SemaPsychiatry- Statistical Analysis Plan

Does the glucagon-like peptide-1 receptor agonist semaglutide prevent deterioration of metabolic state in prediabetic or diabetic patients with schizophrenia treated with the antipsychotic compounds clozapine or olanzapine?

EudraCT: 2020-000102-28
Clinicaltrials.gov: NCT04892199

SAP date/status 18.09.24/ first edition
Protocol version: 03.07.24/ 12th edition

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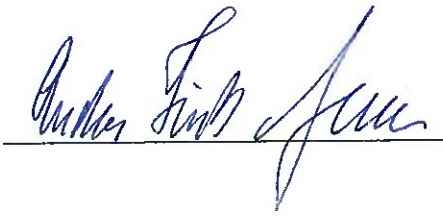

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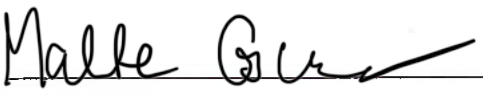

Date: 18.9.24

Abbreviations

AE	Adverse event
ALAT	Alanine aminotransferase
ALP	Alkaline phosphatase
AR	Adverse reaction
ASAT	Aspartate aminotransferase
AUDIT	Alcohol use disorder identification test
BMI	Body mass Index
CRF	Case report form
CGI-S	Clinical Global Impression Severity scale
CVD	Cardiovascular disease
DUDIT	Drug Use Disorders Identification Test
FIB-4	Fibrosis-4
FTND	Fagerström test for nicotine dependence
GAPD	Assessment of Psychosocial Disability
GLP-1	Glucagon-like peptide-1
GLP1-RA	Glucagon-like peptide-1 receptor agonists
HbA1c	Glycated haemoglobin A1c
HDL	High-density lipoprotein
HOMA2-IR	Homeostatic model assessment of insulin resistance
IQR	Interquartile Range
LDL	Low-density lipoprotein
MAR	Missing at random
MIREDIF	Minimum relevant difference
PANSS-6	Positive and Negative Syndrome Scale Six-items
REDCap	Web application for building and managing online surveys and databases
SAE	Serious adverse event
SD	Standard deviation
SQLS	Schizophrenia Quality of Life Scale
SRL	Subject randomisation list
VLDL	Very Low-density lipoprotein

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Introduction

Background and rationale

Patients with schizophrenia have a two-to-three-fold higher mortality compared to the general population.[1–3] Somatic diseases, primarily cardiovascular disease (CVD), are estimated to account for 60% of the excess mortality.[3,4] High prevalence of obesity, metabolic disturbances and type 2 diabetes among patients with schizophrenia largely explain the increased risk of cardiovascular morbidity and increased mortality.[3–5] A recent meta-analysis found that glucose homeostasis is altered from illness onset in schizophrenia, indicating that patients are at increased risk of diabetes.[6]

Antipsychotic medications are effective for treating schizophrenia[7] but the drugs are linked to body weight increase and development of metabolic disturbances and type 2 diabetes.[8,9] Clozapine is the most effective antipsychotic drug and used for treatment-resistant schizophrenia.[10] Unfortunately, clozapine induces the greatest body weight gain and confers a high risk of metabolic disturbances compared to other psychotropic medications.[5,8] The weight gain after clozapine initiation is on average seven kilogram within the first 16 weeks of treatment[11] and around 10% of the patients will develop type 2 diabetes within the first year of treatment with clozapine – and around 35% within the first five years of treatment.[12] Olanzapine is often used in the clinic to treat psychotic events and this compound also induces weight gain and conveys a high degree of metabolic disturbances including prediabetes.[7] Previously, limited effects have been demonstrated for counteracting antipsychotic-induced body weight gain and metabolic disturbances with the switch of antipsychotic therapy, non-pharmacological/behavioural interventions or adjunct pharmacological treatments.[13–17]

Growing evidence suggests a potential effect of an adjunct pharmacological treatment with incretin-based therapies, such as glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RA). Five different GLP-1RAs are approved for use in Europe and the US for type 2 diabetes and two for bodyweight management. Semaglutide, a GLP-1RA with an extended half-life of approximately one week (which permits once-weekly subcutaneous administration)[18] was approved for the treatment of type 2 diabetes by the US Food and Drug Administration (FDA) in 2017 and the European Medicines Agency (EMA) in 2018. In 2021 semaglutide treatment in a higher dose, 2.4mg (Wegovy®) once weekly s.c. administration was approved for treating obesity by the FDA and in 2022 by EMA. Recent studies have shown beneficial effects of liraglutide, semaglutide and albiglutide on major adverse cardiovascular events in patients with type 2 diabetes at high risk of CVD.[18–20] In a recent study, we reported that subcutaneous treatment for 16 weeks with liraglutide as adjunctive treatment to clozapine or olanzapine in schizophrenia-spectrum disorder patients with prediabetes improved HbA1c with approximately 2.3 mmol/mol, glucose tolerance and several other cardiometabolic disturbances and induced a 5.3 kg body weight loss compared to placebo.[21] In the light of these promising findings, there is a need for further studies to elucidate the effect on metabolic state and weight gain of longer-lasting treatment with GLP-1RA in schizophrenia-spectrum disorder patients treated with clozapine or olanzapine. Furthermore, clozapine-induced metabolic changes can be observed already within the first year after initiation of clozapine treatment.[12] Therefore, the effect of add-on therapy with GLP-1RA should be investigated when clozapine- or olanzapine-treated patients fulfil the diagnose for prediabetes or diabetes within a time frame of max 60 months following initiation of clozapine- or olanzapine treatment.

Objectives

We hypothesize that add-on therapy with GLP-1RA, in prediabetic or diabetic schizophrenic patients who have initiated treatment with clozapine or olanzapine, will improve overall glycemic control and mitigate the antipsychotic-induced metabolic disturbances.

Study Methods

Trial design

The SemaPsychiatry trial[22] were a randomised, double-blinded, placebo-controlled clinical trial for 26 weeks and a long term follow-up 1,5 years after the end of participation in the main trial. Comparative treatment regimens were once-weekly injections with semaglutide 1 mg (Ozempic®) or placebo (vehicle) as a supplement to usual psychiatric treatment. Baseline data were collected at the screening session. Follow-up visits were scheduled at weeks 4, 8, 12 (phone call), 16, 20 (phone call), and a final evaluation at week 26. All patients had a baseline DXA-scan at week 1 and repeated at week 25. All participants wore an activity sensor for one week at baseline and again one week after the 26 weeks of treatment.

Randomisation

The participants were block randomized into two groups. The randomization was stratified in terms of age (two levels) and sex (two levels). The supplier of pens (Novo Nordisk A/S) provided a subject randomisation list (SRL) for randomisation purpose. The random allocation sequence (SRL) was uploaded in REDCap in accordance with REDCap's user guide and reference manual. The supplier of pens was responsible for labelling and blinding the semaglutide and semaglutide placebo pens before the beginning of the treatment period.

Sample size

The study was an explorative study, and the required patient population size was based on a significance level (α) of 5%, a power (1-β) of 90%, where β (10%) is the risk of accepting a false hypothesis. Based on data from a recent study in a similar patient population (50), we estimated that the minimum relevant difference (MIREDIF) of HbA1c (primary endpoint) after 26 weeks of intervention is -0.26 mmol/mol and an SD of 0.28 mmol/mol. Thus, with the abovementioned power, significance level, MIREDIF and SD, the trial required 26 patients in each of the two arms, totalling 52 patients. Thus, with an expected dropout rate of 50%, a total of 104 patients were to be randomised.
However, due to a much lower dropout rate than expected, a decision was made in November 2023 to finalise study recruitment in the first quarter of 2024. This decision was made because 33 individuals of the estimated 52 participants had completed the whole study duration at this point, 28 were currently active participants, and only nine individuals had dropped out. The dropout rate could rise to 36% among the final group (still active in the trial) without compromising on having 52 participants complete the study by July 2024.

Framework, Statistical interim analysis and stopping guidance

No superiority, equivalence, or noninferiority hypothesis testing framework will be performed: no interim analysis was performed.

Timing of analysis

All data described under primary- and secondary endpoints will be analysed collectively. All analyses will be carried out with the treatment groups still blinded and labeled as "treatment group 1" and "treatment group 2". Before dividing participants into group 1 and group 2, the statistical analysis plan will be completed, signed, and uploaded at clinicaltrials.gov, and the data set locked. The final unblinding of treatment groups (semaglutide or placebo), will not be carried out until all statistical analyses regarding primary- and secondary outcomes are performed. Posthoc analysis will be performed unblinded. Please see the section regarding this.

Timing of outcome assessments

All visits are planned from the date of the first injection. All irregularities are recorded as protocol deviations and visit "windows" are within 2 weeks (+/-).

Statistical Principles

Confidence and P-values

The level of statistical significance will be with an alpha set at 0.05, two-sided testing, and a corresponding confidence interval of 95%. There will be no adjustment for multiplicity.

Adherence and protocol deviations

Patients were asked to complete a weekly injection diary. The return of the unused trial product was documented in the patient CRF. Face-to-face adherence reminder sessions took place at the initial product dispensing and at each study visit. Adherence to the intervention will be presented as a table of distribution of percentage of weeks with study medication injections in the main treatment period. Protocol deviations will be presented in a table divided into the categories: study procedure, eligibility, and randomisation. Only protocol deviations regarding "lost to follow-up" and "withdrawal" will be summarized in the section named this.

Analysis populations

All analyses will be performed using the intention-to-treat principle on subjects who were randomised and received at least one dose of the trial compound (Ozempic® or placebo).

Trial Population

Screening data

Screening data will be presented in the CONSORT flowchart

Eligibility

Eligible participants are adults aged 18–65 years diagnosed with schizophrenia spectrum disorder according to the criteria of ICD10 or DSM-IV, with HbA1c 35-57mmol/mol and BMI ≥25kg/m^2 who, within the last 60 months, have initiated daily treatment with clozapine and/or and given informed and written consent to participation. Main exclusion criteria include: treatment with coercive measures, treatment with weight-lowering and/or antidiabetic medication within the preceding three months before inclusion, acute suicidal thoughts and/or behaviour, deterioration of psychosis (evaluated by a score of 6 or 7 on the Clinical Global Impression Severity Scale (CGI-S)), and increase in plasma levels of Hba1c >57mmol/mol. For additional exclusion criteria, please see the protocol publication by Sass et al. 2023.[22]

Recruitment

From 9th of September 2021, to 31st of January 2024, 101 individuals were screened for eligibility, and 72 were randomised and started on trial product. Last patient's first visit was performed on 15 February 2024. Last patient last visit was performed on the 16th of august 2024. The final long-term follow-up (1,5 year after trial completion) will take place in February 2026.

Withdrawal/Followup

All patients who have withdrawn from the intervention were encouraged to participate in PANSS-6 interview and a DXA scans at the time of withdrawal. All participants who succeeded the 26 weeks of trial intervention will be contacted for a long-term follow-up after 1.5 years. All other individuals e.g. individuals who withdraw or were lost to follow-up will not be contacted for a long-term follow-up. Drop-out data will be presented in a Kaplan Meyer survival curve.

Baseline Patient characteristics

Baseline characteristics will be descriptively summarised in a table differentiated by the intervention. List of baseline characteristics to be summarised:

- **Sex**
- **Age mean (SD)**
- **Diagnosis**
  - Schizophrenia (F20, F20.1, F20.3, F20.9)
  - Psychosis (F22, F23)
  - Schizoaffective disorder (F25)
- **Duration of diagnose, mean (years)**
- **Treatment (No. (%)**
  - Olanzapine
  - Clozapine
  - Clozapine & Olanzapine
- **Dose (median), mg**
  - Olanzapine
  - Clozapine
- **Clinical characteristics, mean (SD)**
  - Body weight (kg)
  - Waist circumference, cm
  - Hip circumference, cm women
  - Hip circumference, cm men
  - BMI
  - Systolic blood pressure mm Hg
  - Diastolic Blood pressure, mmHg
- **Prediabetes/diabetes criteria**
  - Prediabetes HbA1c 39-47mmol/mol
  - Diabetes HbA1c ≥48mmol/mol
- **Glucose metabolism**
  - HbA1c, mmol/mol
  - Fasting glucose, mmol/l
  - Fasting insulin, pmol/l
  - Fasting C-peptide, pmol/l
  - HOMA2-IR
- **Cholesterol level, median (IQR)**
  - Total, mmol/L
  - LDL, mmol/L
  - HDL, mmol/L

  - VLDL, mmol/L
- **Liver function**
  - Alanine transaminase, U/L
  - Aspartate transaminase, U/L
  - Alkaline phosphatase, U/L
  - Amylase, U/L
  - FIB-4 score
- **Body composition**
  - Visceral fat, mean (SD), gram
  - Android to gynoid fat ratio, median (IQR)
  - Total body fat, median (IQR) %
- **GAPD, total score**
- **CGI-S, total score**
- **PANSS-6, total score**
- **SQLS**
  - Psychosocial
  - Motivation
  - Adverse effects
- **AUDIT, total score**
- **DUDIT, total score**
- **Smoking status**
  - Non-smokers
  - Fagerströms test for nicotine dependence

Analysis

Primary endpoint

The primary endpoint is the change in the glycemic control parameter HbA1c from baseline to follow-up at week 26, adjusted for baseline.

Secondary endpoints

1. Bodyweight (kg) at follow-up after 26 weeks of treatment, adjusted for baseline.
2. Hip circumference (cm) at follow-up after 26 weeks of treatment, adjusted for baseline.
3. Waist circumference (cm) at follow-up after 26 weeks of treatment, adjusted for baseline.
4. waist to hip ratio at follow-up after 26 weeks of treatment, adjusted for baseline.
5. Blood pressure (mmHg) at follow-up after 26 weeks of treatment, adjusted for baseline.
6. Pulse (PR) at follow-up after 26 weeks of treatment, adjusted for baseline.
7. Plasma insulin levels at follow-up after 26 weeks of treatment, adjusted for baseline.
8. Beta-cell function evaluated by the HOMA2-IR score at follow-up after 26 weeks of treatment, adjusted for baseline.
9. Plasma glucagon at follow-up after 26 weeks of treatment, adjusted for baseline.
10. Fasting low-density lipoprotein (LDL) at follow-up after 26 weeks of treatment, adjusted for baseline.
11. Fasting high-density lipoprotein (HDL) at follow-up after 26 weeks of treatment, adjusted for baseline.
12. Fasting triglycerides at follow-up after 26 weeks of treatment, adjusted for baseline.
13. Fasting total cholesterol at follow-up after 26 weeks of treatment, adjusted for baseline.

14. The pancreatic parameter amylase at follow-up after 26 weeks of treatment, adjusted for baseline.
15. The liver parameter alanine aminotransferasee (ALAT) at follow-up after 26 weeks of treatment, adjusted for baseline.
16. The liver parameter gamma-glutamyl transferase (GGT) at follow-up after 26 weeks of treatment, adjusted for baseline.
17. The liver parameter Alkaline phosphatase (ALP) at follow-up after 26 weeks of treatment, adjusted for baseline.
18. FIB-4 fibrosis score at follow-up after 26 weeks of treatment, adjusted for baseline.
19. Positive and Negative Syndrome Scale Six-items (PANSS-6) score at follow-up after 26 weeks of treatment, adjusted for baseline.
20. Clinical Global Impression Severity scale (CGI-S) score at follow-up after 26 weeks of treatment, adjusted for baseline.
21. Alcohol Use Disorders Identification Test (AUDIT) score at follow-up after 26 weeks of treatment, adjusted for baseline.
22. Drug Use Disorders Identification Test (DUDIT) score at follow-up after 26 weeks of treatment, adjusted for baseline.
23. Fagerström test for nicotine dependence (FNTD) score at follow-up after 26 weeks of treatment, adjusted for baseline.
24. Schizophrenia Quality of Life Scale (SQLS) score at follow-up after 26 weeks of treatment, adjusted for baseline.
25. Psychosocial disability (GAPD) rating score at follow-up after 26 weeks of treatment, adjusted for baseline.
26. Body composition assessed by a DXA scan at follow-up after 26 weeks of treatment.
27. Bone density assessed by a DXA scan at follow-up after 26 weeks of treatment.

Analysis methods

For the primary endpoint, a repeated mixed-model analysis of covariance will be used to analyse the change in the level of HbA1c from week 0 to week 26 for the semaglutide and the placebo groups. All changes in secondary endpoints from baseline to the end of the trial will be analysed using repeated mixed-model analyses for continuous outcomes and mixed-model logistic regression for categorical outcomes. For comparison between the two groups, the covariates age, sex, illness duration, treatment group, baseline Clinical Global Impressions Scale severity score and BMI will be included in the analyses together with the baseline value of the relevant variable.

Sensitivity analysis

Exploratory analyses and post hoc sensitivity analyses will be performed to assess the robustness of the primary analyses. Effect sizes (Cohen d) for lowering HbA1c levels and reducing body weight will be calculated by dividing the difference of the means in change from baseline to endpoint (treatment – placebo) by the pooled SD.

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.

Subgroup analysis

We will perform the following subgroup analysis:

- Antipsychotics (clozapin vs olanzapine)

Posthoc analysis

- Plasma semaglutide levels
- Urine and plasma oxidative stress parameters
- Plasma bone markers (vitamin D, calcium (ionized and total), phosphate, magnesium, parathyroid hormone (PTH), procollagen type 1 N-terminal propeptide (PINP), C-terminal telopeptide of type 1 collagen (CTX), osteocalcin (OC))
- Incretin hormones: glucagon-like peptide-1 and -2 (GLP-1 and GLP-2) and gastric inhibitory polypeptide (GIP)
- Proteomic fingerprint
- Preference for sweet and fatty candy obtained by a “clicker test”
- activity measurements collected with a wearable activity device (one week at baseline and one week after last injection)
- Data from the 1.5-year follow-up

Missing data

Missing data will be imputed using the multiple imputation method. However, for multiple imputations to work properly we need to assume that the data are missing at random (MAR) which may not be the case in our study. Consequently, as a sensitivity analysis of handling the missing data, we will consider two realistic alternatives for the missing mechanism: 1) to assume that all non-observed individuals at 26 weeks have reverted to their pre-study HbA1c, 2) to assume that all non-observed individuals at 26 weeks have raised their HbA1c to the baseline-value plus 2 mmol/mol. If only multiple outcomes are missing then we will use a linear mixed-effect model which is an extension of the ANOVA model for analyzing the data.

Additional analysis

Our primary analysis compares treated with untreated in an intention-to-treat (ITT) setup which provides valid estimates of the real-world effects. To get an estimate of the complier-average causal effect we will use information from the questionnaire of the dropouts using the principal stratification approach of Frangakis and Robin.[23]

Harms

Safety data has been collected in the 26 weeks of inclusion and up until 10 weeks after termination of the study for all individuals. Data has been classified as Serious Adverse Events (SAE), Adverse Events (AE), and Adverse Reactions (AR). All collected safety data will be summarised in a table with incidence cases.

Statistical software

All statistical analysis will be performed with RStudio.

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