Effectiveness of integrating a pragmatic pathway for prescribing liraglutide 3.0 mg in weight management services (STRIVE study): a multicentre, open-label, parallel-group, randomized controlled trial

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Summary

Background An effective prescribing pathway for liraglutide 3 mg, an approved obesity pharmacotherapy, may improve treatment access. This trial compared a targeted prescribing pathway for liraglutide 3 mg with multiple stopping rules in specialist weight management services (SWMS) to standard SWMS care.

Methods This phase four, two-year, multicentre, open-label, parallel-group, real-world randomized clinical trial (ClinicalTrials.gov: NCT03036800) enrolled adults with BMI ≥35 kg/m^2 plus prediabetes, type 2 diabetes, hypertension or sleep apnoea from five SWMS in Ireland and UK. Participants were randomly allocated (2:1, stratified by centre and BMI) to SWMS care plus a targeted prescribing pathway for once daily subcutaneous liraglutide 3 mg (intervention) with stopping rules at 16 (≥5% weight loss, WL), 32 (≥10% WL) and 52 weeks (≥15% WL) or to SWMS care alone (control) through an online randomization service. The primary outcome was WL ≥15% at 52 weeks, assessed by complete cases analysis. All randomized participants were included in safety analysis.

Findings From November 28, 2017 to February 28, 2020, 434 participants were screened, and 392 randomized (260 intervention; 132 control), while 294 (201 intervention; 93 control) included in the 52 weeks complete case analysis. More intervention than control participants achieved WL ≥15% at 52 weeks [51/201 (25.4%) vs 6/93 (6.5%); odds ratio 5.18; 95% CI 2.09, 12.88; p < 0.0001]. More adverse events occurred in the intervention (238/260, 91.5%; two deaths) than control (89/132, 67.4%; no deaths) group.

Interpretation A targeted prescribing pathway for liraglutide 3 mg helps more people achieve ≥15% WL at 52 weeks than standard care alone.

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Keywords: Specialist weight management services; Obesity; Liraglutide 3 mg; Multiple stopping rules; Targeted prescribing pathway

Research in context

Evidence before this study

In the UK and Ireland, specialist weight management services (SWMS) can offer intensive lifestyle interventions and/or obesity pharmacotherapy for people with BMI ≥35 kg/m^2 and obesity-related complications. Liraglutide 3 mg is an approved obesity pharmacotherapy with proven efficacy and safety, but there is heterogeneity in treatment response. To ensure treatment is not continued in those who do not respond and to optimise the benefit: risk ratio from medication use, the license specifies that liraglutide 3 mg should be stopped in those with less than 5% weight loss (WL) at 16 weeks. However, the clinical effectiveness of liraglutide 3 mg in SWMS has not been assessed and even with the 5% WL stopping rule, the cost of the medication is precluding its routine long-term use for many patients presenting to SWMS. Developing a clinically effective prescribing pathway for liraglutide 3 mg to target the long-term medication use to people with obesity who achieve ≥15% WL with medication, may optimise the cost-effectiveness and improve access to this treatment.

We searched the PubMed on 7th of May 2023 for articles published from January 1, 2010 to May 7, 2023, with no language restrictions, using the terms "obesity" and "liraglutide" and "randomized controlled trial". We found 214 articles assessing liraglutide treatment, including 18 randomized controlled trials (RCTs) that evaluated liraglutide 3 mg for weight management. A retrospective analysis of the SCALE-Obesity and Prediabetes and SCALE-Diabetes found that the application of a single stopping rule of 4% WL at 16 weeks, is a good predictor of long-term WL. Based on this single stopping rule, 62%–77% of people with obesity would be suitable to continue using liraglutide 3 mg, but only 9%–21% of those who achieved ≥4% WL at 16 weeks managed ≥15% WL at 52 weeks, suggesting a potential role for additional stopping rules at other time points to optimise medication use. Currently, there is lack of pragmatic, multicentre studies assessing the clinical effectiveness of liraglutide 3 mg in conjunction with SWMS programmes, when multiple stopping rules are applied prospectively.

Added value of this study

This study provides important data on the clinical effectiveness of a targeted prescribing pathway for liraglutide 3 mg with multiple prespecified stopping rules (≥5% WL at 16 weeks, ≥10% WL at 32 weeks and ≥15% WL at 52 weeks) for management of obesity in SWMS. Around one fifth of participants randomized to the intervention group passed all the three stopping rules and continued the second year with liraglutide 3 mg. The use of a targeted prescribing pathway for liraglutide 3 mg in SWMS settings resulted in more people achieving ≥15% WL at 52 weeks compared to standard SWMS care alone—from those achieved ≥15% WL at 52 weeks in the intervention group, more than half maintained ≥10% WL at 104 weeks. The results also showed improvements in cardiometabolic risk factors (waist circumference and glycaemia) and in some quality-of-life measures, without new safety signals.

Implications of all the available evidence

STRIVE is the first multicentre clinical trial to show that people with obesity can benefit from a targeted prescribing pathway for liraglutide 3 mg with multiple prespecified stopping rules. The mean WL achieved with the targeted prescribing pathway at 52 weeks was similar to that seen at the liraglutide 3 mg arm in SCALE-Obesity and Prediabetes trial, however, in STRIVE trial this amount of WL was achieved with less people being on liraglutide 3 mg at the end of the first year. This targeted prescribing pathway is consistent with the concept of personalised medicine and may help to optimise the cost-effectiveness of liraglutide 3 mg use.

Introduction

Obesity is a chronic, progressive and relapsing disease.[1] People with BMI ≥35 kg/m^2 represent around 10% of the UK population and are at higher risk of developing obesity-related complications such as prediabetes, type 2 diabetes (T2D), hypertension and obstructive sleep apnoea (OSA).[2]

In the UK and Ireland, specialist weight management services (SWMS) offer the option of intensive lifestyle interventions and/or adjunctive obesity pharmacotherapy in people with BMI ≥35 kg/m^2 and obesity-related complications.[3]

Lifestyle interventions commonly result in 3–5% mean weight loss (WL),[3–5] and even the most intensive lifestyle programmes (involving periods of formula-diet partial meal replacement or total diet replacement) can achieve up to 10% mean WL at 12 months, however maintaining meaningful WL long-term is challenging.[6–9] Although 5–10% WL improves multiple cardiometabolic risk factors, it may not be enough to reverse obesity-related complications such as sleep apnoea and T2D.[10] Approved obesity pharmacotherapies such as liraglutide 3 mg, a glucagon-like peptide-1 receptor agonist

(GLP-1 RA), can be useful adjuncts to lifestyle interventions to support WL ≥10% and even ≥15% and maintenance.[11–14]

The data from clinical trials on WL with liraglutide 3 mg are robust, but its clinical effectiveness in SWMS settings has not been assessed.[11,14,15] Based on a cost-effectiveness analysis, the National Institute for Health and Care Excellence (NICE) approved the use of liraglutide 3 mg in SWMS in December 2020 for people with BMI ≥35 kg/m^2, prediabetes and high cardiovascular risk, with a single stopping rule of ≥5% WL at 16 weeks.[16,17] However, people presented to SWMS with obesity-related complications and normoglycaemia or T2D are not currently eligible for liraglutide 3 mg based on NICE criteria, despite that there is strong evidence from clinical trials that a significant proportion of them can achieve substantial WL (e.g., ≥15% WL) with the medication and subsequent health improvements.[11,14,18] A different, pragmatic and personalised approach is needed in order the long-term liraglutide 3 mg use to be directed to those who will benefit most from it.

Clinical trials with lifestyle interventions as well as with liraglutide 3 mg use demonstrate that greater improvements in obesity-related complications and quality of life occur with greater WL, with maximum benefits observed with these interventions at ≥15% WL.[18–21] Additionally, from the people on liraglutide 3 mg who will pass the ≥5% WL stopping rule at 16 weeks, only 9–21% are expected to achieve ≥15% WL at 52 weeks, suggesting a potential role for additional stopping rules at other time points to optimise further medication use and cost.[16] Hence, the development of a clinically effective prescribing pathway aiming to support people achieving ≥15% WL and at the same time optimise the cost of the medication may improve access to this treatment for people who would likely benefit most from it.

We therefore conducted an open label, real world, randomized controlled trial (RCT) to investigate the clinical effectiveness at 52 and 104 weeks of a targeted prescribing pathway for liraglutide 3 mg with multiple stopping rules (striving to achieve ≥15% WL) as adjunct to standard care in SWMS vs standard SWMS care alone.

Methods

Trial design and participants

The STRIVE study (NCT03036800) was an investigator initiated, two-year, multicentre, open-label, parallel, two group, real-world, pragmatic RCT. Participants were recruited from five SWMS (Dublin, Glasgow, Leicester, Liverpool, and London) with the trial duration of being 104 weeks. Approval for the protocol was obtained from the Medicines and Healthcare products Regulatory Agency (UK Competent authority) and from the Health Products Regulatory Authority (Irish Competent Authority). The study was approved by the Health Research Authority (HRA) and ethical approval as a Clinical Trial of an Investigational Medicinal Product was granted by the North West National Research Ethics Service committee (17/NW/0517) in the UK and by the St Vincent's University Hospital European Research Ethics Committee (2017-002998-20) in Ireland. All trial participants provided written informed consent prior to participation. The study protocol and planned data analysis are published and the latest version of the protocol as well as the statistical analysis plan (SAP) are included with the Supplementary material.[22]

Main inclusion criteria were adults aged 18–75 years who have been referred to SWMS, with stable body weight (<5 kg self-reported weight change over the last 12 weeks) and BMI ≥35 kg/m^2 plus at least one of prediabetes, T2D (being treated with any combination of lifestyle, metformin, sulphonylureas, thiazolidinediones or sodium glucose co-transporters-2), hypertension or OSA.

Key exclusion criteria included type 1 diabetes, T2D treated with insulin, dipeptidyl peptidase-4 inhibitor or GLP-1 RA within the last 6 months, estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73 m^2 over the last 26 weeks, being on obesity pharmacotherapy within 12 weeks prior to randomization and having a history of pancreatitis. Full eligibility criteria can be found at the Supplementary material (protocol and Appendix 1).

Randomisation and masking

Eligible participants were randomly assigned in a 2:1 ratio to a targeted prescribing pathway for liraglutide 3 mg (intervention group) or standard SWMS care alone (control group, Fig. 1), through a validated online system (sealedenvelope.com). Randomisation was stratified by centre and BMI (≥45 kg/m^2; <45 kg/m^2) using random permutated blocks. The study was open-label and participants were informed of the group assignment at baseline. The allocation sequence was generated by sealedenvelope.com ensuring concealment of sequence until randomization performed. Participants were enrolled from the research study team at each site. Randomisation and assignment was done by a delegated member of the study team in each research site.

Control group (standard SWMS care)

A SWMS typically includes a clinician-led multidisciplinary team approach, potentially including a specialist physician, dietitian, nurse, psychologist and physiotherapist. The nature of the standard care in STRIVE study varied between the different sites, as this was a pragmatic real-world study. Participants in the control group followed the best medical practice at the relevant site, typically involving individualized dietary advice to reduce energy intake (that may include a period using formula-diet meal replacement or total diet replacement), accompanied, if available, by a physical activity support programme. Clinician input included the medical assessment of participants, the review of antihypertensive and

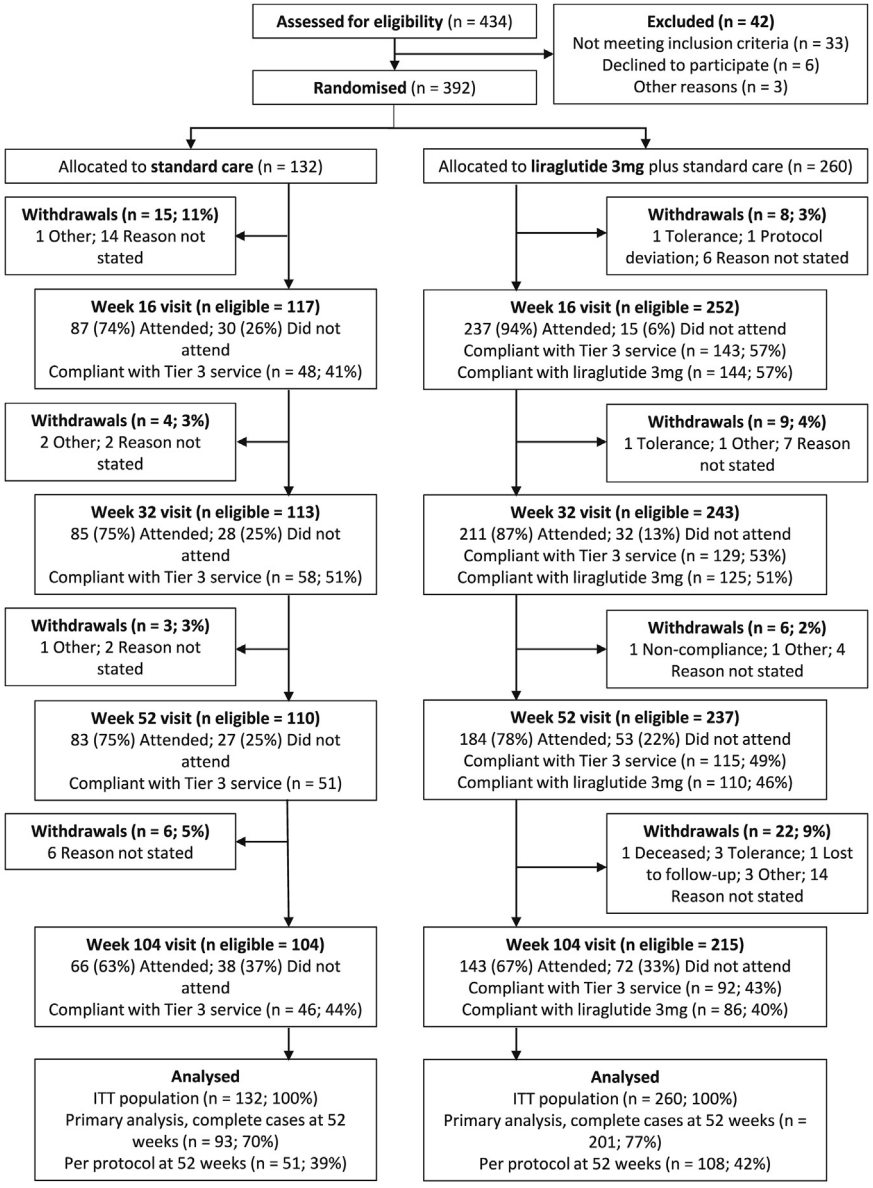

Fig. 1: **Trial profile**.

antidepressant medications and the prescription of obesity pharmacotherapy (i.e., orlistat) at the clinicians' discretion as per local SWMS policy. Participants remained at the SWMS in line with NICE guidance. Participants could be offered treatment options within the duration of the study (including bariatric surgery) according to NICE guidance and the discretion of the local team.

Intervention group (targeted prescribing pathway plus standard care)

Participants in the intervention arm received the same standard care as those in the control arm (i.e., the best medical practice delivered by each site). Additionally, at baseline, liraglutide 3 mg prefilled pens were prescribed to all participants in the intervention arm. Participants were asked to initiate with 0.6 mg dose once daily for the first week and then, in accordance with the summary of product characteristics (SPC), there was gradual dose escalation to an obligatory maximum of 3 mg daily; participants who withdrawn from liraglutide 3 mg use due to inability to tolerate the maximum dose or due to adverse events were offered standard care.

Participants at the intervention arm were informed before initiating liraglutide 3 mg about the multiple prespecified stopping rules and the respective WL thresholds at the different time points (≥5% WL at 16

weeks, ≥10% WL at 32 weeks and ≥15% WL at 52 weeks, Fig. 2). Patients were prescribed liraglutide 3 mg for the duration of the study, unless they did not meet the prespecified WL targets. Participants who did not reach the WL thresholds were also offered standard care.

Outcomes

The primary outcome was the proportion (%) of participants achieving ≥15% WL at 52 weeks with the standard care alone vs a targeted prescribing pathway for liraglutide 3 mg. Prespecified secondary outcomes included weight parameters (mean %WL, mean BMI change, ≥5% WL, ≥10% WL, ≥15% WL), cardiometabolic risk factors (HbA1c, blood pressure, lipids, waist circumference), obesity-related complications (including measures related to glycaemic status, hypertension, dyslipidaemia, OSA), use of medications and quality of life related outcomes at baseline, 52 and 104 weeks (see protocol for full list). Moreover, adherence to SWMS and safety, tolerability and adherence to liraglutide 3 mg were also assessed (Supplementary material, Appendix 2).

Quality of life was assessed by the Euro-QoL-5 Dimensions (EQ-5D) questionnaire and the weight-specific impact of weight on quality of life-lite questionnaire (IWQoL-Lite) at baseline, 52 and 104 weeks. The patient health questionnaire-9 (PHQ-9) measured symptoms of depression. Self-reported physical activity (PA) was evaluated with the short-form of the International Physical Activity Questionnaire (IPAQ). Safety assessments included the number of adverse and serious adverse events.

"Responders" to the intervention was the subgroup of people in the intervention arm who achieved ≥15% WL at the end of the first 52 weeks. Weight loss at 104 weeks for the "responders" group was a secondary outcome.

Weight was measured at baseline and during prespecified time points using calibrated scales.

Changes to the protocol related to primary outcome

All the changes occurred to the protocol can be found at the Supplementary material (Appendix 3).

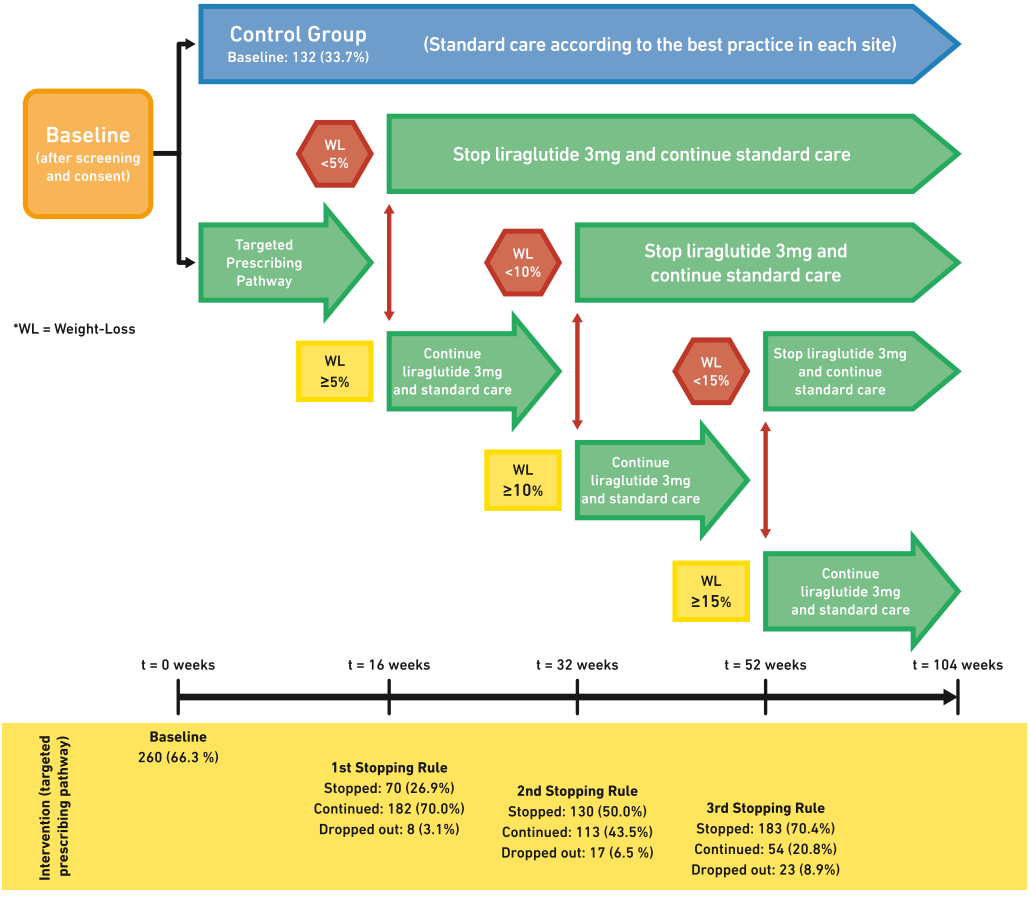

Fig. 2: **Trial design and proportion of participants who passed each stopping rule at the intervention group.**

In response to the COVID-19 pandemic, the following main changes occurred to the protocol for safety reasons and to support data collection for the primary outcome:

1. The visit window for the 52-week visit extended from ±14 days to ±3 months.
2. For participants who were unable to attend face to face the 52-week visit, weight was alternatively obtained during visit window:
   i) by asking participants to weigh themselves at home during a virtual appointment on calibrated scales provided by the study team or
   ii) by extracting the weight record (if available) from routinely collected data such as electronic health records, if participants did not attend neither a virtual or face to face appointment for the 52 weeks visit.

There were 13 participants (14% of complete cases) in the control group and 21 (10.5% of complete cases) in the intervention group from whom routinely collected weight data was used for the primary outcome.

Statistical analysis

It was anticipated that, at 52 weeks, approximately 5% of the standard care participants would achieve ≥15% WL.[11,12] An achievable target for ≥15% WL at 52 weeks in intervention group was 16%.[11,12] Accounting for 25% drop out, 80% power, 5% alpha and 2:1 randomisation, 384 participants (256 intervention; 128 control) needed to be recruited to detect a significant difference between the groups in participants achieving ≥15% WL at 52 weeks. The original recruitment target of 384 participants was increased to 392 (261 intervention; 131 control) based on advice from the Data Safety and Monitoring Committee (DSMC) and Trial Steering Committee (TSC) due to the amount of participant dropouts at the time (Supplementary material, Appendix 3, protocol amendment in March 2020).

The primary analysis compared the proportion of participants achieving ≥15% WL at 52 weeks (primary outcome) between the study arms using a logistic regression model with adjustment for stratification factors (site and baseline BMI) in the complete case population (all randomised participants with data available for the analysed outcome and excluding those who had had bariatric surgery). Missing data were not imputed for the complete cases analysis.

Secondary analyses of the primary outcome were based on intention-to-treat (ITT, all randomized participants in the study) and per-protocol (all randomized participants deemed compliant with their treatment group, see definition at Supplementary material, Appendix 4) populations. As an exploratory post-hoc analysis, an inverse probability weighted (IPW) analysis was conducted with the weights based on factors that may impact missingness of the primary outcome, defined as randomization arm plus factors found to be significantly different at the 10% level between the two randomization arms in terms of whether the primary outcome was missing (age, ethnicity, heart rate).

Secondary outcomes measured at 52 and 104 weeks were analysed based on the complete cases population. Due to the large number of secondary outcomes, it was pre-planned in the SAP that statistical models were only fitted for the secondary anthropometric outcomes to limit the impact of multiple testing.

In all analyses, participants were analysed within the treatment arm to which they were allocated at baseline.

Binary anthropometric outcomes were analysed using logistic regression models and continuous anthropometric outcomes were compared using linear regression models. Additionally, a "responder" analysis was performed, which repeated the analyses of the anthropometric outcomes with the intervention group restricted to participants who achieved ≥15% WL at 52 weeks. Descriptive summaries were produced for the other secondary outcomes without statistical testing. Data on treatment adherence and safety were also summarised and tabulated. The safety analysis population included all participants who randomised into the trial (Supplementary material, Appendix 4).

A DSMC and TSC reviewed the study approximately every six months. As specified at the SAP, there was no blinding of the statisticians. The (unblinded) trial statistician (SB) was responsible for drafting the initial version of the SAP and subsequently preparing reports to the oversight committees for the duration of the trial. The first version of the SAP was approved on July 12, 2022 and the final version of the SAP (August 1, 2022) was signed as complete prior to database lock and release of the data for statistical analysis. The statistician who conducted the statistical analysis for the final report (DHB) had not been involved or unblinded to the data presented in reports to the oversight committees (SB: validated the final statistical analysis).

The trial conducted according to University of Leicester sponsor standard operating procedures (SOPs) (https://le.ac.uk/research/regi/standard-operating-procedures).

All analyses were conducted in STATA v17.0.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. After data lock, the corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between November 28, 2017 and February 28, 2020, 434 potential participants were assessed for eligibility

(Fig. 1) and a total of 392 participants enrolled to the study and randomly assigned to the targeted prescribing pathway with liraglutide 3 mg (n = 260) or the control group (n = 132)—these 392 participants comprised the full analysis set. The last patient last visit was February 25, 2022 and the trial ended as planned. After exclusion of individuals without primary outcome data, a total of 294 (75%) out of 392 participants [n = 201 (77.3%) in the intervention arm and n = 93 (70.5%) in the control arm] were included in the complete cases analysis for the primary outcome at 52 weeks. There was no difference in baseline characteristics at the 5% level between participants with and without primary outcome data (Supplementary material, Supplementary Tables S1 and S2).

Most participants were white (86.5%) and female (64.3%). Mean age (standard deviation, SD) was 51.3 years (10.8), mean weight was 128.4 kg (24.1) and mean BMI was 46.0 kg/m^2 (7.6), with 35.4% of participants having T2D, 15.8% prediabetes, 63.8% hypertension and 49% sleep apnoea. Baseline characteristics were balanced across groups (Table 1).

From the 260 people randomized to the intervention group, 182 (70%) passed the 1st stopping rule at 16 weeks, 113 (43.5%) passed also the second stopping rule at 32 weeks and 54 (20.8%) passed all the three stopping rules at 52 weeks (Fig. 2). A small number of people (n = 3 out of 54) in the intervention arm who were marked as having passed the 15% WL stopping rule, did not actually achieve ≥15% WL at 52 weeks (WL was 14.6%, 14.1% and 12% respectively for these individuals) and were not eligible for the "responder" population analysis (Supplementary material, Supplementary Table S3).

The primary analysis of the primary outcome (complete cases analysis), demonstrates that 25.4% (51 out of 201) of participants at the intervention group achieved ≥15% WL compared with 6.5% (6 out of 93) in the control group at 52 weeks (OR = 5.2; 95% CI = 2.1, 12.9; p < 0.0001, Table 2, Fig. 3). The results of the sensitivity analyses (ITT, per protocol, and IPW-adjusted) for the primary outcome were consistent with the complete cases analysis (Table 2).

Mean (SD) percentage of WL at 52 weeks was 8.1% (7.2) in the intervention and 2.7% (6.8) in the control group [estimated treatment difference (ETD) −5.4 (95% CI −7.0, −3.7), p < 0.0001]. The intervention group was superior to the control group for ≥5% and ≥10% WL at 16, 32 (Supplementary material, Supplementary Table S4) and 52 weeks (Table 2, Fig. 3).

At 104 weeks, the mean (SD) percentage of WL for the intervention group was −5.2% (7.5) compared to −1.2% (8.2) in the control group [ETD of −4.1 (95% CI, −6.4 to −1.8), p < 0.0001]. People in the intervention were more likely to achieve ≥5% WL compared to controls (47.0% vs 27.9%, OR = 2.4; 95% CI = 1.2, 4.8; p = 0.010) at 104 weeks, but there was no difference between groups for ≥10% (24.2% vs 13.1%, p = 0.065) and ≥15% WL (11.4% vs 3.3%, p = 0.07, Table 2, Fig. 3).

Mean BMI and waist circumference were reduced more in the intervention vs control group at 52 and 104 weeks (Table 2).

The "responders" group lost 17.2% (2.4) of initial bodyweight at 52 weeks (n = 51) and 11.0% (6.7) at 104 weeks (n = 42, Fig. 4). At 104 weeks, 78.6% (33 out of 42) of the "responders" maintained ≥5% WL, 54.8% (23 out of 42) maintained ≥10% WL and 28.6% (12 out of 42) maintained ≥15% WL (p ≤ 0.003 for all the comparisons with the control group, Fig. 4, Supplementary material, Supplementary Tables S5 and S6).

As per SAP, no statistical comparisons were planned for the rest of secondary outcomes. Instead, descriptive analyses were performed to explore potential patterns in improvements and these descriptive analyses are presented in the rest of the Results section. For completeness, exploratory ad hoc between group analyses are also presented in Table 3 (difference in change from baseline between groups and p-values).

HbA1c decreased by 6.6 mmol/mol (−0.6%) and 6.0 mmol/mol (−0.6%) respectively at 52 and 104 weeks in the intervention group, while there was minimal change from baseline for controls (Table 3). The number of diabetes agents was similar at baseline for both groups, with small changes at 52 and 104 weeks for both groups.

For people with T2D at baseline, HbA1c improved in the intervention group by 12.6 mmol/mol (−1.2%) and 10.5 mmol/mol (−1.0%) at 52 and 104 weeks respectively, while there were minimal changes from baseline in the control group (Supplementary material, Supplementary Tables S7 and S8). A numerically greater proportion of participants with diabetes achieved HbA1c ≤53 mmol/mol (7%) at the intervention group at 52 and 104 weeks compared to controls (Supplementary material, Supplementary Table S9). Similarly, in people with prediabetes at baseline, there was a reduction of 3.5 mmol/mol (−0.3%) at 52 weeks in the intervention group compared to −0.1 mmol/mol (−0.0%) in the controls (Supplementary material, Supplementary Table S8).

Systolic and diastolic blood pressure (BP) improved for both groups and the absolute systolic and diastolic BP values were similar between the groups both at 52 and 104 weeks (Table 3). More antihypertensive agents were added in the control compared to the intervention group (Table 3). In lipids, there were minimal changes at 52 and 104 weeks for both groups, with a trend towards improved triglycerides in the intervention arm (Table 3). Minimal changes were also observed in lipid-lowering therapies in both groups during the study.

The total IWQoL-Lite score improved at 52 weeks in both groups, with a greater improvement in the intervention group (Table 3). However, at 104 weeks the total IWQoL-Lite declined below baseline levels in both groups (Table 3). The EQ5D visual analogue scale (VAS) improved

Characteristic	Missing values (total)	Control (n = 132)	Intervention (n = 260)	Total (n = 392)
Age, years	0	51.8 ± 10.8	51.1 ± 10.8	51.3 ± 10.8
Gender	0			
Male		53 (40.2)	87 (33.5)	140 (35.7)
Female		79 (59.9)	173 (66.5)	252 (64.3)
Ethnicity	0			
White		114 (86.4)	225 (86.5)	339 (86.5)
Black		11 (8.3)	13 (5.0)	24 (6.1)
South Asian		3 (2.3)	11 (4.2)	14 (3.6)
Mixed/Other		4 (3.0)	11 (4.2)	15 (3.8)
Body weight, kg	0	127.1 ± 21.4	129.0 ± 25.3	128.4 ± 24.1
BMI, kg/m^2	1	45.5 ± 7.3	46.2 ± 7.8	46.0 ± 7.6
BMI ≥ 40 kg/m^2	0	106 (80.3)	207 (79.6)	313 (79.9)
Waist circumference, cm	2	131.8 ± 13.0	132.4 ± 15.6	132.2 ± 14.7
HbA1c, mmol/mol	3	44.7 ± 10.8	46.1 ± 13.7	45.6 ± 12.8
HbA1c, %	3	6.2 ± 1.0	6.4 ± 1.3	6.3 ± 1.2
Glycaemic status	3			
Normoglycaemia		66 (50)	110 (42.3)	176 (44.9)
Prediabetes		20 (15.2)	42 (16.2)	62 (15.8)
T2D remission[a]		3 (2.3)	9 (3.5)	12 (3.1)
T2D		41 (31.1)	98 (37.7)	139 (35.5)
Number of diabetes medications[b]	–			
Does not have diabetes		91 (68.9)	162 (62.3)	253 (64.5)
0		12 (9.1)	35 (13.5)	47 (12.0)
1		22 (16.7)	52 (20.0)	74 (18.9)
2		6 (4.6)	9 (3.5)	15 (3.8)
≥3		1 (0.8)	2 (0.8)	3 (0.8)
Type of diabetes medications[c]	–			
Metformin		28 (68.3)	59 (60.2)	87 (62.6)
Sulphonylureas		1 (2.4)	5 (5.1)	6 (4.3)
Glitazones		1 (2.4)	1 (1.0)	2 (1.4)
SGLT-2 inhibitors		4 (9.8)	6 (6.1)	10 (7.2)
Sleep apnoea	33	68 (51.5)	124 (47.7)	192 (49.0)
Systolic blood pressure, mmHg	1	138.1 ± 17.8	135.8 ± 18.3	136.6 ± 18.1
Diastolic blood pressure, mmHg	1	82.0 ± 12.0	81.4 ± 10.9	81.6 ± 11.3
Hypertension	2	88 (66.7)	162 (62.3)	250 (63.8)
Number of antihypertensive medications, n (%)[b]	–			
Does not have hypertension		44 (33.3)	98 (37.7)	142 (36.2)
0		24 (18.2)	44 (16.9)	68 (17.4)
1		25 (18.9)	55 (21.2)	80 (20.4)
2		22 (16.7)	33 (12.7)	55 (14.0)
≥3		17 (12.9)	30 (11.5)	47 (12.0)
Triglycerides, mmol/L	4	1.9 ± 0.9	1.9 ± 0.9	1.9 ± 0.9
HDL, mmol/L	3	1.3 ± 0.6	1.2 ± 0.3	1.2 ± 0.4
Total cholesterol, mmol/L	2	4.7 ± 1.0	4.8 ± 1.0	4.8 ± 1.0
LDL, mmol/L	13	2.7 ± 0.8	2.7 ± 0.8	2.7 ± 0.8
Statin use[b]	–	31 (23.5)	70 (26.9)	101 (25.8)
Total number of medications[b]	–			
0		30 (22.7)	55 (21.2)	85 (21.7)
1		11 (8.3)	24 (9.2)	35 (8.9)
2		17 (12.9)	17 (6.5)	34 (8.7)
3		9 (6.8)	32 (12.3)	41 (10.5)
4		7 (5.3)	24 (9.2)	31 (7.9)
≥5		58 (43.9)	108 (41.5)	166 (42.4)

(Table 1 continues on next page)

Characteristic	Missing values (total)	Control (n = 132)	Intervention (n = 260)	Total (n = 392)
(Continued from previous page)				
EQ-5D VAS score	12	63.5 ± 20.6	60.8 ± 22.0	61.7 ± 21.5
IWQoL-Lite score	8	34.6 ± 15.6	32.1 ± 16.3	32.9 ± 16.1
Total MET-minutes/week	34	5463.5 ± 7958.6	5246.8 ± 7145.6	5318.2 ± 7412.9

Values are mean ± standard deviation or n (%), BMI: Body Mass Index, HbA1c: glycated haemoglobin, T2D: type 2 diabetes, SGLT-2: sodium glucose co-transporters–2, HDL: High density lipoprotein, LDL: Low density lipoprotein, EQ-5D VAS: Euro-QoL-5 Dimensions Visual Analogue Scale, IWQoL-Lite: impact of weight on quality of life-lite questionnaire, MET: metabolic equivalent of task. [a]Diabetes remission at baseline was defined as HbA1C < 6.5%, not on glucose lowering medication, but with medical history of diabetes. [b]No missing data by definition, i.e., missing values were assumed to be zero medications. [c]Percentages are reported for people with diabetes at baseline (41 people at control group, 98 at intervention, 139 in total). Numbers on individual medications sum to more than the total number on diabetes medications because an individual may be using multiple diabetes medications.

Table 1: **Baseline characteristics for the intention-to-treat population.**

in the intervention group at 52 weeks, but not at 104 weeks (Table 3). There was a greater numerical improvement for all the EQ5D subscales in the intervention than control group both at 52 and 104 weeks (Supplementary material, Supplementary Table S10). The PHQ-9 scores improved numerically in the intervention group at weeks 52 and 104 (Supplementary material, Supplementary Table S10).

At 52 weeks, the total mean metabolic equivalent of task (MET, min/week) increased in both groups by approximately 23% compared to baseline. However, at

	Control		Intervention		Adjusted treatment effect (95% CI)[c]	p-value
	N analysed	N (%) or Mean ± SD	N analysed	N (%) or Mean ± SD		
Weight loss ≥15% (primary outcome)						
52 weeks[b] (Complete case)	93	6 (6.5)	201	51 (25.4)	OR: 5.2 (2.1, 12.9)	<0.0001
52 weeks (ITT)	132	6 (4.6)	260	55 (21.2)[d]	OR: 5.9 (2.5, 14.4)	<0.0001
52 weeks (Per protocol)	51	5 (9.8)	108	40 (37.0)	OR: 5.0 (1.8, 14.0)	0.002
52 weeks (IPW-adjusted)	93	6 (6.5)	201	51 (25.4)	OR: 6.3 (2.4, 16.5)	<0.0001
104 weeks	61	2 (3.3)	132	15 (11.4)	OR: 4.1 (0.9, 18.9)	0.070
Weight loss ≥10%						
52 weeks	93	9 (9.7)	201	90 (44.8)	OR: 8.1 (3.8, 17.2)	<0.0001
104 weeks	61	8 (13.1)	132	32 (24.2)	OR: 2.3 (1.0, 5.5)	0.065
Weight loss ≥5%						
52 weeks	93	29 (31.2)	201	127 (63.2)	OR 4.2 (2.4, 7.2)	<0.0001
104 weeks	61	17 (27.9)	132	62 (47.0)	OR 2.4 (1.2, 4.8)	0.010
Change in weight (% WL)						
52 weeks	93	−2.7 ± 6.8	201	−8.1 ± 7.2	ETD: −5.4 (−7.0, −3.7)	<0.0001
104 weeks	61	−1.2 ± 8.2	132	−5.2 ± 7.5	ETD: −4.1 (−6.4, −1.8)	0.0001
Body mass index (kg/m^2)						
52 weeks	80	43.3 ± 6.4	180	41.4 ± 7.6	–	–
104 weeks	61	43.2 ± 6.8	132	42.6 ± 8.0	–	–
Change in body mass index (kg/m^2)						
52 weeks	80	−1.2 ± 2.8	180	−3.8 ± 3.3	ETD: −2.7 (−3.5, −1.9)	<0.0001
104 weeks	61	−0.5 ± 3.6	132	−2.3 ± 3.3	ETD: −1.9 (−2.9, −0.9)	<0.0001
Waist circumference (cm)						
52 weeks	58	126.0 ± 13.8	137	121.7 ± 14.2	–	–
104 weeks	48	129.9 ± 16.5	101	123.3 ± 15.5	–	–
Change in waist circumference (cm)						
52 weeks	58	−5.6 ± 8.5	137	−8.9 ± 7.9 (n = 137)	ETD: −3.3 (−5.8, −0.8)	0.010
104 weeks	48	−0.9 ± 12.5	101	−6.4 ± 8.4 (n = 101)	ETD: −5.5 (−9.1, −1.9)	0.003

CI: Confidence Interval; ETD: Estimated Treatment Difference; IPW, Inverse Probability Weighting; ITT, Intention To Treat; OR: Odds Ratio; SD, Standard Deviation. [a]All analyses are conducted in the complete case population, unless otherwise specified. [b]Primary analysis (complete case) of primary outcome. [c]Estimates are adjusted for the stratification variables: site and baseline body mass index (≥45 kg/m^2; <45 kg/m^2). [d]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.

Table 2: **Key outcomes (primary outcome, sensitivity analysis of primary outcome and confirmatory secondary endpoints) at 52 and 104 weeks.**[a]

104 weeks, the total MET reduced in the control group compared to baseline, when at the intervention group the total MET increased further (Table 3).

Approximately 90% of participants in the intervention arm were adherent with liraglutide 3 mg use (Supplementary material, Supplementary Table S11). A similar proportion of participants (≈2–3%) in both groups had bariatric surgery by 104 weeks (Supplementary material, Supplementary Table S11).

At 52 weeks, 42.3% of intervention group participants had experienced gastrointestinal symptoms compared with 3.0% of controls, but generally the symptoms were mild (Supplementary material, Supplementary Table S12). Five people in the intervention arm discontinued liraglutide 3 mg due to adverse events over the 104 weeks period. There were 33 people (12.7%) at the intervention group who experienced serious adverse events (SAEs) compared to 11 (8.3%) in the control group during the study (Table 4). Two deaths (one due to metastatic cancer with unknown primary site and the other due to ischaemic bowel disease) and two cases of pancreatitis were reported in the

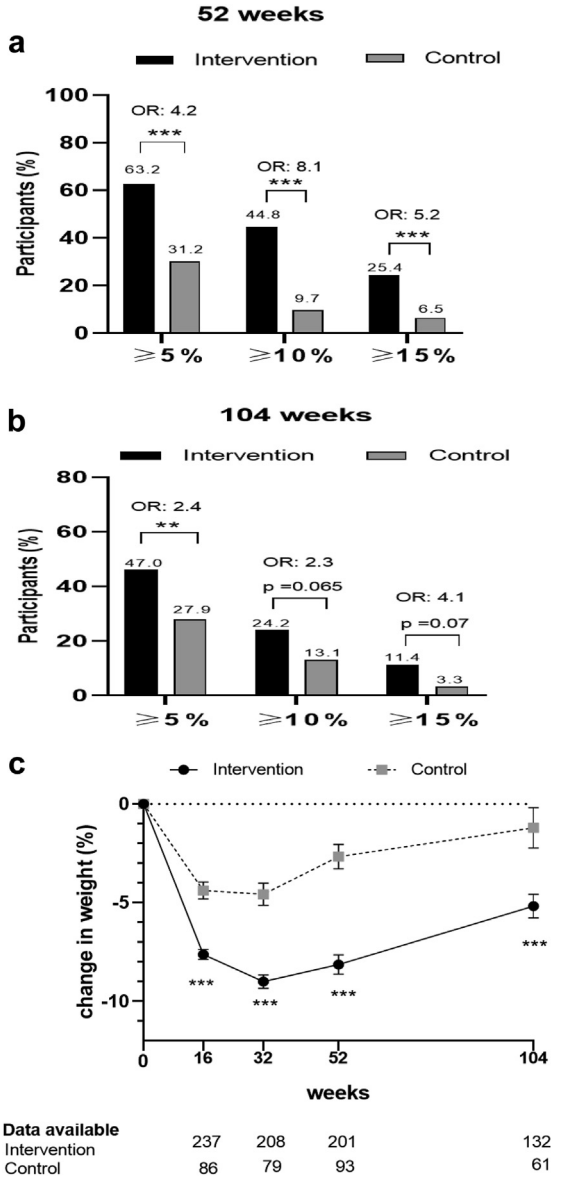

***Fig. 3:* Weight loss outcomes.** Data shown for complete cases population, OR = odds ratio, **p = 0.01, ***p < 0.0001. (a) The proportion of participants in the control and intervention group who lost at least 5%, 10%, and 15% of their baseline bodyweight at week 52, (b) The proportion of participants in the control and intervention group who lost at least 5%, 10%, and 15% of their baseline bodyweight at week 104 (c) Mean relative change in bodyweight for the complete case population in the control and the intervention group. Data shown are the observed means with standard error of the mean (SEM).

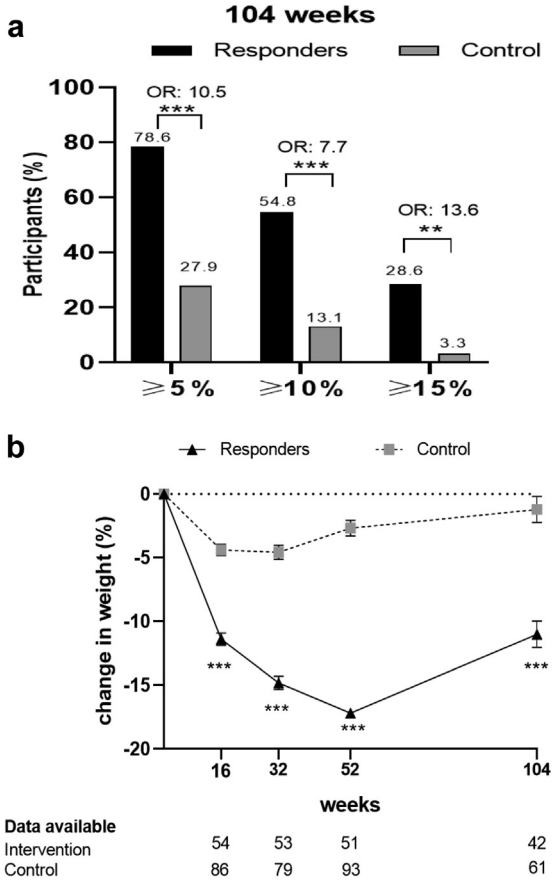

***Fig. 4:* "Responders" population and body weight.** Data shown is the complete case analysis for the "responders" population, OR = odds ratio, **p = 0.003, ***p < 0.0001. (a) The proportion of participants in the control group and the "responders" group who lost at least 5%, 10%, and 15% of their baseline bodyweight at week 104. (b) Mean relative change in bodyweight for the complete case population at the control group and the "responders" group. Data shown are the observed means with standard error of the mean (SEM).

	Baseline		Change from baseline		Difference in change from baseline between groups[b]	
	Control	Intervention	Control	Intervention	Adjusted mean difference (95% CI)[c]	p-value[b]
HbA1c (%)						
52 weeks	6.4 ± 1.1 (n = 51)	5.9 ± 0.9 (n = 129)	−0.0 ± 0.5	−0.6 ± 1.2	−0.57 (−0.91, −0.23)	0.001
104 weeks	6.5 ± 1.1 (n = 44)	6.2 ± 1.2 (n = 78)	0.0 ± 1.0	−0.6 ± 1.4	−0.65 (−1.11, −0.19)	0.006
HbA1c (mmol/mol)						
52 weeks	46.2 ± 12.4 (n = 51)	40.7 ± 10.1 (n = 129)	−0.2 ± 6.0	−6.6 ± 13.0	−6.15 (−9.90, −2.41)	0.001
104 weeks	47.1 ± 12.2 (n = 44)	44.5 ± 12.9 (n = 78)	0.6 ± 10.3	−6.0 ± 14.8	−7.23 (−12.28, −2.19)	0.005
Total number of agents for diabetes						
52 weeks	0.4 ± 0.7 (n = 93)	0.4 ± 0.6 (n = 202)	0.1 ± 0.4	0.0 ± 0.2	−0.07 (−0.13, −0.01)	0.030
104 weeks	0.5 ± 0.9 (n = 64)	0.5 ± 0.9 (n = 142)	0.2 ± 0.6	0.2 ± 0.6	0.00 (−0.17, 0.17)	0.987
Systolic blood pressure (mmHg)						
52 weeks	136.1 ± 15.0 (n = 62)	133.3 ± 17.1 (n = 139)	−3.2 ± 17.3	−3.9 ± 16.7	−0.72 (−5.85, 4.41)	0.784
104 weeks	134.3 ± 13.7 (n = 51)	128.7 ± 16.5 (n = 94)	−5.6 ± 17.8	−2.0 ± 16.1	3.00 (−2.61, 8.62)	0.292
Diastolic blood pressure (mmHg)						
52 weeks	81.3 ± 10.3 (n = 62)	82.3 ± 10.4 (n = 139)	−1.9 ± 11.2	−0.6 ± 9.7	1.18 (−1.91, 4.28)	0.452
104 weeks	81.3 ± 7.1 (n = 51)	79.7 ± 10.5 (n = 94)	−3.1 ± 11.8	−0.6 ± 11.5	2.05 (−1.71, 5.80)	0.283
Total number of agents for hypertension						
52 weeks	1.2 ± 1.4 (n = 93)	1.0 ± 1.2 (n = 202)	0.2 ± 0.8	0.1 ± 0.5	−0.07 (−0.22, 0.08)	0.345
104 weeks	1.3 ± 1.5 (n = 64)	1.0 ± 1.2 (n = 142)	0.2 ± 0.9	0.0 ± 0.4	−0.20 (−0.37, −0.03)	0.021
LDL cholesterol (mmol/L)						
52 weeks	2.6 ± 0.9 (n = 49)	2.7 ± 0.9 (n = 125)	−0.1 ± 0.7	0.0 ± 0.7	0.08 (−0.16, 0.32)	0.511
104 weeks	2.9 ± 1.0 (n = 42)	2.7 ± 0.9 (n = 79)	0.1 ± 0.8	0.1 ± 0.7	−0.06 (−0.34, 0.22)	0.655
HDL cholesterol (mmol/L)						
52 weeks	1.3 ± 0.3 (n = 51)	1.3 ± 0.3 (n = 131)	0.1 ± 0.2	0.1 ± 0.2	−0.02 (−0.08, 0.04)	0.439
104 weeks	1.2 ± 0.3 (n = 42)	1.3 ± 0.3 (n = 79)	0.0 ± 0.2	0.1 ± 0.2	0.05 (−0.02, 0.13)	0.157
Total cholesterol (mmol/L)						
52 weeks	4.6 ± 1.0 (n = 52)	4.7 ± 1.1 (n = 131)	−0.1 ± 0.7	−0.1 ± 0.9	−0.04 (−0.31, 0.23)	0.753
104 weeks	4.7 ± 1.1 (n = 42)	4.6 ± 1.0 (n = 80)	0.0 ± 0.9	−0.0 ± 0.8	−0.04 (−0.36, 0.28)	0.806
Triglycerides (mmol/L)						
52 weeks	1.8 ± 0.9 (n = 51)	1.6 ± 0.9 (n = 126)	−0.1 ± 0.6	−0.3 ± 0.7	−0.15 (−0.39, 0.08)	0.196
104 weeks	1.7 ± 1.3 (n = 41)	1.6 ± 0.7 (n = 78)	0.1 ± 1.1	−0.3 ± 0.8	−0.38 (−0.73, −0.03)	0.034
Total number of agents for dyslipidaemia						
52 weeks	0.3 ± 0.5 (n = 93)	0.3 ± 0.5 (n = 202)	0.0 ± 0.2	0.0 ± 0.2	−0.01 (−0.06, 0.04)	0.821
104 weeks	0.3 ± 0.5 (n = 64)	0.4 ± 0.5 (n = 142)	0.0 ± 0.2	0.1 ± 0.3	0.02 (−0.05, 0.09)	0.556
EQ-5D–VAS						
52 weeks	65.3 ± 19.3 (n = 60)	64.8 ± 20.5 (n = 132)	−2.7 ± 17.7	2.6 ± 23.6	5.62 (−0.85, 12.10)	0.088
104 weeks	65.6 ± 20.1 (n = 50)	60.2 ± 21.9 (n = 101)	−0.1 ± 20.9	−1.5 ± 27.1	−0.17 (−8.76, 8.41)	0.968
IWQoL- Lite (total)						
52 weeks	48.2 ± 21.9 (n = 63)	51.2 ± 22.6 (n = 139)	12.2 ± 13.6	17.5 ± 18.1	5.70 (0.87, 10.53)	0.021
104 weeks	31.5 ± 16.3 (n = 53)	28.7 ± 11.9 (n = 105)	−5.7 ± 15.6	−4.3 ± 14.1	1.54 (−3.46, 6.54)	0.543
Total MET (minutes/week)						
52 weeks	6119.0 ± 10662.8 (n = 55)	5841.6 ± 7859.4 (n = 120)	1153.4 ± 9238.4	1092.0 ± 6351.7	48.0 (−2303.0, 2399.0)	0.968
104 weeks	4336.9 ± 6892.7 (n = 47)	7177.0 ± 9683.0 (n = 90)	−558.7 ± 8972.5	2435.6 ± 9420.6	3687.0 (327.9, 7046.2)	0.032

Values are mean ± standard deviation. HbA1c: glycated haemoglobin, LDL: Low density lipoprotein, HDL: High density lipoprotein, EQ-5D-VAS: Euro-QoL-5 Dimensions-Visual Analogue Scale, IWQoL-Lite: impact of weight on quality of life-Lite questionnaire, MET: metabolic equivalent of task. [a]Due to the large number of secondary outcomes, it was pre-planned in the Statistical Analysis Plan (SAP) that statistical models were only fitted for the secondary anthropometric outcomes to limit the impact of multiple testing. [b]The between group analysis (difference in change from baseline between groups) is an exploratory ad hoc analysis not planned at the SAP. [c]Estimates are adjusted for the stratification variables: site and baseline BMI (≥45 kg/m^2; <45 kg/m^2).

Table 3: **Other secondary outcomes at 52 and 104 weeks from the complete cases analysis.**[a]

intervention group compared to no cases in the controls. The DSMC assessed both death cases and were of opinion that there were unlikely to be related to liraglutide 3 mg use. Overall, safety and tolerability were consistent with the GLP-1 RA class.

Discussion

The STRIVE study is the first multicentre RCT assessing the clinical effectiveness of liraglutide 3 mg in people with obesity when used with multiple prospectively applied stopping rules. Around 21% (54 out of

	Control			Intervention		
	Patients (n = 132)	Events	Events per 100 patient-years	Patients (n = 260)	Events	Events per 100 patient-years
Any AEs	89 (67.4)	310	116.7	238 (91.5)	1329	270.3
SAEs	11 (8.3)	19	7.2	33 (12.7)	47	9.6
Fatal events	0	0	0.0	2 (0.8)	2	0.4
Expected AEs*						
Nausea	0	0	0.0	95 (36.5)	127	26.0
Constipation	4 (3.0)	4	1.5	84 (32.3)	98	20.1
Diarrhoea	1 (0.8)	1	0.4	66 (25.4)	84	17.2
Vomiting	1 (0.8)	1	0.4	37 (14.2)	46	9.4
Abdominal Pain	1 (0.8)	1	0.4	29 (11.2)	38	7.8
Dyspepsia	0	0	0.0	28 (10.8)	32	6.6
Flatulence	0	0	0.0	26 (10.0)	30	6.1
Fatigue	2 (1.5)	2	0.8	21 (8.1)	23	4.7
Dizziness	3 (2.3)	3	1.1	17 (6.5)	20	4.1
Gastro-oesophageal reflux	0	0	0.0	20 (7.7)	20	4.1
Hypoglycaemia	0	0	0.0	11 (4.2)	17	3.5
Gastritis	1 (0.8)	1	0.4	6 (2.3)	6	1.2
Injection site reactions	0	0	0.0	4 (1.5)	4	0.8
Expected SAEs*						
Other	0	0	0.0	5 (1.9)	6	1.2
Pancreatitis	0	0	0.0	2 (0.8)	2	0.4
Cholecystitis	0	0	0.0	1 (0.4)	1	0.2
Diarrhoea	0	0	0.0	1 (0.4)	1	0.2

AE, Adverse Event; SAE, Serious Adverse Event. *Expected AEs and SAEs were collected on an additional case report form (CRF) to the AE log.

Table 4: **Adverse events and serious adverse events.**

260) of the participants in the intervention group passed all the three stopping rules and continued receiving liraglutide 3 mg in the second year. More people achieved ≥15% WL with the use of a targeted prescribing pathway for liraglutide 3 mg vs standard care at 52 weeks (25.4% vs 6.5% in individuals with primary outcome data). There were no new safety signals for liraglutide 3 mg.

The STRIVE study differs from the large SCALE programme studies of liraglutide 3 mg for weight management (SCALE-Obesity and Prediabetes and SCALE-Diabetes) in study design (multiple prospective stopping rules, open label, real-world setting with different intensity lifestyle interventions) and study population (higher baseline BMI, with all participants having BMI ≥35 kg/m^2 and more than one third of participants with T2D).[11,14]

In STRIVE, 70% of participants randomized to the intervention and initiated on liraglutide 3 mg met the European Medicine Agency stopping rule of ≥5% WL by week 16–this is consistent with a retrospective analysis of SCALE-Diabetes and SCALE-Obesity and Prediabetes, in which 62%–77% of people met the stopping rule of ≥4% WL at week 16.[16] In STRIVE, there was no individual who failed the 5% WL stopping rule or even the 10% WL stopping rule at 32 weeks and subsequently managed to achieve ≥15% WL at 52 weeks.

Around 20% (51 out of 260) of participants in the STRIVE intervention arm (excluding those having bariatric surgery) managed ≥15% WL at one year. A single-centre study combining liraglutide 3 mg with intensive lifestyle interventions [including intensive behavioural therapy (IBT) or IBT plus a period of meal replacement diet] resulted in 28–36% of participants achieving ≥15% WL at one year.[13] However, multicentre studies using intensive lifestyle interventions (SCALE-IBT, liraglutide 3 mg plus IBT delivered in primary care) or moderate intensity lifestyle interventions (SCALE-Obesity and Prediabetes) in combination with liraglutide 3 mg resulted in more modest WL, with 14.4–18.1% of participants achieving ≥15% WL at the first year.[11,23]

The mean %WL at 52 weeks with the targeted prescribing pathway (–8.1%) was similar to the mean %WL reported at the intervention arm of SCALE-Obesity and Prediabetes and the SCALE-IBT at one year.[11,23] Our study achieved these outcomes with less overall medication use compared to other clinical trials of liraglutide 3 mg (estimated mean number of weeks that each participant used liraglutide 3 mg over the first year of STRIVE was ≈36). Nevertheless, more people in the STRIVE study were able to achieve ≥15% WL and ≥10% WL at 52 weeks with the targeted prescribing pathway compared to the liraglutide 3 mg arm in SCALE-Obesity and Prediabetes trial, but less people achieved ≥5% WL

(63% vs 73% in complete cases analysis)[11]; this suggests that the distribution of WL at the intervention arm of the STRIVE may be different to SCALE-Obesity and Prediabetes trial, due to multiple stopping rules.

During the second year, some weight regain was observed in the intervention group (mean %WL at 104 weeks was −5.2), which was more apparent than the control group. The SWMS support was stopped for many of participants in both groups by the end of the first year in STRIVE study, in part due to the COVID-19 pandemic, but also as SWMS are often funded to provide care for one year. Moreover, a substantial number of people in the intervention group (n = 59/260, 22.7%) who achieved ≥10% WL at 52 weeks had to come off liraglutide 3 mg due to the 3rd stopping rule—this is likely to have resulted in clinically important weight regain during the second year at this population, similar to what was observed in the STEP-1 trial extension with semaglutide 2.4 mg.[24]

However, even in the "responders" group, who continued receiving liraglutide 3 mg up to 104 weeks, there was weight regain during the second year, which may be partly explained by the STRIVE study design which promoted increased motivation to achieve specific WL targets during the first year (to continue with liraglutide 3 mg) and the reduced intensity of lifestyle interventions at the second year. The mean %WL for this subgroup was −11.0% at 104 weeks and this amount of WL can still provide important health benefits [Supplementary material, Supplementary Table S6 (waist circumference) and exploratory analysis, Supplementary material, Supplementary Table S13].[10,25]

In the control group, the maximum mean WL achieved at 32 weeks, and was −4.6%, after which weight was gradually regained resulting in WL of −2.7% at 52 weeks and −1.2% at 104 weeks. This is consistent with clinical trials incorporating a 500 kcal deficit diet/day.[11,26] We should acknowledge that the COVID-19 pandemic affected the delivery of lifestyle interventions during the study, however the proportion of people in the control group achieving ≥5% WL at 26 and 52 weeks (43% and 31.2% respectively) is in accordance with previously published data for SWMS outcomes.[3,5] The open label design of the study may also have affected the efficacy results, as people randomized to control group may have had less motivation to adhere to the lifestyle programme and engage with the SWMS compared to people randomized to the intervention group who needed to achieve specific WL targets to continue on the medication.

For people with T2D at baseline, the HbA1c reduction at 52 weeks in the intervention group was similar to what was observed in the SCALE-Diabetes study, despite fewer people using liraglutide 3 mg.[14] The HbA1c reduction for people with T2D was also maintained at 104 weeks in the intervention group.

The baseline total IWQoL score was lower in STRIVE study compared to other similar studies, likely due to the severity of the disease in this population.[27] IWQoL scores improved at the end of the first year for both groups, however this improvement was not maintained in the second year. The lack of SWMS support for majority of participants during the second year, the impact of the COVID-19 pandemic and the weight regain during the second year of the STRIVE study may all have contributed.

The safety profile of liraglutide 3 mg was as expected, but it appears that in STRIVE study fewer people withdrew from the intervention arm due to adverse events compared to the SCALE programme studies. The fact that many participants stopped liraglutide 3 mg early during the STRIVE trial due to stopping rules as well as the open label design may explain this finding.[14,15]

The main strengths of the study include the pragmatic, real-world and multicentre study design, the large and representative sample size of people attending SWMS, and the two year follow-up. Our study probably provides an accurate estimate of the expected outcomes with liraglutide 3 mg use in people with obesity when multiple stopping rules are prospectively applied.

STRIVE has also important limitations—despite that it was intentionally designed as real world study, the open label design and the provision of information to participants at baseline regarding their group assignment may have affected the efficacy and safety results of the study. Moreover, another limitation is that 25% of data was missing for the primary outcome at 52 weeks and 51% of weight data was missing at 104 weeks. The transition to virtual research consultations and virtual clinics for safety reasons in response to the COVID-19 pandemic resulted in self-reported body weight assessments, more missing secondary and patient-reported outcomes at 52 and 104 weeks than expected and impacted on the delivery of lifestyle interventions. The study design did not allow people unable to tolerate the maximum dose of liraglutide 3 mg to continue on lower doses of the medication. Additionally, the exact impact of the multiple stopping rules on the study outcomes could not be clearly identified, as there was no control group using liraglutide 3 mg without multiple stopping rules. Longer follow-up of the subgroup of responders would also help us understand whether the observed weight regain over the second year continues.

Given the high cost of liraglutide 3 mg and the heterogeneity in treatment response, directing the long-term medication use to those likely to benefit most may also optimise the cost-effectiveness of medication use. As liraglutide 3 mg will lose patent protection over next years, its cost is expected to reduce and this may boost further the cost-effectiveness of the medication use with the described prescribing pathway. The prespecified 15% WL threshold in STRIVE pathway to determine if one should continue long-term on liraglutide 3 mg is similar to the mean WL achieved with the new pharmacotherapies for obesity, semaglutide 2.4 mg

and tirzepatide.[28,29] However, the cost of the new obesity pharmacotherapies is likely to preclude wide access and/or their long-term use.[26] For example, in the UK, NICE has approved semaglutide 2.4 mg use for maximum of 2 years, for people seen in SWMS with BMI ≥35 kg/m^2 and at least one obesity-related complication, with a stopping rule of ≥5% WL at 6 months.[30] In countries and healthcare systems where access to new obesity pharmacotherapies will be limited, the STRIVE prescribing pathway for liraglutide 3 mg could be an effective and maybe cost-effective approach to help people achieve and maintain clinically beneficial WL. Additionally, the concept of prescribing pathways with multiple stopping rules aiming for at least 15% WL may offer a logical and personalized approach to optimize the cost for any new obesity pharmacotherapy.

In conclusion, the results of the STRIVE RCT demonstrate that using liraglutide 3 mg in real-world SWMS as part of a targeted prescribing pathway with multiple stopping rules aiming to achieve ≥15% WL, resulted in greater and sustained WL compared to standard SWMS care alone over two years, with 21% of participants randomized to the targeted prescribing pathway passing all the three stopping rules and continuing on the medication. Improvements in cardiometabolic risk factors and in some parameters of the quality of life during the first year were confirmed without new safety signals. The suggested targeted prescribing pathway for liraglutide 3 mg offers a pragmatic and personalised approach which directs the long-term medication use to people likely to benefit more and optimises its cost. A cost-effectiveness analysis of the STRIVE study will inform whether national healthcare systems could offer liraglutide 3 mg to people with obesity based on this targeted prescribing pathway.

Contributors

DP: co-investigator; conceptualisation; literature search; data verification; methodology; investigation; visualization; writing–original draft, WAN: investigation; project administration; writing–review and editing, JZML: investigation; project administration; writing–review and editing, JC: investigation; project administration; writing–review and editing, DHB: formal analysis; data curation; data verification; methodology, writing—review and editing, SB: Formal analysis; data curation; data verification; methodology, writing—review and editing, ML: primary investigator, conceptualization, investigation, writing—review and editing BMG: primary investigator, conceptualization, methodology, investigation; supervision, writing–review and editing, DOS: primary investigator; conceptualization; writing—review and editing, DRW: primary investigator; investigation; methodology; writing—review and editing, JPHW: primary investigator; conceptualization; investigation; methodology; supervision; writing—review and editing, CWlR: primary investigator; conceptualization; methodology; supervision; writing–review and editing, MJD: chief investigator; conceptualisation; methodology; data verification; funding acquisition; supervision; writing–review and editing. All authors approved the final version.

Data sharing statement

The corresponding author (MJD) is the custodian of the data and will provide deidentified participant data on reasonable request (melanie.davies@uhl-tr.nhs.uk), with the completion of a data access agreement.

Declaration of interests

DP has received honoraria and support for attending meetings and/or travel from Novo Nordisk and reports grants from Novo Nordisk, Novo Nordisk UK Research Foundation, Academy of Medical Sciences/Diabetes UK and Health Education East Midlands. DP is also a Trustee for the Association of the Study of Obesity (ASO) and a member of the academic subcommittee of the Association of the British Clinical Diabetologists (ABCD). WAN does not report conflict of interest. JZML does not report conflict of interest. JC reports educational grants from Novo Nordisk. DHB is an independent consultant who is contracted to work on projects, including those in relation to obesity and diabetes. SB does not report conflict of interest. ML reports grants from Novo Nordisk, National Institute for Health Care and Research (NIHR), All Saints Educational Trust and Diabetes UK. ML also reports honoraria from Novo Nordisk, Eli Lilly and Nestle, consulting fees from Counterweight Ltd and has received support for attending meetings and/or travel by EASD nutritional study group. BMG is a shareholder of Reset Health and reports honoraria from Novo Nordisk and Janssen and she has received support for attending meeting or travel by Novo Nordisk. BMG reports also grant from Novo Nordisk and consulting fees from Novo Nordisk, Prizer and Johnson and Johnson. BMG is the Chair of Obesity Management Collaborative- UK and co-chair of the EASO Task Force. DOS does not report conflict of interest. DRW reports research funding support from Novo Nordisk and National Institute for Health Care and Research (NIHR). DRW is also chairing the data and safety monitoring committee for an investigator initiated study funded by Novo Nordisk. JPHW reports consultancy/advisory board work contracted via the University of Liverpool (no personal payment) for Altimmune, AstraZeneca, Boehringer Ingelheim, Lilly, Cytoki, Napp, Novo Nordisk, Menarini, Mundipharma, Pfizer, Rhythm Pharmaceuticals, Sanofi, Saniona, Tern, Shionogi & Ysopia in relation to obesity and type 2 diabetes. JPHW is named grantholder (at University of Liverpool) for research grants for clinical trials from AstraZeneca and Novo Nordisk and has received fees for clinical trials (at Liverpool University Hospitals NHS Foundation Trust) by Novo Nordisk, Lilly and Rhythm Pharmaceuticals. JPHW reports personal lecture fees from AstraZeneca, Boehringer Ingelheim, Napp, Medscape and Novo Nordisk in relation to lectures about diabetes and/or obesity and has received support for attending meeting or travel by Novo Nordisk. JPHW reports editorial work for Springer Nature (Medicine Matters Diabetes website) and he is past president of the World Obesity Federation, and a board member of the World Obesity Federation. JPHW reports also fees (paid to University of Liverpool) from AstraZeneca for being a Data and Safety Monitoring Board member for a clinical trial and he is also the speciality lead for the Metabolic and Endocrine Speciality Group of the NIHR Clinical Research Network, a member of the Rank Prize Funds Nutrition Committee, a previous member of the RCP committee on Nutrition, Weight and Health and an advisor on obesity treatments for NICE. CWlR reports grants from the Irish Research Council, Science Foundation Ireland, Anabio, and the Health Research Board. He serves on the advisory boards of Novo Nordisk, Herbalife, GI Dynamics, Eli Lilly, Johnson & Johnson, Altimmune, Irish Life Health and Boehringer Ingelheim and reports honoraria for presentations from Novo Nordisk, Herbalife, Johnson and Johnson, Eli Lilly, Boehringer Ingelheim, Rhythm Pharmaceuticals and Currax Pharmaceuticals. CWlR has received support to attend meetings and/or travel from Novo Nordisk, Herbalife, Johnson and Johnson, Eli Lilly and Boehringer Ingelheim. CWlR is a member of the Irish Society for Nutrition and Metabolism outside the area of work commented on here. He was the previous chief medical officer and director of the Medical Device Division of Keyron in 2021. Both of these were unremunerated positions. CWlR was a previous investor in Keyron, which develops endoscopically implantable medical devices intended to mimic the surgical procedures of sleeve gastrectomy and gastric bypass. The product has only been tested in rodents and none of Keyron's products are currently licensed. They do not have any contracts with other companies to put their products into clinical practice. No patients have been included in any of Keyron's studies and they are not listed on the stock market. CWlR was gifted stock holdings in September, 2021 and divested all stock holdings in

Keyron in September, 2021. He continues to provide scientific advice to Keyron for no remuneration. CWlR provides also service to Beyond BMI, a private obesity clinic providing obesity care. MJD has received grants in support of investigator and investigator initiated trials from Novo Nordisk, Sanofi Aventis, Eli Lilly, Boehringer Ingelheim, Astrazeneca and Janssen. MJD reports consulting fees from Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Sanofi, and honoraria for lectures from Eli Lilly, Sanofi Aventis, Boehringer Ingelheim, Novo Nordisk, AstraZeneca, Novartis, Napp Pharmaceuticals and Amgen. Moreover, MJD is an advisory board member for Novo Nordisk, Sanofi Aventis, Eli Lilly, Boehringer Ingelheim, Lexicon, Pfizer, Medtronic, Zealnd Pharma, AstraZeneca and ShouTi Pharma Inc.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2024.100853.

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