaglutide 2.4 mg in patients with poor weight-loss following bariatric surgery.	
Short Title	BARI-STEP	
Sponsor Protocol Number	142522	
Clinical Phase	Phase 3b	
Trial Design	Double-blinded, randomised, placebo-controlled, two -arm, parallel group trial.	
Trial Participants	Patients aged 18-65 years with poor weight loss following bariatric surgery (<20% of their total weight ≥ 1 year after primary gastric bypass or primary sleeve gastrectomy).	
Planned Sample Size	70 subjects (35 subjects in each arm)	
Treatment duration	Minimum of 18 months, maximum of 20 months	
Follow up duration	74 weeks	
Planned Trial Period	Approximately 26 months from when first participant enrolled to last participant follow-up.	
	Objectives	**Outcome Measures/Endpoints**
Primary	The primary objective of this trial is to compare the efficacy of 68 weeks of subcutaneous semaglutide 3.0 mg/ml or 3.2 mg/ml at a dose of 2.4mg per week versus placebo administration, as an adjunct to diet and exercise, on %WL in participants with poor weight-loss following primary GB or SG at the end of the 68 weeks of treatment.	The primary outcome of this trial is %WL from the baseline visit to 68 weeks of treatment. Percentage weight loss will be calculated using the following formula: %WL = [(weight at the baseline visit–weight at the end of the 68-week treatment period)/ weight at the baseline visit] x 100, measured at the end of treatment.
Secondary	To investigate the effects of semaglutide 3.0 mg/ml or 3.2 mg/ml at a dose of 2.4mg per week compared to placebo upon metabolic and inflammatory indices and HRQoL.	The secondary outcomes of this trial are: 1. The percentage of participants receiving subcutaneous semaglutide 3.0 mg/ml or 3.2 mg/ml at a dose of

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

		2.4mg per week versus placebo who after 68 weeks achieve: •A body weight reduction ≥10% •A body weight reduction ≥15% •A body weight reduction ≥20% 2. The effect of 68 weeks of subcutaneous semaglutide 3.0 mg/ml or 3.2 mg/ml at a dose of 2.4mg per week versus placebo administration upon glycaemia, pre-diabetes and T2D by comparing: •Change in circulating HbA1c levels. •Change in circulating HbA1c levels in participants with pre-diabetes at baseline. •Change in circulating HbA1c levels in participants with T2D at baseline. •The number of pharmacological agents required for the management of T2D in participants with pre-existing T2D at baseline. 3. The effect of 68 weeks of subcutaneous semaglutide 3.0 mg/ml or 3.2 mg/ml at a dose of 2.4mg per week versus placebo administration upon BP and hypertension by comparing: •Systolic and diastolic BP. •Systolic and diastolic BP in participants with pre-existing hypertension. • The number of pharmacological agents required for the management of hypertension in participants with pre-existing hypertension.

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

		4. The effect of 68 weeks of subcutaneous semaglutide 3.0 mg/ml or 3.2 mg/ml at a dose of 2.4mg per week versus placebo administration upon: •Change in lipids and inflammatory markers (HsCRP and inflammatory cytokines). •Change in food cravings. •Change in HRQoL measures. 5. The relationship between GLP-1 levels at baseline and %WL at 68 weeks.
Investigational Medicinal Product(s)	Active IMP from 18 November 2022 to 04 November 2024*: Semaglutide 3.0 mg/ml solution for injection in pre-filled pen. Active IMP from 05 November 2024 to end of trial: Semaglutide 3.2 mg/ml solution for injection in pre-filled pen. Placebo IMP: Same composition as the IMP, but no active ingredient. *This date marks the expiry of the current stock of semaglutide 3.0 mg/ml. Semaglutide 3.0mg/ml is no longer being manufactured for release in the United Kingdom therefore as of 05 November 2024, the licensed semaglutide 3.2 mg/ml will be used for the trial. The maintenance dose remains at 2.4 mg of semaglutide.	
Formulation, Dose, Route of Administration	Semaglutide, 3.0 mg/ml or 3.2 mg/ml at a dose of 2.4 mg per week, subcutaneous injection in pre-filled pen.	

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

iii. ROLE OF TRIAL SPONSOR AND FUNDER

University College London (UCL) will act as sponsor for this trial. As Sponsor, UCL will provide insurance for the clinical trial and undertake to ensure that the above trial is conducted in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended), the UK Policy Framework for Health and Social Care Research 3rd edition 2017 (as amended) and all applicable regulatory requirements.

Sponsor will provide the main REC and the MHRA with Development Safety Update Reports (DSUR) which will be written in conjunction with the trial team and the Sponsor's office. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

iv. KEY WORDS

Bariatric surgery, obesity, poor weight loss, semaglutide, GLP-1,

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

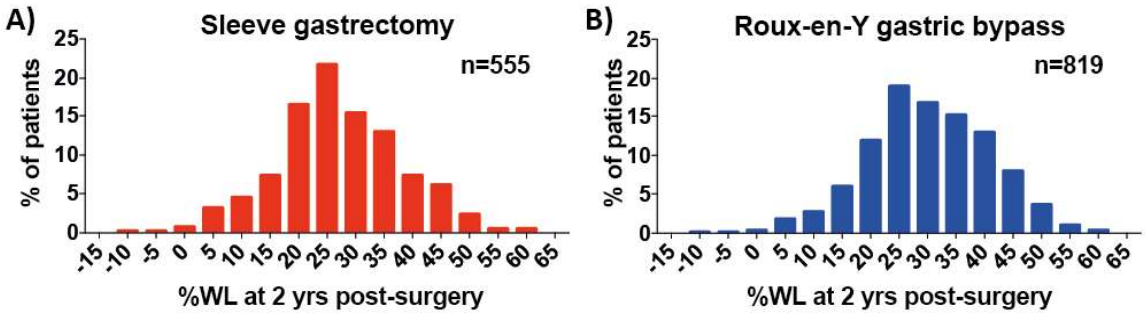
1 BACKGROUND

Obesity and its associated co-morbidities represent a global health threat causing 3.4 million preventable deaths annually. Bariatric surgery is the most effective treatment for patients with severe obesity producing sustained weight-loss with reduced morbidity and mortality. As a consequence of its unparalleled health benefits, bariatric surgery has been widely adopted with ~500,000 operations undertaken annually world-wide [1]. In the UK, patients with severe obesity, defined as a body mass index (BMI) of ≥40 kg/m^2, or ≥35 kg/m^2 with an obesity-associated co-morbidity, are eligible for bariatric surgery in accordance with National Institute for Health and Clinical Excellence (NICE) Guidelines [2].

1.1 Variability in weight-loss response following bariatric surgery

Gastric bypass (GB), including Roux-en-Y Gastric Bypass (RYGB) and One Anastomosis Gastric Bypass (OAGB), and sleeve gastrectomy (SG) are the commonest bariatric procedures performed globally [1]. Whilst at a population level these operations are highly effective at reducing weight and obesity-associated morbidity and mortality, it is now clear that, at the level of the individual, weight-loss following GB and SG is highly variable [3-7]. Figure 1 shows the variability in 2-year percentage weight-loss (%WL) following RYGB and SG from our unit[3]. Given the associated surgical risks, procedure cost and the need for lifelong nutritional monitoring there is an urgent unmet clinical need to identify those with a poor weight loss response, improve weight-loss following bariatric surgery and maximise the health benefits for bariatric surgery patients. Currently, there are no available pharmacological treatments for patients with poor weight loss after surgery and the only therapeutic option is revision surgery, which carries a mortality risk and is difficult to access.

Figure 1: Weight-loss in patients who undergo sleeve gastrectomy or Roux-en-Y gastric bypass is highly variable



A) Percentage weight loss (%WL) in patients 2 years after sleeve gastrectomy.
B) %WL in patients 2 years after Roux-en-Y gastric bypass.

1.2 The importance of maximising post-surgery weight-loss

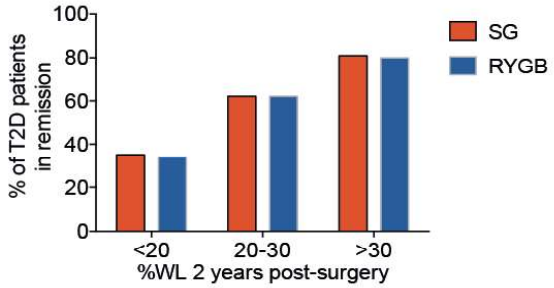
Following GB and SG, glycaemic control improves rapidly by weight-loss independent mechanisms [8]. However, there is increasing evidence that long-term T2D remission depends on weight-loss [9-11]. In our patients, complete T2D remission rates at 2-years post-surgery (defined as HbA1c <6%, off all medication for more than 12 months) are determined by %WL, independent of procedure type [12](Figure 2). Importantly, multivariate

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

logistic regression analysis correcting for confounding baseline factors shows that the odds of complete T2D remission increase by 10% for every additional 1% WL. Therefore, our data highlight the important clinical impact that small changes in %WL have on T2D remission, which has been shown to lead to a reduction in long-term microvascular disease outcomes [13].

Furthermore, the resolution and/or improvement of multiple obesity-related co-morbidities including hypertension, dyslipidaemia, obstructive sleep apnoea and non-alcoholic steatohepatitis following bariatric surgery positively correlate with increasing %WL [14-17]. In contrast, patients with poor weight loss have fewer metabolic benefits and weight regain leads to relapse of co-morbidities [14, 15]. In addition, greater improvements in HRQoL outcomes following bariatric surgery are reported with greater weight-loss [18, 19]. Taken together these findings represent a strong rationale for maximising weight-loss following bariatric surgery.

Figure 2: Rate of remission of type 2 diabetes (T2D) following sleeve gastrectomy or Roux-en-Y gastric bypass is determined by weight-loss independent of procedure type



Percentage of patients with T2D at the time of surgery in complete remission at 2 years after sleeve gastrectomy (n=118) or Roux-en-Y gastric bypass (n=116) plotted according to percent weight-loss category (<20%, 20-30% and >30%).

2 RATIONALE

Liraglutide 3.0 mg (6mg/ml), a once daily subcutaneously injected glucagon-like peptide-1 (GLP-1) receptor analogue, has been shown to lead to significant weight loss in people with obesity and is licensed for weight management as an adjunct to lifestyle modification in people with obesity. The SCALE study (ClinicalTrials.gov number, NCT01272219), a 56-week double-blind trial, investigating liraglutide 3.0 mg versus placebo in people with obesity or overweight without T2D (BMI>30 kg/m^2 or >27 kg/m^2 with dyslipidaemia or hypertension) in addition to lifestyle modification, showed a mean %WL of 8.0 ± 6.7% in patients treated with liraglutide 3.0 mg compared to 2.6 ± 5.7% in the placebo group[20]. 63% of patients treated with liraglutide compared to 27.1% in the placebo group lost ≥5% body weight. 33% of liraglutide-treated patients lost ≥10% compared to 10.6% in the placebo group. The trial also showed greater reductions in HbA1c, fasting glucose and fasting insulin levels in the liraglutide 3.0 mg group compared to the placebo group. Patients in the liraglutide 3.0 mg group also had higher SF-36 scores, indicating improved physical and mental health and higher IWQoL-Lite scores (indicating better quality of life) compared to the placebo group. Overall, the SCALE trial demonstrated that liraglutide 3.0 mg, used as an adjunct to diet and exercise, leads to reduced body weight and improved metabolic health.

Liraglutide 3.0 mg was first used in the post-bariatric surgery population by Wharton *et al*. in a population of 117 post-bariatric surgery patients with poor weight loss, in order to determine if this would differ in three types of

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

bariatric procedure: RYGB, SG and gastric banding [21]. The majority of patients in this study had undergone RYGB (45.3%) or gastric banding (42.7%). A significant weight loss was noted in all participants from 2 months following initiation of liraglutide 3.0 mg compared to baseline, which was maintained following 1 year of treatment ($p<0.05$). %WL was 6.6 ± 7.1% following RYGB with 24.5% of patients achieving ≥ 10% WL; 4.9 ± 5.6% following gastric banding with 12.0% achieving ≥ 10% WL and 3.6 ± 3.0% post-SG. No significant differences were seen in weight loss between the three procedures. Nausea was the most commonly reported side effect, reported by 29.1% patients. Three participants discontinued due to an adverse event, which in two cases was an allergic reaction and one participant developed pancreatitis.

Suliman *et al.* performed a prospective study using liraglutide 3.0 mg in people with obesity and people with poor weight-loss outcomes following bariatric surgery[22]. 787 patients were treated for ≥16 weeks and their median % WL was 6.4% with 23% achieving ≥ 10% WL. The study showed no difference in %WL in patients who had not had bariatric surgery and those who had poor weight loss outcomes following bariatric surgery. The majority of adverse events reported were mild gastrointestinal side effects and treatment was discontinued in one participant due to pancreatitis.

We performed a 24-week randomised-controlled double-bind trial of liraglutide 3.0 mg versus placebo in patients with poor weight loss following RYGB or SG and a sub-optimal meal-stimulated GLP-1 response (EudraCT 2017-002407-10). 70 patients ≥1 year following either RYGB or SG with <20% weight loss and a suboptimal meal-stimulated GLP-1 response were randomised to either receive liraglutide 3.0 mg or placebo for 24 weeks in addition to diet and lifestyle counselling.
This study showed that patients treated with liraglutide 3.0mg had mean weight loss of 9.41 ±5.84% at the end of the 24-week treatment period compared to 1.10 ± 5.26% in the placebo group with an estimated treatment effect of -8.80 (95% CI -11.86 to -5.73) ($p<0.005$). 77.4% of participants in the liraglutide group lost >5% compared to 9.3% in the placebo group ($p<0.001$). 32.2% of patients in the liraglutide arm had ≥10% WL and 16.1% ≥15% WL. No participants in the placebo group lost ≥10% of their body weight (10% WL: 32.2% vs. 0% $p<0.05$; ≥15% WL: 16.1% vs. 0% $p<0.05$). Our findings highlight larger %WL compared to both the SCALE trial, despite a shorter duration, and the open label studies by Wharton *et al.* and Suliman *et al.*

Liraglutide 3.0 mg was well tolerated in our study. There were no serious adverse events in either group. The most commonly reported adverse events were nausea and constipation. Vomiting was only reported by 3% of patients in the liraglutide 3.0 mg arm and by 3% of participants in the placebo arm. In contrast in the SCALE study, vomiting was reported in 16.3% in the liraglutide 3.0 mg arm versus 4.1% in the placebo arm. Our findings illustrate that liraglutide 3.0 mg represents an effective, safe treatment to improve %WL for patients with poor weight loss following RYGB and SG.

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

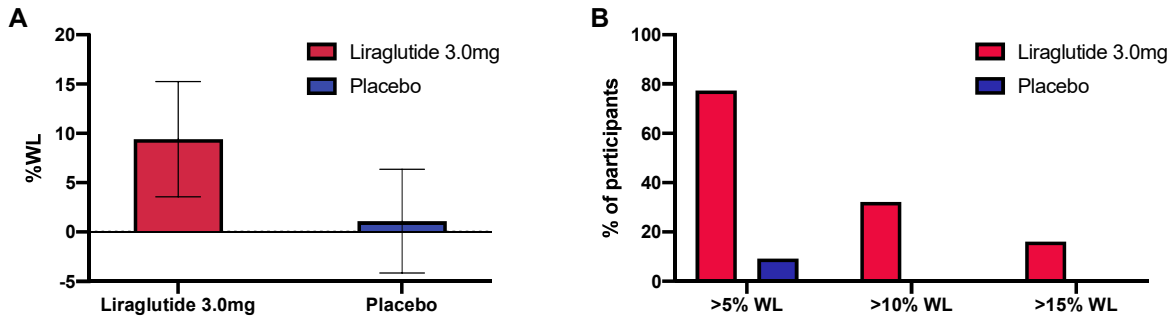


Figure 3: Mean weight loss at 24-weeks in liraglutide 3.0 mg vs placebo in patients with poor weight loss ≥1 year following either RYGB or SG (A) and percentage of participants achieving ≥ 5%, ≥ 10% and ≥ 15% in liraglutide 3.0 mg vs placebo (B)

Semaglutide is a long-acting GLP-1R agonist, which is injected subcutaneously once weekly for the treatment of type 2 diabetes mellitus. At present, semaglutide for weight management has been granted marketing authorisation in the UK as of 24th September 2021 (PL number PLGB 04668/0433). The Semaglutide Treatment Effect in People with obesity (STEP) is a phase 3 clinical trial programme comprised of five different trials, with the aim of evaluating the efficacy and safety of semaglutide 3.0 mg/ml administered subcutaneously once weekly, for weight management in people with obesity or overweight.

In STEP 1, 1,961 adults with obesity or overweight, without T2D, were being randomly assigned in a 2:1 manner to receive semaglutide 3.0 mg/ml or placebo as an adjunct to lifestyle intervention for 68 weeks. Mean body weight change from baseline to week 68 was −14.9% in the semaglutide 3.0 mg/ml group vs. −2.4% with placebo (estimated treatment difference: −12.4% [95% confidence interval: −13.4%; −11.5%]; p<0.0001. Nausea and diarrhoea (typically transient and mild-to-moderate) were the most common adverse events with semaglutide 3.0 mg/ml; these subsided with time. Treatment discontinuation due to gastrointestinal events more frequently with semaglutide 3.0 mg/ml (4.5%) than placebo (0.8%). Treatment discontinuation in STEP 1 was lower compared to the SCALE trial where 9.9% in the liraglutide 3.0 mg group withdrew due to adverse events and 2.9% in the placebo group[20].

The Coronavirus Infectious Disease 2019 (COVID-19) pandemic has highlighted the need to maximise health outcomes for people living with obesity. People living with obesity are at an increased risk of developing severe disease with COVID-19 and obesity is associated with an increased mortality from COVID-19[23]. Obesity leads to a pro-inflammatory state with increased production of inflammatory cytokines, which can result in impaired immune responses in people with obesity. Together with increased prevalence of co-morbidities and the mechanical stress of adiposity on lung function, this impaired immune function and inflammatory state have been proposed as a link between obesity and poor outcomes with COVID-19[24, 25]. In addition to improvement in co-morbidities, bariatric surgery has been shown to improve immune function[26]. Importantly, a study investigating outcomes in people with obesity who had undergone bariatric surgery and lost weight following their operation, showed lower rates of hospital and intensive care admission in patients with obesity who developed COVID-19[24].

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

Data from the STEP program illustrate that semaglutide 3.0 mg/ml is more efficacious compared to liraglutide 3.0 mg/ml: 75% of people achieved ≥10% weight loss with semaglutide 3.0 mg/ml versus 33% with liraglutide 3.0 mg/ml. More importantly 55% achieved ≥ 15% weight loss with semaglutide 3.0 mg/ml versus 14% with liraglutide 3.0 mg/ml. Considering the promising results from our trial showing liraglutide 3.0 mg leads to approximately 10% WL in patients with poor weight loss following bariatric surgery and the results from the STEP program, we hypothesise that semaglutide 3.0 mg/ml or 3.2 mg/ml will lead to greater weight loss and health improvement compared to placebo in patients with poor weight loss following GB or SG. We plan a 68-week double-blind randomised placebo-controlled trial to assess the efficacy of semaglutide 3.0 mg/ml or 3.2 mg/ml in people with <20% WL ≥ 1 year following GB or SG, in terms of %WL, number of patients achieving ≥ 10% WL, ≥15% WL, >20% WL, metabolic and inflammatory markers and health economics/quality of life parameters.

2.1 Assessment and management of risk

The table below summarises the risks, frequencies and mitigations of the Investigational Medicinal Product (IMP). and Non-Investigational Medicinal Products (NIMP).

Name of IMP	**Potential risk**	**Risk Frequency**	**Risk Management**
Semaglutide 3.0 mg/ml or 3.2 mg/ml	Injection site reactions	Common	1. Participants will be trained on injection technique and instructed to follow the dose escalation schedule.
	Nausea, Vomiting, Constipation, Diarrhoea, Abdominal Pain, Fatigue, Headache	Very Common	1. Close monitoring by trial investigators. Antiemetics will provided if required to manage gastrointestinal side effects. 2. Participants will be given a 24-hour Contact Card and a drug diary.
	Dizziness, Gastritis, Gastrooesophageal reflux disease, Dyspepsia, Eructation, Flatulence, Abdominal distension, Cholelithiasis, Hair loss	Common	

The table below summarise the risks and mitigations of all tests and/or procedures above standard care that are being performed:

Intervention	**Potential risk**	**Severity Grading**	**Risk Management**
Blood Test/Cannulation	Bruising	Mild	1.Performed by trained healthcare professionals.

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

	Pain Bleeding Infection	Mild Mild/Moderate Moderate/Severe	2.Follow trust standard operational procedures. 3.Provision of 24h contact card

This trial is categorised as: Type B = Somewhat higher than the risk of standard medical care

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

In patients with poor weight-loss following GB or SG, to determine whether 68 weeks of subcutaneous semaglutide 3.0 mg/ml or 3.2 mg/ml with diet and exercise counselling causes greater %WL and reduction in adiposity than placebo with diet and exercise counselling, and to estimate the extent of any reduction. Investigation will also be carried out with regard to improvement in metabolic and inflammatory indices and HRQoL.

3.1 Primary objective

The primary objective of this trial is to compare the efficacy of 68 weeks of subcutaneous semaglutide 3.0 mg/ml or 3.2 mg/ml at a dose of 2.4 mg per week versus placebo administration, as an adjunct to diet and exercise, on %WL in participants with poor weight-loss following primary GB or SG at the end of the 68 weeks of treatment.

3.2 Secondary objectives

1. To compare the percentage of participants receiving subcutaneous semaglutide 3.0 mg/ml or 3.2 mg/ml at a dose of 2.4 mg per week versus placebo who after 68 weeks achieve:

- A body weight reduction ≥10%
- A body weight reduction ≥15%
- A body weight reduction ≥20%

2. The effect of 68 weeks of subcutaneous semaglutide 3.0 mg/ml or 3.2 mg/ml at a dose of 2.4 mg per week versus placebo administration upon glycaemia, pre-diabetes and T2D by comparing:

- Change in circulating HbA1c levels.
- Change in circulating HbA1c levels in participants with pre-diabetes at baseline.
- Change in circulating HbA1c levels in participants with T2D at baseline.
- The number of pharmacological agents required for the management of T2D in participants with pre-existing T2D at baseline.

3. The effect of 68 weeks of subcutaneous semaglutide 3.0 mg/ml or 3.2 mg/ml at a dose of 2.4 mg per week versus placebo administration upon BP and hypertension by comparing:

- Systolic and diastolic BP.

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

- Systolic and diastolic BP in participants with pre-existing hypertension.
- The number of pharmacological agents required for the management of hypertension in participants with pre-existing hypertension.

4. To compare the effect of 68 weeks of subcutaneous semaglutide 3.0 mg/ml or 3.2 mg/ml at a dose of 2.4 mg per week versus placebo administration upon:

- Change in circulating lipids and inflammatory markers (HsCRP and inflammatory cytokines).
- Changes in food cravings
- Change in HRQoL measures.

5. To investigate the relationship between fasted and meal-stimulated active GLP-1 levels at baseline and %WL at 68 weeks.

3.3 Outcome measures/endpoints

3.3.1 Primary endpoint/outcome

The primary outcome of this trial is %WL from the baseline visit to 68 weeks of treatment. Percentage weight loss will be calculated using the following formula: %WL = [(weight at the baseline visit–weight at the end of the 68-week treatment period)/ weight at the baseline visit] x 100, measured at the end of treatment.

3.3.2 Secondary endpoints/outcomes

The secondary outcomes of this trial are:

1. The percentage of participants receiving subcutaneous semaglutide 3.0 mg/ml or 3.2 mg/ml at a dose of 2.4 mg per week versus placebo who after 68 weeks achieve:
    - A body weight reduction ≥10%
    - A body weight reduction ≥15%
    - A body weight reduction ≥20%

2. The effect of 68 weeks of subcutaneous semaglutide 3.0 mg/ml or 3.2 mg/ml at a dose of 2.4 mg per week versus placebo administration upon glycaemia, pre-diabetes and T2D by comparing:

- Change in circulating HbA1c levels.
- Change in circulating HbA1c levels in participants with pre-diabetes at baseline.
- Change in circulating HbA1c levels in participants with T2D at baseline.
- The number of pharmacological agents required for the management of T2D in participants with pre-existing T2D at baseline.

3. The effect of 68 weeks of subcutaneous semaglutide 3.0 mg/ml or 3.2 mg/ml at a dose of 2.4 mg per week versus placebo administration upon BP and hypertension by comparing:

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

- Systolic and diastolic BP.
- Systolic and diastolic BP in participants with pre-existing hypertension.
- The number of pharmacological agents required for the management of hypertension in participants with pre-existing hypertension.

4. The effect of 68 weeks of subcutaneous semaglutide 3.0 mg/ml or 3.2 mg/ml at a dose of 2.4 mg per week versus placebo administration upon:
    - Change in lipids and inflammatory markers (HsCRP and inflammatory cytokines).
    - Change in food cravings.
    - Change in HRQoL measures.

5. The relationship between GLP-1 levels at baseline and %WL at 68 weeks.

3.3.3 Table of endpoints/outcomes

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective The primary objective of this trial is to compare the efficacy of 68 weeks of subcutaneous semaglutide 3.0 mg/ml or 3.2 mg/ml at a dose of 2.4 mg per week versus placebo administration, as an adjunct to diet and exercise, on %WL in participants with poor weight-loss following primary GB or SG at the end of the 68 weeks of treatment.	Percentage weight loss will be calculated using the following formula: %WL = [(weight at the baseline visit–weight at the end of the 68-week treatment period)/ weight at the baseline visit] x 100, measured at the end of treatment. The mean difference in %WL at 68 weeks between the groups will be analysed using linear regression, adjusting for stratification variables and any baseline variables which are not balanced between the groups. Mean difference in %WL will be reported with 95% confidence interval. The assumptions of the model will be checked, and a suitable transformation/non-parametric method will be used where the assumptions are not met. All available data will be analysed as randomised. Bias due to missing data will be investigated and dealt as appropriate.	At baseline and at each follow-up visit, corresponding to weeks: 1, 2, 4 ,6, 8, 10, 12, 14, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 and 68.

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

Secondary Objectives 1. To compare the percentage of participants receiving subcutaneous semaglutide 3.0 mg/ml or 3.2 mg/ml at a dose of 2.4 mg per week versus placebo who after 68 weeks achieve: •A body weight reduction ≥10% •A body weight reduction ≥15% •A body weight reduction ≥20% 2. The effect of 68 weeks of subcutaneous semaglutide 3.0 mg/ml or 3.2 mg/ml at a dose of 2.4 mg per week versus placebo administration upon glycaemia, pre-diabetes and T2D by comparing: •Change in circulating HbA1c levels. •Change in circulating HbA1c levels in participants with pre-diabetes at baseline. •Change in circulating HbA1c levels in participants with T2D at baseline. •The number of pharmacological agents required for the management of T2D in participants with pre-existing T2D at baseline. 3. The effect of 68 weeks of subcutaneous semaglutide 3.0 mg/ml or 3.2 mg/ml at a dose of 2.4 mg per week versus placebo administration upon BP and hypertension by comparing: •Systolic and diastolic BP. •Systolic and diastolic BP in participants with pre-existing hypertension. •The number of pharmacological agents required for the management of hypertension in	The results of the secondary analysis will be treated as exploratory. Continuous outcomes will be analysed using separate linear regression models, adjusting for stratification variables and any baseline variables which are not balanced between the groups. Mean differences in each outcome will be reported with 95% confidence intervals. The assumptions of each model will be checked, and a suitable transformation/non-parametric method will be used where the assumptions are not met.	Evaluation of secondary outcome measure taken at 68 weeks after randomisation.

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

participants with pre-existing hypertension. 4. To compare the effect of 68 weeks of subcutaneous semaglutide 3.0 mg/ml or 3.2 mg/ml at a dose of 2.4 mg per week versus placebo administration upon: •Change in circulating lipids and inflammatory markers (HsCRP and inflammatory cytokines). •Changes in food cravings •Change in HRQoL measures. 5. To investigate the relationship between fasted and meal-stimulated active GLP-1 levels at baseline and %WL at 68 weeks.		

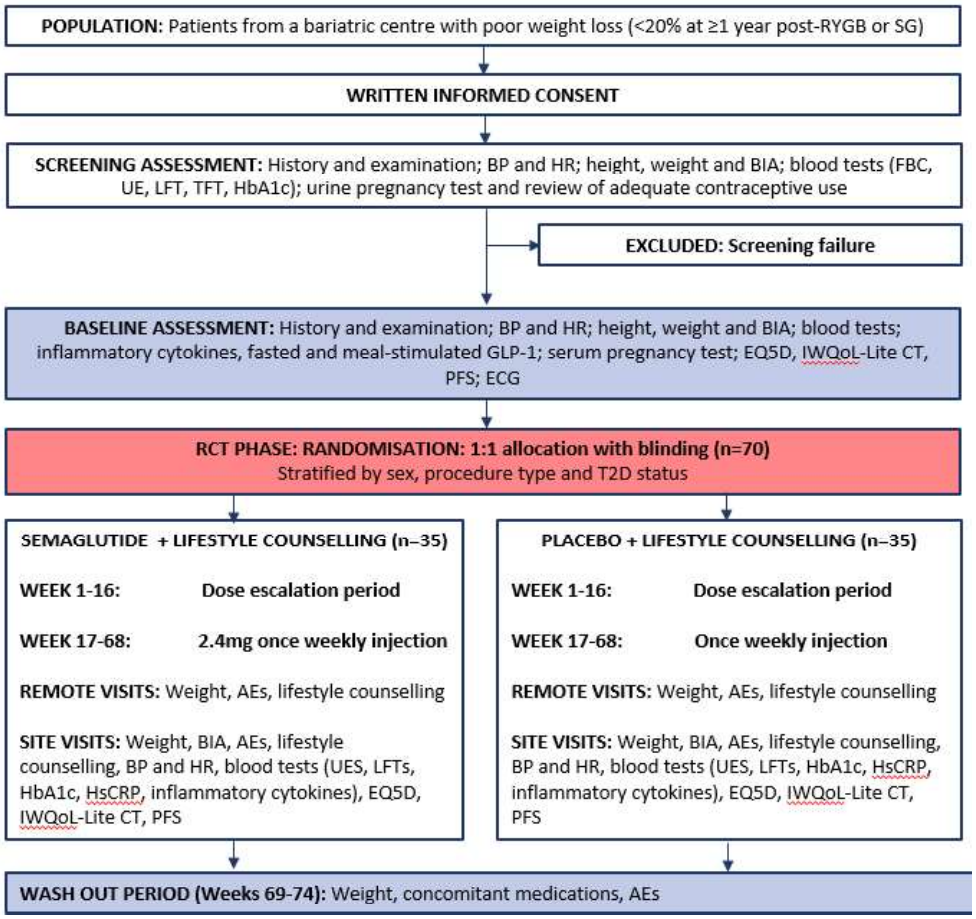
4 TRIAL DESIGN

This study is a 68-week double-blind, randomised, placebo-controlled, two-arm, parallel group trial (Figure 4). The purpose of this trial is to evaluate the therapeutic effects of semaglutide 3.0 mg/ml or 3.2 mg/ml in patients with 'poor' weight loss (<20% WL) following bariatric surgery. Enrolled participants will be randomised 1:1 to receive semaglutide at a dose of 2.4 mg per week or placebo, stratified for sex, procedure type and T2D. The primary outcome will be %WL following 68 weeks of treatment. 35 participants will be randomised to receive semaglutide 2.4mg (n = 35) or placebo (n = 35) for 68 weeks. An identical placebo containing no active ingredients will be used as a comparator to evaluate the real treatment effect. Treatment allocation will be concealed from patients and investigators.

Semaglutide 3.0 mg/ml or 3.2 mg/ml at dose of 2.4 mg will be used and will follow a 16-week dose escalation protocol. Follow-up visits will take place at 1, 2 ,4 ,6, 8, 10, 12, 14, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 and 68 weeks after randomisation. The majority of these visits will be carried out remotely. Data including weight, adverse events and concomitant medication use will be collected at each visit. The visits at weeks 6, 14, 32, 52 and 68 will be carried out in person, to allow a targeted physical examination to be performed and blood samples to be taken for biochemical monitoring. Participants will remain in the trial for an additional 6-week wash out period with remote monitoring visits at week 70 and 74.

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

4.1 Trial Flow Chart



5 TRIAL SETTING

This is a single centre trial and will be conducted at University College London Hospitals (UCLH). At first, suitable patients will be identified by the bariatric team during their post-surgery follow-up visits at face-to-face or virtual clinic appointments, and through database search and asked if they are interested to take part in the study. Participants will be recruited from the Bariatric Clinics at University College London Hospital (UCLH).

6 PARTICIPANT ELIGIBILITY CRITERIA

Study population: patients, 1 year or more following primary GB or primary SG, with poor weight-loss response (<20% WL) will be invited to participate. There will be no waivers to the inclusion and exclusion criteria.

The Sponsor does NOT allow the use of “protocol waivers” or departures from the approved inclusion/exclusion criteria of the protocol. Occurrences of this nature may constitute a serious breach and be reportable to the MHRA.

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

6.1 Inclusion Criteria

1. Patients, ≥1 year primary GB or primary SG, with poor weight-loss (<20% WL) that is not caused by either a surgical or psychological problem.
2. Adults, 18-65 years inclusive.
3. Females of childbearing potential and female partners of male participants must be willing to use highly effective method of contraception (hormonal or barrier method of birth control; abstinence) (Appendix 2) from the time consent is signed until 2 months after treatment discontinuation.
4. Male participants with partners of childbearing potential must use barrier methods of contraception for the duration of the trial until 2 months after treatment discontinuation.
5. Females of childbearing potential must have a negative serum pregnancy test within 7 days prior to randomisation. NOTE: Subjects are considered not of childbearing potential if they are surgically sterile (i.e. they have undergone a hysterectomy, bilateral salpingectomy or bilateral oophorectomy) or they are postmenopausal.
6. A self-reported ≤5 % variation in body weight over preceding 3 months.
7. Fluent in English and able to understand and complete questionnaires.
8. Participants capable to provide written informed consent and comply with the trial protocol.

6.2 Exclusion criteria

1. Bariatric surgical procedure other than GB and SG, or revision bariatric surgery of any operation type.
2. Personal history of type I diabetes or type II diabetes mellitus currently treated with insulin.
3. Concomitant use of GLP-1R agonist or DPPIV-inhibitors.
4. Female who is pregnant, breast-feeding, or intends to become pregnant.
5. Current participation in other clinical intervention trial.
6. History of suicidal attempt in the previous 5 years or untreated severe depression or mental health condition assessed by direct questioning.
7. Symptomatic gallstone disease
8. Uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg).
9. Renal impairment measured as glomerular infiltration rate (eGFR <15 ml/min 1.73 m^2)
10. Known or suspected hypersensitivity to semaglutide or any of the excipients involved in their formulation.
11. Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.
12. History of malignant neoplasms within the past 5 years prior to screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed.
13. Personal history of acute pancreatitis 180 days before screening or chronic pancreatitis.
14. Uncontrolled thyroid disease.
15. History of stroke, unstable angina, acute coronary syndrome, congestive heart failure New York Heart Association class III-IV within the preceding 12 months.
16. Untreated clinically significant arrhythmias.
17. Diabetic gastroparesis.
18. Concomitant usage of medications that cause weight gain or weight loss.
19. Known or suspected abuse of alcohol or recreational drugs.
20. Severe hepatic impairment diagnosed via liver function blood tests and clinical evaluation

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

21. Any additional factor, which in the investigator's opinion, might jeopardise the subject's safety or compliance with the trial protocol.

7 TRIAL PROCEDURES

A schedule of all trial assessments and procedures is set-out in Appendix 1.

7.1 Recruitment

Participant recruitment will only commence following written confirmation by the Sponsor, and the trial site has been issued a Trust Confirmation of Capacity and Capability and Open to Recruitment Letter. The clinical bariatric teams at UCLH will identify patients potentially fulfilling the eligibility criteria either when these attend follow-up clinics, or through search of existing databases. Patients will be considered to be enrolled into the trial following: consent, baseline assessments, randomisation, allocation of the participant trial number and intervention.

7.1.1 Participant Identification

Participant recruitment at a site will only commence when the trial has:

1. Been initiated by the Sponsor (or it's delegated representative), and
2. Issued with the 'Open to Recruitment' letter.

7.2 Informed Consent

The person taking consent will be GCP trained, suitably qualified and experienced, and have been delegated this duty by the CI on the Staff Signature and Delegation of Tasks Log. At first, suitable patients will be identified by the bariatric team during their post-surgery follow-up visits at face-to-face or virtual clinic appointments and asked if they are interested to take part in the study. In addition, potentially suitable patients might be identified through database searches by members of the clinical team. In this instance, patients who have expressed their interest in participating in research projects will be approached by the clinical team (via email, phone call) to see whether they might be interested in the trial. Information about interested subjects will be collected by the clinical team onto the study screening log and the contact will be logged in their medical records. Verbal consent or email consent (for those contacted by email who email back) will be sought from patients before they are approached by a research investigator who will explain the screening procedure as well as the aims, methods, anticipated benefits and potential risks of the study and provide a copy of the Participant Information Sheet (PIS). The investigator will also explain that patients are under no obligation to undergo screening and enter the trial and that they can withdraw at any time without having to give a reason. Those patients interested in taking part in the trial will be invited to attend a face-to-face visit in order to undergo screening for this trial. Written informed consent will only be sought after a minimum of 24 hours after being sent the PIS. When attending the screening visit, potential participants will be asked to sign two copies of the study consent form, which will be also countersigned by the research investigator conducting the assessment: one copy will be for the participant to retain and the other will be filed in the study site file (a copy will be also uploaded in the patient's medical records). However, consent will not denote enrolment into the study. Participants will be informed that their suitability to participate in the study will only be confirmed following review of screening data and that they may be excluded based on the study's inclusion and exclusion criteria. The consent process will be documented in the medical notes for a clear audit trail.

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

If a participant does not meet all the inclusion and exclusion criteria no further action will be taken and the participant will be informed that, for their own safety, it is not appropriate they continue with the study. Screening failure patients might be contacted for other research studies should they be interested (the option of being considered for future research is included in the consent form and they have consented to this). In addition, depending on the reason for screening failure, such patients might be contacted again in the future and asked if willing to be re-screened, should they still wish to take part to the trial. A research investigator will notify participants of screening outcome via phone call or email. The investigator will explain again study aims, methods, anticipated benefits and potential risks to qualifying patients and answer any questions they may have. The investigator will also explain that participants are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason. No clinical trial procedures will be conducted prior to the participant giving consent by signing the Consent Form.

The investigator obtaining consent will register the participant by entering all screening data regarding the participant on the database. The system will then assign a unique participant identification number (PIN) to that participant that needs to be recorded on the consent form. No eligibility waivers or deviations will be permitted. If new safety information results in significant changes in the risk/benefit assessment, the PIS and consent form will be reviewed and updated if necessary and subjects will be re-consented as appropriate. Therefore, the version and date of the PIS and ICF in use at the time will be recorded in the medical notes.

7.3 Screening

Interested eligible patients will be invited to attend a screening assessment visit. On the day of the screening visit, the investigator will explain the trial, the procedures involved and will answer any questions the participants may have. Before any procedure is carried out, participants will be asked to sign 2 copies of the trial consent form, which will be countersigned by the research investigator conducting the visit. One copy of the consent form will be given to the participant to keep for their records and the second copy will be filed in the trial site file. All participants who have consented for the trial must meet all the inclusion and exclusion criteria as set out in section 6.1 and 6.2. No eligibility waivers or deviations will be permitted.

The following screening procedures will be carried out:

- Physical examination.
- Vital signs (heart rate (HR) and blood pressure (BP).
- Medical history and co-morbidities.
- Concomitant medications.
- Urine pregnancy test for women of childbearing potential.
- Weight and height.
- Blood tests:
    - Haematology: full blood count.
    - Serum biochemistry: renal, liver and thyroid function, HbA1c.

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

Following the visit, once all data related to the screening visit has been obtained, the investigator (a qualified healthcare professional) will review the data to ensure that the participant is eligible to take part in the trial. An investigator will call/email the patient to notify of the outcome of screening, answer their questions and explain possible next steps (depending on outcome). Subjects who are deemed not to be eligible will be advised that they will be unable to be re-screened at a later date.

All pre-treatment procedures will be carried out as specified in the schedule of assessments (Appendix 1).

7.4 The randomisation Procedures

Participant registration will be undertaken centrally by the coordinating trial team.
Following participant consent, and confirmation of eligibility (see section 7.3 - Screening) the registration procedure described below will be carried out.

Participants are considered to be enrolled into the trial following: consent, pre-treatment screening assessments (see section 7.3 - Screening), confirmation of eligibility, completion of the registration, and allocation of the participant trial number by the central coordinating team.

7.4.1 Method of implementing the randomisation/allocation sequence

Following participant consent, screening and baseline measure collection, the randomisation procedure will be remotely carried out through an online randomisation service (Sealed Envelope Ltd.), with provision to enable unblinding if required. Subjects will be randomly (stratified block randomisation with varying block sizes) assigned in a 1:1 ratio to receive either semaglutide 2.4 mg or placebo, stratified for sex, type of surgical procedure and T2D status. The investigator will provide participant's initials, date of birth and stratification information before a randomisation code can be generated for each participant. Both participants and investigators will be blinded to study-group assignments. Once randomisation has been performed, no group allocation will be disclosed. A randomisation notification email will be sent to the pharmacist reporting the participant randomisation code; this randomisation code will reveal group allocation when identified in the code list. Only the trial coordinator and the trial pharmacist will have access to the code list. The blinding of the trial will be maintained throughout the trial until all data entry and processing are complete, the database has been locked and data analysis performed. Participants will be given a 24-hour Contact Card for emergency unblinding if required, medical support, or for any enquiries they have throughout the study period. For details on unblinding procedure refer to the trial Randomisation, Unblinding and Code break SOP.

7.5 Blinding

Both participants and all study staff carrying out trial visits/collecting study data will be blinded to study-group assignments. The study drugs, i.e., IMP and NIMP, will be identical in appearance. The only difference will be the lack of the active ingredient (semaglutide) in the placebo formulation. The blinding of the trial will be maintained throughout the trial until all data entry and processing are complete, the database has been locked and primary analysis performed.

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

7.5.1 Unblinding

During the trial, trial code will only be broken for valid medical or safety reasons e.g., in the case of a serious adverse event where it is necessary for the treating health care professional to know which treatment the participant is receiving before providing appropriate treatment. Subject always to clinical need, where possible, members of the research team will remain blinded. For details on unblinding procedure refer to the trial Randomisation, Unblinding and Code break SOP.

In the event a code is required to be unblinded a formal request to the holder of the code break list, or their delegate, will be made and the unblinded information obtained. The pharmacist and the Trial Co-ordinator will be the solely holders of the code list which will be provided by Sealed Envelope and will unblind via sealedenveleops.com. In the event a code is required to be unblinded, a formal request to the holder of the code break list will be made and the unblinded information obtained.

The CI/PI will document the breaking of the code and the reasons for doing so on the CRF/data collection tool, in the site file and medical notes. It will also be documented at the end of the study in any final study report and/or statistical report. The CI/Investigating team will notify the JRO (acting on behalf of the Sponsor) in writing as soon as possible following the code break detailing the necessity of the code break.

The Sponsor will also notify the relevant authorities as required. The written information will be disseminated to the Data and Safety Monitoring Committee (DSMC) for review in accordance with the DSMC Charter.

7.5.2 Emergency Unblinding

The trial code should only be broken for valid medical or safety reasons e.g., in the case of a serious adverse event where it is necessary for the investigator or treating health care professional to know which treatment the participant is receiving before the participant can be treated. Subject to clinical need, where possible, members of the research team should remain blinded. If a treating physician, who is not the CI/PI/trial investigator, requires the treatment to be unblinded in an emergency situation, they should notify the Investigating team that an emergency unblinding is required for a trial subject. The investigator/research team will provide this information as quickly as possible. On receipt of the treatment allocation details the CI/PI/trial investigator, or treating health care professional, will deal with the participant's medical emergency as appropriate.

In the event a code is required to be unblinded a formal email request, or phone call, to the holder of the code break list will be made and the unblinded information obtained. The pharmacist and the Trial Co-ordinator will be the solely holders of the code list. Outside normal working hours, UCLH Pharmacy will not provide unblinding support, therefore, any request will be dealt by the Trial coordinator. The pharmacist and trial manager will unblind via sealedenvelope.com.

7.6 Baseline Data

Prior to the scheduled assessment, a member of the study team will contact the participants to remind them to fast for 12 hours prior to the study visit and drink only water, as detailed in the PIS. They will be advised to avoid heavy exercise and alcohol consumption the evening prior to the visit. This contact will be noted in the medical records. The following baseline assessments will be carried out:

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

- Sociodemographic data.
- Physical examination.
- Vital signs (HR and BP).
- Serum pregnancy test for women of childbearing potential.
- Weight.
- BIA.
- ECG
- Blood tests:
    - Haematology: full blood count.
    - Serum biochemistry: renal, liver and thyroid function, HbA1c (If baseline visit >7 days from screening), glucose, lipids
    - HsCRP and inflammatory cytokines
    - Fasted and meal-stimulated GLP-1 levels: Prior to and 30 minutes after a standardised liquid meal. (Patients will be given a choice of cannulation or venepuncture when drawing baseline bloods for GLP-1 level analysis)
- Questionnaires:
    - ✓ Impact of weight on quality of life-lite (IWQOL-Lite CT)
    - ✓ SF-36 physical functioning score
    - ✓ Power of food questionnaire
    - ✓ EuroQol-5D (EQ-5D) [28, 29]
- Counselling on lifestyle modification (500-kcal deficient diet and 150 minute of physical activity/week and resistance exercise).
- Distribution of:
    - ✓ Scale
    - ✓ Drug diary
    - ✓ Semaglutide 3.0 mg/ml or 3.2 mg/ml /placebo pre-filled pens, injection and sharps bins.
- Subcutaneous injection training. Participants will be contacted by the study team to assess their injection technique. They will be offered additional injection training by the research investigator as required.

7.7 Trial Assessments

68-week trial of once weekly subcutaneously injected escalating semaglutide 3.0 mg/ml or 3.2 mg/ml or placebo as an adjunct to diet and exercise. Participants will receive on-going counselling for diet and exercise throughout the trial period by healthcare professionals. Semaglutide 3.0 mg/ml or 3.2 mg/ml and placebo will be supplied as a solution for injection in a pre-filled dial-a-dose pen-injector containing placebo or semaglutide 3.0 mg/ml or 3.2 mg/ml. Study medication will only be administered once all visit 2 assessments have been completed and the relevant safety reports have been obtained. All eligibility criteria have to be fulfilled and no exclusion criteria must be identified.

7.8 Long term follow-up assessments

Follow-up trial visits to monitor participants will be carried out at week 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 and 68 weeks. The majority of these visits will be carried out remotely. Data including weight, adverse events and concomitant medication use will be collected at each visit. The visits at weeks 6, 14, 32, 52 and 68 weeks will be carried out in person for safety purpose, to allow a targeted physical examination to be performed and blood samples to be taken for biochemical monitoring.

Docusign Envelope ID: F60CEFFC-8A22-436F-AE83-0299BDD1E22D

Visits 3-5, 7-9, 11-14, 16-19, 21-23: Intervention phase remote visits (Weeks 1, 2, 4, 8, 10, 12, 16, 20, 24, 28, 36, 40, 44, 48, 56, 60, 64) (+/- 3 days, +/- 7 days from visit 16 onwards)

The following will be assessed at each of the trial visits:

- Weight (using the scales provided to the participants).
- Concomitant medications.
- Compliance with trial treatment.
- Nutritional and exercise counselling.
- Adverse events (AE) review.

Visits 6, 10, 15, 20: Intervention phase site visits (Weeks 6, 14, 32, 52) (+/- 3 days; +/- 7 days for visit 20)

The following will be assessed at each of the trial visits:

- Targeted physical examination.
- Vital signs (HR and BP).
- Weight.
- BIA.
- Blood tests:
    - Haematology: full blood count.
    - Serum biochemistry: renal, liver, HbA1c.
    - HsCRP and inflammatory cytokines
- Questionnaires:
    - ✓ Impact of weight on quality of life-lite (IWQOL-Lite CT)
    - ✓ SF-36 physical functioning score
    - ✓ Power of food questionnaire
    - ✓ EuroQol-5D (EQ-5D) [28, 29]
- Concomitant medications.
- Adverse event (AE) review.
- Review of:
    - ✓ Drug diary

Visit 24: End-of-treatment assessment (Week 68 +/- 7 days)

The following assessments will be carried out following the last dose of semaglutide 3.0 mg/ml or 3.2 mg/ml /placebo:

- Physical examination.
- Vital signs (HR and BP).
- Urine pregnancy test for women of childbearing potential.
- Weight.
- BIA.
- ECG.
- Blood tests:
    - Haematology: full blood count.
    - Serum biochemistry: renal, liver and thyroid function, glucose, lipids, HbA1c (If baseline visit >7 days previously).
    - HsCRP and inflammatory cytokines
- Questionnaires:
    - ✓ Impact of weight on quality of life-lite (IWQOL-Lite CT)