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The glucagon like peptide-1 analogue dulaglutide to prevent antipsychotic induced weight gain – a study protocol proposal

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Abstract:

Introduction: *Schizophrenia spectrum disorders are characterized by delusions, hallucinations and perceptual disturbances and lead to increased personal and economic burden. Besides psychotherapy, antipsychotic medications are the main treatment option, although inducing major side effects such as weight gain. However, no standard to prevent weight gain in these patients has yet been established. The proposed study protocol aims at analyzing whether the glucagon-like-peptide-1 (GLP-1) analogue dulaglutide (Trulicity®), an agent reducing appetite and weight, can prevent antipsychotic induced weight gain in patients with a schizophrenia spectrum disorder.*

Methods: *The proposed study protocol is a 24-week two-group, double-blind, multicenter, randomized, placebo-controlled superiority trial comparing the GLP-1 analogue dulaglutide to placebo. Patients suffering from a schizophrenia spectrum disorder and newly treated with olanzapine or clozapine are eligible. A total of 154 participants will be recruited (77 in each arm).*

Intervention and outcome: *Eligible patients will receive dulaglutide (0.75mg/week) or placebo subcutaneously once weekly for 24 weeks. An additional follow-up assessment will be performed 52 weeks after randomization. The primary outcome is mean percentage weight change after 24 weeks calculated as ratio of the initial weight and will be treated as a continuous variable.*

Discussion: *There is a need for studies investigating GLP-1 analogues preventive effect in patients receiving antipsychotics and weight gain risk. There is evidence that GLP-1 analogues are effective in reducing weight, but the preventive potential has not yet been studied. The proposed study would provide information on both whether the intervention prevents weight gain and whether this contributes to well-being, long-time adherence and overall therapeutic success in patients with a schizophrenia spectrum disorder.*

Keywords: *Schizophrenia spectrum disorder, clozapine, olanzapine, GLP-1*

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INTRODUCTION

Schizophrenia spectrum disorders are a heterogeneous disease group with symptoms like delusions, hallucinations, and perceptual disturbances which result in impaired functioning in various social settings such as interpersonal relationships, parenting, and self-care (Harris et al., 2013). Schizophrenia spectrum disorders are ranked among the world's leading causes of long-term disability, and affect about 1% of the world's population (Harris et al., 2013; McGrath, Saha, Chant, & Welham, 2008). Antipsychotic medications are the main pharmacological treatment option for patients with this disorder. However, antipsychotic medications can cause severe side effects such as extrapyramidal symptoms, tardive dyskinesia, and weight gain (Alberti et al., 2009).

Weight gain is most common in patients treated with second generation antipsychotics (SGAs) and

especially in those receiving olanzapine, clozapine, and quetiapine (Bak, Fransen, Janssen, van Os, & Drukker, 2014; Perez-Iglesias et al., 2008). The average weight gain is 5-10 kg (Association, 2004; Bak et al., 2014) but may progress to morbid obesity (Perez-Iglesias et al., 2008). Weight gain may lead to metabolic changes, dyslipidemia, type 2 diabetes, cardiovascular diseases, and ultimately premature death (Alberti et al., 2009). Besides markedly impairing the patient's quality of life (Harris et al., 2013), weight gain leads to reduced adherence and hence poor disease control (Velligan et al., 2009). Controlling weight gain associated with SGAs in patients with schizophrenia spectrum disorders is expected to improve health risks, increase the patient's quality of life, and reduce the associated economic burden.

Treatment to prevent weight gain is being investigated in several trials as it is considered to be more beneficial than treatment to reduce weight after it has been gained (Bennett et al., 2013; Gillman & Ludwig, 2013). Few studies have investigated preventing weight gain with life style intervention and metformin (Baptista et al., 2007; Varuni A de Silva et al., 2015). However, the limited success of these studies is likely the reason why these findings are not yet incorporated in clinical practice, nor guidelines.

GLP-1 is an incretin hormone synthesized in endocrine L cells located at the intestinal mucosa and is released after food intake (Drucker & Nauck, 2006). The GLP-receptor is widespread throughout the body and its activation increases the glucose-induced pancreatic insulin secretion, decreases glucagon secretion, inhibits gastric emptying and reduces appetite (Gutniak, Ørkov, Holst, Ahrén, & Efendić, 1992; Gutzwiller et al., 1999). Studies showed that GLP-1 analogues were effective in reducing weight (average weight loss -5kg) and improve glycemic control (HbA1c -0.2%) in obese schizophrenic patients with type 2 diabetes and in obese non-diabetic schizophrenic patients on SGAs (Astrup et al., 2012; Larsen et al., 2017; Lykkegaard et al., 2008; Vilsbøll, Christensen, Junker, Knop, & Gluud, 2012). This positive effect has also been shown in non-psychiatric patients with little difference between the GLP-1 analogues (Dungan et al., 2014).

However, to our knowledge no study has yet explored the usefulness of GLP-1 analogues in preventing weight gain in patients with a schizophrenia spectrum disorder newly treated with SGAs. The aim of this proposal is to study whether the GLP-1 analogue dulaglutide (Trulicity®) in comparison to placebo can prevent weight gain induced by the SGAs olanzapine and clozapine, and hence prevent the negative consequences of weight gain, and thereby increase patients' compliance and quality of life.

METHODS

Objective

The aim is to study the efficacy of the GLP-1 analogue dulaglutide in preventing weight gain in patients with a schizophrenia spectrum disorder treated with the SGAs olanzapine or clozapine after 24 weeks.

Design

The proposed trial is a two-group parallel, double-blind, multicenter, randomized, placebo-controlled superiority trial.

Study setting

All adult patients with a schizophrenia spectrum disorder will be screened at the in- and out-patient department of psychiatry of three tertiary care hospitals in Switzerland. Psychiatric practitioners at these sites will be informed about the trial and invited to refer eligible patients to the study investigators.

Participants

Inclusion criteria are age 18-65 years, a schizophrenia spectrum disorder using the Structured Clinical Interview for DSM-5 (SCID-5) (Lobbestael, Leurgans, & Arntz, 2011), newly treated with olanzapine or clozapine (within 1 month) and informed consent as documented by signature.

Exclusion criteria are pregnancy or breastfeeding, BMI <20kg/m2 or >30kg/m2, diabetes mellitus, treatment with oral corticosteroids, renal insufficiency (GFR <30ml/min/1.73m^2), and abnormal liver function (ALT and AST > 3 times above norm).

Randomization and blinding

Patients' allocation to the experimental or the placebo arm will be concealed with a pre-specified computer-generated randomization list and will be kept at the pharmacy of the main study site. The randomization between the two study arms will be 1:1 with random sized blocks of 4 and 6, stratified by site and medication (olanzapine and clozapine).

Generator and executor of randomization will be separated. The study drug will be prepared prior to the trial initiation, will be concealed by the main study center pharmacy (either 24 injections of 0.75mg dulaglutide or placebo), and will be stored appropriately. The numbered trial medications will be delivered to the site investigator

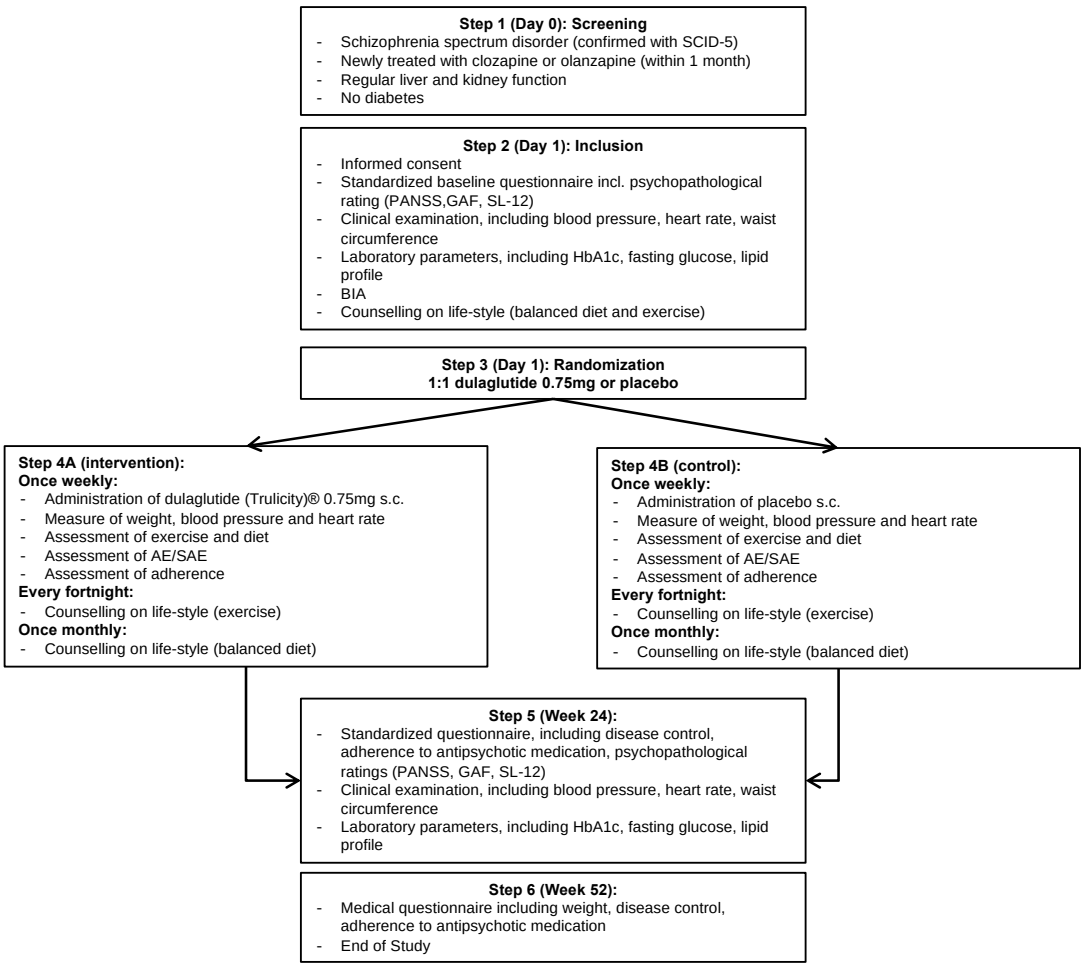

Figure 1: Study flow chart. Abbreviation: PANSS = Positive and Negative Symptom Scale, GAF = Global Assessment of Functioning, SL-12 = Quality of Life Questionnaire Short Form-12, SCID-5 = Structured Clinical Interview for DSM-5.

and will be administered by the study nurse to the respective patient. By this method, patients and investigators will be blinded to allocation. Unblinding prior to study completion should be avoided, unless patients' safety (serious adverse event, SAE) is at risk and unblinding is deemed necessary for appropriate treatment. If an SAE occurs e.g., gastrointestinal disease requiring hospitalization, life-threatening malnutrition, or death, the data safety monitoring board (DSMB) will be contacted and asked for authorization of unblinding.

In the case of an SAE that deemed related to the study drug, the participant will receive no further study medication, data collected until drop-out will be considered for statistical analysis (intention to treat analysis).

Adherence

Medication and protocol adherence are important issues especially in a trial including psychiatric patients, since adherence in this population can be as low as 60% compared to 80% in the general population (Caminati et al., 2016; Zipursky, 2014). The study drug has to be administered once weekly subcutaneously. To maximize adherence, a study nurse will pass by the patient's home for the weekly visits or while the patient is visiting his treating psychiatrist. The visit will follow a safety protocol and the study nurse will report to the investigator in case of safety (e.g., serious gastrointestinal problems, local reactions at injection site) or compliance issues (e.g., reschedule appointment, refuse injection).

Study Protocol

The study flow chart is shown in figure 1 and the study schedule in figure 2. The study duration for the patients will be 52 weeks. The trial medication will be administered weekly during the first 24 weeks, and one additional follow-up will be performed 52 weeks after randomization.

• Screening: Patients will be screened daily in the in- and out-patient's department of the participating sites by the site investigators.

• Baseline assessment: Once informed consent has been acquired and the SCID-5 has confirmed the presence of a schizophrenia spectrum disorder, blood samples will be collected for screening. After fulfilling all eligibility criteria, patients will be randomized. Baseline measurement of vital parameters, weight, height, waist-hip ratio, baseline blood sampling (random glucose, glycated hemoglobin, lipid profile), and baseline BIA (bioelectrical impedance analysis to assess muscle and fat mass) will take place. Patients will be informed about a healthy lifestyle, including balanced diet and exercise. Psychopathological ratings will be assessed by the site investigator using the Positive and Negative Symptom Scale (PANSS) (Kay, Flszbein, & Opfer, 1987), the Global Assessment of Functioning (GAF) (Hall, 1995), and the Quality of Life questionnaire Short Form-12 (SF-12) (Ware, Kosinski, & Keller, n.d.). For every site investigator who is performing the SCID-5 or the PANSS, a four-day training program including practice sessions will be performed. Once inter-rater agreement reaches 90%, the training will be considered successful.

• Follow-up assessment: Patients will receive weekly visits by a blinded study nurse for injection of the study drug, measurement of vital parameters, weight, and adverse events, especially gastrointestinal complications and local site reaction. Patients will receive physiotherapy every two weeks with individual assessment meetings and personalized exercises. Patients will receive smart watches to objectively assess the amount of performed exercise. The focus will be on cardiovascular and endurance exercise to maximize weight stability. Once monthly, patients should present themselves to the study site for a group meeting where

	Screening	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24	Week 52
Study Visit		V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25
Eligibility assessment	X																										
Informed consent	X																										
SCID-5	X																										
Medical history	X																										
Blood sampling	X																									X	X
Inclusion / randomization		X																									
Psychopathological ratings		X																								X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight, height, BMI		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BIA		X																								X	
Life-style counselling Diet		X				X				X				X		X				X				X			
Life-style counselling Activity		X		X		X		X		X		X		X		X		X		X		X		X		X	
Study drug		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
New medication			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medication adherence			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Figure 2: Study visit.

Abbreviation: SCID-5 = Structured Clinical Interview for DSM-5, BMI = Body mass index, BIA = Body impedance analysis

they will be informed about healthy lifestyle. A nutritionist will explain a balanced diet using the "healthy eating plate" (https://www.hsph.harvard.edu/nutrition source/). After 24 weeks, patients will have the last regular visit including measurements of vital parameters, weight, height, waist-hip ratio, blood sampling (random glucose, glycated hemoglobin, lipid profile), and BIA. If the visit is missed, the treating psychiatrist can be contracted to help collect data. If no contact is possible, the last weight measurement will be considered for the main outcome.

• End of study visit: After 52 weeks, patients will have a follow-up visit assessing change of weight, blood sampling (random glucose, glycated hemoglobin, lipid profile), BIA and psychopathological ratings.

Endpoints

The primary outcome is mean percentage weight change after 24 weeks calculated as ratio of the initial weight and will be treated as a continuous variable. Body weight is a clinically relevant outcome and the main risk factor for metabolic changes (Millstein, 2014).

The following secondary endpoints will be considered:

• Mean change of BMI after 24 weeks (reasoning: BMI is a valid marker for weight change) (Millstein, 2014)

• Mean change in weight after 1 year (reasoning: to evaluate treatment persistence)

• Mean change of proportion of fat mass and muscle mass measured by a bioelectrical impedance analysis (BIA) after 24 weeks (reasoning: to assess changes of body composition)

• Mean change in glycated hemoglobin (HbA1c) after 24 weeks and 52 weeks (reasoning: to assess development of prediabetes and diabetes due to weight gain and use of SGAs)

• Adherence to antipsychotic therapy defined as intake of at least 80% of the prescribed antipsychotic medication by patient's interview, and if relevant reason for discontinuation (reasoning: to assess influence of weight gain on therapy adherence)

• Disease control and relapse rate of schizophrenia spectrum disease assessed using the PANSS (reasoning: to assess influence of weight gain and GLP-1 analogues on underlying disease)

• Quality of life using the SF-12 at inclusion, after 12, 24 and 52 weeks (reasoning: to assess patient's well-being on GLP-1 analogues and SGAs)

• Difference in adverse events and serious adverse events between the two groups (reasoning: to assess tolerance of GLP-1 analogues)

Data Management and Safety Monitoring

The trial will use a Data Coordination Center (DCC) located at the main site. The central DCC will be involved throughout the trial, starting from the draft of the data management plan and its regular review and update up to trial closure. Collected data will be captured in an electronic case report form (eCRF) compliant to good clinical practice (GCP), which will be accessible via a standard browser and password protected for authorized persons. An audit trail system will maintain a record of initial entries and changes (reasons for changes, time and date of changes, user identification of entry and changes). The DSMB will meet every 3 months.

Sample Size Estimation

The main outcome of this study will be mean percentage weight change after 24 weeks calculated as ratio of the initial weight and will be treated as a continuous variable. Sample size was estimated to identify a clinically relevant difference (5-7% weight difference (Bak et al., 2014)) between the two groups using a two-sided two-sample t-test, with an alpha of 0.05 and a power of 90%. The following assumptions were applied in the calculations:

• mean weight gain of 9% (SD 8%) in the placebo group after 24 weeks (Bak et al., 2014)

• mean weight gain of 4% (SD 8%) in the GLP-1 group after 24 weeks (Larsen et al., 2017)

• drop-out rate of 30% (Zipursky, 2014)

Based on these assumptions, 77 patients should be recruited in each study arm, or 154 patients total, to ensure the required 54 evaluated patients in each arm.

Statistical Analysis

Categorical variables will be expressed as count and percentage, continuous variables as mean and standard deviation (SD) or median and interquartile range (IQR) based on their distribution pattern. Normality of the data will be assessed graphically using a histogram or a quantile-quantile plot and confirmed using the Kolmogorov-Smirnov test.

The analysis of the primary outcome, weight change in percentage after 24 weeks of treatment, will be considered as continuous variable using a t-test. The primary analysis will be based on the intention to treat principle (ITT). Sensitivity analysis for the primary endpoint will be a per protocol analysis, a repeated measure ANOVA including monthly weight changes, and a logistic regression model based on dichotomized weight gain in percentage (<7% vs >7%, considered a clinically relevant weight gain (Bak et al., 2014)) at 24 weeks.

Analysis of secondary outcomes will be performed by t-tests or Wilcoxon rank-sum tests for continuous data and chi-square test or Fisher's exact test for categorical data. As the medication at investigation has been proven to be safe in several trials, an interim analysis for safety is not required (Astrup et al., 2009; Marso et al., 2016).

For all statistical tests, we will consider a two-sided alpha level of 0.05 for statistical significance and will use Stata 14 (Stata Corp, College Station, TX).

Missing Data

Missing data will be assessed at the end of the trial for the primary endpoint. If missing data is found to be less than 5%, a complete case analysis will be conducted. If the missing data is found to be more than 5%, the data will be analyzed for any systematic differences between missing data and complete data using logistic regression, with baseline characteristics such as weight, medication, BMI, and duration of schizophrenia spectrum disorder with an alfa of 5%. The main data imputation method will be multiple imputation using baseline weight, age, sex, and duration of schizophrenia spectrum disorder as explanatory variables.

Registration

The trial will be registered on www.clinicaltrials.gov and kofam.ch.

DISCUSSION

Even with the potential efficacy of SGAs reducing psychotic symptoms, the risk of side effects and especially weight gain often leads to poor therapy adherence and high relapse rate. GLP-1 analogues have been proven to be beneficial in reducing weight gain (Astrup et al., 2012; Lykkegaard et al., 2008). However, the potential effect of GLP-1 analogues preventing weight gain has not yet been studied. The proposed study would provide information on whether GLP-1 analogue prevent weight gain and whether this contributes to better therapy adherence and disease control in patients with a schizophrenia spectrum disorder.

Patients with a schizophrenia spectrum disorder may require SGAs when suffering from an acute psychotic episode and with insufficient response to other antipsychotic medication. Olanzapine and clozapine are among the best medications to reduce psychotic symptoms but have the highest weight gain profile and metabolic changes. Most existing trials have focused on reducing weight in overweight and obese schizophrenic patients (Larsen et al., 2017; Lykkegaard et al., 2008). Life-style interventions failed to show significant weight reduction in comparison to placebo while metformin and GLP-1 analogues showed promising results (Varuni Asanka de Silva et al., 2016; Green et al., 2015; Lykkegaard et al., 2008). However, preventing weight gain in the first place might is considered to be more beneficial than treatment to reduce weight after it has been gained (Varuni Asanka de Silva et al., 2016).

During acute psychosis, when change to the mentioned SGAs is most common, patients have a reduced ability to provide informed consent. Thus, we propose to include patients within the first month after starting these medications to reach the required dose and to give patients time to recover from the initial acute phase. It has been shown that the highest weight gain occurs during the first couple of months after initiating treatment (Association, 2004; Bak et al., 2014), however, starting the intervention within the first month is an acceptable timeframe.

In the proposed trial, we plan to investigate the GLP-1 analogue dulaglutide 0.75mg as prevention of weight gain for patients newly treated with the SGAs olanzapine and clozapine over a 24-week trial. We chose the GLP-1 analogue dulaglutide as it is administered once weekly in comparison to other GLP-1 analogues that need to be administered daily, but with comparable efficacy (Dungan et al., 2014). As this trial focuses on preventing and not treating antipsychotic induced weight gain, we chose the smaller dose of 0.75mg weekly. With this dose, the gastrointestinal side effects are known to be lower which should reduce drop-out rate in our patient population and hence decrease attrition bias (Dungan et al., 2014). The choice of a 24-week trial was based on similar weight reducing trials (Chen et al., 2013; Dungan et al., 2014). In a shorter trial the between-subject variability might be larger and hence no difference would be seen, a longer trial might increase drop-out rate, therefore increase attrition bias.

Adherence is especially difficult in psychiatric patients (Zipursky, 2014). To increase adherence and reduce patients' effort, we propose home visits from the study nurse for weekly study drug injections. We are aware that this will increase manpower and the costs of the study; however, we believe that the increased adherence is more important and increases the feasibility of the study. Furthermore, we have assumed a comparably high drop-out rate to ensure a sufficient sample size for the analysis.

A challenge of the trial is the heterogeneous underlying population, as we intend to include patients ranging from first episode to chronic schizophrenia, which might affect internal validity. Nevertheless, our focus is on the weight gain due to the SGAs olanzapine and

clozapine regardless the disease state. Furthermore, it is unclear whether weight gaining and subsequent reduction from GLP-1 analogues is comparable between olanzapine and clozapine. However, studies have shown the highest weight gain effect using these two medications and thus we think it is important to investigate both these medications (Bak et al., 2014) and a subgroup analysis will be performed to test for a potential difference. Last but not least, we are aware that the proposed trial is challenging, requires motivated patients (which might affect external validity) and dedicated personnel to ensure a low drop-out rate and high adherence. Regardless, we believe that this trial benefit if GLP-1 proves to be effective in preventing weight gain justifies the required effort.

In conclusion, the proposed study would be the first to investigate the GLP-1 analogue dulaglutide in preventing weight gain in patients with a schizophrenia spectrum disorder. Our hypothesis is that GLP-1 analogues would prevent weight gain in patients receiving SGAs and thus decrease the negative consequences of weight gain, leading to an increased compliance and quality of life.

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Conflict of interest and financial disclosure

The authors followed the International Committee or Journal of Medical Journals Editors (ICMJE) form for disclosure of potential conflicts of interest. All listed authors concur with the submission of the manuscript. The final version has been approved by all authors. The authors have no financial or personal conflicts of interest.

Abbreviation

ALT	Alanine Transaminase
ANOVA	Analysis of Variance
AST	Aspartate Transaminase
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
CTU	Clinical Trial Unit
DCC	Data Coordination Center
DSMB	Data Safety Monitoring Board
eCRF	electronic Case Report Form
GAP	Global Assessment of Functioning
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GLP	Glucagon-like-peptide
IQR	Interquartile Range
ITT	Intention to Treat
PANSS	Positive and Negative Symptom Scale
SCID-5	Structured Clinical Interview for DSM-5
SD	Standard Deviation
SF-12	Quality of Life Questionnaire Short Form-12
SGAs	Second Generation Antipsychotics

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