Table of content

Summary of changes to the statistical analysis plan

The original statistical analysis plan is described in the original protocol, version 1.2 provided below.

Before any unblinding of treatment groups was performed, the final statistical analysis plan was uploaded to clinicaltrials.gov. All analyses were carried out with the treatment groups still blinded and labeled as "treatment group A" and "treatment group B". If requested, the Email correspondence with the unblinded nurse regarding unblinding can be forwarded.

In the original statistical analysis plan missing data were handled by last observation carried forward. However, a decision was made to use mixed model of repeated measurements to reduce the risk of bias. Mixed model was used for all analyses including the primary endpoint (change in glucose tolerance).

Furthermore, the study was intended to be exploratory with an estimated sample size of 100 participants. However, it was possible to perform a precise power calculation based on unpublished baseline data from individuals with and without impaired glucose tolerance (IGT) following a 4-hour 75-grams OGTT from the study: "The Impact of Liraglutide on Glucose Tolerance and the Risk of Type 2 Diabetes in Women With Previous Pregnancy-induced Diabetes".(1)

The power calculation resulted in a sample size of 96 participants, similar to the initial estimation.

Reference List

1. Foghsgaard S, Vedtofte L, Mathiesen ER et al. The effect of a glucagon-like peptide-1 receptor agonist on glucose tolerance in women with previous gestational diabetes mellitus: protocol for an investigator-initiated, randomised, placebo-controlled, double-blinded, parallel intervention trial. BMJ Open 2013;3(10):e003834.

Final statistical analysis plan

Power calculation

A sample size of 96 participants (48 in each group) was estimated, with two-sided t-testing, an α of 5% and a power of 90%. The power calculation was based on the primary outcome measurement: Change in glucose tolerance. The glucose tolerance was estimated by the total Area Under the Curve (AUC) following a 4-hour 75-grams Oral Glucose Tolerance Test (OGTT). The expected mean total AUC for the plasma glucose excursion following a 4-hour 75-grams OGTT was estimated as 1695 (SD 158) and 1800 (SD 158) after 16 weeks of treatment for the liraglutide and liraglutide placebo group, respectively. The difference in total AUC was based on unpublished data in individuals with and without Impaired Glucose Tolerance (IGT) following a 4-hour 75-grams OGTT at baseline from the study: "The Impact of Liraglutide on Glucose Tolerance and the Risk of Type 2 Diabetes in Women With Previous Pregnancy-induced Diabetes".(1)

Procedure

All analyses will be carried out with the treatment groups still blinded and labeled as "treatment group A" and "treatment group B". Before dividing participants into group A and group B, the statistical plan was completed and uploaded on clinicaltrials.gov, and the data set was locked. The final unblinding of treatment groups (liraglutide or liraglutide placebo), will not be carried out until all statistical analyses are performed. All analyses will be performed using SAS 9.4, with α set at 0.05 and two-sided testing.

All efficacy analyses will be performed using a modified intention-to-treat principle. All participants who were randomized, received at least one dose of the trial compound (liraglutide or liraglutide placebo) and who had at least one assessment after baseline will be included in the efficacy analyses. All safety analyses will be performed in the intent-to-treat sample that includes all participants, who were randomized and received at least one dose of the trial compound (liraglutide or liraglutide placebo).

Primary endpoint

The primary endpoint is the change in glucose tolerance following a 4-hour 75-grams OGTT from week 0 to week 16. During the 4-hour 75-grams OGTT, blood was sampled at fixed time points: -

15, -10, 0, 5, 10, 15, 20, 30, 40, 50, 60, 90, 120, 150, 180, and 240 minutes. An analysis of covariance (ANCOVA) will be use to analyze change in glucose tolerance from week 0 to week 16 using mixed model analyses for the plasma glucose levels for the liraglutide and the liraglutide placebo group, respectively. In case of relevant baseline differences between the two groups, demographic, illness or treatment parameters will be included in the model as fixed effects together with the baseline value of the OGTTs as a covariate.

Secondary endpoints

Blood was also sampled for analyses of C-peptide, glucagon and incretin hormones in response to the glucose load at the same fixed time points during the OGTT. Change in secretion of C-peptide, glucagon and incretin hormones from week 0 to week 16 will also be evaluated using mixed model ANCOVA analyses for the liraglutide and liraglutide placebo group, respectively. In case of relevant baseline differences between the two groups, demographic, illness or treatment parameters will be included in the model as fixed effects together with the baseline value of the relevant variable as a covariate.

Most secondary endpoints were repeated every 4 weeks. Few secondary endpoints were only repeated at week 0 and 16. For all repeated measurements a mixed model ANCOVA analyses will be use to analyze mean change in continuous outcomes from week 0 to week 16 for the liraglutide and the liraglutide placebo group, respectively. In case of relevant baseline differences between the two groups, demographic, illness or treatment parameters will be included in the model as fixed effects together with the baseline value of the relevant variable as a covariate. Change in categorical outcomes from week 0 to week 16 will be analyzed using mixed model logistic regression with the same fixed effects and covariates as described for the continuous outcomes.

For secondary endpoints without repeated measurements, missing data imputations will be made using Multiple Imputation of Chained Equations (MICE).

For continuous outcomes without repeated measurements, outcomes will be analyzed using ANCOVA to detect differences between the liraglutide and the liraglutide placebo group. In the model baseline demographic, illness or treatment parameters will be included. Categorical outcomes without repeated measurements will be analyzed using a multiple mixed effect logistic

regression analysis model, where baseline demographic, illness or treatment parameters will be included.

Subgroup and sensitivity analyses

Subgroup and sensitivity analyses will be performed to assess the robustness of the primary analyses. These analyses will be performed using regression analysis for continuous outcomes and logistic regression for categorical outcomes. The analyses will consider clinically or mechanistically relevant baseline and intra-treatment variables, including:

- Gender
- Smoking
- Antipsychotics (clozapine vs olanzapine; monopharmacy vs polypharmacy with other antipsychotic medications)
- Lipid profile
- Liver function
- Different groups of dysglycaemia:
    a. HbA1c: 43 mmol/mol ≤ HbA1c ≤ 47 mmol/mol, vs
    b. Impaired fasting glucose (IFG): Fasting plasma glucose (FPG): 6.1 mmol/l ≤ FPG ≤ 6.9 mmol/l and HbA1c < 48 mmol/mol, vs
    c. Impaired glucose tolerance (IGT): two-hour plasma glucose after 75-g oral glucose tolerance test >7.8 mmol/l with a FPG < 7.0 mmol/l and HbA1c < 48 mmol/mol
- IGT < 11.1 mmol/l vs IGT >11.0 mmol/l
- Liraglutide treatment (1.2 mg vs 1.8 mg liraglutide)
- Weight
- Add-on psychotropic drugs/classes (antidepressants, anxiolytics etc. vs no add-on)
- Antihypertensive treatment vs no antihypertensive treatment
- Lipid lowering treatment vs no lipid lowering treatment
- Changes in antipsychotic medication (> 20 % change in dose vs < 20 % change in dose vs no changes in dose for clozapine or olanzapine, respectively)
- Inhalation steroid vs no inhalation steroid
- Body composition
- Insulin resistance

- Beta-cell function
- Incretin hormones
- Psychopathologic rating scales
- Alcohol consumption
- Length of disease
- Diagnosis (schizophrenia vs schizotypal disorder vs paranoid psychosis)
- Side effects
- Serious adverse events

Summary of changes in the protocol

Protocol version	Amendment	Approval from the Danish Health Authority	Approval from the Ethics Committee
Version 1.2	First final protocol	March 15, 2013	March 27, 2013
Version 1.3	Screening for eligible patients in hospital records	N/A. Only the Ethics Committee had to approve the amendment	August 20, 2013
Version 1.4	Sub-study: "Cambridge". Extra blood sampling for proteomic fingerprinting	December 12, 2013	November 25, 2013
Version 1.5	Expansion of recruitment area. Still single site study	N/A. Only the Ethics Committee had to approve the amendment	January 16, 2014
Version 2.0	1-year follow-up	September 17, 2014	September 3, 2014
Version 2.1	Adding second site: Aalborg	January 19, 2015	January 12, 2015
Version 3.0	Modification of inclusion criteria: Expansion of definition of prediabetes. Prolongation of study period.	June 2, 2015	May 12, 2015
Version 3.1	Sub-study: Examination of 10 healthy controls for baseline comparisons	October 23, 2015	October 23, 2015
Version 3.2	Prolongation of study period	February 22, 2016	February 5, 2016

Original protocol, version 1.2

CLINICAL TRIAL PROTOCOL

Compound VICTOZA®

Protocol title

Does a GLP-1 receptor agonist change glucose tolerance in antipsychotic-treated patients?

EudraCT number: 2013-000121-31

UTN-number: U1111-1128-3404

Protocol date/status 11-1-2013; final (version 2)

SPONSOR-INVESTIGATOR
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Professor
Department of Psychiatry O Sign: _____
Psychiatric Centre Copenhagen
University of Copenhagen, Denmark Date: _____

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Head of Diabetes Research Division
Department of Internal Medicine Sign: _____
Gentofte Hospital
University of Copenhagen, Denmark Date: _____

MONITORATION OF THE STUDY ACCORDING TO GCP
The GCP Unit, University of Copenhagen, Bispebjerg Hospital, Bygning 51, 3., Bispebjerg Bakke 23, 2400 Copenhagen NV.

FINANCIAL SUPPORT
The study has not yet received financial support.

COLLABORATORS
Peter W Jepsen, MD, PhD and Thomas Middelbo, MD, PhD, Department of Psychiatry O, Psychiatric Centre Copenhagen, University of Copenhagen, Denmark

Novo Nordisk A/S affiliate contact person: Esben Selmer Buhl, MD, PhD, Medical Advisor, Clinical, Medical and Regulatory Affairs, Novo Nordisk Scandinavia AB, Region Denmark

Novo Nordisk A/S: Supplier of intervention medication (Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injectors and Liraglutide placebo, 3.0 mL pre-filled pen-injectors

Protocol summary

Compound	Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injector (Victoza®) vs. Liraglutide placebo, 3.0 mL pre-filled pen-injector
Study title	Does a GLP-1 receptor agonist change glucose tolerance in antipsychotic-treated patients?
Scientific group	Tina Vilsbøll MD DMSs, Diabetes Research Division, Gentofte Hospital, and Anders Fink-Jensen MD DMSc, Department O (Rigshospitalet), Psychiatric Centre Copenhagen, University of Copenhagen, Denmark
Study location	Diabetes Research Division, Gentofte Hospital, University of Copenhagen, DK-2900 Hellerup, Denmark and Department O (Rigshospitalet), Psychiatric Centre Copenhagen, DK-2100 Copenhagen, Denmark.
Key dates	Start of recruitment Q1, 2013 Last treatment Q3, 2015 Recruitment duration 30 months
Objective	To investigate the effects of the GLP-1 receptor agonist Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injector (Victoza®) vs. Liraglutide placebo, 3.0 mL pre-filled pen-injector.
Study design	Double-blind, randomized, placebo-controlled, 16-weeks clinical trial
Patients	Volunteers with a diagnosis of schizophrenia, schizotypal disorder or paranoid psychosis between age 18 years and 65 years with dysglycaemia, a body mass index (BMI) ≥27 kg/m^2 and on antipsychotic medical treatment.
Sample size	Hundred patients will be included in the study.
Procedure	At inclusion, patients will be randomized to Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injector or Liraglutide placebo, 3.0 mL pre-filled pen-injector and blood sampling and DEXA scan will be performed. In addition blood pressure, OGTT, self-reported dietary, height, waist circumference and exercise are recorded and the patients are rated by use of the Schizophrenia Quality of Life Scale (SQLS), the Clinical Global Impression - Severity Scale (CGI-S), the Clinical Global Improvement Scale (CGI-S), Alcohol Use Disorders Identification Test (AUDIT) and the Global Assessment of Psychosocial Disability (GAPD) scale. The patients

	will be treated for 16 weeks with daily subcutaneous injection of Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injector or Liraglutide placebo, 3.0 mL pre-filled pen-injector. The initial daily dose of Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injector will be 0.6 mg for one week, 1.2 mg the following week and then 1.8 mg for the remaining 14 weeks treatment period. At follow up, week 4, 8, 12 and 16, the majority of tests will be repeated (se table 1).
Endpoints	The primary endpoint is the change from baseline in glucose tolerance (measured by area under the curve (AUC) for the plasma glucose (PG) excursion following a 4-hour 75 g Oral Glucose Tolerance Test (OGTT). Secondary endpoints include changes of dysglycaemia (impaired fasting glucose (IFG), impaired glucose tolerance (IGT), combined IFG/IGT or diabetes), changes in body weight, waist circumference, blood pressure, secretion of incretin hormones, insulin sensitivity and beta cell function, evaluated by homeostatic model assessment (HOMA), DEXA scanning (body composition), lipid profile, liver function, dietary, exercise records and measures of psychopathology, alchohol use and quality of life.
Safety	Blood samples will be collected during the entire study period to monitor safety parameters.
Study duration	Sixteen weeks

TABLE OF CONTENTS

1 INTRODUCTION

1.1 Clinical experience

Metabolic disturbances, overweight and obesity in antipsychotic-treated patients are a major clinical problem (1) that most likely results from the interaction of medication, genes and lifestyle factors such as physical inactivity and possible high fat diet. However, the mechanisms underlying antipsychotic cardiometabolic adverse effects are incompletely understood (2).

Recently, glucagon-like peptide-1 (GLP-1) based therapy was introduced to the marked for the treatment of type 2 diabetes (3). GLP-1 is an incretin hormone, which is secreted from endocrine L-cells of the small intestine in response to nutrients in the gut lumen (4). GLP-1 conveys an insulinotropic effect via GLP-1 receptors on the beta cells of pancreas and inhibits the secretion of glucagon from the alpha cells of the pancreas, which together lower the blood glucose level (4). Thus, GLP-1 is central for glycaemic control. Both of these effects are strictly glucose-dependent (more pronounced at higher levels of blood glucose) and the effect ceases as the level of blood glucose reaches values below 4-5 mmol/L. Therefore, the GLP-1 receptor (GLP-1R) agonist keeps the blood glucose at normal levels without increasing the risk of hypoglycaemia (5). Liraglutide, one of the GLP-1R agonists, has 97% homology with naturally occurring GLP-1 hormone but has a significant longer half-life (12–14 hours).

Antipsychotic medication treatment is often associated with obesity and metabolic disorders (1,2). Psychiatric patients on antipsychotic treatment, especially those who are overweight or obese and/or who have metabolic disturbances, are often encouraged to increase physical activity. Studies with type 2 diabetes patients have shown that different types of exercise interventions with supervised training have positive effects on glycaemic control (6). Exercise improves the aerobic capacity and muscular strength, which is often related to fat loss, increased muscle mass, increased cardiovascular fitness and improved glycaemic control. Exercise-induced fat loss and increase in muscle mass may improve glycaemic control and insulin sensitivity in these patients, even in the absence of absolute weight loss. However, in clinical practice exercise interventions in antipsychotic treated patients has often proven to be difficult (7). Another possibility includes instructions about a healthier food intake (7). This has proven efficacious in some patients, but not in others, and there exist a large group of patients where healthy life style interventions has only very little effect. Another possibility, if patients are treated with a weight-increasing agent, would be to shift medical treatment to a compound with less weight-increasing potential (8,9). However, two of the most potent weight-inducing antipsychotics, clozapine and olanzapine are also two of the most efficacious antipsychotic compounds and especially clozapine is often used to treat patients with only minor effects of other obtainable antipsychotic compounds (10). Consequently, switch of antipsychotic treatment is often not possible in these cases.

While a number of add-on treatments have been tried to mitigate antipsychotic induced weight gain, a recent meta-analysis of 32 studies in 1,482 patients found only 5 agents to be superior to placebo (11). Due to adverse effects, fenfluramine and sibutramine, two of these agents, have since been removed from the market. Reboxetine had the lowest effect and cannot be used in bipolar disorder. Thus, only metformin and topiramate, both leading to approximately 2.5-3.0 kg

weight loss compared to placebo, are the only currently usable augmentation agents (11). Nevertheless, little is known about metabolic advantages of these two add-on agents, and most studies were small (11).

Consequently, there exist a large and important group of antipsychotic treated patients who are in urgent need for medical interventions to improve their metabolic status, so risk factors for that life-shortening cardiovascular morbidity can be reduced. In this context, it is promising that studies have shown that patients with type 2 diabetes treated with GLP-1R agonists improve glycaemic control. The proposed study will attempt to extend these beneficial findings to the psychiatric population receiving antipsychotic medication treatment.

1.2 Benefits and risks

Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injector (Victoza®) is approved and marketed as non-insulin, once-daily medication for patients with T2DM. Besides control of the PG levels, Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injector may provide the additional benefit of body weight loss. The patients in the present study suffer from schizophrenia and obesity and we expect to see improved glucose tolerance in patients treated with Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injector. The risks attributed to Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injector are mainly related to gastrointestinal symptoms. The most common adverse events include nausea, vomiting, headache and diarrhoea, which most often cease with time (weeks). Less commonly, the patients may experience stomach pain, constipation, fever, reflux, gastritis or dizziness. Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injector can be injected subcutaneously in the abdomen, in the thigh or in the upper arm. Patients will receive detailed information in writing and orally about the risk of adverse events. If the patients find the adverse events unacceptable, they are free to withdraw from the study without any further explanation.

1.3 Clinical trial regulations

The trial will be monitored by the GCP unit of Copenhagen University. The clinical trial will be conducted in compliance with the protocol, according to ICH E6: Good Clinical Practice: Consolidated guideline, CPMP/ICH/135/95, and national guidelines including Clinical Trials Directive 2001/20/EC. The trial can be subjected to quality audit.

2 OBJECTIVES OF THE TRIAL

The objective of this study is to investigate long term (16 weeks) effects of Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injector or Liraglutide placebo, 3.0 mL pre-filled pen-injector

on glucose tolerance in patients with a diagnosis of schizophrenia, schizotypal disorder or paranoid psychosis between age 18 years and 65 years with dysglycaemia, a body mass index (BMI) ≥27 kg/m2 and on antipsychotic medical treatment with clozapine or olanzapine.

3 INVESTIGATIONAL TRIAL DESIGN

3.1 Study endpoints

3.1.1 Primary endpoint

The primary endpoint is the change in glucose tolerance from baseline (measured by area under the curve (AUC) for the plasma glucose (PG) excursion following a 4-hour 75 g oral glucose tolerance test (OGTT)) to follow up at week 16 or to last observation if study participation is stopped earlier.

3.1.2 Secondary endpoints

Secondary endpoints include changes of dysglycaemia (impaired fasting glucose (IFG), impaired glucose tolerance (IGT), combined IFG/IGT or diabetes), changes in body weight, waist circumference, blood pressure, secretion of incretin hormones, insulin sensitivity and beta cell function, evaluated by homeostatic model assessment (HOMA), DEXA scanning (body composition), lipid profile, liver function, dietary, exercise records and measures of psychopathology, alchohol use and quality of life from baseline to follow up at week 16 or to last observation if study participation is stopped earlier.

3.2 Study design

A double-blind, randomized, parallel, placebo-controlled clinical trial has been chosen in accordance with the trial objectives.

3.3 Comparative treatment regimes

Treatment with: 1) Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injector or 2) Liraglutide placebo, 3.0 mL pre-filled pen-injector.

3.4 Randomisation and blinding

Patients will be randomized to treatment with 1) Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injector or 2) Liraglutide placebo, 3.0 mL pre-filled pen-injector. The randomization will be carried out by drawing sealed opaque envelopes with the randomization code.

The supplier of Victoza® pens, i.e. Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injectors and placebo pens, i.e. Liraglutide placebo, 3.0 mL pre-filled pen-injectors (Novo Nordisk) will be responsible for labelling and blinding the Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injectors and Liraglutide placebo, 3.0 mL pre-filled pen-injectors before beginning of the treatment period and for generating the randomization

code. An emergency code will be kept at Gentofte Hospital and Psychiatric Centre Copenhagen if a patient develops adverse events that demand knowledge on the treatment, the code may be broken.

3.5 Description of investigational drug and placebo drug

Victoza® (Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injector) is supplied in pens for injection containing 1.8 mg of the GLP-1 agonist liraglutide in 3.0 ml sterile water with disodiumphosphate and propylenglycol, and phenol for conservation (pH 8.15). Commercial pens will be used. Direction for use (DFU)wil be given together with trial products.

Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injector

The initial daily dose will be 0.6 mg for one week, 1.2 mg the following week and then 1.8 mg for the remaining treatment period. Patients who, due to adverse events, do not tolerate up-titration to 1.2 or 1.8 mg Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injector will remain on 0.6 or 1.2 mg of Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injector, respectively. The injection is administered once daily.

Liraglutide placebo, 3.0 mL pre-filled pen-injector

The Liraglutide placebo, 3.0 mL pre-filled pen-injectors contain "Victoza-vehicle" (no active drug) and are administered in the same way and volume as Victoza®. The Liraglutide placebo, 3.0 mL pre-filled pen-injectors are specially packed for this study and will be used in the study only.

3.6 Drug storage

The pens are delivered in separate boxes. Storage and in-use conditions: Not in use: The Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injectors must be stored in a refrigerator at a temperature between +2°C and + 8°C. Store away from the freezer compartment. Do not freeze and do not use if it has been frozen. In-use: After first opening, the Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injectors can be stored for one month at temperatures between 10°C and 30°C or in a refrigerator (2°C-8°C).. The pens must be protected from all sources of light, and the pen caps should be kept on when the pen is not in use. The Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injectors should not be used if it does not appear clear and colourless

3.7 Drug accountability

One investigator will be responsible for drug accountability. For each patient treated, the batch number of the pen must be documented and the patients will be asked to return the pens after usage. After verification of the drug accountability, proper destruction of the used pens will be ensured.

3.8 Study duration

The full study period constitutes 16 weeks.

3.9 Trial timetable

The anticipated timetable for the trial is:

Start of recruitment	March 2013
End of recruitment	May 2015
Last treatment	September 2015

4 PATIENT SELECTION

4.1 Number of patients and target population

Planned number of subjects to be screened (i.e. documented informed consent): 150 (Screen failure rate = 15-20 %). Number of subjects planned to be randomized and started on trial product: 125. Number of subjects expected to complete the trial: 100.

Hundred patients will be included. The patients will be recruited via Psychiatric Center Copenhagen or via other psychiatric centres in the Capitol Region of Copenhagen. Recruitment will take place through direct contact or through contact by mail or telephone. The expected number of dropouts is difficult to estimate, since similar interventions with daily subcutaneous injections have not, to our knowledge, been performed before among psychiatric patients. In the study by Astrup et al., 16 persons out of 90 (18%) in the liraglutide, 1.8 mg group over the 20 weeks trial period. We will expect the withdraw to be a little higher in our patient population over time, but this effect is expected to be counteracted by our shorter study duration. Consequently, we expect a drop-out rate of 20 % in our study population over the 16 weeks trial period. At least eighty patients have to complete the full 16 week trial. If the drop out rate should turn out to be higher than 20 %, more patients will be included in order to reach the goal of eighty patients completing the study. In that case change in sample size will be documented in a substantial protocol amendment.

4.2 Patient screening

Eligible patients will be informed about the possibility to participate in this study. Before any trial related procedures are performed, the patient must be thoroughly informed about the study and he/she must sign and date the informed consent form. A pre-treatment evaluation will be carried out to screen the patients according to inclusion and exclusion criteria (see Treatment Procedure).

4.3 Inclusion criteria

- Informed oral and written consent
- Diagnosed with schizophrenia, schizotypal disorder or paranoid psychosis according to the criteria of ICD10 (International Classification of Diseases, World Health Organization) or the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, the American Psychiatric Association)
- and on stable antipsychotic treatment with either clozapine or olanzapine for at least 6 months (without dose change for at least 30 days)
- Stable co-medications for at least 30 days.
- Age ≥18 years and ≤65 years
- Stable weight (defined as less than 5% change in weight over the last 3 month before inclusion)
- BMI ≥27 kg/m^2
- Dysglycaemia (IFG, i.e. fasting plasma glucose level from 6.1 mmol/L to 6.9 mmol/L or IGT, i.e. two-hour glucose levels of 7.8 to 11.0 mmol on the 75-g oral glucose tolerance test and a fasting plasma glucose of less than 7.0 mmol/L).

4.4 Exclusion criteria

- Compulsory treatment
- Females of child bearing potential who are pregnant, breast-feeding or have intention of becoming pregnant or are not using adequate contraceptive measures
- Subjects treated with corticosteroids or other hormone therapy (except estrogens)
- Any active substance abuse or dependence for the past 6 months (except for nicotine)
- Impaired hepatic function (liver transaminases >2 times upper normal limit)
- Impaired renal function (se-creatinine >150 µM and/or macroalbuminuria)
- Impaired pancreatic function (acute or chronic pancreatitis and/or amylase >2 times upper normal limit)
- Cardiac problems defined as decompensated heart failure (NYHA class III or IV), unstable angina pectoris and/or myocardial infarction within the last 12 months
- Uncontrolled hypertension (systolic blood pressure >180 mmHg, diastolic blood pressure >100 mmHg)
- Any condition that the investigator feels would interfere with trial participation
- Receiving any investigational drug within the last 3 months
- Use of weight-lowering pharmacotherapy within the preceding 3 month
- Type 1 or 2 diabetes with HbA1c > 6.5%

4.5 Patient withdrawal

Completion or trial termination for any reason will be fully documented in the clinical record form (CRF) pages. Patients are free to withdraw from the trial at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason for withdrawal may be withdrawal of consent,

treatment failure, adverse event(s), pregnancy discovered during the trial, significant worsening (Clinical Global Impressions-Improvement (CGI-I) score of 6 or 7 (much or very much worse), Change in the dosing of olanzapine or clozapine of more than 20% or loss to follow-up. The reason(s) will be recorded in the CRF. Dropouts will be replaced until 80 patients have completed the treatment period. Data from dropouts will be included in data processing. Patients withdrawing from the trial should be encouraged to go through the same final evaluations as patients completing the trial according to the protocol with special focus on safety. The aim is to record data in the same way as for patients who complete the trial. Otherwise data will be recorded as consented by the patient. This will be documented in the CRF.

5 TREATMENT PROCEDURE

The study consists of a pre-treatment evaluation followed by a 16 weeks treatment period where patients are randomized to treatment with either 1) liraglutide (subcutaneous injections using Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injectors) or 2) placebo (subcutaneous injections, using Liraglutide placebo, 3.0 mL pre-filled pen-injectors).

5.1 Pre-treatment evaluation

Before screening, all patients will be provided oral and written information about the trial, including the most common adverse events, and the procedures involved in the study. All subjects will be fully informed, verbally and in writing, of their rights and responsibilities while participating in the trial. They will have the opportunity to ask questions, have ample time to consider participation and must give both signed and dated consent to be included in the trial. The total duration of the trial for a patient will be 16 weeks. Each patient will attend regular visits (every 4 weeks) to the clinic in order to draw blood samples, evaluate side effects, global illness severity and measure body weight and waist circumference. Antipsychotic medication and possible IGF / IGT / dysglycaemia history will also be optained.

Pre-treatment evaluation will only be performed after the patient has agreed to participate and has signed and dated the informed consent form. No treatment will be initiated before the signed consent has been given. If the patient meets all inclusion criteria, an appointment for the first visit will be set up. The clinical examinations will be conducted at the three community mental health centres and wards affiliated with Psychiatric Centre Copenhagen. If not enough patients can be included from til centre, other psychiatric centres in the Capital Region of Copenhagen will be included.

5.2 Treatment evaluation

A 75 g-oral glucose tolerance test (OGTT) will be performed at baseline and after 16 weeks of treatment in all participants. The procedures are as follows: 75 g water-free glucose dissolved in 300 ml H_2O is to be ingested during the first 5 minutes of the test. Blood is sampled from a cannula inserted in a cubital vein 15, 10 and 0 min before oral intake of the glucose load and 5, 10, 15, 20, 30, 40, 50, 60, 90, 120, 150, 180 and 240 min after. At each time-point blood is drawn for serum / plasma analyses for glucose, insulin, C-peptide, glucagon, intact and total GLP-1 and GIP,

622 respectively. During both experimental days the hand with the cannula is kept in a heating box (42
623 ^{o}C) throughout the test.

624 After baseline examinations the groups will be randomized to receive blinded treatment with
625 either liraglutide s.c. using Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injectors or placebo, using
626 Liraglutide placebo, 3.0 mL pre-filled pen-injectors.

627 Victoza®/Liraglutide placebo, 3.0 mL pre-filled pen-injector is administered subcutaneously one time
628 daily in the entire treatment period (Day 1-7: 0.6 mg Victoza®/Liraglutide placebo, 3.0 mL pre-filled pen-
629 injector; Day 8-14: 1.2 mg Victoza/Liraglutide placebo, 3.0 mL pre-filled pen-injector; Day 15 and rest of the
630 study: 1.8 mg Victoza®/Liraglutide placebo, 3.0 mL pre-filled pen-injector). Patients who, due to adverse
631 events, do not tolerate up-titration to 1.8 mg Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injector will
632 remain on 1.2 mg of Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injector. The patients are instructed in
633 injection technique. Compliance and adverse events are noted during the entire period. If the patient
634 cannot self inject Victoza®/Liraglutide placebo, 3.0 mL pre-filled pen-injector, a contact person will assist.
635 Assisting contact persons, i.e. assisting nurses, are blinded to the treatment too.

636

637 **Table 1: Study flow chart**

638

	Screening (max 2 weeks before week 0)	Inclusion (week 0)	Follow-up (week 4)	Follow-up (week 8)	Follow-up (week 12)	Follow-up (week 16)
Introduction, informed content, blood screening	X					
Drug dispensing		X		X		
Blood sampling		X	X	X	X	X
Weight		X	X	X	X	X
Blood pressure		X	X	X	X	X
OGTT		X				X
DEXA scanning		X				X
Self-reported dietary		X	X	X	X	X
Heigth		X				
Waist circumference		X	X	X	X	X
Exercise records		X	X	X	X	X
The Schizophrenia Quality of Life Scale (SQLS)		X				X
Clinical Global Impression, Improvement (CGI-I)		X				X
Clinical Global Impression, Severity (CGI-S)		X				X
Global Assessment of Function (GAF)		X				X

	Screening (max 2 weeks before week 0)	Inclusion (week 0)	Follow-up (week 4)	Follow-up (week 8)	Follow-up (week 12)	Follow-up (week 16)
Alcohol Use Disorders Identification Test (AUDIT)		X				X

6 ASSESSMENT OF EFFICCY

6.1 Clinical response

The clinical response of Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injector compared to Liraglutide placebo, 3.0 mL pre-filled pen-injector is assessed by monitoring the change from baseline in glucose tolerance (measured by area under the curve (AUC) for the plasma glucose (PG) excursion following a 4-hour 75 g oral glucose tolerance test (OGTT) at inclusion (week 0) and at follow up, week 16. In addition, a number of secondary endpoints are included too.

6.2 Blood samples

Glycaemic control is evaluated by an OGTT and level of HbA1c on the day of inklusion (basal level) and after 16 weeks of treatment. The endocrine pancreas function is assessed by plasma concentrations of insulin, C-peptide and plasma glucagon. Additionally levels of incretin hormones will be evaluated in the fasting state and after oral glucose (amount of blood max 150 ml. per test)

7 ASSESSMENT OF SAFETY

7.1 Serious adverse event (SAE) and serious adverse reactions (SAR)

7.1.1 Definition of SAE and SAR

SAE, i.e. there exists a relationship between the drug or the experiment and the untoward effect, and SAR, i.e. a noxious event occurring in a treated patient in an experiment, which is not necessarily related to the treatment is any untoward medical occurrence that at any dose:

1) results in death or

2) is life-threatening or

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

3) requires inpatient hospitalization or prolongation of existing hospitalization[1] or

4) results in persistent or significant disability/incapacity[2], or

5) is a congenital anomaly/birth defect

and is either known (SAE or suspected (SAR)

In addition, medical and scientific judgment is required to decide if prompt notification is required in other situations, i.e. any event which the investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the subject or required intervention to prevent one of the outcomes listed above, or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug.

Reporting of SAE and SAR

The investigators must immediately report any SAE and SAR to the sponsor occurring between the treatment with study drug and completion of last follow-up, i.e., 1 month after the treatment, whether or

[1] Complications occurring during hospitalisation are AEs and are SAEs if they cause prolongation of the current hospitalisation. Hospitalisation for elective treatment of a pre-existing non worsening condition is not, however, considered an AE. The details of such hospitalisations must be recorded on the medical history/physical examination page of the CRF.

[2] An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions.

not considered related to study drug. All pregnancies occurring during the study, although not SAEs, should be reported using the SAE reporting procedures and will be reported directly to Novo Nordisk.

The investigator should not wait to receive additional information to fully document the event before notifying a SAE, although additional information may be requested. Where applicable, information from relevant laboratory results, hospital records and autopsy reports should be obtained. The investigators are also required to submit follow-up reports until such time as the SAE or SUSAR has resolved or in the case of permanent impairment, until the SAE or SUSAR stabilizes.

The sponsor will report all SAEs to the Ethics Committees (IECs) and all SARs to the Danish Medical Agency once a year together with a report on the safety of the study patients. All SAEs and SARs will be reported to Novo Nordisk within 15 days from the investigator getting knowledge of the case. Details of SAEs and SARs will be noted on the adverse event pages in the CRF. There will be no formal follow-up after last patient visit but all patients have the opportunity to contact the investigators in case of uncertainties. Instances of death, congenital abnormality or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigators at any time after cessation of study medication and linked by the investigators to this study should be reported.

7.1.3 Suspected unexpected serious adverse reaction (SUSAR)

Any serious adverse event that is unexpected will immediately be reported by sponsor to the Danish Medical Agency. SUSARs that result in death or are life-threatening will be reported to the Danish Medical Agency at the latest 7 days after the sponsor has been notified about it. After reporting the SUSAR, the sponsor will provide the Danish Medical Agency all relevant further information on the course of case within 8 days. SUSARs that do not result in death or are not life-threatening will be reported to the Danish Medical Agency at the latest 15 days after sponsor has been notified about the SUSAR. Any report will be followed by comments about any consequences for the research project. Sponsor will moreover report any SUSARs to the marketing authorization holder (Novo Nordisk).

7.2 Adverse event

7.2.1 Definition of adverse event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. All events occurring after the subject has signed the study consent form should be reported as an adverse event.

7.2.2 Reporting of adverse event

AEs related to the treatment according to the investigator will be recorded in the CRF. All reported AE's will be followed up until resolved or as clinically required.

7.2.3 Assessment of adverse event

AEs may be reported spontaneously by the patient through open (non-leading) questioning during the study. As far as possible, all AEs must be described by their duration (start and stop date), severity (mild, moderate, or severe), relationship to treatment (yes, uncertain, no), and according to the need of other specific therapy. The onset of AEs will be classified relative to the stage of treatment.

7.3 Reporting at the end of the study

All SAEs, SARs, SUSARs, and AEs will be reported to the Danish Medical Agency at the end of the study.

8 STATISTICAL EVALUATION

8.1 Statistical analyses

All analyses will be performed using the intent-to-treat principle on subjects who were randomized and received at least one dose of the trial compound (Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injector or Liraglutide placebo, 3.0 mL pre-filled pen-injector). Missing data will be imputed using a last-observation-carried-forward (LOCF) methods. Analyses will be performed using SPSS, with alpha set at 0.05.

The primary outcome will be change in glucose tolerance from baseline. Secondary outcomes include changes in blood pressure, fasting glucose, fasting insulin sensitivity and beta cell function (evaluated by HOMA), fat mass and fat percentage (measured by DEXA scanning), liver function, lipid profiles, triglycerides, body weigth, waist circumference and dietary and exercise behaviours (evaluated with 24 hour recall and 7 day recall, respectively) as well as quality of life.

All *continuous outcomes*, i.e., change in metabolic parameters, weight, body composition parameters, and exercise and diet behaviour, will be analyzed using ANOVA from baseline to last observation endpoint. In case, relevant baseline demographic, illness or treatment parameters differ significantly between the two groups, these parameters will be included in an ANCOVA model. *Categorical outcomes*, ie, shift from obesity, overweight, hyperglycemia, hypertrigyceridemia etc to the next lower risk category at last observed endpoint, will be analyzed using chi square analyses. In case, relevant baseline demographic, illness or treatment parameters differ significantly between the two groups, these parameters will be included in a multivariate logistic regression analysis model.

8.2 Justification of sample size

The study is an explorative study and the required patient population size (see above) is based on significance level (α) of 5%, a power (1-β) of 80%, where β (20%) is the risk of accepting a

hypothesis that is false, an estimated minimum relevant difference (MIREDIF) of the area under the curve (AUC) for the PG excursion following an OGTT after 16 weeks of intervention. Thus, with the above-mentioned power, significance level, MIREDIF and SD, the trial requires 50 patients in each arm; a total of 100 patients.

8.3 Disposition of patients

Efficacy results will be presented for the per-protocol (PP) efficacy population and intent-to-treat (ITT) efficacy population.

Per-protocol (PP) efficacy population:

This population consists of all treated patients. Only observed data will be part of the per-protocol analysis.

Intent-to-treat (ITT) efficacy population:

This population will consist of the entire population for whom any aspect of treatment was initiated. This population will be analyzed using the LOCF method to impute missing values and to avoid possible bias introduced by non-random dropout of patients.

8.4 End of the study before time

The study will be stopped for a given patient if this patient wishes to withdraw from the study or in case of extraordinary circumstances that makes it impossible for the patient to complete the study. Moreover, extraordinary events that prevent the study to be carried through will lead to interruption of the whole study for all participating patients, which will be informed about the decision and the reason for ending the study before time.

9 DATA MANAGEMENT

9.1 Source data identification and source data verification

Patient information collected in the CRF but not recorded in the patient notes is regarded as source data. However, the patient's participation and any serious adverse events related to the study treatment should be documented in the patient hospital files. In the process of ensuring data completeness and accuracy, source data verification (SDV) should be performed. The patients will be informed in writing about the need for SDV. SDV will be performed by the GCP monitors. To be able to do SDV, the investigators will require and review relevant part of the patient hospital files.

9.2 Subject data protection

Patient number, initials, date of birth and sex will identify the patients in the CRFs. The sponsor-investigator is responsible for keeping a list of all randomized patients including patient numbers, full names and date of

birth. In addition, the sponsor-investigator will prepare a list of patients who were screened for participation of the trial but were not randomized and the reason for non-eligibility. The patients will be informed in writing that the results will be stored and analyzed in a computer according to national laws, as applicable, and that patient confidentiality will be maintained.

9.3 Data handling

All data obtained during the study will be documented in the individual CRF. The reasons for any missing data must be noted in the CRF. Corrections should be made legibly, dated and initialed. Incorrect entries must not be covered by correction fluid, or obliterated, or made illegible in any way. Source data, source documents, CRF, protocol and amendments, drug accountability forms, correspondence, patient identification list, informed consent forms, and other essential GCP documents will be retained for at least 15 years after the part is completed at the study site. Patient data will be entered continuously into the database by the sponsor-investigator.

10 ADMINISTRATIVE PROCEDURES

10.1 Insurance

The investigators make sure that the participation of the patients in the study is covered by insurance via the hospital.

10.2 Ethics committee (EC) / institutional review board

The trial protocol, including the patient information and informed consent to be used, must be approved by the regional EC. Written approval must be obtained before enrolment of any subjects into the trial. It is the responsibility of the sponsor-investigator to obtain the letter of approval. The investigators will ensure that this study is conducted in full conformance with the Edinburgh, Scotland (2000), amendment to the Declaration of Helsinki 1964 and with national laws and regulations for clinical research. The sponsor-investigator is responsible for informing the ethics committees and regulatory authorities of any SAE and/or major amendments to the protocol as per national requirements. The sponsor-investigator should file all correspondence and notify the ethics committees and regulatory authorities when the study is completed.

10.3 Ethical considerations

This study is not considered as having any ethical problems. The treatment is associated with minimal discomfort for the participating patients comprising blood sample collection and daily injection of Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injector or Liraglutide placebo, 3.0 mL pre-filled pen-injector in the subcutis in the abdomen, in the thigh or in the upper arm. Common adverse events are mild to moderate transient gastrointestinal symptoms (nausea, vomiting and diarrhoea) and headache affecting around 10-15% of treated patients. Less commonly, the patients may experience stomach pain, anorexia, constipation, fever, reflux, gastritis, dizziness, tiredness and upper airway infection. Rare adverse events comprise acute pancreatitis, thyroid adenoma and angioedema.

When collecting blood, some patients may experience minor discomfort when the needle penetrates the skin and rarely a small bleeding occurs. The amount of blood collected during the entire study period is around 600 ml and only patients with normal blood haemoglobin will be included.

Symptoms of hypoglycaemia such as sweating, tremor, confusion, nausea, nervousness, weakness, hunger, trouble speaking, palpitations, anxiety and irritability can be experienced by some patients.

Patients will be treated on highest tolerated dose of Liraglutide 6.0 mg/mL, 3.0 mL pre-filled pen-injector. Severe systemic adverse events are not expected.

The patients will receive thorough verbal and written information about the risk of developing the mentioned adverse events. Verbal and written informed consent will be obtained from patients prior to participation in accordance with current rules. It will be emphasized in the declaration of consent that participation in the project is voluntary and that patients may withdraw their consent to participate at any time without providing a reason and without any consequences for the patient's current or future treatment by the health service.

The participating patients will receive a study number when entering the study. All data forms and blood samples will only be labelled with the patient's initials and study number. The sponsor-investigator is responsible for keeping a list separately for all randomized patients containing patient numbers, full names and date of birth. Extra plasma and white blood cells will be stored for up to 10 years after the end of the study for repeated measurements in case of error analysis or the need for more analyses. The use of these samples will demand a new approval. The protocol will be notified to the Danish Data Protection Agency, The Danish Ethics Committee and the Danish Medicines Agency.

10.4 Patient informed consent

The investigators are responsible for giving the patients complete verbal and written information about the nature, purpose, and possible risks and benefits of the trial. The patients must also be notified that they are free to withdraw from the trial at any time. The patients should have reasonable time to read and understand the information before signing. The sponsor-investigator is responsible for obtaining signed and oral EC-approved informed consent from all subjects before performing any trial-related procedures.

A copy of the patient information and of the patient informed consent form will be given to the patients. The signed consent form will be kept by the sponsor-investigator, either in the patient hospital file or in the sponsor-investigator's study file.

Participating patients will be informed about the result of the study if they express a wish for this.

10.5 Regulatory affairs

A notification will be submitted to national authorities before commencement of the trial, as applicable according to local regulations. Notifications and reports will be filed according to ICH E6(R1): GCP: Consolidated guideline, CPMP/ICH/135/95, and national guidelines including Clinical Trials Directive 2001/20/EC.

10.6 Trial monitoring

Prior to the start of the study, the sponsor-investigator will ensure that the other investigators are familiar with the protocol, CRFs and other study documents and procedures. The sponsor-investigator will be visited on a regular basis by the monitor, who will check trial procedures, including safety assessments, drug handling, data recording and SDV. The monitor will be allowed to review relevant hospital records to confirm that required protocol procedures are being followed and check consistency between patient record and CRF. Incorrect or missing entries onto the CRFs will be addressed as data queries and must be corrected immediately. Trial monitoring will not jeopardize patient confidentiality. The trial will be monitored by the GCP unit of Copenhagen University. The clinical trial will be conducted in compliance with the protocol, according to ICH E6: Good Clinical Practice: Consolidated guideline, CPMP/ICH/135/95, and national guidelines including Clinical Trials Directive 2001/20/EC. The trial can be subjected to quality audit.

10.7 Trial audits and inspections

The patients will be informed in writing about the possibility for audits and/or inspections. The audit and/or inspection might be performed by the hospital institutional review board/ethics committee or regulatory authority. In these cases, relevant part of the patient records will be required and reviewed.

11 CONFIDENTIALITY AND COMMUNICATION OF RESULTS

11.1 Publication

At the end of the trial one or more manuscripts will be prepared for publication in scientific journals. The investigators will be given 14 days to review and comment on any manuscript/abstract or other means intended for publication or presentation of the data. While it is the intention that the sponsor-investigator will be the first author, the published international guidelines for authorship (International Committee of Medical Journal Editors, 1997) will be adhered to; i.e. 'All persons designed as authors should qualify for authorship. Each author should have participated sufficiently in the work to take public responsibility for the content'.

The final decision on the order of authorship will be decided when the study has been finalized. The results from the study may moreover be presented as posters or oral presentations at national and/or international conferences. The trial will be registered at www.clinicaltrials.gov according to the requirements from the US Food and Drug Administration (FDA) and the International Committee of Medical Journal Editors.

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13 Budget (in DKK)

Running costs

Blood sampling analyses	No. of subjects	Total samples	Price per sample	Total price
Screening packages	100	100	1.700	170.000
Blood samples during experiment (Glucose, C-peptide, insulin, HbA1C, cholesterol, triglycerides)				250.000
Total price for blood sampling analyses				**420.000**
Subject reimbursement				
DKK 4.000 per subject	100		4.000	400.000
Total price for subject reimbursement				**400.000**
Utensils/other costs				
Cannulas, syringes, tubes, storage boxes etc.				350.000
DEXA-scan	100	200	2.000	400.000
Total price for utensils/other				**750.000**
Total running costs				**1.570.000**

Salary

Technical staff	
Lab-technician ; 100% of full time for 24 months, clinical experiments and analyses	600.000
Psychiatric nurse; 100% of full time for 24 months	700.000
Total salary costs	**1.300.000**

Total budget (DKK)	**2.870.000**