Clinical trial results:
Effectiveness and cost of integrating a protocol with use of liraglutide 3.0mg into an obesity service (STRIVE Study)

Summary

EudraCT number	2017-002998-20
Trial protocol	GB
Global end of trial date	25 February 2022

Results information

Result version number	v1 (current)
This version publication date	11 March 2023
First version publication date	11 March 2023

Trial information

Trial identification

Sponsor protocol code	UNOLE0626

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03036800
WHO universal trial number (UTN)	U1111-1189-5726
Other trial identifiers	REC: 17/NW/0517

Notes:

Sponsors

Sponsor organisation name	University of Leicester Research Governance Office - Sponsor
Sponsor organisation address	Leicester General Hospital, Gwendolen Road, Leicester, United Kingdom, LE5 4PW
Public contact	Professor Melanie Davies, University of Leicester, +44 0116 258 6481, melanie.davies@uhl-tr.nhs.uk
Scientific contact	Professor Melanie Davies, University of Leicester, +44 0116 258 6481, melanie.davies@uhl-tr.nhs.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 February 2022
Global end of trial reached?	Yes
Global end of trial date	25 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective will be to compare the proportion of participants with severe and complicated obesity (defined as BMI ≥35 kg/m2 with at least one major obesity-related comorbidity) achieving weight loss ≥15% at 1 year (52 weeks) with a targeted prescribing pathway (i.e. use of LIRA 3mg according to a pre-specified protocol in combination with standard care provided in Tier 3 services) versus standard care provided in Tier 3 services alone.

Protection of trial subjects:

Severe and complicated obesity' is a substantial health problem that is defined as a body mass index (BMI) ≥35kg/m2 with at least one major obesity-related comorbidity. In England, the proportion of adults with severe and complicated obesity has risen alarmingly over the last two decades. Approximately 10% of the adult population in England now has a BMI ≥35kg/m2. In this group, 8-16% have type 2 diabetes mellitus (T2DM), imposing colossal direct and indirect healthcare costs.
In the United Kingdom, standard care for patients with severe and complicated obesity is currently variable, but generally includes referral to a 'Tier 3' or specialist weight management service, which comprises a multi-disciplinary team of experts, including psychological support. Depending on the centre, this team uses a combination strategy of optimal diet and lifestyle advice, meal replacements, and pharmacological therapies to facilitate weight loss. According to current guidelines, individuals with severe and complicated obesity qualify for bariatric surgery, which is one of the treatment options also available in a Tier 3 specialist weight management service. However, the majority of patients prefer not to have surgical interventions for their obesity, but are unable to achieve adequate long term weight loss with currently available non-surgical options. All participants will be reviewed regularly by the study clinician via face to face and telephone consultations. Those on the liraglutide arm will have additional visit to those on the control arm. All adverse events will be monitored at each study visit and all serious adverse events will be reported to the sponsor within the agreed timelines. All AE's and SAE's will be followed up at each study visit. The safety of the participants will be monitored very closely.

Background therapy:

Liraglutide 3.0 mg (LIRA 3mg) has been recently approved for the treatment of obesity by the European Medicines Agency (EMA) and Food and Drug Administration (FDA), as evidence from large randomised controlled trials (RCTs) has demonstrated that it is a safe and effective treatment option for obesity in diverse patient groups.
The majority of the trials involving LIRA 3mg have been placebo controlled, have included patients with BMI as low as 27 kg/m2, and have all continued LIRA 3mg treatment from the start of treatment for up to 3 years, irrespective of individual effectiveness, even for patients who fail to lose any weight. Best clinical practice would suggest that patients who fail to lose weight should not be continued on treatment because they are exposed to increased risk of adverse effects without significant benefit in terms of weight loss. Moreover, being randomised, with the uncertainty as to whether an active agent is being given, is a disincentive to compliance with diet and exercise advice for some patients. Effect sizes may be affected by the strict protocols of an RCT and these data may not be optimal for health economic analyses as real-world applicability and generalisability of RCTs are limited. Nonetheless, within the populations studied, LIRA 3mg resulted in ≥15% weight loss in 14% of patients, compared with 3.5% of patients with placebo, a reduction which is likely to generate major health benefits and long-term cost-savings, especially if weight loss can be maintained. Among obese patients with T2DM, weight loss is less, but the potential cost-savings are greater.

Evidence for comparator:

Post-hoc analysis of the SCALE Obesity trial comparing "early responders" (lost ≥5% of their starting weight after 16 weeks of LIRA 3mg treatment) with "early non-responders" (lost <5% of their starting weight after 16 weeks of LIRA 3mg treatment) found that 24.2% of early responders had lost ≥15% of their bodyweight at 56 weeks compared with 1.8% of early non-responders. A different model for the use of LIRA 3mg has been suggested by the SCALE Maintenance study which required a substantial

weight loss (≥5% of the baseline weight) with lifestyle changes (including meal replacement strategies) during a period of 12 weeks prior to commencing the drug. The study resulted in 26% of patients achieving ≥15% weight loss one year after treatment with LIRA 3mg compared with 6% of patients on placebo. Overall, these results suggest that the patients who are more likely to achieve clinically significant long-term weight loss with LIRA 3mg are those who achieve ≥5% weight loss during the first 12-16 weeks either with lifestyle changes or with LIRA 3mg treatment.
It would be unethical to prescribe LIRA 3mg to all patients with severe and complicated obesity because the risk of adverse events would be increased without any likely benefit to the patient. Moreover, the cost of LIRA 3mg is likely to preclude routine use for the full range of patients included in clinical trials, or for all patients who currently present for treatment in 'Tier 3' obesity services in the UK. Conversely, there is strong evidence that LIRA 3mg can lead to substantial weight reduction in some patients with severe and complicated obesity, thus it is imperative that this treatment is available to those who would benefit from it. We therefore propose testing a targeted prescribing pathway that would provide a pragmatic means by which to optimise the use of LIRA 3mg in a specialist obesity service.

Actual start date of recruitment	28 November 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Ireland: 124
Country: Number of subjects enrolled	United Kingdom: 268
Worldwide total number of subjects	392
EEA total number of subjects	124

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	341
From 65 to 84 years	51
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from five sites across the UK & Ireland.
Sites: University Hospitals Leicester, Guys & St Thomas Hospital London, Aintree University Hospital Liverpool, Glasgow Royal Infirmary and St Vincent's Dublin.
Recruitment open: 22/11/2017
First recruit: 28/11/2017
Last recruit: 28/02/2020
Recruitment closed: 29/02/2020

Pre-assignment

Screening details:

Participants were screened for eligibility by their age, ability to understand English and give consent, their BMI, a stable body weight, whether they had been referred to their local tier 3 service and having one of the following: pre-diabetes, diabetes, hypertension and/or obstructive sleep apnoea. We screened a total of 434 participants.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard care (control group)

Arm description:

Participants in the control group will follow the best medical care provided by the Tier 3 service at their site. This typically involves dietary advice to reduce energy intake, accompanied by a physical activity programme, both supported by behavioural change techniques with regular professional contacts. The nature of the standard care will vary between the different Tier 3 services at each site, as this is a pragmatic 'real-world' study. Clinician input will include the medical assessment of participants for severe and complicated obesity and the prescription of anti-obesity drugs as per local Tier 3 service policy. Those patients taking antihypertensive or antidepressant medication will be assessed and it will be at the clinician's discretion as to whether these medications are changed. Participants will remain routinely in the Tier 3 service and may also be offered treatment options within the duration of the study, including bariatric surgery, in line with NICE guidance.

Arm type	Control

No investigational medicinal product assigned in this arm

Arm title	Liraglutide 3mg (intervention)

Arm description:

Participants in the intervention group received the same standard care as those in the control group plus liraglutide 3mg was prescribed. Dose escalation of liraglutide occurred according to a pre-specified titration protocol, from 0.6mg to a maximum of 3.0mg daily. The liraglutide dose was initiated at 0.6mg and then increased to 1.2mg in Week 2, 1.8mg in Week 3, 2.4mg in Week 4, and 3.0mg in Week 5. Participants in the LIRA arm were made aware that continued use of LIRA 3mg was based upon their response to the treatment in terms of them achieving pre-defined weight loss targets at 16, 32 and 52 weeks. Stopping rule one: only those who had lost ≥5% of their baseline weight were offered further treatment with LIRA 3mg for another 16 weeks. Stopping rule two: only those who had lost ≥10% of their baseline weight were offered another 20 weeks. Stopping rule three: only those who had lost ≥15% of their baseline weight were offered another 52 weeks on LIRA 3mg.

Arm type	Intervention
Investigational medicinal product name	Liraglutide 3mg
Investigational medicinal product code	
Other name	Saxenda
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Intramuscular use

Dosage and administration details:

Saxenda 6mg/ml solution for injection in pre-filled pen in which 1ml of solution contains 6mg of liraglutide (human glucagon like peptide1 (GLP1) analogue produced by recombinant DNA technology in Saccharomyces Cerevisiae). One prefilled pen contains 18mg liraglutide in 3ml and can deliver doses of 0.6mg, 1.2mg, 1.8mg, 24.mg or 3mg via subcutaneous injection only. The IMP was formulated and supplied by Novo Nordisk for this trial.

Number of subjects in period 1	Standard care (control group)	Liraglutide 3mg (intervention)
Started	132	260
Completed	132	260

Period 2

Period 2 title	Week 16
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard care (control group)

Arm description:

Participants in the control group will follow the best medical care provided by the Tier 3 service at their site. This typically involves dietary advice to reduce energy intake, accompanied by a physical activity programme, both supported by behavioural change techniques with regular professional contacts. The nature of the standard care will vary between the different Tier 3 services at each site, as this is a pragmatic 'real-world' study. Clinician input will include the medical assessment of participants for severe and complicated obesity and the prescription of anti-obesity drugs as per local Tier 3 service policy. Those patients taking antihypertensive or antidepressant medication will be assessed and it will be at the clinician's discretion as to whether these medications are changed. Participants will remain routinely in the Tier 3 service and may also be offered treatment options within the duration of the study, including bariatric surgery, in line with NICE guidance.

Arm type	Control

No investigational medicinal product assigned in this arm

Arm title	Liraglutide 3mg (intervention)

Arm description:

Participants in the intervention group received the same standard care as those in the control group plus liraglutide 3mg was prescribed. Dose escalation of liraglutide occurred according to a pre-specified titration protocol, from 0.6mg to a maximum of 3.0mg daily. The liraglutide dose was initiated at 0.6mg and then increased to 1.2mg in Week 2, 1.8mg in Week 3, 2.4mg in Week 4, and 3.0mg in Week 5. Participants in the LIRA arm were made aware that continued use of LIRA 3mg was based upon their response to the treatment in terms of them achieving pre-defined weight loss targets at 16, 32 and 52 weeks. Stopping rule one: only those who had lost ≥5% of their baseline weight were offered further treatment with LIRA 3mg for another 16 weeks. Stopping rule two: only those who had lost ≥10% of their baseline weight were offered another 20 weeks. Stopping rule three: only those who had lost ≥15% of their baseline weight were offered another 52 weeks on LIRA 3mg.

Arm type	Intervention

Investigational medicinal product name	Liraglutide 3mg
Investigational medicinal product code	
Other name	Saxenda
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Intramuscular use

Dosage and administration details:

Saxenda 6mg/ml solution for injection in pre-filled pen in which 1ml of solution contains 6mg of liraglutide (human glucagon like peptide1 (GLP1) analogue produced by recombinant DNA technology in Saccharomyces Cerevisiae). One prefilled pen contains 18mg liraglutide in 3ml and can deliver doses of 0.6mg, 1.2mg, 1.8mg, 24.mg or 3mg via subcutaneous injection only. The IMP was formulated and supplied by Novo Nordisk for this trial.

Number of subjects in period 2	Standard care (control group)	Liraglutide 3mg (intervention)
Started	132	260
Completed	117	252
Not completed	15	8
Tolerance	-	1
Reason not stated	15	6
Protocol deviation	-	1

Period 3

Period 3 title	Week 32
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard care (control group)

Arm description:

Participants in the control group will follow the best medical care provided by the Tier 3 service at their site. This typically involves dietary advice to reduce energy intake, accompanied by a physical activity programme, both supported by behavioural change techniques with regular professional contacts. The nature of the standard care will vary between the different Tier 3 services at each site, as this is a pragmatic 'real-world' study. Clinician input will include the medical assessment of participants for severe and complicated obesity and the prescription of anti-obesity drugs as per local Tier 3 service policy. Those patients taking antihypertensive or antidepressant medication will be assessed and it will be at the clinician's discretion as to whether these medications are changed. Participants will remain routinely in the Tier 3 service and may also be offered treatment options within the duration of the study, including bariatric surgery, in line with NICE guidance.

Arm type	Control

No investigational medicinal product assigned in this arm

Arm title	Liraglutide 3mg (intervention)

Arm description:

Participants in the intervention group received the same standard care as those in the control group plus liraglutide 3mg was prescribed. Dose escalation of liraglutide occurred according to a pre-specified titration protocol, from 0.6mg to a maximum of 3.0mg daily. The liraglutide dose was initiated at 0.6mg

and then increased to 1.2mg in Week 2, 1.8mg in Week 3, 2.4mg in Week 4, and 3.0mg in Week 5. Participants in the LIRA arm were made aware that continued use of LIRA 3mg was based upon their response to the treatment in terms of them achieving pre-defined weight loss targets at 16, 32 and 52 weeks. Stopping rule one: only those who had lost ≥5% of their baseline weight were offered further treatment with LIRA 3mg for another 16 weeks. Stopping rule two: only those who had lost ≥10% of their baseline weight were offered another 20 weeks. Stopping rule three: only those who had lost ≥15% of their baseline weight were offered another 52 weeks on LIRA 3mg.

Arm type	Intervention
Investigational medicinal product name	Liraglutide 3mg
Investigational medicinal product code	
Other name	Saxenda
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Intramuscular use

Dosage and administration details:

Saxenda 6mg/ml solution for injection in pre-filled pen in which 1ml of solution contains 6mg of liraglutide (human glucagon like peptide1 (GLP1) analogue produced by recombinant DNA technology in Saccharomyces Cerevisiae). One prefilled pen contains 18mg liraglutide in 3ml and can deliver doses of 0.6mg, 1.2mg, 1.8mg, 24.mg or 3mg via subcutaneous injection only. The IMP was formulated and supplied by Novo Nordisk for this trial.

Number of subjects in period 3	Standard care (control group)	Liraglutide 3mg (intervention)
Started	117	252
Completed	113	243
Not completed	4	9
Tolerance	-	1
Reason not stated	4	8

Period 4

Period 4 title	Week 52
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard care (control group)

Arm description:

Participants in the control group will follow the best medical care provided by the Tier 3 service at their site. This typically involves dietary advice to reduce energy intake, accompanied by a physical activity programme, both supported by behavioural change techniques with regular professional contacts. The nature of the standard care will vary between the different Tier 3 services at each site, as this is a pragmatic 'real-world' study. Clinician input will include the medical assessment of participants for severe and complicated obesity and the prescription of anti-obesity drugs as per local Tier 3 service policy. Those patients taking antihypertensive or antidepressant medication will be assessed and it will be at the clinician's discretion as to whether these medications are changed. Participants will remain routinely in the Tier 3 service and may also be offered treatment options within the duration of the study, including bariatric surgery, in line with NICE guidance.

Arm type	Control

No investigational medicinal product assigned in this arm

Arm title	Liraglutide 3mg (intervention)

Arm description:

Participants in the intervention group received the same standard care as those in the control group plus liraglutide 3mg was prescribed. Dose escalation of liraglutide occurred according to a pre-specified titration protocol, from 0.6mg to a maximum of 3.0mg daily. The liraglutide dose was initiated at 0.6mg and then increased to 1.2mg in Week 2, 1.8mg in Week 3, 2.4mg in Week 4, and 3.0mg in Week 5. Participants in the LIRA arm were made aware that continued use of LIRA 3mg was based upon their response to the treatment in terms of them achieving pre-defined weight loss targets at 16, 32 and 52 weeks. Stopping rule one: only those who had lost ≥5% of their baseline weight were offered further treatment with LIRA 3mg for another 16 weeks. Stopping rule two: only those who had lost ≥10% of their baseline weight were offered another 20 weeks. Stopping rule three: only those who had lost ≥15% of their baseline weight were offered another 52 weeks on LIRA 3mg.

Arm type	Intervention
Investigational medicinal product name	Liraglutide 3mg
Investigational medicinal product code	
Other name	Saxenda
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Intramuscular use

Dosage and administration details:

Saxenda 6mg/ml solution for injection in pre-filled pen in which 1ml of solution contains 6mg of liraglutide (human glucagon like peptide1 (GLP1) analogue produced by recombinant DNA technology in Saccharomyces Cerevisiae). One prefilled pen contains 18mg liraglutide in 3ml and can deliver doses of 0.6mg, 1.2mg, 1.8mg, 24.mg or 3mg via subcutaneous injection only. The IMP was formulated and supplied by Novo Nordisk for this trial.

Number of subjects in period 4	Standard care (control group)	Liraglutide 3mg (intervention)
Started	113	243
Completed	110	237
Not completed	3	6
Non compliance	-	1
Reason not stated	3	5

Period 5

Period 5 title	Week 104
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard care (control group)

Arm description:

Participants in the control group will follow the best medical care provided by the Tier 3 service at their site. This typically involves dietary advice to reduce energy intake, accompanied by a physical activity programme, both supported by behavioural change techniques with regular professional contacts. The nature of the standard care will vary between the different Tier 3 services at each site, as this is a pragmatic 'real-world' study. Clinician input will include the medical assessment of participants for severe and complicated obesity and the prescription of anti-obesity drugs as per local Tier 3 service

policy. Those patients taking antihypertensive or antidepressant medication will be assessed and it will be at the clinician's discretion as to whether these medications are changed. Participants will remain routinely in the Tier 3 service and may also be offered treatment options within the duration of the study, including bariatric surgery, in line with NICE guidance.

Arm type	Control

No investigational medicinal product assigned in this arm

Arm title	Liraglutide 3mg (intervention)

Arm description:

Participants in the intervention group received the same standard care as those in the control group plus liraglutide 3mg was prescribed. Dose escalation of liraglutide occurred according to a pre-specified titration protocol, from 0.6mg to a maximum of 3.0mg daily. The liraglutide dose was initiated at 0.6mg and then increased to 1.2mg in Week 2, 1.8mg in Week 3, 2.4mg in Week 4, and 3.0mg in Week 5. Participants in the LIRA arm were made aware that continued use of LIRA 3mg was based upon their response to the treatment in terms of them achieving pre-defined weight loss targets at 16, 32 and 52 weeks. Stopping rule one: only those who had lost ≥5% of their baseline weight were offered further treatment with LIRA 3mg for another 16 weeks. Stopping rule two: only those who had lost ≥10% of their baseline weight were offered another 20 weeks. Stopping rule three: only those who had lost ≥15% of their baseline weight were offered another 52 weeks on LIRA 3mg.

Arm type	Intervention
Investigational medicinal product name	Liraglutide 3mg
Investigational medicinal product code	
Other name	Saxenda
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Intramuscular use

Dosage and administration details:

Saxenda 6mg/ml solution for injection in pre-filled pen in which 1ml of solution contains 6mg of liraglutide (human glucagon like peptide1 (GLP1) analogue produced by recombinant DNA technology in Saccharomyces Cerevisiae). One prefilled pen contains 18mg liraglutide in 3ml and can deliver doses of 0.6mg, 1.2mg, 1.8mg, 24.mg or 3mg via subcutaneous injection only. The IMP was formulated and supplied by Novo Nordisk for this trial.

Number of subjects in period 5	Standard care (control group)	Liraglutide 3mg (intervention)
Started	110	237
Completed	104	215
Not completed	6	22
Adverse event, serious fatal	-	1
Tolerance	-	3
Reason not stated	6	17
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Standard care (control group)

Reporting group description:

Participants in the control group will follow the best medical care provided by the Tier 3 service at their site. This typically involves dietary advice to reduce energy intake, accompanied by a physical activity programme, both supported by behavioural change techniques with regular professional contacts. The nature of the standard care will vary between the different Tier 3 services at each site, as this is a pragmatic 'real-world' study. Clinician input will include the medical assessment of participants for severe and complicated obesity and the prescription of anti-obesity drugs as per local Tier 3 service policy. Those patients taking antihypertensive or antidepressant medication will be assessed and it will be at the clinician's discretion as to whether these medications are changed. Participants will remain routinely in the Tier 3 service and may also be offered treatment options within the duration of the study, including bariatric surgery, in line with NICE guidance.

Reporting group title	Liraglutide 3mg (intervention)

Reporting group description:

Participants in the intervention group received the same standard care as those in the control group plus liraglutide 3mg was prescribed. Dose escalation of liraglutide occurred according to a pre-specified titration protocol, from 0.6mg to a maximum of 3.0mg daily. The liraglutide dose was initiated at 0.6mg and then increased to 1.2mg in Week 2, 1.8mg in Week 3, 2.4mg in Week 4, and 3.0mg in Week 5. Participants in the LIRA arm were made aware that continued use of LIRA 3mg was based upon their response to the treatment in terms of them achieving pre-defined weight loss targets at 16, 32 and 52 weeks. Stopping rule one: only those who had lost ≥5% of their baseline weight were offered further treatment with LIRA 3mg for another 16 weeks. Stopping rule two: only those who had lost ≥10% of their baseline weight were offered another 20 weeks. Stopping rule three: only those who had lost ≥15% of their baseline weight were offered another 52 weeks on LIRA 3mg.

Reporting group values	Standard care (control group)	Liraglutide 3mg (intervention)	Total
Number of subjects	132	260	392
Age categorical Units: Subjects			
Adults (18-64 years)	113	228	341
From 65-84 years	19	32	51
Age continuous Units: years			
arithmetic mean	51.81	51.10	
standard deviation	± 10.77	± 10.81	-
Gender categorical Units: Subjects			
Female	79	173	252
Male	53	87	140
Ethnic Group Units: Subjects			
White	114	225	339
Black	11	13	24
South Asian	3	11	14
Mixed/Other	4	11	15
Body Mass Index Units: Subjects			
<40 kg/m2	25	53	78
≥40 kg/m2	106	207	313
Missing	1	0	1

Smoking Status Units: Subjects			
Never smoker	71	144	215
Ex-smoker	48	90	138
Current smoker	13	25	38
Missing	0	1	1
Glycaemic Status Units: Subjects			
Normogylcaemia	66	110	176
Prediabetes	20	42	62
Diabetes remission	3	9	12
Diabetes	41	98	139
Missing	2	1	3
Hypertension Status Units: Subjects			
No	44	96	140
Yes	88	162	250
Missing	0	2	2
Sleep apnoea status Units: Subjects			
No	54	113	167
Yes	68	124	192
Missing	10	23	33
Type of diabetes medication Units: Subjects			
SGLT-2	4	6	10
Metformin	28	59	87
Sulphonylureas	1	5	6
Glitazones	1	1	2
Missing	0	1	1
N/A	98	188	286
Statin use Units: Subjects			
No	101	190	291
Yes	31	70	101
Number of all medications Units: Subjects			
None	30	55	85
One	11	24	35
Two	17	17	34
Three	9	32	41
Four	7	24	31
Five and over	58	108	166
Number of diabetes medications Units: Subjects			
Does not have diabetes	91	162	253
None	12	35	47
One	22	52	74
Two	6	9	15
3 and over	1	2	3
Number of antihypertensive medications			

Units: Subjects			
Does not have hypertension	44	98	142
None	24	44	68
One	25	55	80
Two	22	33	55
3 and over	17	30	47
Weight			
Units: kilogram(s)			
arithmetic mean	127.09	129.02	
standard deviation	± 21.42	± 25.33	-
Body mass index			
Units: kg/m2			
arithmetic mean	45.52	46.22	
standard deviation	± 7.25	± 7.75	-
Heart rate			
Units: beats/minute			
arithmetic mean	78.37	78.27	
standard deviation	± 12.24	± 11.21	-
Waist circumference			
Units: centimetre			
arithmetic mean	131.81	132.44	
standard deviation	± 12.95	± 15.56	-
HbA1c			
Units: millimole/mole			
arithmetic mean	44.71	46.10	
standard deviation	± 10.79	± 13.72	-
HbA1c			
Units: percent			
arithmetic mean	6.24	6.36	
standard deviation	± 0.99	± 1.27	-
Systolic blood pressure			
Units: mmHg			
arithmetic mean	138.12	135.77	
standard deviation	± 17.79	± 18.26	-
Diastolic blood pressure			
Units: mmHg			
arithmetic mean	81.99	81.35	
standard deviation	± 12.04	± 10.94	-
LDL cholesterol			
Units: millimole(s)/litre			
arithmetic mean	2.70	2.71	
standard deviation	± 0.83	± 0.84	-
HDL cholesterol			
Units: millimole(s)/litre			
arithmetic mean	1.25	1.24	
standard deviation	± 0.55	± 0.30	-
Total cholesterol			
Units: millimole(s)/litre			
arithmetic mean	4.74	4.76	
standard deviation	± 0.95	± 1.00	-
Triglycerides			
Units: millimole(s)/litre			

arithmetic mean	1.86	1.85	
standard deviation	± 0.94	± 0.94	-
Average total MET Units: minutes/week			
arithmetic mean	5463.48	5246.83	
standard deviation	± 7958.59	± 7145.63	-

End points

End points reporting groups

Reporting group title	Standard care (control group)

Reporting group description:

Participants in the control group will follow the best medical care provided by the Tier 3 service at their site. This typically involves dietary advice to reduce energy intake, accompanied by a physical activity programme, both supported by behavioural change techniques with regular professional contacts. The nature of the standard care will vary between the different Tier 3 services at each site, as this is a pragmatic 'real-world' study. Clinician input will include the medical assessment of participants for severe and complicated obesity and the prescription of anti-obesity drugs as per local Tier 3 service policy. Those patients taking antihypertensive or antidepressant medication will be assessed and it will be at the clinician's discretion as to whether these medications are changed. Participants will remain routinely in the Tier 3 service and may also be offered treatment options within the duration of the study, including bariatric surgery, in line with NICE guidance.

Reporting group title	Liraglutide 3mg (intervention)

Reporting group description:

Participants in the intervention group received the same standard care as those in the control group plus liraglutide 3mg was prescribed. Dose escalation of liraglutide occurred according to a pre-specified titration protocol, from 0.6mg to a maximum of 3.0mg daily. The liraglutide dose was initiated at 0.6mg and then increased to 1.2mg in Week 2, 1.8mg in Week 3, 2.4mg in Week 4, and 3.0mg in Week 5. Participants in the LIRA arm were made aware that continued use of LIRA 3mg was based upon their response to the treatment in terms of them achieving pre-defined weight loss targets at 16, 32 and 52 weeks. Stopping rule one: only those who had lost ≥5% of their baseline weight were offered further treatment with LIRA 3mg for another 16 weeks. Stopping rule two: only those who had lost ≥10% of their baseline weight were offered another 20 weeks. Stopping rule three: only those who had lost ≥15% of their baseline weight were offered another 52 weeks on LIRA 3mg.

Reporting group title	Standard care (control group)

Reporting group description:

Participants in the control group will follow the best medical care provided by the Tier 3 service at their site. This typically involves dietary advice to reduce energy intake, accompanied by a physical activity programme, both supported by behavioural change techniques with regular professional contacts. The nature of the standard care will vary between the different Tier 3 services at each site, as this is a pragmatic 'real-world' study. Clinician input will include the medical assessment of participants for severe and complicated obesity and the prescription of anti-obesity drugs as per local Tier 3 service policy. Those patients taking antihypertensive or antidepressant medication will be assessed and it will be at the clinician's discretion as to whether these medications are changed. Participants will remain routinely in the Tier 3 service and may also be offered treatment options within the duration of the study, including bariatric surgery, in line with NICE guidance.

Reporting group title	Liraglutide 3mg (intervention)

Reporting group description:

Participants in the intervention group received the same standard care as those in the control group plus liraglutide 3mg was prescribed. Dose escalation of liraglutide occurred according to a pre-specified titration protocol, from 0.6mg to a maximum of 3.0mg daily. The liraglutide dose was initiated at 0.6mg and then increased to 1.2mg in Week 2, 1.8mg in Week 3, 2.4mg in Week 4, and 3.0mg in Week 5. Participants in the LIRA arm were made aware that continued use of LIRA 3mg was based upon their response to the treatment in terms of them achieving pre-defined weight loss targets at 16, 32 and 52 weeks. Stopping rule one: only those who had lost ≥5% of their baseline weight were offered further treatment with LIRA 3mg for another 16 weeks. Stopping rule two: only those who had lost ≥10% of their baseline weight were offered another 20 weeks. Stopping rule three: only those who had lost ≥15% of their baseline weight were offered another 52 weeks on LIRA 3mg.

Reporting group title	Standard care (control group)

Reporting group description:

Participants in the control group will follow the best medical care provided by the Tier 3 service at their site. This typically involves dietary advice to reduce energy intake, accompanied by a physical activity programme, both supported by behavioural change techniques with regular professional contacts. The nature of the standard care will vary between the different Tier 3 services at each site, as this is a pragmatic 'real-world' study. Clinician input will include the medical assessment of participants for severe and complicated obesity and the prescription of anti-obesity drugs as per local Tier 3 service policy. Those patients taking antihypertensive or antidepressant medication will be assessed and it will be at the clinician's discretion as to whether these medications are changed. Participants will remain routinely in the Tier 3 service and may also be offered treatment options within the duration of the study, including bariatric surgery, in line with NICE guidance.

Reporting group title	Liraglutide 3mg (intervention)

Reporting group description:

Participants in the intervention group received the same standard care as those in the control group plus liraglutide 3mg was prescribed. Dose escalation of liraglutide occurred according to a pre-specified titration protocol, from 0.6mg to a maximum of 3.0mg daily. The liraglutide dose was initiated at 0.6mg and then increased to 1.2mg in Week 2, 1.8mg in Week 3, 2.4mg in Week 4, and 3.0mg in Week 5. Participants in the LIRA arm were made aware that continued use of LIRA 3mg was based upon their response to the treatment in terms of them achieving pre-defined weight loss targets at 16, 32 and 52 weeks. Stopping rule one: only those who had lost ≥5% of their baseline weight were offered further treatment with LIRA 3mg for another 16 weeks. Stopping rule two: only those who had lost ≥10% of their baseline weight were offered another 20 weeks. Stopping rule three: only those who had lost ≥15% of their baseline weight were offered another 52 weeks on LIRA 3mg.

Reporting group title	Standard care (control group)

Reporting group description:

Participants in the control group will follow the best medical care provided by the Tier 3 service at their site. This typically involves dietary advice to reduce energy intake, accompanied by a physical activity programme, both supported by behavioural change techniques with regular professional contacts. The nature of the standard care will vary between the different Tier 3 services at each site, as this is a pragmatic 'real-world' study. Clinician input will include the medical assessment of participants for severe and complicated obesity and the prescription of anti-obesity drugs as per local Tier 3 service policy. Those patients taking antihypertensive or antidepressant medication will be assessed and it will be at the clinician's discretion as to whether these medications are changed. Participants will remain routinely in the Tier 3 service and may also be offered treatment options within the duration of the study, including bariatric surgery, in line with NICE guidance.

Reporting group title	Liraglutide 3mg (intervention)

Reporting group description:

Participants in the intervention group received the same standard care as those in the control group plus liraglutide 3mg was prescribed. Dose escalation of liraglutide occurred according to a pre-specified titration protocol, from 0.6mg to a maximum of 3.0mg daily. The liraglutide dose was initiated at 0.6mg and then increased to 1.2mg in Week 2, 1.8mg in Week 3, 2.4mg in Week 4, and 3.0mg in Week 5. Participants in the LIRA arm were made aware that continued use of LIRA 3mg was based upon their response to the treatment in terms of them achieving pre-defined weight loss targets at 16, 32 and 52 weeks. Stopping rule one: only those who had lost ≥5% of their baseline weight were offered further treatment with LIRA 3mg for another 16 weeks. Stopping rule two: only those who had lost ≥10% of their baseline weight were offered another 20 weeks. Stopping rule three: only those who had lost ≥15% of their baseline weight were offered another 52 weeks on LIRA 3mg.

Reporting group title	Standard care (control group)

Reporting group description:

Participants in the control group will follow the best medical care provided by the Tier 3 service at their site. This typically involves dietary advice to reduce energy intake, accompanied by a physical activity programme, both supported by behavioural change techniques with regular professional contacts. The nature of the standard care will vary between the different Tier 3 services at each site, as this is a pragmatic 'real-world' study. Clinician input will include the medical assessment of participants for severe and complicated obesity and the prescription of anti-obesity drugs as per local Tier 3 service policy. Those patients taking antihypertensive or antidepressant medication will be assessed and it will be at the clinician's discretion as to whether these medications are changed. Participants will remain routinely in the Tier 3 service and may also be offered treatment options within the duration of the study, including bariatric surgery, in line with NICE guidance.

Reporting group title	Liraglutide 3mg (intervention)

Reporting group description:

Participants in the intervention group received the same standard care as those in the control group plus liraglutide 3mg was prescribed. Dose escalation of liraglutide occurred according to a pre-specified titration protocol, from 0.6mg to a maximum of 3.0mg daily. The liraglutide dose was initiated at 0.6mg and then increased to 1.2mg in Week 2, 1.8mg in Week 3, 2.4mg in Week 4, and 3.0mg in Week 5. Participants in the LIRA arm were made aware that continued use of LIRA 3mg was based upon their response to the treatment in terms of them achieving pre-defined weight loss targets at 16, 32 and 52 weeks. Stopping rule one: only those who had lost ≥5% of their baseline weight were offered further treatment with LIRA 3mg for another 16 weeks. Stopping rule two: only those who had lost ≥10% of their baseline weight were offered another 20 weeks. Stopping rule three: only those who had lost ≥15% of their baseline weight were offered another 52 weeks on LIRA 3mg.

Subject analysis set title	Complete cases at 52 weeks
Subject analysis set type	Full analysis

Subject analysis set description:

Complete cases at 52 weeks - Standard care and Liraglutide

Subject analysis set title	Intention-to-treat at 52 weeks
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intention-to-treat at 52 weeks - Standard care and Liraglutide arm	
Subject analysis set title	Per protocol at 52 weeks
Subject analysis set type	Per protocol
Subject analysis set description: Per protocol at 52 weeks - Standard care and Liraglutide arm	
Subject analysis set title	Responder at 52 weeks
Subject analysis set type	Full analysis
Subject analysis set description: Responder at 52 weeks - Standard care and Liraglutide arm	
Subject analysis set title	Complete cases primary outcome - Control arm
Subject analysis set type	Full analysis
Subject analysis set description: Complete cases at 52 weeks - Standard care	
Subject analysis set title	Complete cases primary outcome - Liraglutide arm
Subject analysis set type	Full analysis
Subject analysis set description: Complete cases at 52 weeks - Liraglutide	
Subject analysis set title	Per protocol primary outcome - Control arm
Subject analysis set type	Per protocol
Subject analysis set description: Per protocol at 52 weeks - Standard care	
Subject analysis set title	Per protocol primary outcome - Liraglutide arm
Subject analysis set type	Per protocol
Subject analysis set description: Per protocol at 52 weeks - Liraglutide arm	
Subject analysis set title	Intention-to-treat - Control
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intention-to-treat - 52 weeks - Standard care	
Subject analysis set title	Intention-to-treat - Liraglutide
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intention-to-treat - 52 weeks - Liraglutide	

Primary: Binary outcome indicating whether weight loss of ≥15% was achieved at 52 weeks

End point title	Binary outcome indicating whether weight loss of ≥15% was achieved at 52 weeks

End point description:

N.B. For participants who did not attend the week 52 visit, routine data was used to obtain the weight measurement.
N.B. Four participants that achieved the primary outcome in the intention-to-treat population had bariatric surgery before week 52 and so were not eligible for the complete cases population.
Numbers given for reporting group subjects analysed are based on the primary analysis population, complete case population.

End point type	Primary

End point timeframe:

Compare the proportion of participants with severe & complicated obesity achieving weight loss ≥15% at 1 year (52 weeks) with a targeted prescribing pathway (i.e. use of LIRA 3mg in combination with standard care (tier 3)) vs standard care alone (tier 3).

End point values	Standard care (control group)	Liraglutide 3mg (intervention)	Complete cases primary outcome - Control arm	Complete cases primary outcome - Liraglutide arm
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	93	201	93	201
Units: Number	6	51	6	51

End point values	Per protocol primary outcome - Control arm	Per protocol primary outcome - Liraglutide arm	Intention-to-treat - Control	Intention-to-treat - Liraglutide
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	51	108	132	260
Units: Number	5	40	6	55

Statistical analyses

Statistical analysis title	Primary analysis of primary outcome

Statistical analysis description:

A logistic regression model will be used with a binary indicator showing whether or not ≥15% weight loss was achieved at 52 weeks as the outcome, randomisation group (intervention or control) as the main covariate, & the stratification factors of site(non-ordinal categorical variable) & baseline BMI (>45kg/m2; <45kg/m2) as additional covariates. The adjusted odds ratio with 95% CI & p-value will be presented.
This analysis uses the complete cases population, therefore missing data isn't imputed

Comparison groups	Complete cases primary outcome - Control arm v Complete cases primary outcome - Liraglutide arm
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.09
upper limit	12.88

Statistical analysis title	ITT of primary outcome

Statistical analysis description:

The analysis of the primary outcome in the ITT population, uses the same model as the primary

analysis. Missing primary outcome data are imputed for the ITT analysis; this will be done by assuming that these participants did not achieve ≥15% weight loss at 52 weeks, which is a conservative approach.

Comparison groups	Liraglutide 3mg (intervention) v Standard care (control group)
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.45
upper limit	14.4

Statistical analysis title	Per Protocol analysis of primary outcome
Statistical analysis description:	
The same model as specified for the primary outcome was fitted using the per-protocol population	
Comparison groups	Per protocol primary outcome - Control arm v Per protocol primary outcome - Liraglutide arm
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.81
upper limit	14.01

Secondary: Referral rates to other obesity interventions (intention-to-treat) - Tier 4

End point title	Referral rates to other obesity interventions (intention-to-treat) - Tier 4
End point description:	
Number of participants referred to Tier 4 for bariatric surgery over the 104 weeks study period.	
End point type	Secondary
End point timeframe:	
104 weeks	

End point values	Standard care (control group)	Liraglutide 3mg (intervention)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	150		
Units: Number				
No	64	125		
Yes	5	25		

Statistical analyses

No statistical analyses for this end point

Secondary: Long-term maintenance (defined as the proportion of patients maintaining ≥15% weight loss at 104 weeks among those who achieved ≥15% weight loss at 52 weeks)

End point title	Long-term maintenance (defined as the proportion of patients maintaining ≥15% weight loss at 104 weeks among those who achieved ≥15% weight loss at 52 weeks)
End point description:	
Proportion of participants maintaining weight loss of ≥15% among those who lost ≥15% at 52 weeks	
End point type	Secondary
End point timeframe:	
104 weeks	

End point values	Standard care (control group)	Liraglutide 3mg (intervention)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	41		
Units: Number	2	12		

Statistical analyses

Statistical analysis title	≥15% weight loss at 2yrs in those ≥15% at 1yr

Statistical analysis description:

A Logistic regression model was fitted with the binary variable of ≥15% weight loss at 2yrs as the outcome, the main covariate being randomised arm and adjusting for for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2) as well. This was fitted for individuals with weight loss of ≥15% at 1yr.

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.601
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	4.24

Secondary: Absolute BMI (kg/m2) at 52 weeks

End point title	Absolute BMI (kg/m2) at 52 weeks

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Standard care (control group)	Liraglutide 3mg (intervention)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	180		
Units: kg/m2				
arithmetic mean (standard deviation)				
Baseline	44.41 (± 5.71)	45.20 (± 7.19)		
Follow-up	43.25 (± 6.42)	41.37 (± 7.63)		
Change from baseline	-1.17 (± 2.84)	-3.84 (± 3.29)		

Statistical analyses

Statistical analysis title	Complete case analysis of change in BMI from BL

Statistical analysis description:

Linear regression with change in BMI from baseline as the outcome, randomised group as the main covariate, adjusting also for covariates of site and BMI strata.

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)
Number of subjects included in analysis	260
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	-1.91

Secondary: Absolute waist circumference (cm) at 52 weeks

End point title	Absolute waist circumference (cm) at 52 weeks

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Standard care (control group)	Liraglutide 3mg (intervention)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	137		
Units: centimetre				
arithmetic mean (standard deviation)				
Baseline	131.57 (± 13.73)	130.62 (± 13.87)		
Follow-up	125.99 (± 13.81)	121.74 (± 14.19)		
Change from baseline	-5.58 (± 8.48)	-8.88 (± 7.89)		

Statistical analyses

Statistical analysis title	Analysis of change in waist circumference

Statistical analysis description:

Carried out in the complete case population. Linear regression with change in waist circumference from BL as the outcome, randomised arm as the main covariate, adjusting also for site and BMI strata.

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	-3.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.77
upper limit	-0.8

Secondary: Improving obesity-related co-morbidities (obstructive sleep apnoea, prediabetes, diabetes, hypertension, dyslipidaemia, depression) 52 weeks

End point title	Improving obesity-related co-morbidities (obstructive sleep apnoea, prediabetes, diabetes, hypertension, dyslipidaemia, depression) 52 weeks

End point description:

This will be assessed by the Kings College Obesity Staging (KCOS) score. The score is 0-3.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Standard care (control group)	Liraglutide 3mg (intervention)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	145		
Units: number				
Normal health at baseline	0	0		
Normal health at follow-up	0	1		
At risk of disease at baseline	5	6		
At risk of disease at follow-up	12	23		
Established disease at baseline	41	97		
Established disease at follow up	43	108		
Advanced disease at baseline	17	42		
Advanced disease at follow up	8	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Improving obesity-related co-morbidities (obstructive sleep apnoea, prediabetes, diabetes, hypertension, dyslipidaemia, depression) 104 weeks

End point title	Improving obesity-related co-morbidities (obstructive sleep apnoea, prediabetes, diabetes, hypertension, dyslipidaemia, depression) 104 weeks

End point description:

This will be assessed by the Kings College Obesity Staging (KCOS) score. The score is 0-3.

End point type	Secondary

End point timeframe:

104 weeks

End point values	Standard care (control group)	Liraglutide 3mg (intervention)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	115		
Units: number				
Normal health at baseline	0	0		
Normal health at follow-up	0	2		

At risk of disease at baseline	4	5		
At risk of disease at follow-up	10	16		
Established disease at baseline	37	84		
Established disease at follow up	35	86		
Advanced disease at baseline	10	26		
Advanced disease at follow up	6	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Referral rates to other obesity interventions (intention-to-treat) Per site bariatric referrals

End point title	Referral rates to other obesity interventions (intention-to-treat) Per site bariatric referrals

End point description:

Referrals for bariatric surgery by 104 weeks by site.

End point type	Secondary

End point timeframe:

104 weeks

End point values	Standard care (control group)	Liraglutide 3mg (intervention)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	25		
Units: number				
Dublin	3	3		
Glasgow	0	0		
Leicester	0	10		
Liverpool	1	2		
London	1	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Referral rates to other obesity interventions (intention-to-treat) - Had bariatric surgery by week 104

End point title	Referral rates to other obesity interventions (intention-to-treat) - Had bariatric surgery by week 104

End point description:

Had bariatric surgery by 104 weeks

End point type	Secondary

End point timeframe:

104 weeks.

End point values	Standard care (control group)	Liraglutide 3mg (intervention)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	148		
Units: number				
No	64	142		
Yes	4	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Attended at least 70% of scheduled Tier 3 appointments by 52 weeks

End point title	Attended at least 70% of scheduled Tier 3 appointments by 52 weeks

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Standard care (control group)	Liraglutide 3mg (intervention)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	200		
Units: number				
No	1	0		
Yes	51	115		
Attended week 52 visit but variable missing	37	85		

Statistical analyses

No statistical analyses for this end point

Secondary: Attended at least 70% of scheduled Tier 3 appointments by 104 weeks

End point title	Attended at least 70% of scheduled Tier 3 appointments by 104 weeks

End point description:

End point type	Secondary

End point timeframe:
104 weeks

End point values	Standard care (control group)	Liraglutide 3mg (intervention)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	143		
Units: number				
No	0	0		
Yes	46	92		
Attended week 104 visit but variable missing	20	51		

Statistical analyses

No statistical analyses for this end point

Secondary: Stopped treatment with liraglutide 3mg due to adverse effects by 52 weeks

End point title	Stopped treatment with liraglutide 3mg due to adverse effects by 52 weeks

End point description:

End point type	Secondary

End point timeframe:
52 weeks

End point values	Liraglutide 3mg (intervention)			
Subject group type	Reporting group			
Number of subjects analysed	114			
Units: number				
No	111			
Yes	3			
Missing	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Stopped treatment with liraglutide 3mg due to adverse effects by 104 weeks

End point title	Stopped treatment with liraglutide 3mg due to adverse effects

	by 104 weeks

End point description:

End point type	Secondary

End point timeframe:

104 weeks

End point values	Liraglutide 3mg (intervention)			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: number				
No	53			
Yes	2			
Missing	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Compliant with liraglutide 3mg treatment up to 52 weeks

End point title	Compliant with liraglutide 3mg treatment up to 52 weeks[1]

End point description:

End point type	Secondary

End point timeframe:

52 weeks

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome is for up to 52 weeks and therefore we've had to select baseline rather than 52 weeks since it includes individuals that withdrew from the trial before 52 weeks.
This was defined using the questionnaire answers as detailed in Appendix 7 of the SAP, and so includes all participants (i.e., not only those who attended the visit) up to the point when they stopped treatment or withdrew from the study.

End point values	Liraglutide 3mg (intervention)			
Subject group type	Reporting group			
Number of subjects analysed	260			
Units: number				
No	23			
Yes	233			
Missing	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Compliant with liraglutide 3mg treatment up to 104 weeks

End point title	Compliant with liraglutide 3mg treatment up to 104 weeks[2]

End point description:

End point type	Secondary

End point timeframe:

104 weeks

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome is for up to 104 weeks and therefore we've had to select baseline rather than 104 weeks since it includes individuals that withdrew from the trial before 104 weeks.
This was defined using the questionnaire answers as detailed in Appendix 7 of the SAP, and so includes all participants (i.e., not only those who attended the visit) up to the point when they stopped treatment or withdrew from the study.

End point values	Liraglutide 3mg (intervention)			
Subject group type	Reporting group			
Number of subjects analysed	260			
Units: number				
No	27			
Yes	229			
Missing	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Stopped liraglutide 3mg treatment at 16 weeks

End point title	Stopped liraglutide 3mg treatment at 16 weeks

End point description:

End point type	Secondary

End point timeframe:

16 weeks

End point values	Liraglutide 3mg (intervention)			
Subject group type	Reporting group			
Number of subjects analysed	260			
Units: number				
No	181			
Yes	79			
Missing	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Stopped liraglutide 3mg treatment at 32 weeks

End point title	Stopped liraglutide 3mg treatment at 32 weeks

End point description:

End point type	Secondary

End point timeframe:

32 weeks

End point values	Liraglutide 3mg (intervention)			
Subject group type	Reporting group			
Number of subjects analysed	181			
Units: number				
No	110			
Yes	71			
Missing	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Stopped liraglutide 3mg treatment at 52 weeks

End point title	Stopped liraglutide 3mg treatment at 52 weeks

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Liraglutide 3mg (intervention)			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: number				
No	53			
Yes	57			
Missing	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Completed 52 weeks of the Tier 3 programme despite stopping liraglutide 3mg by 16 weeks

End point title	Completed 52 weeks of the Tier 3 programme despite stopping liraglutide 3mg by 16 weeks

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Liraglutide 3mg (intervention)			
Subject group type	Reporting group			
Number of subjects analysed	260			
Units: number				
No	60			
Yes	19			
N/A (still using liraglutide 3mg at 16 weeks)	181			
Missing	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Completed 52 weeks of the Tier 3 programme despite stopping liraglutide 3mg by 32 weeks

End point title	Completed 52 weeks of the Tier 3 programme despite stopping liraglutide 3mg by 32 weeks

End point description:

End point type	Secondary

End point timeframe:
52 weeks

End point values	Liraglutide 3mg (intervention)			
Subject group type	Reporting group			
Number of subjects analysed	181			
Units: number				
No	49			
Yes	22			
N/A (still using liraglutide at 32 weeks)	110			
Missing	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Started on anti-obesity drugs at 52 weeks

End point title	Started on anti-obesity drugs at 52 weeks

End point description:

End point type	Secondary

End point timeframe:
52 weeks

End point values	Standard care (control group)	Liraglutide 3mg (intervention)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	206		
Units: number				
No	92	3		
Yes	1	203		

Statistical analyses

No statistical analyses for this end point

Secondary: Started on anti-obesity drugs at 104 weeks

End point title	Started on anti-obesity drugs at 104 weeks

End point description:

End point type	Secondary

End point timeframe:
104 weeks

End point values	Standard care (control group)	Liraglutide 3mg (intervention)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	147		
Units: number				
No	64	144		
Yes	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Weight loss of ≥5% from baseline

End point title	Weight loss of ≥5% from baseline

End point description:

End point type	Secondary

End point timeframe:
16, 32, 52 and 104 weeks

End point values	Standard care (control group)	Liraglutide 3mg (intervention)	Standard care (control group)	Liraglutide 3mg (intervention)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	86	237	79	208
Units: number	34	186	34	158

End point values	Standard care (control group)	Liraglutide 3mg (intervention)	Standard care (control group)	Liraglutide 3mg (intervention)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	93	201	61	132
Units: number	29	127	17	62

Statistical analyses

Statistical analysis title	16 week weight loss of ≥5% from baseline

Statistical analysis description:
This was carried out using the complete case population. A logistic regression with a binary outcome of

Weight loss of ≥5% from baseline was fitted. The main covariate was randomised arm, with the model also being adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)
Number of subjects included in analysis	323
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	10.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.26
upper limit	19.48

Statistical analysis title	32 week weight loss of ≥5% from baseline

Statistical analysis description:

This was carried out using the complete case population. A logistic regression with a binary outcome of Weight loss at 32 weeks of ≥5% from baseline was fitted. The main covariate was randomised arm, with the model also being adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.86
upper limit	9.36

Statistical analysis title	52 week weight loss of ≥5% from baseline

Statistical analysis description:

This was carried out using the complete case population. A logistic regression with a binary outcome of Weight loss at 52 weeks of ≥5% from baseline was fitted. The main covariate was randomised arm, with the model also being adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)

Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.39
upper limit	7.22

Statistical analysis title	104 week weight loss of ≥5% from baseline

Statistical analysis description:

This was carried out using the complete case population. A logistic regression with a binary outcome of Weight loss at 104 weeks of ≥5% from baseline was fitted. The main covariate was randomised arm, with the model also being adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.23
upper limit	4.84

Secondary: Weight loss of ≥10% from baseline

End point title	Weight loss of ≥10% from baseline

End point description:

End point type	Secondary

End point timeframe:

16, 32, 52 and 104 weeks

End point values	Standard care (control group)	Liraglutide 3mg (intervention)	Standard care (control group)	Liraglutide 3mg (intervention)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	86	237	79	208
Units: number	9	60	14	110

End point values	Standard care (control group)	Liraglutide 3mg (intervention)	Standard care (control group)	Liraglutide 3mg (intervention)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	93	90	61	132
Units: number	9	90	8	32

Statistical analyses

Statistical analysis title	16 week weight loss of ≥10% from baseline

Statistical analysis description:

This was carried out using the complete case population. A logistic regression with a binary outcome of Weight loss at 16 weeks of ≥10% from baseline was fitted. The main covariate was randomised arm, with the model also being adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)
Number of subjects included in analysis	323
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.14
upper limit	12.39

Statistical analysis title	32 week weight loss of ≥10% from baseline

Statistical analysis description:

This was carried out using the complete case population. A logistic regression with a binary outcome of Weight loss at 32 week of ≥10% from baseline was fitted. The main covariate was randomised arm, with the model also being adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)

Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	6.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.32
upper limit	12.86

Statistical analysis title	52 week weight loss of ≥10% from baseline

Statistical analysis description:

This was carried out using the complete case population. A logistic regression with a binary outcome of Weight loss at 52 weeks of ≥10% from baseline was fitted. The main covariate was randomised arm, with the model also being adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	8.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.8
upper limit	17.16

Statistical analysis title	104 week weight loss of ≥10% from baseline

Statistical analysis description:

This was carried out using the complete case population. A logistic regression with a binary outcome of Weight loss at 104 weeks of ≥10% from baseline was fitted. The main covariate was randomised arm, with the model also being adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.065
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.28

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	5.47

Secondary: Weight loss of ≥15% from baseline

End point title	Weight loss of ≥15% from baseline

End point description:

End point type	Secondary

End point timeframe:

16, 32, 52 and 104 weeks

End point values	Standard care (control group)	Liraglutide 3mg (intervention)	Standard care (control group)	Liraglutide 3mg (intervention)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	86	237	79	208
Units: number	2	10	5	32

End point values	Standard care (control group)	Liraglutide 3mg (intervention)	Standard care (control group)	Liraglutide 3mg (intervention)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	93	201	61	132
Units: number	6	51	2	15

Statistical analyses

Statistical analysis title	16 week weight loss of ≥15% from baseline

Statistical analysis description:

This was carried out using the complete case population. A logistic regression with a binary outcome of Weight loss at 16 weeks of ≥15% from baseline was fitted. The main covariate was randomised arm, with the model also being adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)
Number of subjects included in analysis	323
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.206
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	14.34

Statistical analysis title	32 week weight loss of ≥15% from baseline

Statistical analysis description:

This was carried out using the complete case population. A logistic regression with a binary outcome of Weight loss at 32 week of ≥15% from baseline was fitted. The main covariate was randomised arm, with the model also being adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.023
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.17
upper limit	8.9

Statistical analysis title	52 week Weight loss of ≥15% from baseline

Statistical analysis description:

N.B. This is the primary analysis of the primary outcome and is included again here for completeness of looking at this outcome over the different time points.

This analysis was carried out in the complete case population. A logistic regression model was fitted for the binary outcome of Weight loss at 52 weeks of ≥15% from baseline. The main covariate was randomised arm and the model was also adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Liraglutide 3mg (intervention) v Standard care (control group)
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.09
upper limit	12.88

Statistical analysis title	104 week Weight loss of ≥15% from baseline

Statistical analysis description:

This analysis was carried out in the complete case population. A logistic regression model was fitted for the binary outcome of Weight loss at 104 weeks of ≥15% from baseline. The main covariate was randomised arm and the model was also adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	18.93

Secondary: Absolute weight (kg) at 16 weeks

End point title	Absolute weight (kg) at 16 weeks

End point description:

End point type	Secondary

End point timeframe:

16 weeks

End point values	Standard care (control group)	Liraglutide 3mg (intervention)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	237		
Units: kg				
arithmetic mean (standard deviation)				
Baseline	125.31 (± 20.95)	127.49 (± 23.62)		
Follow-up	119.77 (± 20.61)	117.88 (± 23.20)		
Change from baseline	-5.54 (± 5.87)	-9.61 (± 5.38)		

Statistical analyses

Statistical analysis title	16 week absolute weight change from baseline

Statistical analysis description:

This analysis was carried out in the complete case population. A linear regression model was fitted for the outcome of absolute weight change from BL at 16 weeks (kg). The main covariate was randomised arm and the model was also adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)
Number of subjects included in analysis	323
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	-4.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.85
upper limit	-3.4

Secondary: Absolute weight (kg) at 32 weeks

End point title	Absolute weight (kg) at 32 weeks

End point description:

End point type	Secondary

End point timeframe:

32 weeks

End point values	Standard care (control group)	Liraglutide 3mg (intervention)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	208		
Units: kg				
arithmetic mean (standard deviation)				
Baseline	125.76 (± 20.61)	125.92 (± 23.21)		
Follow-up	120.06 (± 21.43)	114.64 (± 22.81)		
Change from baseline	-5.70 (± 7.16)	-11.27 (± 7.70)		

Statistical analyses

Statistical analysis title	32 week absolute weight change from baseline

Statistical analysis description:

This analysis was carried out in the complete case population. A linear regression model was fitted for

the outcome of absolute weight change from BL at 32 weeks (kg). The main covariate was randomised arm and the model was also adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Odds ratio (OR)
Point estimate	-5.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.76
upper limit	-4.02

Secondary: Absolute weight (kg) at 52 weeks

End point title	Absolute weight (kg) at 52 weeks

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Standard care (control group)	Liraglutide 3mg (intervention)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	201		
Units: kg				
arithmetic mean (standard deviation)				
Baseline	128.28 (± 20.66)	126.40 (± 23.57)		
Follow-up	125.07 (± 23.25)	116.25 (± 24.41)		
Change from baseline	-3.21 (± 8.66)	-10.15 (± 9.45)		

Statistical analyses

Statistical analysis title	52 week absolute weight change from baseline

Statistical analysis description:

This analysis was carried out in the complete case population. A linear regression model was fitted for the outcome of absolute weight change from BL at 52 weeks (kg). The main covariate was randomised arm and the model was also adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)

Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Odds ratio (OR)
Point estimate	-6.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.03
upper limit	-4.71

Secondary: Absolute weight (kg) at 104 weeks

End point title	Absolute weight (kg) at 104 weeks

End point description:

End point type	Secondary

End point timeframe:

104 weeks

End point values	Standard care (control group)	Liraglutide 3mg (intervention)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	132		
Units: kg				
arithmetic mean (standard deviation)				
Baseline	126.15 (± 19.95)	124.86 (± 23.80)		
Follow-up	124.89 (± 23.66)	118.35 (± 24.09)		
Change from baseline	-1.27 (± 10.30)	-6.51 (± 9.28)		

Statistical analyses

Statistical analysis title	104 week absolute weight change from baseline

Statistical analysis description:

This analysis was carried out in the complete case population. A linear regression model was fitted for the outcome of absolute weight change from BL at 104 weeks (kg). The main covariate was randomised arm and the model was also adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)

Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Odds ratio (OR)
Point estimate	-5.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.34
upper limit	-2.53

Secondary: Absolute BMI (kg/m2) at 104 weeks

End point title	Absolute BMI (kg/m2) at 104 weeks

End point description:

End point type	Secondary

End point timeframe:

104 weeks

End point values	Standard care (control group)	Liraglutide 3mg (intervention)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	132		
Units: kg/m2				
arithmetic mean (standard deviation)				
Baseline	43.73 (± 5.23)	44.90 (± 7.42)		
Follow-up	43.24 (± 6.78)	42.59 (± 7.99)		
Change from baseline	-0.49 (± 3.57)	-2.30 (± 3.29)		

Statistical analyses

Statistical analysis title	104 week absolute BMI change from baseline

Statistical analysis description:

This analysis was carried out in the complete case population. A linear regression model was fitted for the outcome of absolute BMI change from BL at 104 weeks. The main covariate was randomised arm and the model was also adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)

Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Odds ratio (OR)
Point estimate	-1.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.91
upper limit	-0.86

Secondary: Absolute change in waist circumference (cm) at 104 weeks

End point title	Absolute change in waist circumference (cm) at 104 weeks

End point description:

End point type	Secondary

End point timeframe:

104 weeks

End point values	Standard care (control group)	Liraglutide 3mg (intervention)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	101		
Units: centimetre				
arithmetic mean (standard deviation)				
Baseline	130.81 (± 11.72)	129.76 (± 14.16)		
Follow-up	129.89 (± 16.45)	132.34 (± 15.49)		
Change from baseline	-0.93 (± 12.54)	-6.42 (± 8.44)		

Statistical analyses

Statistical analysis title	104 week waist circumference change from baseline

Statistical analysis description:

This analysis was carried out in the complete case population. A linear regression model was fitted for the outcome of change in waist circumference from BL at 104 weeks (cm). The main covariate was randomised arm and the model was also adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)

Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Regression, Linear
Parameter estimate	Odds ratio (OR)
Point estimate	-5.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.09
upper limit	-1.94

Secondary: Weight loss of ≥5% from baseline (responder population)

End point title	Weight loss of ≥5% from baseline (responder population)
End point description: Responder population.	
End point type	Secondary
End point timeframe: 16, 32, 52 and 104 weeks	

End point values	Standard care (control group)	Liraglutide 3mg (intervention)	Standard care (control group)	Liraglutide 3mg (intervention)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	86[3]	54[4]	79[5]	53[6]
Units: number	34	54	34	53

Notes:
[3] - Responder population
[4] - Responder population
[5] - Responder population
[6] - Responder population

End point values	Standard care (control group)	Liraglutide 3mg (intervention)	Standard care (control group)	Liraglutide 3mg (intervention)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	93[7]	51[8]	61[9]	42[10]
Units: number	29	51	17	33

Notes:
[7] - Responder population
[8] - Responder population
[9] - Responder population
[10] - Responder population

Statistical analyses

Statistical analysis title	Responder popn week 104 weight loss of ≥5% from BL

Statistical analysis description:

This analysis was carried out in the responder population. A logistic regression model for the binary outcome of week 104 weight loss of ≥5% from BL was fitted. The covariate was randomised arm , with the model also being adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	10.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.83
upper limit	28.97

Secondary: Weight loss of ≥10% from baseline (responder population)

End point title	Weight loss of ≥10% from baseline (responder population)
End point description:	
Responder population.	
End point type	Secondary
End point timeframe:	
16, 32, 52 and 104 weeks	

End point values	Standard care (control group)	Liraglutide 3mg (intervention)	Standard care (control group)	Liraglutide 3mg (intervention)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	86[11]	54[12]	79[13]	53[14]
Units: number	9	34	14	53

Notes:

[11] - Responder population

[12] - Responder population

[13] - Responder population

[14] - Responder population

End point values	Standard care (control group)	Liraglutide 3mg (intervention)	Standard care (control group)	Liraglutide 3mg (intervention)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	93[15]	51[16]	61[17]	42[18]
Units: number	9	51	8	23

Notes:

[15] - Responder population

[16] - Responder population

[17] - Responder population

Statistical analyses

Statistical analysis title	Responder popn week 16 weight loss of ≥10% from BL

Statistical analysis description:

This analysis was carried out in the responder population. A logistic regression model for the binary outcome of week 16 weight loss of ≥10% from BL was fitted. The covariate was randomised arm , with the model also being adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	23.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.55
upper limit	70.67

Statistical analysis title	Responder popn week104 weight loss of ≥10% from BL

Statistical analysis description:

This analysis was carried out in the responder population. A logistic regression model for the binary outcome of week 104 weight loss of ≥10% from BL was fitted. The covariate was randomised arm , with the model also being adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	7.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.75
upper limit	21.6

Secondary: Weight loss of ≥15% from baseline (responder population)	
End point title	Weight loss of ≥15% from baseline (responder population)
End point description: Responder population.	
End point type	Secondary
End point timeframe: 16, 32, 52 and 104 weeks	

End point values	Standard care (control group)	Liraglutide 3mg (intervention)	Standard care (control group)	Liraglutide 3mg (intervention)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	86[19]	54[20]	79[21]	53[22]
Units: number	2	8	5	24

Notes:

[19] - Responder population

[20] - Responder population

[21] - Responder population

[22] - Responder population

End point values	Standard care (control group)	Liraglutide 3mg (intervention)	Standard care (control group)	Liraglutide 3mg (intervention)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	93[23]	51[24]	61[25]	42[26]
Units: number	6	51	2	12

Notes:

[23] - Responder population

[24] - Responder population

[25] - Responder population

[26] - Responder population

Statistical analyses

Statistical analysis title	Responder popn week 16 weight loss of ≥15% from BL

Statistical analysis description:

This analysis was carried out in the responder population. A logistic regression model for the binary outcome of week 104 weight loss of ≥15% from BL was fitted. The covariate was randomised arm , with the model also being adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	6.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.16
upper limit	32.32

Statistical analysis title	Responder popn week 32 weight loss of ≥15% from BL

Statistical analysis description:

This analysis was carried out in the responder population. A logistic regression model for the binary outcome of week 32 weight loss of ≥15% from BL was fitted. The covariate was randomised arm , with the model also being adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	11.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.8
upper limit	34.67

Statistical analysis title	Responder popn week104 weight loss of ≥15% from BL

Statistical analysis description:

This analysis was carried out in the responder population. A logistic regression model for the binary outcome of week 104 weight loss of ≥15% from BL was fitted. The covariate was randomised arm , with the model also being adjusted for the stratification variables: site and baseline body mass index (>45kg/m2; <45kg/m2).

Comparison groups	Standard care (control group) v Liraglutide 3mg (intervention)
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	13.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.47
upper limit	75.09

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded throughout the study (BL-Wk104) whether serious or not. Members of research team asked participants about AEs at each study visit and recorded these on AE/SAE logs and reported SAEs as per sponsor and regulatory requirements.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	2.0

Reporting groups

Reporting group title	Standard care (control group)

Reporting group description:

Participants in the control group will follow the best medical care provided by the Tier 3 service at their site. This typically involves dietary advice to reduce energy intake, accompanied by a physical activity programme, both supported by behavioural change techniques with regular professional contacts. The nature of the standard care will vary between the different Tier 3 services at each site, as this is a pragmatic 'real-world' study. Clinician input will include the medical assessment of participants for severe and complicated obesity and the prescription of anti-obesity drugs as per local Tier 3 service policy. Those patients taking antihypertensive or antidepressant medication will be assessed and it will be at the clinician's discretion as to whether these medications are changed. Participants will remain routinely in the Tier 3 service and may also be offered treatment options within the duration of the study, including bariatric surgery, in line with NICE guidance.

Reporting group title	Liraglutide 3mg (intervention)

Reporting group description:

Participants in the intervention group received the same standard care as those in the control group plus liraglutide 3mg was prescribed. Dose escalation of liraglutide occurred according to a pre-specified titration protocol, from 0.6mg to a maximum of 3.0mg daily. The liraglutide dose was initiated at 0.6mg and then increased to 1.2mg in Week 2, 1.8mg in Week 3, 2.4mg in Week 4, and 3.0mg in Week 5. Participants in the LIRA arm were made aware that continued use of LIRA 3mg was based upon their response to the treatment in terms of them achieving pre-defined weight loss targets at 16, 32 and 52 weeks. Stopping rule one: only those who had lost ≥5% of their baseline weight were offered further treatment with LIRA 3mg for another 16 weeks. Stopping rule two: only those who had lost ≥10% of their baseline weight were offered another 20 weeks. Stopping rule three: only those who had lost ≥15% of their baseline weight were offered another 52 weeks on LIRA 3mg.

Serious adverse events	Standard care (control group)	Liraglutide 3mg (intervention)	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 132 (8.33%)	47 / 260 (18.08%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm malignant	Additional description: Site unspecified.		
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			

Haemorrhage			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hernia repair			
subjects affected / exposed	0 / 132 (0.00%)	2 / 260 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nail operation	Additional description: therapeutic procedures		
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Therapeutic procedure			
subjects affected / exposed	0 / 132 (0.00%)	2 / 260 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Febrile infection			
subjects affected / exposed	1 / 132 (0.76%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain	Additional description: and discomfort		
subjects affected / exposed	0 / 132 (0.00%)	2 / 260 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Immune system disorders			
Anaphylactic reaction	Additional description: and anaphylactoid responses		
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vulvovaginal disorder			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm	Additional description: and obstruction.		
subjects affected / exposed	2 / 132 (1.52%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural infection	Additional description: and inflammation		
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary thrombosis	Additional description: thrombotic and embolic conditions		
subjects affected / exposed	1 / 132 (0.76%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Auscultation	Additional description: Cardiac auscultatory investigations		
subjects affected / exposed	1 / 132 (0.76%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Limb fracture			
subjects affected / exposed	1 / 132 (0.76%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle injury	Additional description: Tendon and ligament injuries.		
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury	Additional description: Non-site specific		
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Conduction disorder			
subjects affected / exposed	1 / 132 (0.76%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 132 (0.00%)	2 / 260 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis	Additional description: Noninfectious		
subjects affected / exposed	1 / 132 (0.76%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia supraventricular			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Transient cerebrovascular event			
subjects affected / exposed	1 / 132 (0.76%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis	Additional description: Acute and chronic.		
subjects affected / exposed	0 / 132 (0.00%)	2 / 260 (0.77%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal vascular occlusion and infarction			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatobiliary disorders			
Bile duct infections and inflammations			

subjects affected / exposed	0 / 132 (0.00%)	2 / 260 (0.77%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis	Additional description: and cholelithiasis		
subjects affected / exposed	0 / 132 (0.00%)	3 / 260 (1.15%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal lithiasis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Posterior pituitary disorder			
subjects affected / exposed	1 / 132 (0.76%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain	Additional description: Musculoskeletal and connective tissue pain and discomfort		
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue disorder			
subjects affected / exposed	0 / 132 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal infection			
subjects affected / exposed	3 / 132 (2.27%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Female reproductive tract disorder			

subjects affected / exposed	1 / 132 (0.76%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 132 (0.76%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 132 (0.76%)	2 / 260 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection	Additional description: and muscle infections.		
subjects affected / exposed	1 / 132 (0.76%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 132 (1.52%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 132 (0.00%)	3 / 260 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Standard care (control group)	Liraglutide 3mg (intervention)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	89 / 132 (67.42%)	238 / 260 (91.54%)	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 132 (1.52%)	38 / 260 (14.62%)	
occurrences (all)	2	49	
Neurological symptom			

subjects affected / exposed	6 / 132 (4.55%)	27 / 260 (10.38%)	
occurrences (all)	6	31	
General disorders and administration site conditions			
Asthenic conditions			
subjects affected / exposed	3 / 132 (2.27%)	30 / 260 (11.54%)	
occurrences (all)	3	32	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 132 (6.06%)	72 / 260 (27.69%)	
occurrences (all)	8	92	
Dyspepsia			
subjects affected / exposed	0 / 132 (0.00%)	38 / 260 (14.62%)	
occurrences (all)	0	44	
Flatulence			
subjects affected / exposed	0 / 132 (0.00%)	33 / 260 (12.69%)	
occurrences (all)	0	39	
Gastrointestinal pain			
subjects affected / exposed	5 / 132 (3.79%)	37 / 260 (14.23%)	
occurrences (all)	6	48	
Gastrointestinal hypomotility			
subjects affected / exposed	12 / 132 (9.09%)	93 / 260 (35.77%)	
occurrences (all)	12	117	
Nausea			
subjects affected / exposed	5 / 132 (3.79%)	109 / 260 (41.92%)	
occurrences (all)	5	183	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	15 / 132 (11.36%)	34 / 260 (13.08%)	
occurrences (all)	16	43	
Infections and infestations			
Ear infection			
subjects affected / exposed	10 / 132 (7.58%)	5 / 260 (1.92%)	
occurrences (all)	12	6	
Influenza			
subjects affected / exposed	5 / 132 (3.79%)	14 / 260 (5.38%)	
occurrences (all)	5	15	

Lower respiratory tract infection			
subjects affected / exposed	17 / 132 (12.88%)	41 / 260 (15.77%)	
occurrences (all)	22	63	
Upper respiratory tract infection			
subjects affected / exposed	8 / 132 (6.06%)	18 / 260 (6.92%)	
occurrences (all)	8	19	
Urinary tract infection			
subjects affected / exposed	5 / 132 (3.79%)	21 / 260 (8.08%)	
occurrences (all)	8	26	
Viral infection			
subjects affected / exposed	7 / 132 (5.30%)	36 / 260 (13.85%)	
occurrences (all)	8	41	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 March 2018	Changes made to management of sleep apnoea patients and tests. Removal of lipase blood test and exclusion criteria. Addition of lipase for confirming a suspected case of acute pancreatitis where amylase levels are normal, change to GLP-1 exclusion. Transfer responsibility for Trial Management and associated activities from the LCTU to the LDC. To add the use of Participant Identification Centre's (PIC) where applicable for recruitment purposes. Recruitment period error corrected to 'up to 24months' and '4-6 patients/month' to reflect the study contract with funder and the current REC approved LPLV timeframes which have not altered. Clarification to table visit windows (weeks vs no's) and visualisation of the titration profile for Appendix 3. Additional information given in the key. Administrative changes for clarity and to correct errors that do not alter the study procedures.
08 June 2018	(REC approved SA1-UK v3; HPRA non-acceptance (not approved) is addresses in this SA2-UK v4) Same as above clarifying concerns raised by HPRA in non-acceptance of SA1-UK.
07 January 2019	Change to the visit schedule to allow for some visits to be classified as optional. For participants in both arms of the study visits held at 2/52 (visit 3), 4/52 (visit 4), 12/52 (visit 6), 20/52 (visit 8), 40/52 (visit 10) and 78/52 (visit 12/13) will be defined as 'optional' to reduce study burden and maximise participant retention, as per the visit schedule (see Protocol, Appendix 3); Remove wording included in error following previous amendment sleep study capture in schedule, and Secondary Outcomes (see Protocol, Appendix 3; and Section 7.3; Clarification of reference ranges for TSH in terms of eligibility in the protocol to be amended to reflect the different normal ranges labs at each site used. This was highlighted at a recent monitoring visit where the 'normal' range stated in the protocol was different to that used in routine clinical assessment at site due the variable of local pathology laboratory reference ranges (see Protocol, Section 7.3); Update the exclusion criteria clarifying the time scale since weight loss procedures/surgery and the scope to allow for removal of gastric bands and gastric balloon whilst still be eligible for the study (see Protocol, Section 7.3). The consent form has been modified to include an extra question (question 3) surrounding lost to follow up and non attendance. This has been added as optional with yes or no boxes. Questions 8 and 10 have also been changed to optional yes or no boxes. Update to the current SmPC. Version 12/2016 will be replaced by version 06/2018.
20 February 2019	Change to add a legal representative in Ireland due to Brexit coming into force on 29th March 2019. Clinical trials legislation required that the sponsor or legal representative of the sponsor is established in the EU/EEA. Change of the legal representative for the Strive study from University of Leicester to the University College Dublin. Sponsor responsibilities will continue to reside with University of Leicester but the University College Dublin will act as the legal representative for the study in the EU/EEA.
26 March 2020	This was to update the recruitment target, which was increased from 384 to 392 and to update the recruitment end date which was amended from 31/12/2019 to 29/02/2020.

19 May 2020	As a result of the COVID19 global pandemic a risk assessment was conducted and an urgent safety measure was sent to the MHRA. The study team made several changes to the management and running of the trial due to the risks associated with face to face visits during the pandemic, in summary these include: provision of scales for participants to weigh themselves at home, adapted study drug deliveries/returns procedures, and virtual consultations via phone or video call. During this period the BP/HR measurements for those participants who do not have a home monitor and blood sampling for V11 and V13 visits will not be conducted. Addition of monetary incentive for all participants to aid retention, as suggested by the data monitoring safety committee (DMSC) and the trial steering committee (TSC). Extended the visit window for V11 primary end-point to support data collection; from+/- 14 days to +/- 3 months. QoL questionnaires to be issued to participants at an interim time point during the COVID19 pandemic. The study end date and recruitment target was amended in March 2020 as an NSA for all UK sites. Dublin site (IRE) requested that this be submitted as a substantial amendment so this has been added for IRE as part of this amendment (detailed in the IRE protocol).
29 January 2021	Update to the current SmPC. Version 5.0 will be replaced by version 10.0. The study end date has been updated from 30/04/2022 to 30/06/2022. Update to the details around COVID-19 in section 8.10.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Although the trial was not interrupted during COVID-19 we did issue an USM to the REC & MHRA during the pandemic to explain that certain aspects of the trial would not be possible, however measures were put in place to ensure participant safety.

Notes: