# The use of liraglutide 3.0 mg daily in the management of overweight and obesity in people with schizophrenia, schizoaffective disorder and first episode psychosis: results of a pilot randomised double-blind placebo-controlled trial

Running title: Liraglutide and the management of overweight and obesity in severe mental illness

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## Abstract

### Background

People with severe mental illness are 2-3 times more likely to be overweight and obese than the general population and this is associated with significant morbidity and premature mortality. This study investigated the feasibility and acceptability of using liraglutide 3.0 mg daily to address this problem.

### Materials and Methods

Design: Double-blind, randomised, placebo-controlled pilot trial.

Setting: Mental health centres and primary care within Southern Health NHS Foundation Trust.

Participants: Adults with schizophrenia, schizoaffective, or first-episode psychosis prescribed antipsychotic medication who were overweight or obese.

Intervention: Once daily subcutaneous liraglutide or placebo, titrated to 3.0 mg daily, for 6 months.

Primary outcome: recruitment, consent, retention and adherence.

Secondary exploratory outcomes: weight, HbA1c and Brief Psychiatric Rating Scale.

### Results

799 individuals were screened for eligibility. The commonest reasons for exclusion were ineligibility (44%) and inability to make contact (28%). The acceptance rate, as a proportion of all eligible participants, was 12.2%. The commonest stated reason why eligible candidates declined to participate related to the study specific medication and protocol (n= 50). 47 participants were randomised with 79% completing the trial. Participants in the liraglutide arm had lost a mean 5.7±7.9 kg compared with no significant weight change in the placebo group (treatment difference −6.0 kg, p=0.015). BMI, waist circumference and HbA1c reduced in the intervention group.

### Conclusions

This study supports the need for a larger randomised controlled trial to evaluate use of liraglutide (maximum dose 3.0 mg daily) in the management of obesity in people with severe mental illness.

## Background

The prevalence of overweight and obesity is 2-3 times higher among people with schizophrenia than in the general population (1). Weight gain occurs early in the natural history of schizophrenia with a significant proportion of people with first episode psychosis being overweight prior to treatment. Substantial weight gain, often more than 7%, occurs rapidly within 6-8 weeks after antipsychotic treatment initiation (2). Longer term observational studies have indicated that weight gain continues for at least 4 years albeit at a slower rate (3).

Lifestyle and pharmacological interventions lead to clinically and cost-effective reductions in body weight in the general population (4); however, lifestyle intervention studies in people with severe mental illness have shown mixed effects on weight reduction (5-7). A wide variety of pharmacological treatments have been subject to clinical studies (8), but currently no drug treatments are licensed for the treatment of antipsychotic-associated weight gain or obesity, apart from of orlistat. The use of orlistat is extremely limited due to high discontinuation rates (9, 10). Despite metformin having little effect on body weight in the general population, this drug has been extensively studied in people taking antipsychotic drugs. Over a period of 3-6 months, the average weight loss is 3.3 kg (11).

Liraglutide is a glucagon-like peptide-1 receptor agonist that has been successfully used in the treatment of type 2 diabetes for over a decade. In addition to effective lowering of HbA1c, its use also led to significant weight loss, which prompted the development of a higher dose formulation specifically for the treatment of obesity. Five clinical trials demonstrated that liraglutide 3.0 mg daily achieve clinically significant weight-loss and liraglutide 3.0 mg daily was approved for the treatment of obesity in December 2014 (12).

Despite the need for daily injections, GLP-1 receptor agonists may have potential benefits over metformin, including greater weight reduction, daily rather than multiple daily dosing and a licence for the treatment of weight loss in the case of liraglutide. Three studies have evaluated the use of GLP-1 receptor agonists as a treatment for antipsychotic-induced weight gain, two using exenatide and one using liraglutide (13-15). A meta-analysis of these studies reported a mean 3.71 kg greater weight loss after 16 weeks of treatment in people treated with the GLP-1 receptor agonists (16). Weight loss was greater in those treated with clozapine or olanzapine compared with other antipsychotics. Although these studies suggest a potential use of GLP-1 receptors agonists to treat antipsychotic-induced weight gain, the doses used were the diabetes doses rather than obesity dose.

The aim of this pilot study was therefore to compare the use of liraglutide (maximum dose 3.0 mg daily) with placebo in obese or overweight people with schizophrenia, schizoaffective disorder or first episode psychosis to assess the feasibility and acceptability of delivering a full-scale trial evaluating its use in people with schizophrenia and other severe mental illness.

## Methods

## Design

The study protocol for this trial has been published previously (17). In brief, we conducted a double blind randomised controlled pilot trial between 24 July 2018 (first patient, first visit), and 5 May 2020 (last patient, last visit) in mental health centres and primary care in Southern Health NHS Foundation Trust, UK (Figure 1).

## Participants

The trial team aimed to recruit a maximum of 60 participants through in-patient and community mental health teams and local general practices. Eligible participants were adults aged 18 to 75 years with a diagnosis of schizophrenia, schizoaffective disorder or first episode psychosis and who had been prescribed antipsychotic medication for at least one month. Participants had a body mass index (BMI; calculated as weight in kilograms divided by height in metres squared) *≥*30 kg/m² (obese), or *≥*27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related consequence, such as dysglycaemia (pre-diabetes or type 2 diabetes), hypertension, dyslipidaemia or obstructive sleep apnoea. The main exclusion criteria comprised contraindications to liraglutide (e.g. pancreatitis or eGFR <30 ml/min/1.73 m2), use of other pharmacological products for weight management, substance abuse, or sub-optimally managed diabetes defined by HbA1c >8% (64 mmol/mol). A complete list of inclusion and exclusion criteria is available in appendix 1 (17).

**Study procedures**

Participants were provided with oral and written information and gave written informed consent. After baseline assessments, participants were randomised in a 1:1 ratio to either once daily subcutaneous liraglutide or matching placebo using simple randomisation with permuted blinded block size. Novo Nordisk prepared and provided the subject randomisation list using a computer-based programme. All participants, carers, and study personnel except the pharmacy team were blinded to treatment assignment. The participants followed a fixed up-titration schedule of 0.6 mg per week to a daily dose of 3.0mg. Participants who did not tolerate up-titration remained on the highest tolerable dose. Each participant attended study visits every 4 weeks where concomitant medications and adverse events were documented. Clinical data were collected (secondary endpoints) including weight and blood samples at the baseline, 3- and 6-month visits. All participants received standardised written information about healthy eating, physical activity and smoking but responses to this advice were not monitored.

## End points

The primary objective of the trial was to investigate the feasibility and acceptability of delivering a full-scale trial. The study gathered data on time to reach recruitment target, number of eligible participants required to be screened, participant attrition rate and estimate of adherence to the investigational medicinal product. Adherence to trial medication was defined as taking at least 70% of prescribed trial medication. Key secondary exploratory outcomes included changes in body weight, BMI, waist circumference, blood pressure; glycaemia, lipid profile and Brief Psychiatric Rating Scale from baseline to the end of trial.

## Data Analysis

Data were analysed on an intention-to-treat basis, as the most conservative approach, in accordance with the trial’s detailed statistical analysis plan. A per protocol analysis was not undertaken but this may have amplified the treatment effect and therefore increase the risk of type I error. Imputation of data was not done as this was a feasibility trial and these analyses were exploratory. Sub-group analysis was not undertaken because of the small numbers in the study. Continuous variables were analysed by mean or median, with groups compared statistically using either paired t-test or Wilcoxon signed rank test as appropriate. Data are presented as mean ± SD. Categorical variables were presented as n (%) with groups compared using chi-squared or Fisher’s exact tests. The difference in weight change between groups was analysed using generalised linear models, both unadjusted and adjusted for covariates that were identified as potential confounders in univariate testing. Estimated mean change was reported with 95% confidence intervals. All statistical tests were 2-sided with statistical significance assumed at 0.05.

**Governance**

The study was conducted in keeping with Good Clinical Practice (GCP) and the International Conference of Harmonisation (ICH) standards. South Central - Hampshire B Research Ethics Committee (REC) approved the study on the 17 April 2018 (Reference: 18/SC/0085). Southern Health NHS Foundation Trust sponsored the study (SHT325). The trial was registered with the WHO Primary Registries Universal Trial Number (UTN) is U1111-1203-0068 and the European Clinical Trials Database (EudraCT) number: 2017-004064-35. The day-to-day management of the trial was co-ordinated by the research team and oversight was maintained by the Trial Steering Committee.

## Results

### Pilot and feasibility outcomes

Between 17 July 2018 and 31 October 2019, 799 individuals were screened for eligibility and 321 people were invited to a screening visit, of whom 55 attended and 47 entered the trial as shown in the CONSORT diagram (Figure 2). The commonest reasons for exclusion were ineligibility (44%) and inability to contact the individual (28%). 12.2% of all eligible participants attended the screening visit and 10.5% were randomised. The main stated reason why eligible candidates declined to take part was the study specific medication or protocol (14%).

24 men and 23 women (43.9 ± 11.0 years) were randomised to liraglutide (maximum dose 3.0mg daily) or placebo for 6 months. The time to reach this recruitment figure was 67 weeks and 2 days. Mean recruitment was 0.7 people per week (95% CI 0.6 - 0.8).

10 participants (7 in the intervention arm; 3 in the placebo arm) were not available for follow up as per the research protocol. Six withdrew and four were lost to follow up. The difference in participant attrition between arms was not statistically significant (P=0.180). 17 intervention participants and 20 placebo arm participants completed the 6-month trial.

Two participants in the intervention arm were unable to titrate to the maximum dose of liraglutide. One reached a maximum tolerated dose of 1.2 mg daily and the other 2.4 mg daily. 12 participants withdrew from the trial medication but continued to attend study visits, five of whom were in the liraglutide arm and seven in the placebo arm. 25 participants continued the trial medication from baseline until the final visit. 23 of these 25 participants took the trial medication as prescribed (11 in the intervention arm and 12 in the placebo arm). Adherence did not change between 3 and 6 months of treatment.

### Secondary exploratory outcomes

At baseline, the groups were largely balanced, however, the placebo group were on average 6.3 kg heavier, despite a higher proportion of men, who are on average heavier than women, in the intervention arm (62% vs. 39%) (Table 1). Most participants had an established diagnosis of schizophrenia or schizoaffective disorder. The participants reported mild-to-moderate psychiatric symptoms and were prescribed a range of antipsychotic medications, including clozapine (n= 13; 28%) (Table 2).

Three participants had missing weight data at 6 months, two in the intervention arm and one in the placebo arm, because the restrictions imposed by the Covid pandemic meant that the final in-person assessment could not completed. Thus, the intention-to-treat analysis was performed on 15 intervention participants and 19 control participants.

After 6 months, participants in the intervention group lost a mean 5.7 ± 7.9 kg (4.5%; 95% CI -8.3% to -0.8%) in body weight while there was no weight change in the placebo group (0.3 ± 5.7 kg [0.0%; 95% CI -2.5% to 3.1%]). The estimated treatment difference between groups was −6.0 kg (95% CI: -10.8 to -1.3; P = 0.015) (Table 3). There were statistically significant improvements in BMI, Brief Psychiatric Rating Scale and HbA1c for participants treated with liraglutide. 53% of those who completed the trial on the trial medication in the intervention arm lost ≥5% of their body weight compared to 10% of the placebo participants (P = 0.007) (Table 4).

None of the four participants with type 2 diabetes had any changes in the type or dose of their diabetes medication during the trial. Overall, there were nine changes to antipsychotic medication prescriptions during the trial. Three participants started or stopped an antipsychotic medication and six had a dose change, but these were similar between arms.

The most frequent adverse events were gastrointestinal, and these were more common (72% of those reported) in the intervention arm, in keeping with the known side effect profile of liraglutide. There was one case of gallstones in the intervention group but there were no episodes of pancreatitis or pancreatic cancer. Other adverse events were similar between groups and 65% of all reported adverse events were mild (Table 5). There were five serious adverse events during the trial, four in the placebo group and one in the intervention group (Appendix 2). There were no serious adverse reactions or serious unexpected serious adverse reactions during the trial.

## Discussion

This is the first trial to assess the use of the GLP-1 receptor agonist, liraglutide, at the higher 3.0 mg daily dose licensed for the treatment of overweight and obesity in people with severe mental illness. The study successfully collected data on recruitment, eligibility, consent, attrition and adherence to the study medication. The study also provided useful pilot data about the potential clinical effectiveness of liraglutide 3.0 mg daily in the management of obesity in people with schizophrenia and schizoaffective disorder.

Recruitment for this trial proved more challenging than initially expected and the trial was stopped for pragmatic reasons in agreement with the trial steering committee after a 3-month extension to the recruitment period when 47 participants had been randomised. The number of case notes that had been pre-screened for eligibility was almost four times the number predicted and the acceptance rate was lower than estimated. Southern Health was a study site for the STEPWISE study, which evaluated the use of a group-based structured education lifestyle intervention to support weight loss in people with schizophrenia (18). In the STEPWISE study, the research team screened 180 people for eligibility, invited 101 people to take part and recruited 55 people over an 8-month period. As the inclusion and exclusion criteria were similar between the studies, we had expected a similar rate of recruitment for the current study. The time commitment between the studies was broadly comparable and so the likely reason for the difference is the use of an injectable medication. A full-scale trial will need to account for this and consider ways of reducing this barrier.

Our screening to randomization rate (10.5%) was lower than that seen in the other two GLP‑1 receptor agonist studies in this patient population that reported the randomisation rate (Larsen et al 48% and Siskind et al 22%). In these studies as well as ours, the main documented reason for non-participation was ineligibility (13, 15). The CODEX study was also unable to reach its initial recruitment target, ultimately randomising 28 participants from a target of 60 participants (13).

In contrast to the difficulties in recruitment, once an individual was recruited, retention and adherence to medication were in line with expectations. Analysis of the attrition rates in previous studies of pharmacological treatments of obesity, including liraglutide, shows that around a third of individuals do not complete the study, which is consistent with the 78% completion rate in our study (19, 20). Treatment adherence in previous trials was ~70%, which again is similar to this trial (21). Retaining participants in obesity trials is challenging because they are aware if they do not lose weight. If the treatment is ineffective, participants may be unwilling to continue treatment, particularly if they are experiencing medication adverse effects. However, the results of the current study suggest there are no differences between people with schizophrenia and the general population in this regard.

Despite the low numbers who completed the study, there was a clinically significant treatment effect on weight in those who completed treatment with liraglutide. The weight reduction in this pilot trial was greater than the weight loss seen in the other GLP-1 receptor agonist studies in this population (16) and was almost comparable with the 5.7% – 8.0% weight loss seen in the SCALE phase III clinical trial programme (20, 22-24). In the SCALE Obesity and Prediabetes trial, whose participants were most similar to our study, those treated with the liraglutide 3.0 mg group lost a mean 8.4 kg of body weight after 56 weeks of treatment, compared with 6.0 kg in our study after 6 months of treatment (20). In addition to the presence of a severe mental illness, there are other important differences in the participant characteristics between the studies. Baseline mean BMI was higher in the SCALE Obesity and Prediabetes trial (38.3 kg/m2) and 78% of participants were female.

Consistent with our trial, weight loss in the other GLP-1 receptor agonist trials in people with antipsychotic induced weight gain was also associated with reductions in HbA1c and improvement in cardiometabolic measurements (blood pressure and cholesterol levels) in the GLP-1 receptor agonist groups (16).

### Strengths and limitations of the trial

Key strengths included the randomised placebo controlled design of the trial, the retention rate, zero errors in the database check, the joint mental and physical health team working and impact the intervention made to a number of the participants, especially the ones who lost more than 5% of their body weight. As judged by the baseline characteristics, the trial recruited a broad representative group of people with schizophrenia taking a range of different antipsychotic medications.

Limitations include the exclusion of non-English speakers and failure to reach the planned sample size, which led to some imbalance in baseline characteristics. The trial did not allow for any data collection after cessation of the trial medication to observe what happened to weight post-treatment cessation. The trial was funded by the investigational drug manufacturer and this could lead to potential bias. In order to mitigate against this bias, the trial was sponsored by Southern Health NHS Foundation Trust, which had the responsibility for the initiation, management, conduct, analysis, reporting and publication of the trial. A further limitation is the lack of a formal assessment of diet and physical activity before and during the trial. However, given our experience during the STEPWISE trial with a similar patient group, we do not believe that any weight change is likely to be attributable to the provision of standardised lifestyle advice (18). Finally, 6-month data from the final participants were missing because the trial had to stop with the introduction of Covid-19 restrictions.

### Impact for future research

Several key research question regarding the use of injectable weight loss medications remain for this patient population. Although encouraging, the results of this study would need to be confirmed in a fully powered trial. How to identify those who are sufficiently motivated to benefit most from an injectable weight loss intervention would be valuable in order to inform how this treatment could be delivered as part of routine care.

Although liraglutide 3.0 mg daily is currently the only licensed GLP-1 receptor agonist for the treatment of obesity, there is on-going studies of other GLP-1 receptor agonists for this indication. Semaglutide 1 mg, a once weekly GLP-1 receptor agonist, has been shown to lead to significantly greater weight loss than that seen with liraglutide 1.2mg daily (diabetes dose) in people with type 2 diabetes in the SUSTAIN-10 trial (5.8 vs 1.9 kg) (25). A phase 2 study of semaglutide 2.4 mg once weekly demonstrated a mean weight loss of up to -13.8% for those treated with semaglutide (26) and five phase III studies are now on-going as part of the Semaglutide Treatment Effect in People with obesity STEP programme (27). The use of a once weekly preparation may appeal to those who declined to take part in this study because of the need for daily injections with liraglutide. A once weekly preparation may also allow the injections to be administered by healthcare professionals where necessary.

## CONCLUSION

Obesity adversely affects the physical health, quality of life and psychological well-being of people with severe mental illness. This pilot study explored the feasibility and practical issues of conducting a trial assessing liraglutide as a possible treatment for obesity in people with severe mental illness and provided data to estimate important parameters to help its design. Although recruitment to this pilot study was challenging, once participants were enrolled, retention and adherence to the trial medication was similar to previous studies of liraglutide 3mg daily in the general population. Those who were randomised to liraglutide experienced clinically relevant weight loss, which was consistent with previous trials. This study supports the need for a larger definitive randomised controlled trial to evaluate the use of liraglutide (maximum dose 3.0 mg daily) in the management of obesity in people with severe mental illness.

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# DECLARATIONS

## Availability of data and material

Not available

## Competing interests

CAW, HCP, PP, SR and KT are employees of Southern Health NHS Foundation Trust. HCP received fees for lecturing, consultancy work and attendance at conferences from Novo Nordisk. SR received fees for speaking at conferences from Janssen, Lundbeck and Otsuka. KBK received fees for advisory board participation, consultancy work and attendance at conferences from the following: Sanofi, Roche Diabetes Care, Lifescan, Novo Nordisk, Silvercloud, Senseonics. RIGH received fees for lecturing, consultancy work and attendance at conferences from the following: Boehringer Ingelheim, Eli Lilly, Janssen, Lundbeck, Novo Nordisk, Novartis, Otsuka, Sanofi, Sunovion, Takeda, MSD.

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## Authors contribution

RIGH, HCP, SR, PP, KT, KBK and CAW wrote the original protocol. RIGH, HCP, SR, PP, KBK and CAW were co-applicants on the Investigator Led Novo Nordisk grant application. CAW, HCP, SR, PP, KBK, KT, CR, RP, JM and RIGH refined the protocol. CAW ran the trial. KN analysed the data. All authors critically reviewed the manuscript.

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**Figure legends**

**Figure 1: Trial design**

**Figure 2: CONSORT Diagram.**

**\***the analysis was performed according to intention-to-treat as per the pre-specified statistical analysis plan and so included those who had withdrawn from treatment or who did not take the medication as prescribed

### Table 1: Baseline characteristics

|  |  |  |
| --- | --- | --- |
| **Variable** | **Study Arm** |  |
| **Intervention (n=24)** | **Control (n=23)** | **P-value** |
| **Age (years)** | 42.7 ± 11.325.0 – 64.0 | 45.4 ± 10.721.0 – 63.0 | 0.554t |
| **Sex** |  |  | **0.036c** |
| **Female** | 9 (38%) | 14 (61%) |  |
| **Male** | 15 (62%) | 9 (39%) |  |
| **Diagnosis** |  |  | 0.879 |
| **First Episode Psychosis** | 1 (4%) | 1 (4%) |  |
| **Schizophrenia** | 15 (62%) | 13 (56%) |  |
| **Schizoaffective disorder** | 8 (33%) | 9 (39%) |  |
| **Ethnicity** |  |  | 0.325c |
| **Other Ethnic Group** | 3 (13%) | 6 (26%) |  |
| **White British, Irish, Other** | 21 (88%) | 17 (74%) |  |
| **Smoking status\*** |  |  | 0.412c |
| **Current Smoker** | 13 (62%) | 7 (32%) |  |
| **Never Smoked** | 5 (24%) | 7 (32%) |  |
| **Previous Smoker** | 3 (14%) | 8 (36%) |  |
| **Diagnosis of type 2 diabetes** |  | 0.287c |
| **No** | 23 (96%) | 20 (87%) |  |
| **Yes** | 1 (4%) | 3 (13%) |  |
| **Height (m)** | 1.72 ± 0.131.32 – 1.97 | 1.71 ± 0.111.50 - 1.90 | 0.079t |
|  **Weight (kg)** | 111.4 ± 25.576.6 - 171.2 | 117.7 ± 23. 573.6 - 162.8 | 0.535t |
| **Body mass index (kg/m2)** | 37. 5 ± 6.929.4 – 50.9 | 41.0 ± 6.730.2 – 59.7 | 0.059t |
| **Waist circumference (cm)** | 123.8 ± 20.195.0 – 175.0 | 130.6 ± 14.0 112.0 – 158.0 | 0.187t |
| **Systolic blood pressure (mmHg)** | 130 ± 2493 - 197 | 134 ± 15113 - 169 | 0.086t |
| **Diastolic blood pressure (mmHg)** | 92 ± 2368 - 174 | 93 ± 781 - 112 | 0.537t |
|  **Brief psychiatric rating scale**  | 38 ± 1421 – 80 | 31 ± 918 – 51 | 0.076t |
| **HbA1c (mmol/mol)** | 37 ± 625 - 49 | 40 ± 531 - 47 | 0.166t |
| **HbA1c (%)** | 5.5 ± 0.64.5 – 6.7 | 5.8 ± 0.55.0 – 6.5 | 0.651t |
| **Fasting plasma glucose (mmol/l)** | 5.2 ± 0.54.5 – 6.0 | 5.1 ± 0.73.9 - 6.6 | 0.771t |
| **Fasting lipids (mmol/l)** |  |  |  |
| **Total cholesterol** | 5.0 ± 1.03.7 - 6.6 | 5.0 ± 1.22.9 - 6.8 | 0.974t |
| **HDL cholesterol** | 1.3 ± 0.30.8 - 2.1 | 1.4 ± 0.30.9 - 2.3 | 0.192t |
| **LDL cholesterol** | 3.1 ± 0.82.0 - 4.4 | 2.7 ± 1.01.3 - 4.3 | 0.202t |
| **Non-HDL cholesterol** | 3.7 ± 1.01.6 - 5.7 | 3.6 ± 1.11.7 - 5.1 | 0.711t |
| **Triglycerides**  | 1.8 ± 0.80.8 - 3.6 | 1.8 ± 0.80.9 - 3.7 | 0.965t |

***t: Two independent sample T-TEST with equal variance; c: Chi-square Test***

Data are mean ± SD; range or percentage. \*Data are missing from 2 participants in the intervention arm and one in the placebo arm. HbA1c:glycated haemoglobin; HDL: high density lipoprotein, LDL: low density lipoprotein

**Table 2. Antipsychotic medication used by participants**

|  |  |  |  |
| --- | --- | --- | --- |
| **Medication** | **Liraglutide** | **Placebo** | **P-Value** |
| **Antipsychotic Medication** | 1 (4%) | 2 (9%) | 0.458 |
|  Aripiprazole | 1 (4%) | 2 (9%) |  |
|  Aripiprazole (IM) | 0 (0%) | 2 (9%) |  |
|  Clozapine | 3 (12%) | 6 (26%) |  |
|  Flupenthixol | 4 (17%) | 3 (13%) |  |
|  Olanzapine | 2 (8%) | 0 (0%) |  |
| Paliperidone | 4 (17%) | 1 (4%) |  |
| Quetiapine | 1 (4%) | 2 (9%) |  |
| Risperidone | 1 (4%) | 2 (9%) |  |
| Zuclopenthixol Decanoate | 2 (8%) | 1 (4%) |  |
| Amisulpiride | 1 (4%) | 1 (4%) |  |
| **Multiple antipsychotic medication** | 5 (21%) | 3 (13%) | 0.321 |

Oral medication unless stated. IM: intramuscular

### Table 3: Secondary exploratory outcomes

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Change from Baseline to 6 months** | **Liraglutide (n=15)** | **Placebo (n=19)** | **Mean change between arms** | **P -value\*** |
| **Weight in kilograms (kg)**  | **-5.7± 7.9****-10.1 to -1.4** | **0.3 ± 5.7****-2.5 to 3.1** | **-6.0** **-10.8 to -1.36** | **0.015** |
| **% weight**  | **4.5± 6.20****-8.3 to -0.8** | **0.0 ± 4.2****-1.9 to 2.1** | **-4.6****-8.4 to -0.7** | **0.021** |
| **Body mass index (kg/m2)** | **-1.7± 2.6****-3.2 to -0.3** | **0.0 ± 1.8****-0.9 to 0.9** | **-1.76** **-3.31 to -0.20** | **0.028** |
| **Waist circumference (cm)** | -5.3 ± 9.2-10.8 to 0.3 | 1.9 ± 4.6-0.4 to 4.2 | **-7.2****-12.3 to -2.1** | **0.008** |
| **Brief Psychiatric Rating Score**  | **-10.6 ± 12.1****-17.6 to -3.6** | -**4.3 ± 8.8****-8.4 to -0.1** | -6.3-13.6 to 1.0 | 0.088 |
| **HbA1c (mmol/mol)** | **-3.3 ± 2.8****-5.2 to -1.4** | 0.3 ± 2.4-1.2 to 1.8 | **-3.6****-5.9 to -1.3** | **0.003** |
| **Fasting plasma glucose (mmol/l)** | -0.2 ± 0.8-0.8 to 0.3 | 0.4 ± 0.9-0.2 to 0.9 | -0.6-1.3 to 0.1 | 0.081 |
| **Systolic blood pressure (mmHg)**  | -3 ± 14-12 to 6 | -6 ± 17-15 to 3 | 3(-9 to 15) | 0.600 |
| **Diastolic blood pressure (mmHg)** | 2 ± 14-6 to 11 | -2 ± 7-6 to 1 | 5-3 to 12 | 0.231 |
| **Lipids (mmol/l):**  |  |  |  |  |
| **Total Cholesterol**  | -0.3 ± 0.6-0.8 to 0.1 | 0.0 ± 0.5-0.3 to 0.3 | -0.3-0.8 to 0.2 | 0.198 |
| **HDL cholesterol**  | 0 ± 0.2-0.1 to 0.1 | -0.1 ± 0.2-0.2 to 0.0 | 0.1-0.1 to 0.2 | 0.205 |
| **LDL cholesterol**  | -0.2 ± (0.5)-0.7 to 0.2 | 0.1 ± (0.3)-0.2 to 0.3 | -0.3-0.8 to 0.1 | 0.141 |
| **Non-HDL cholesterol**  | -0.3 ± 0.6-0.7 to 0.1 | 0.1 ± 0.4-0.2 to 0.3 | -0.4-0.8 to 0.0 | 0.071 |
| **Triglycerides**  | 0 ± 0.8-0.5 to 0.5 | 0 ± 0.4-0.3 to 0.3 | 0.0 -0.5 to 0.5 | 0.942 |

***\* Two Independent Sample T-Test P-value***

Data are mean change ± SD: 95% CI*.* BMI: body mass index; HDL: high density lipoprotein, LDL: low density lipoprotein

### Table 4: 3 month and 6 month weight change of at least 5%

|  |  |  |
| --- | --- | --- |
|  | **Study arm**  |  |
| **Participants with ≥ 5% weight change**  | **Liraglutide** | **Placebo** | **P value** |
| **3 month** **6 month**  | 8 (50%)8 (53%) | 1 (5%)2 (10%) | **0.005\*****0.007\*** |

\* Chi-square Test, p value statistically significant at 5%. Data are number and percentage

**Table 5: Adverse events**

|  |  |  |
| --- | --- | --- |
| Adverse Event | Liraglutide | Placebo |
| Gastrointestinal |  |  |
|  Vomiting | 6 (11%) | 3 (6%) |
|  Nausea | 7 (12%) | 4 (9%) |
|  Diarrhoea | 9 (16%) | 4 (9%) |
|  Constipation | 5 (9%) | 2 (4%) |
|  Dyspepsia | 10 (17%) | 0 (0%) |
|  Gallstones | 1 (2%) | 0 (0%) |
|  Blood in stool | 1 (2%) | 1 (2%) |
| Respiratory |  |  |
|  Upper respiratory tract infection | 7 (12%) | 12 (25%) |
|  Asthma | 0 (0%) | 1 (2%) |
| Musculoskeletal | 4 (7%) | 2 (4% |
| Neurological | 8 (15%) | 7 (15%) |
| Dermatological | 0 (0%) | 1 (2%) |
| Other infection | 1 (2%) | 6 (13%) |
| Gynaecological | 1 (2%) | 1 (2%) |
| Haematological | 0 (0%) | 3 (6%) |

Data are N (%)

Appendices:

**Appendix 1: Full list of inclusion and exclusion criteria**

Adults were eligible to participate in the study if they:

1. were aged 18-75 years old.
2. had a clinical diagnosis of schizophrenia or schizoaffective disorder (defined by ICD-10 codes F20 and F25) or first episode psychosis using case note review. There was no limit on the duration of illness for those with schizophrenia or schizoaffective disorder but first episode psychosis was defined as less than 3 years since presentation to the mental health team or first antipsychotic prescription.
3. were being treated with an antipsychotic, with a minimum duration of 1 month prior to entry in to the trial. No restriction was placed on the class or generation of antipsychotic
4. were able to give written informed consent.
5. Ability and willingness to take liraglutide or placebo.
6. were able to speak and read English.
7. had a body mass index (BMI, calculated as weight in kilograms (kg) divided by height in meters squared) *≥* 30 kg/m² (obese), or *≥* 27 kg/m² to < 30 kg/m² (overweight) in the presence of at least one weight-related consequence such as dysglycaemia (pre-diabetes or type 2 diabetes), hypertension, dyslipidaemia or obstructive sleep apnoea.

People were excluded from the study if they had a:

1. Physical illnesses, e.g. cancer, that could seriously reduce their life expectancy or ability to participate in the trial
2. A co-existing physical health problem that would, in the opinion of the principal investigator, independently impact on metabolic measures or weight, e.g. Cushing’s syndrome, poorly controlled Type 2 diabetes defined by HbA1c >8% (64 mmol/mol).
3. Inflammatory bowel disease and diabetic gastroparesis
4. Contraindications to Liraglutide: Hypersensitivity to liraglutide or to any of the excipients.
	1. Any condition which in the investigator’s opinion might jeopardise participant’s safety or compliance with the protocol.
	2. Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. Family is defined as a first degree relative.
	3. History or presence of pancreatitis (acute or chronic).
	4. History of diabetic ketoacidosis.
	5. Any of the following: myocardial infarction, stroke, hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening.
	6. Participants presently classified as being in New York Heart Association Class IV.
	7. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.
	8. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of <30 ml/min/1.73 m2 as defined by KDIGO 2012 classification.
	9. Impaired liver function, defined as alanine aminotransferase (ALT) ≥2.5 times upper normal limit at screening.
	10. Proliferative retinopathy or maculopathy requiring acute treatment.
	11. Presence or history of malignant neoplasms within the past 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma in-situ is allowed.
5. Use of other pharmacological products for weight management.
6. Mental illnesses that could seriously reduce their ability to participate in the trial, including significant suicidality.
7. Current pregnancy or a desire to become pregnant. Mothers who were less than 6 months post-partum or breastfeeding were also be excluded. In line with the current EU licence and advice from the MHRA, sponsor and manufacturer, any women who could become pregnant during the trial but were unwilling to use a highly effective method of birth control (e.g. such as implants, injectables, combined oral contraceptives, intrauterine devices, sexual abstinence or vasectomised partner) were not eligible for the trial.
8. Significant alcohol or substance misuse which, in the opinion of the principal investigator, would limit participant’s ability to participate in the trial.
9. A diagnosis or tentative diagnosis of psychotic depression or mania.
10. A primary diagnosis of learning disability or cognitive impairment which would impair participant’s ability to self-administer trial medication.
11. Lack of capacity. Those who lose capacity any time during the study will not be eligible to continue and will be withdrawn from the study immediately with no further study procedures carried out.
12. History of type 1 diabetes.
13. Current or previous use of incretin based therapies (GLP-1 receptor agonist or DPP-4 inhibitors) or insulin.

**Appendix 2: Details of Serious Adverse Events**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **SAE number** | **Description** | **Outcome** | **On IMP** | **Intervention or placebo arm** | **Un-blinded during trial** | **Withdrawn** |
| **1** | Unconscious, admitted to hospital | Recovered | No | Intervention | No | No |
| **2** | Musculoskeletal chest pain requiring admission to hospital | Recovered | Yes | Placebo | No | No  |
| **3** | NSTEMI requiring admission to hospital | Recovered | Yes | Placebo | Yes | Yes |
| **4** | Self-harm  | Recovered | Yes | Placebo | No | No |
| **5** | Chest pain, requiring admission to hospital. Investigations for pulmonary embolism were negative | Recovered | Yes | Placebo | No | No |