CLINICAL TRIAL PROTOCOL

COMPOUND SEMAGLUTID (WEGOVY®) S.C. ONCE-WEEKLY

PROTOCOL TITLE: DOES THE GLUCAGON-LIKE PEPTIDE 1 (GLP-1) RECEPTOR AGONIST SEMAGLUTIDE REDUCE ALCOHOL INTAKE IN PATIENTS WITH ALCOHOL USE DISORDER AND COMORBID OBESITY?

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Protocol summary

Compound	Semaglutid s.c. vs placebo
Study title	Does the glucagon-like peptide 1 (GLP-1) receptor agonist (GLP-1RA) semaglutide reduce alcohol intake in patients with alcohol use disorder and comorbid obesity?
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Study location	Psychiatric Center Copenhagen, Frederiksberg, and Neurobiology Research Unit, Inge Lehmanns Vej 6, Rigshospitalet.
Key dates	Start of recruitment Q2, 2023 Last treatment Q4, 2026
Objective	To investigate the effects of the GLP-1RA semaglutide s.c. vs placebo on alcohol consumption in patients diagnosed with alcohol use disorder and comorbid obesity.
Study design	Randomised, double-blind, placebo-controlled, single-site, 26-weeks clinical trial

Patients	Patients diagnosed with alcohol use disorder and body mass index (BMI) ≥30 kg/m^2, between 18 and 70 years of age (both included).
Sample size	One hundred and eight patients will be included.
Procedure	Patients will be treated for 26 weeks with semaglutide subcutaneously (s.c.) once weekly or placebo. The medication will be provided as a supplement to standardised cognitive behavioural therapy. A subgroup of the patients will have two brain scans (magnetic resonance spectroscopy (MRS) and functional magnetic resonance imaging (fMRI)) conducted in one scan session at week 0 and 26.
Endpoints	The primary endpoint is the percentage-point reduction in total number of heavy drinking days, defined as days with an excess intake of 48/60 grams of alcohol per day (women and men, respectively) from baseline to follow-up after 26 weeks of treatment, measured by the timeline followback (TLFB) method. Secondary endpoints include changes in total alcohol consumption (g/30 days measured with the TLFB method), changes in the number of days without alcohol consumption, drinks per day, time to relapse defined as time to first alcohol intake, time to first heavy drinking day, change in the Penn alcohol craving scale (PACS) score, changes in alcohol use disorders identification test (AUDIT) score, changes in drug use disorders identification test (DUDIT) score, changes in WHO risk drinking levels, changes in Fibrosis-4 (FIB4) score, changes in the blood parameters gamma-glutamyltransferase (GGT), alanine aminotransferase (ALAT), phosphatidyl-ethanol (PEth), mean cell volume (MCV), changes in body weight, blood pressure, pulse, changes in the overall glycaemic control parameter haemoglobin A1c (HbA1c), and changes in the World health organisation quality of life score (WHOQOL-BREF). In addition to the clinical outcome parameters, the possible neuroanatomical underpinnings of semaglutide will be investigated by use of fMRI. The changes in brain gamma-aminobutyric acid (GABA) levels will be investigated with an MRS scan.
Safety	Blood samples will be collected regularly during the study to monitor safety parameters, and a 24/7 open phone line will be available.
Study duration	26 weeks of treatment and a safety follow-up phone call 5 weeks after trial end.

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DOES THE GLUCAGON-LIKE PEPTIDE 1 (GLP-1) RECEPTOR AGONIST SEMAGLUTIDE REDUCE ALCOHOL INTAKE IN PATIENTS WITH ALCOHOL USE DISORDER AND COMORBID OBESITY

1 INTRODUCTION

1.1 BACKGROUND

Alcohol use disorder (AUD) is a chronic brain disorder characterised by loss of control of alcohol intake, a negative state when not consuming alcohol, and compulsive alcohol behaviour, leading to relapse.[1] Up to 50% of patients with AUD experience alcohol withdrawal symptoms such as anxiety, tremors, and nausea, and some require medical detoxification treatment.[2] Globally, alcohol use is a huge burden, and an estimated 280 million people globally suffer from AUD.[3] In 2016, three million deaths were caused by the harmful use of alcohol. In Denmark, approximately 20% of the population consumes more alcohol per week than the Danish Health and Medicines Authority recommends and can thus be characterised as having excessive alcohol consumption. 14% of the Danish population has a harmful consumption of alcohol and 3% fulfils the criteria for AUD.[4] Despite this, the treatment gap is wide compared to other mental health disorders[5] - a Danish study has reported an all-cause cumulative 15-year mortality rate of 29% after a first-time hospital contact due to alcohol.[6] This high mortality rate might be due to medical conditions and complications such as alcoholic liver disease, injuries,[1] fracture,[6] heart disease, stroke, cancer,[7] or suicide.[8] In this perspective, AUD has serious consequences for the individual but also for families and friends[7] and the society due to higher health care[6] and socio-economical costs.[2,3] This is also why alcohol is reported as the most harmful drug of addiction; the harm to both users and others taken into consideration.[9]

1.2 TREATMENT OF ALCOHOL USE DISORDER

1.2.1 PSYCHOLOGICAL TREATMENT

AUD is a heterogeneous disorder, and several behavioural- and psychological treatments are available.[2] However, cognitive behavioural therapy (CBT) is among the treatments with the highest empirical support.[10–12] Both CBT and other psychosocial interventions, e.g., motivational interviewing (MI) or motivational enhancement therapy, are intensive one-to-one sessions where the patient and the therapist develop strategies to prevent relapse and deal with trigger situations.[13] Also, other treatment modalities exist, e.g., 12-step support groups and self-help groups.[13] In Denmark, and according to Danish-[14], the National institute for health and care excellence (NICE)[15]-, and the American psychiatric association (APA)[16] guidelines, patients diagnosed with mild AUD are recommended only psychological intervention, but an add-on of pharmacological treatment is recommended in patients with moderate to severe AUD. The underlying neuroanatomical basis of alcohol addiction and the treatment effects of CBT are not yet established, but functional Magnetic Resonance Imaging (fMRI) studies have begun to elucidate the neuroanatomical basis.[17] Alcohol-dependent patients have been found to display exaggerated dorsal anterior cingulate cortex (dACC) activation during an fMRI spatial working memory task, perhaps reflecting decreased neural capacity due to distracting alcohol-related thoughts.[18] Interestingly, it was also recently demonstrated that alcohol-dependent patients display exaggerated neural activation to alcohol-associated cues in mesocorticolimbic networks and that it is reversed with psychological therapy.[17]

1.2.2 PHARMACOLOGICAL TREATMENT

Only three pharmacological treatments, disulfiram, acamprosate, and naltrexone, are approved by both the European Medicines Agency (EMA)[19] and the United States Food and Drug Administration (FDA). A single compound, nalmefene, is only approved by the EMA.[20] They are an important aid in the treatment of people with AUD. The FDA approved the anti-craving medication acamprosate (Campral®) in 2004.[21] Its chemical structure is related to gamma-aminobutyric acid (GABA), and evidence suggests that the effects of acamprosate are due to interactions with the neurotransmitters glutamate, restoring the imbalance of neuronal excitation and inhibition caused by chronic alcohol exposure.[22] Acamprosate is recommended in both Danish and other clinical guidelines as a first-line treatment.[14–16,23] The anti-craving medication naltrexone (Adepend®) was approved as an oral formulation by the FDA in 1994 and as a long-acting injection formulation in 2006. Naltrexone is an opioid receptor antagonist, blocking the mu-opioid receptors primarily and, to a lesser extent, the kappa-opioid receptors.[21] Danish and other clinical guidelines recommend naltrexone as a first-line treatment.[15,16,23] Disulfiram (Antabus®) inhibits aldehyde dehydrogenase, which metabolises acetaldehyde, the toxic metabolite of alcohol. the inhibition combined with alcohol consumption causes the "disulfiram-ethanol" reaction, i.e., nausea, vomiting, headache, facial flush, hypotension, sweating, palpitations, restlessness, exhaustion, confusion, and rarely cardiovascular relapse.[20,21] The therapeutic effect of disulfiram is most likely the fear of the adverse effects, i.e., punishment.[20,21] A systematic review including eleven randomised clinical trials reports that disulfiram affects short-term abstinence, i.e., days until relapse and number of drinking days, but long-term trials are missing.[24] A meta-analysis including 22 clinical trials reports no difference between treatment groups in the blinded studies. However, in open-label studies, disulfiram is a safe and efficacious treatment.[25] According to Danish-[14], NICE-,[15] APA-,[16] and British association for psychopharmacology (BAP)[23] guidelines, disulfiram is recommended as a second-line treatment. Nalmefene (Selincro®) is only approved by the EMA[1] and is not evaluated in the APA[16] or NICE[15] guidelines. Nalmefene is a mu- and delta-opioid receptor antagonist and a kappa-opioid receptor partial agonist. It is recommended as a treatment for patients with a high drinking risk level,[26] and is to be ingested when tempted to consume alcohol.[20] In Denmark, alcohol treatment is free of charge and is offered within 14 days. The standard treatment is therapeutic sessions, combined with pharmacological therapy if needed, i.e. acamprosate, naltrexone, disulfiram or nalmefene.[14] Given the diverse biological processes that contribute to alcohol use disorder, new medications are needed to provide a broader spectrum of treatment options. Some people may respond to a medication that helps with craving, others to a medication that relieves impulsivity, and others may respond to a medication that reverses the negative emotional state of withdrawal or protracted withdrawal.

1.3 GLUCAGON-LIKE PEPTIDE 1 (GLP-1)

In the search for new treatments of AUD and other drugs of abuse, the focus has been on the incretin hormone glucagon-like peptide 1 (GLP-1).[27–32] GLP-1 is an endogenous 30-amino acid peptide hormone produced by cleavage of the prohormone proglucagon. GLP-1 is produced in the L-cells in the small intestines and is released in response to food intake. It is hastily inactivated with a half-life of only 3-5 minutes by the enzyme dipeptidyl peptidase 4 (DPP-4).[33] GLP-1 potentiates insulin secretion, suppresses glucagon secretion, regulates overall glycaemic control, and regulates appetite and food intake by slowing down gastric emptying.[34,35] These effects are strictly glucose-dependent (more pronounced at higher blood glucose levels), and the effect ceases as the blood glucose level reaches values below 4-5 mmol/l.[36] Importantly, GLP-1 is also produced in the nucleus tractus solitarius (NTS) of the brain stem and is released as a neurotransmitter in the ventral

tegmental area (VTA) and nucleus accumbens (NAc).[37] GLP-1 receptors (GLP-1R) are also expressed in brain regions involved in reward and addiction (VTA, NAc, septal nucleus, hypothalamus, and amygdala).[38–43]

1.3.1 GLP-1 RECEPTOR AGONISTS

GLP-1-based therapy was introduced to the market in 2006, and since then, several GLP-1 (GLP-1RAs) have been approved for treating type 2 diabetes. The GLP-1RA semaglutide (Ozempic®) 1 mg subcutaneously (s.c.) was approved for the treatment of type 2 diabetes in 2017 and cardiovascular risk reduction in patients with type 2 diabetes in 2020. In 2014 was, the first GLP-1 RA liraglutide (Saxenda®) approved for the treatment of obesity (BMI >30 kg/m^2).[44] The proposed GLP-1RA semaglutide is reported to be superior to previous GLP-1 RAs approved for weight loss,[45] and was approved by the FDA in June 2021 (Wegovy®). The first once-daily oral GLP-1RA, semaglutide (Rybelsus®), was approved to treat patients with type 2 diabetes in 2019. This represents a paradigm shift and a possible attractive treatment alternative to injectable therapy in the future.[46] Several pre-clinical studies report of GLP-1RAs crossing the blood-brain barrier to some extent,[47–50] and semaglutide is reported to access the brainstem, septal nucleus, and hypothalamus.[47] One randomised clinical trial in patients with Parkinson's Disease reported that the GLP-1RA exenatide in a clinically relevant dose crosses the blood-brain barrier.[51] Earlier studies[52] and case reports[53] have reported an increased risk of pancreatitis or pancreatic cancer in patients with type 2 diabetes when treated with GLP-1RAs. This increased risk may have limited the enthusiasm for testing GLP-1RAs as a treatment of AUD, as patients with AUD are already at higher risk for pancreatitis and pancreatic cancer.[54] However, a systematic review and meta-analysis including three high-quality randomised clinical trials and 18.700 diabetes patients treated with GLP-1RAs or placebo found no significant association.[55] These findings are supported in a recent meta-analysis including more than 55.000 patients,[56] and in a study comparing the risk of pancreatitis[57] or pancreatic cancer[58] between the treatment with GLP-1RAs and other therapies of diabetes. In our recent clinical trial investigating the GLP-1RA exenatide as a potential treatment of alcohol use disorder in 127 patients for 26 weeks, no incidences of pancreatitis or raised plasma levels of pancreatic enzymes were reported.[59]

1.3.2 PRE-CLINICAL RESEARCH, GLP-1 RECEPTOR AGONISTS, AND ALCOHOL

Several GLP-1RAs have been evaluated in pre-clinical addiction models regarding their effects on alcohol consumption in mice, rats, and nonhuman primates. In a conditioned place preference (CPP) model, pre-clinical trials report decreased or abolished alcohol place preference when animals are pre-treated with systemic exenatide,[60,61] exenatide injections in the NTS,[62] or NAc.[63] The same results are reported for the GLP-1RA, liraglutide.[64] In a two-bottle-choice paradigm, pre-treatment with exenatide administered systemically,[60,61,65] or injected centrally into the VTA,[61,66] NTS,[62] NAc, dorsal hippocampus, lateral hypothalamus,[66] NAc shell[63,66] or laterodorsal tegmental area,[63] is reported to reduce the rodent alcohol intake. It is also reported of decreased alcohol administration in an operant self-administration paradigm when rodents are treated systemically with exenatide[60] or centrally in the VTA.[67] Most pre-clinical addiction studies are performed with exenatide or liraglutide,[68] but the effects of semaglutide are also reported in a pre-clinical trial in rats.[69] The effects of GLP-1RAs on alcohol intake have been tested in nonhuman primates with long-term alcohol experience.[70] Alcohol-preferring African vervet monkeys were treated with exenatide/vehicle for five weeks or liraglutide/vehicle for two weeks to obtain steady-state. After this period, alcohol was reintroduced for two weeks, combined with the assigned treatment. Both treatments reduced alcohol intake without signs

of nausea.[70] We have recently demonstrated that semaglutide potently inhibits alcohol intake in non-human primates (unpublished data, Figure 1).

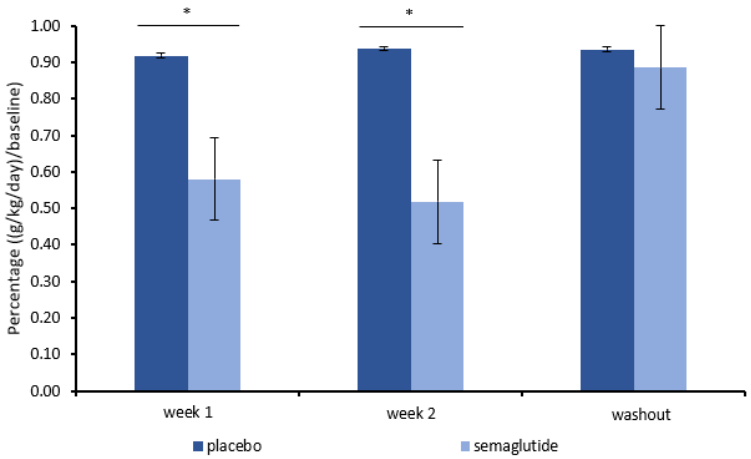

***Figure 1**. Mean weekly alcohol consumption (gram alcohol/kg(weight of the animal)/day) adjusted for baseline consumption in non-human primates (n=20) treated with semaglutide or placebo for two weeks, followed by a washout period (the second week after the end of treatment) (unpublished data). The study is performed at the same research facilities as reported in Thomsen et al.[70] *p < 0.05*

1.3.3 HUMAN STUDIES, NATIVE GLP-1, GLP-1 RECEPTOR AGONIST, AND ALCOHOL

Clinical trials investigating the effects of alcohol on gastrointestinal hormones in healthy controls report no changes in plasma GLP-1 levels after ingestion of alcohol,[71–74] or after intravenous alcohol.[71] However, one study in patients diagnosed with type 2 diabetes, consuming alcohol and a fat-rich meal reported decreased postprandial GLP-1 levels.[75] It is thus uncertain whether the result can be attributed to the ingested alcohol or other nutrients. A large human genetic association study comprising four smaller studies reports an association between AUD and the GLP-1R 168Ser allele. The 168Ser/Ser genotype is associated with increased alcohol consumption and a higher fMRI blood-oxygen-level-dependent (BOLD) response in the globus pallidus when receiving a reward notification in the Monetary Incentive Delay task.[76] The authors suggest that people with the 168Ser/Ser allele might have a more dysfunctional reward system, causing a vulnerability to the development of AUD.[76] The potential alcohol-reducing effects of GLP-1RAs in humans were first reported in a conference abstract in 2011. A cross-sectional review conducted on patients with type 2 diabetes treated with liraglutide for three months reported a reduction in alcohol intake.[77] However, the data were – to the best of our knowledge - never published in a peer-reviewed journal. Only one clinical trial investigating the effects of a GLP-1RA in patients with AUD has been reported, and this was done by our research group.[59] The trial was a randomised, placebo-controlled, double-blinded clinical trial including 127 patients with AUD treated with exenatide or placebo once-weekly.[59] Our primary endpoint was reduction in heavy drinking days, defined as days with consumption of more than 60/48 (men/women) grams of alcohol per day.[78] Although we observed a dramatic reduction in number of heavy drinking days in both treatment groups, the reduction did not differ between groups, i.e., a reduction of 26.8 percentage points in the placebo group and 19.6 percentage points in the exenatide group (p=0.37). Also, we did not find a significant difference in total alcohol intake between the groups either (p=0.86) (secondary endpoint). Due to the known weight-lowering effects of GLP-1RAs, we performed an exploratory analysis of baseline body mass index (BMI) subgroups. In the subgroup of patients with a baseline BMI >30 kg/m^2 (n=30), exenatide reduced heavy drinking days by 24 percentage points (95% CI -44 to -3, p=0.034) and total alcohol intake per 30 days by 1,205 grams (95% CI -

2,206 to -204, p=0.026) relative to the placebo group. The overall alcohol reduction of 1,205 grams per 30 days equals 40 grams per day, the same as a 1-level reduction in WHO alcohol risk levels, which is associated with a reduction in consequences and increases in mental health functioning.[79] A subgroup of the patients underwent fMRI at baseline and week 26. Our data showed a significant reduction in alcohol cue reactivity in the ventral- and dorsal striatum and putamen in the exenatide group compared to the placebo group. These findings imply that patients with AUD treated with exenatide have reduced incentive salience, i.e. a reduced sensitivity to alcohol-associated visual cues.[80] Alcohol cue-reactivity was also reduced in the exenatide group compared to the placebo group in the septal area, a brain area playing a pivotal role in reward[81] and with high expression of GLP-1Rs.[82]

1.3.4 Pre-clinical research, GLP-1 receptor agonists, and dopamine

Dopamine is considered to play a central role in the awarding, and addictive properties of drugs of abuse and alcohol,[83] and GLP-1 producing neurons projecting from the NTS to the VTA and the NAc core- and shell has been identified.[37] GLP-1R stimulation in the NTS increases expression of dopamine-related genes, cf. mRNA encoding tyrosine hydroxylase, which is required for the synthesis of dopamine in the VTA. However, the expression of dopamine receptors or dopamine transporters (DAT) in the NAc is reported not to be altered by exenatide.[84] Several pre-clinical studies have tried to elucidate how GLP-1 systems modulate dopamine signalling. Microdialysis and fast-scan cyclic voltammetry studies report attenuated alcohol-induced accumbal dopamine release after systemically injected liraglutide-,[64] and exenatide,[60] and after exenatide injections directly into NTS.[62] Exenatide also attenuates cocaine-, amphetamine-, and nicotine-induced increases in accumbal or lateral septal dopamine levels in rats.[82,85–88] However, GLP-1RAs do not seem to suppress baseline dopamine levels, as opposed to stimulated ones.[85,87] But how GLP-1R stimulation affects dopamine function is less clear. In brain slices from the lateral septum, an area previously associated with reward,[81] GLP-1R stimulation increases DAT expression on the neuronal cell surface in mice[82] and in the striatum of rats.[89] However, other studies report unaffected striatal DAT availability after GLP-1R stimulation in mice,[89] knock-out mice,[89] and in the NAc in rats.[85]

1.3.5 Human, GLP-1 receptor agonists and dopamine

To the best of our knowledge, we were the first research group to investigate the acute effects of the GLP-1RA, exenatide twice daily, on DAT availability in healthy controls.[89] Ten healthy volunteers with no record of alcohol- or other substance use disorder were assessed with a single-photon emission computerised tomography (SPECT) DAT-scan while receiving placebo- and exenatide infusions. However, we found no acute changes in DAT availability.[89] This result is in line with a clinical trial in Parkinson's patients, reporting no significant changes in SPECT DAT availability, after 48 weeks of treatment, with the GLP-1RA exenatide once weekly.[51] However, in our recent clinical trial including patients with AUD,[59] we found a significantly lower DAT availability after 26 weeks of treatment with exenatide compared to placebo, which might be a compensatory mechanism for the decreased dopamine activity previously reported in patients with AUD.[90]

1.3.6 GLP-1 receptor agonists and GABA/Dopamine

The precise mechanism of GLP-1RA regulation of dopamine has not been elucidated yet. Recent pre-clinical and clinical data indicate an involvement of the GABAergic transmitter system, which modulates dopamin-

ergic homeostasis.[91–93] GABA and glutamate are the brain's primary inhibitory and excitatory neurotransmitters.[91] Although the magnetic resonance spectroscopy (MRS) measurements of GABA reflect the whole tissue (i.e., neurotransmitter pool + extracellular space + neuronal cell body), data from epilepsy studies imply that GABAergic activity is related to the concentration of GABA in the brain.[94,95] Imaging studies using MRS have reported of acute ethanol administration in healthy individuals reduces cortical brain levels of the inhibitory neurotransmitter GABA,[92] and that GABA-A receptors are downregulated after prolonged ethanol withdrawal in patients with AUD compared to healthy individuals.[91] Pre-clinical studies have reported GLP-1Rs on cortical glutamatergic and GABAergic nerve terminals in rats[96] and mice.[93] Moreover, the GLP-1RA exenatide is reported to increase cortical and hippocampal GABA release, and the GLP-1R antagonist exendin-3 can abolish the effect.[93]

2 OBJECTIVES OF THE TRIAL

Based on the identified medical need for novel molecular targets in the medical treatment of alcohol use disorder and the promising data of GLP-1R stimulation in alcohol-mediated behaviour in rodents, non-human primates, patients with type 2 diabetes, and exploratory data from patients with AUD and comorbid obesity, we aim to investigate whether these beneficial findings on alcohol consumption can be a novel treatment of patients with AUD and comorbid obesity. This study aims to investigate the effects of the GLP-1RA semaglutide on alcohol intake in patients with AUD and comorbid obesity (BMI ≥30) (primary endpoint). The trial is a 26-week, double-blinded, randomised, placebo-controlled, single-site, clinical trial. The possible neuromolecular and neuroanatomical underpinnings will be investigated, in a subgroup of the patients, using fMRI and MRS brain-imaging at week 0 and week 26.

2.1 HYPOTHESES

Treatment with semaglutide will:

- Cause a greater decrease in alcohol consumption compared with placebo, measured as the total number of heavy drinking days, in patients with AUD with comorbid obesity
- Cause a reduced fMRI BOLD response compared with placebo in reward processing regions (ventral and dorsal striatum, putamen, nucleus accumbens, and caudate), including the septal area.
- Cause a greater increase in brain GABA levels compared with placebo, measured with an MRS-scan

3 INVESTIGATIONAL TRIAL DESIGN

3.1 STUDY ENDPOINTS

3.1.1 PRIMARY ENDPOINT

Change in alcohol consumption, defined as the change in percentage of heavy drinking days during a period of 30 consecutive days* (see beneath), after 26 weeks of treatment adjusted for baseline (percentage points (pp)). A heavy drinking day is defined as more than 60/48 grams (men/women) of alcohol in one day, measured with the validated timeline followback (TLFB) method.[97]

The 30-day period will be the 30 consecutive days with the biggest alcohol intake (most heavy drinking days **and the largest amount of total alcohol intake) out of the 40 days prior to the evaluation, measured by the TLFB method.*

3.1.2 SECONDARY ENDPOINTS

Changes from baseline to last assessment after 26 weeks of treatment with semaglutide vs placebo in:

- Change in heavy drinking days during a period of 30 consecutive days* (see beneath), after 26 weeks of treatment adjusted for baseline (percentage points (pp)) and maximum tolerable semaglutide dose given.
- Change in heavy drinking days during a period of 30 consecutive days* (see beneath), after 26 weeks of treatment adjusted for baseline (percentage points (pp)) and weight loss during the 26 weeks of treatment.
- Total alcohol consumption (gram/last 30 consecutive days*)
- Number of days without alcohol consumption (last 30 consecutive days*)
- Drinks per day (last 30 consecutive days*)
- Time to relapse, defined as the time to first alcohol intake
- Time to first heavy drinking day
- Reduction in WHO alcohol risk level (last 30 consecutive days*)
- Penn Alcohol Craving Scale (PACS) score
- Alcohol Use Disorder Identification Test (AUDIT) score
- Drug Use Disorders Identification Test (DUDIT) score
- Fibrosis-4 (FIB4) score
- Measures of health (WHOQOL-BREF) score
- Fagerströms Test for Nicotine Dependence score
- Blood gamma-glutamyl transferase (GGT)
- Blood alanine transaminase (ALAT)
- Plasma levels of phosphatidyl ethanol (PEth)
- Blood mean cell volume (MCV)
- Body weight
- Blood pressure
- Pulse
- Waist circumference
- Glycaemic control parameters (HbA1c)
- Brain GABA levels (cortical, caudate, and putamen) assessed by MRS brain scans
- Brain alcohol cue-response in reward-processing brain regions (ventral and dorsal striatum, putamen, nucleus accumbens, and caudate), including the septal area assessed by fMRI brain scans

The 30-day period will be the 30 consecutive days with the biggest alcohol intake (most heavy drinking days,* ***and* *the largest amount of total alcohol) out of the 40 days prior to the evaluation, measured by the TLFB method.*

3.2 STUDY DESIGN AND DURATION

A 26-week long, randomised, double-blinded, placebo-controlled, single-site, clinical trial, including 26 weeks of treatment, plus up to four weeks extra for the patients participating in the brain imaging part of the study (two weeks before treatment initiation to be sure no patients have benzodiazepines leftovers in the body from alcohol withdrawal treatment and one week after treatment cessation to be sure the scanner is available in case of unpredictable events. No extra injections will be given in this timeslot of three weeks). All included patients will be contacted by telephone five weeks after last visit, to evaluate safety data.

3.3 THE ANTICIPATED TIMETABLE FOR THE TRIAL

Start of recruitment	Q2 2023
End of recruitment	Q4 2025
Last treatment	Q4 2026

3.4 STUDY SCHEDULE

3.4.1 SCREENING

Before the screening, all patients will be provided with oral and written information about the trial, including the most common adverse events and the procedures involved in the study. All patients will be fully informed, verbally and in writing, of their rights and responsibilities while participating in the trial. Screening examinations will only be performed after the patient has agreed to participate and has signed and dated the written informed consent form. The complete recruitment procedure is described in detail later.

3.4.1.1 WOMEN OF CHILDBEARING POTENTIAL

Women of childbearing potential (WOCBP) i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile (hysterectomy, bilateral salpingectomy and bilateral oophorectomy) will be informed of the risk of possible human teratogenicity/fetotoxicity in early pregnancy,[98] and the demand of using contraceptives (during the whole study period plus additional two months), considered as highly effective (combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable) intrauterine device – IUD, IUS, bilateral tubal occlusion, vasectomised partner, sexual abstinence).[99]

3.4.2 SCREENING EXAMINATIONS

At the screening assessment, the patient will be asked about his/her alcohol intake in the previous 40 days. The information will be recorded via the timeline followback (TLFB) method. The patient will be asked questions about his/her lifetime alcohol consumption, alcohol preference, previous treatment, and general information about psychosocial factors, i.e., education level, employment, and marital status, name and contact-information for a close relative. Height, weight, waist circumference, blood pressure, and pulse will be registered. Questionnaires (the clinical institute withdrawal assessment of alcohol scale-revised (CIWA-Ar), major depression inventory (MDI) score, AUDIT, DUDIT, PACS, Fagerströms questionnaire and WHOQOL-BREF) will be performed. Current somatic symptoms, i.e., gastrointestinal-symptoms, will be registered to obtain somatic baseline information. Daily medications will be registered. Safety blood samples will be collected (see Table 1 for a specification). A blood sample will be saved for an investigational biobank and a biobank for future research (described in the section about ethical considerations). The assessment will last 3 hours. Patients who fulfil any of the exclusion criteria or do not meet inclusion criteria (listed in later sections of the protocol) will be excluded. A list of all excluded patients will be kept in the case report form (CRF).

3.4.3 EXAMINATIONS DURING AND AT THE END OF THE TRIAL

At weeks 6, 8, 12, 16, and 20 parts of the baseline examinations will be repeated. At week 26, the final examination will take place, repeating the baseline examinations. The examination will last 1,5 hours. See Appendix 1 for a complete schedule of events during the study period. All included patients will be contacted by telephone five weeks after last visit, to evaluate safety data.

3.4.4 COGNITIVE BEHAVIOURAL THERAPY (CBT)

During the 26 weeks of inclusion, the patients will receive up to ten sessions of standardised cognitive behavioural therapy (CBT) by a blinded, experienced nurse trained in CBT. During the sessions, psychoeducation, motivation, drinking goals, self-control, behavioural analysis of drinking risk situations, general problem-solving (cravings and feelings), relapse prevention, and life-time alcohol use (ALCO-Life) will be assessed.[12] After the last therapy session, patients will be asked to give feedback on all individual sessions, i.e. what sessions had the highest impact and why.

3.5 BRAIN-IMAGING

In addition to these clinical outcome parameters, we will explore the neuromolecular- and anatomical underpinnings of the potential therapeutic effects of semaglutide in a subgroup of patients who are treated with either semaglutide or placebo. To assess this, a combined MRS/fMRI-scan (70 patients) will be performed at baseline and after 26 weeks of treatment. The patients will be included continuously until 70 patients have completed the baseline scan. To ensure safety, patients going in the scanner will be tested with an alcohol breath test and the CIWA-Ar score just before starting preparations for the scans. The CIWA-Ar score has to be below nine, and the patients have to be able to perform a simple neurological test. Otherwise, a new appointment will be scheduled. Patients will be asked to abstain from smoking or use of other nicotine products for one hour preceding the scan-session. Just before entering the MRI scanner, the patients are asked to provide a urine sample, which will be tested for cocaine, amphetamine, THC, methadone, morphine, and benzodiazepine. If positive, this will be registered as a potential bias and will not have any consequences for the patients. During the scan, the patients will lie on their backs with their heads resting in a holder containing the 1H observation coil. For patients treated with benzodiazepines due to alcohol withdrawal symptoms, the first fMRI scan will be scheduled 12 days after the last intake, as earlier studies have demonstrated impaired task performance after the consumption of benzodiazepines.[100] The scan methods are described in the following sections. The combined MRI session lasts in total approximately two hours, and the total time in the scanner for each patient is approximately one hour. All MRI scan methods are non-invasive.

3.5.1 FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI)

3.5.1.1 FMRI EQUIPMENT AND ANALYSIS

During functional magnetic resonance imaging (fMRI), images are presented on an opaque screen, which can be viewed by participants through angled mirrors. Task presentation is performed using Presentation software (Version 9.9, Neurobehavioral Systems, Inc., Albany, California) and E-Prime (version 2.0, Psychology Software Tools, Inc., Sharpsburg, PA). Pre-processing and resting-state statistical analyses are performed using SPM8 (Wellcome Department of Cognitive Neurology, London, United Kingdom) (alcohol cue sensitivity task), FEAT (FMRIB Expert Analysis Tool) (spatial working memory task). Structural MRI data (e.g. atrophy) is

analysed with FIRST (FMRIB's Integrated Registration and Segmentation Tool) and SIENA/FSL-VBM (structural brain change analysis and voxel wise analysis of grey-matter density), and structural connectivity reflected by diffusion tensor imaging (DTI) with the FMRIB's Diffusion Toolbox (FDT), which are part of FSL (FMRIB Software Library version 5.0.2.2) (www.fmrib.ox.ac.uk/fsl). Behavioural data and craving ratings will be analysed using SPSS (Statistical Package of the Social Sciences, Version 19 by IBM). To assess the association between behaviour/craving, group (semaglutide or control), session (first or second scan), and stimulus category (alcohol or neutral stimuli), a repeated-measures analysis of variance is conducted with craving as a dependent variable, group as between-subject factor and session and stimulus category as within-subject factors.

3.5.1.2 Resting state

Resting state functional connectivity will be investigated while the patient rest in the scanner, but without falling asleep. Task duration is ten minutes.

3.5.1.3 Alcohol cue sensitivity

Sixty alcohol-related and 45 neutral stimuli are presented using a block design. The task is presented in a block paradigm to maximise sensitivity for BOLD signal change. Each block consists of five stimuli, each presented for four seconds. Alcohol-related pictures are taken from a validated picture series.[101] Neutral control cues are taken from the International Affective Picture System.[102] Following each block, the patients rate the intensity of their alcohol craving on a visual analogue scale ranging from 0 (no craving) to 100 (extremely extensive craving). The task duration is 12 min. An example of the visual stimuli is provided in Figure 1.

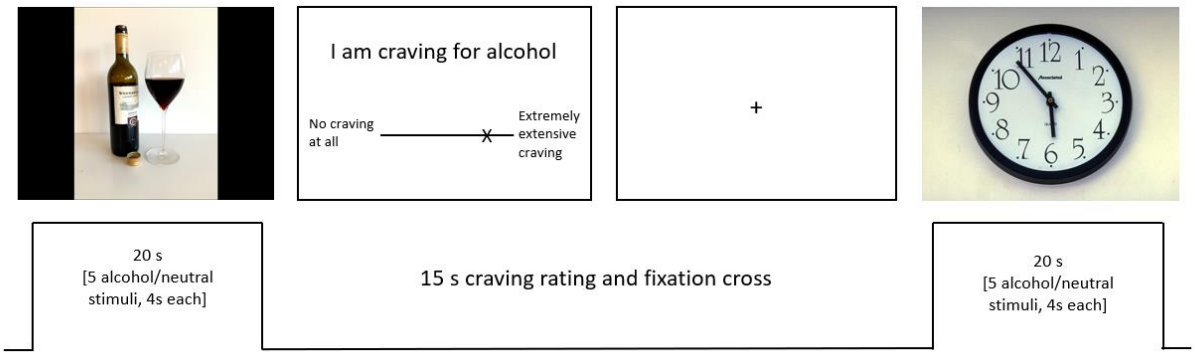

Figure 1

3.5.1.4 Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) will be investigated while the patient rest in the scanner, but without falling asleep. Task duration is 10 minutes.

3.5.2 Magnetic Resonance Spectroscopy (MRS)

3.5.2.1 MRS acquisition and analyses

MR images will be obtained for anatomical localisation, and a volume will be chosen in grey matter for the measurements of GABA (using J-editing), and glutamate (using STEAM or semi-LASER). Unsuppressed acquisitions of water will also be acquired for subsequent quantification. The scan will last 20 minutes, including

positioning of the patient and scanner calibration. The data will be inspected for signs of motion, aligned, and averaged to optimise signal-to-noise ratios. The data will be fitted in the spectral domain using LCModel[103] and referenced to tissue creatine and unsuppressed tissue water. Tissue creatine can be a useful parameter because it is acquired simultaneously with the other metabolites and is generally stable across conditions (except in cases of major brain compromise such as cancer and stroke). However, because there is potential for tissue creatine to change, tissue water will also be acquired as a reference for comparison of neurochemical levels. We and others have found that the differencing approach is generally more sensitive to small chemical changes, analogous to a paired t-test compared to group t-tests. We have already conducted a pilot study in Copenhagen with healthy controls (unpublished) and have succeeded in setting up the GABA spectra brain levels measurements (Figure 2).

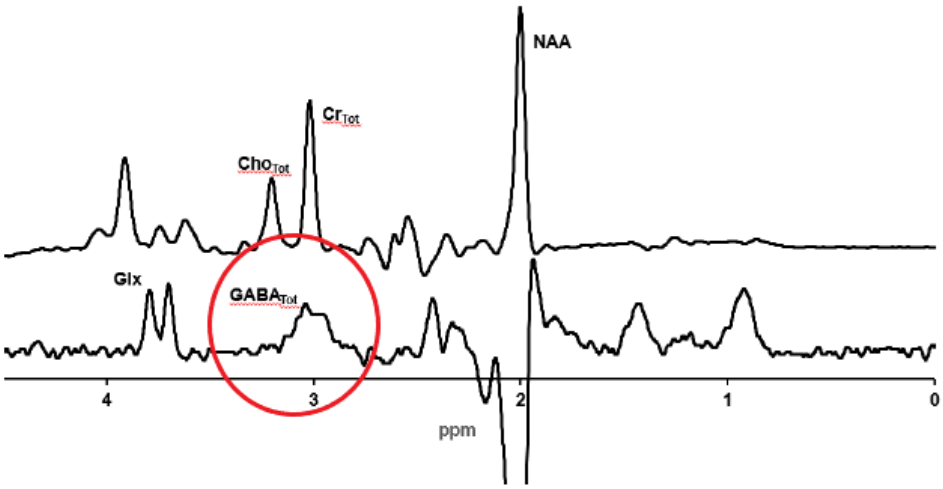

Figure 2. MRS GABA findings: GABA spectra brain levels from healthy controls

3.6 BLOOD SAMPLES (TABLE 1)

Blood sample	Screening, week 0	Week 6	Week 12	Week 20	End of trial, week 26
PEth	X	X	X	X	X
Proteomics	X				X
Plasma semaglutide	X				X
Biobank for future research	X				X
Haemoglobin	X				X
Thrombocytes	X				X
MCV	X				X
Leukocytes	X				X
Leukocytes, differential count	X				X
INR	X				X
HbA1c	X		X		X
Amylase	X	X	X	X	X
Albumin	X				X
GGT	X		X		X
ALAT	X		X		X
ASAT	X		X		X
Cholesterol	X				X
Triglycerides	X				X
HDL	X				X
LDL	X				X
D-vitamin	X				X
Cobalamin	X				X
Natrium (Na+)	X				X
Potassium (K+)	X				X
Creatinine	X		X		X
eGFR	X		X		X
Plasma hCG (females of childbearing potential (WOCBP))*	X				X
TSH	X				X

*Table 1. Blood samples during the study. PEth denotes phosphatidylethanol; MCV, mean cell volume; INR, international normalised ratio; HbA1c, glycated haemoglobin; GGT, gamma-glutamyl transferase; ALAT, alanine aminotransferase; ASAT, alkaline phosphatase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; hCG, human chorionic gonadotropin; TSH, thyroid-stimulating hormone. *in case of delayed menstrual periode (over one month between menstruations) a plasma hCG confirmation of absence of pregnancy be performed.*

3.7 RANDOMISATION AND BLINDING

The participants will be randomised into two groups, with 54 patients in each group. The randomisation will be stratified in terms of age, sex, and baseline alcohol consumption (i.e., the number of heavy drinking days and total alcohol consumption before inclusion measured by the TLFB). For this stratified randomisation, the randomisation tool in REDCap will be used. REDCap is a secure web application for building and managing online surveys and databases. The technical parts of setting up the randomisation tool will be carried out in close corporation with an expert in statistics, who will ensure the correct function of the tool before study start.

After screening the patient, i.e., ensuring that all inclusion criteria and none of the exclusion criteria are fulfilled the patient will be included in the study by the investigators. All included patients will be randomised. Only un-blinded personnel will have access to the randomisation module of REDCap, and he/she will be responsible for carrying out the randomisation of the patients. Patients, investigators, other caregivers performing assessments, and persons performing data analysis will remain blinded from the time of randomisation until the time of database unlock. To maintain the blinding of the patients, un-blinded personnel will prepare the injection in a separate room and give the injection immediately after. To maintain blinding, the patients will be blindfolded, as the injection is given in the abdomen or upper arm. If not blindfolded, the patients will be able to see if they are given the active or the placebo drug, as these two are very different in appearance. This blinding method has been used before, unproblematic for the patients or the investigators.[59] As the active pen makes a small sound when released, the patients will be provided with music in their ears. In case of emergencies, i.e., situations that require immediate un-blinding, the investigators will be able to change their user rights in REDCap and get access to the randomisation tool. In the randomisation tool, it is possible to reveal treatment based un study ID, i.e., get information about the specific patient without breaking all randomisation codes. All activity performed in REDCap by the investigators is logged, i.e., any change in user rights or un-blinding will be logged by the program.

3.8 TREATMENT REGIMES

Comparative treatment regimes in 26 weeks of treatment with:

- semaglutide 2.4 mg s.c. once-weekly, or
- placebo s.c. once-weekly

3.9 DRUGS USED IN THIS STUDY

3.9.1 DRUG DESCRIPTIONS

3.9.1.1 SEMAGLUTIDE

Semaglutide 1 mg/1,5mL pre-filled pen-injector is supplied in pens for injection containing the GLP-1RA semaglutide in sterile water with disodium phosphate and propylene glycol and phenol for conservation (pH 8.15): The initial weekly dose will be 0.25 mg for four weeks (week 1-4) (see Table 2).

Semaglutide 2 mg/1,5mL pre-filled pen-injector is supplied in pens for injection containing the GLP-1RA semaglutide in sterile water with disodium phosphate and propylene glycol and phenol for conservation (pH 8.15): The weekly dose will be 0.5 mg for four weeks (week 5-8) (see Table 2).

Semaglutide 4 mg/3mL pre-filled pen-injector is supplied in pens for injection containing the GLP-1RA semaglutide in sterile water with disodium phosphate and propylene glycol and phenol for conservation (pH 8.15): The weekly dose will be 1 mg for four weeks (week 9-12) (see Table 2).

Semaglutide 6,8 mg/3mL pre-filled pen-injector is supplied in pens for injection containing the GLP-1RA semaglutide in sterile water with disodium phosphate and propylene glycol and phenol for conservation (pH 8.15): The weekly dose will be 1.7 mg for four weeks (week 13-17) (see Table 2).

Semaglutide 9,6 mg/3mL pre-filled pen-injector is supplied in pens for injection containing the GLP-1RA semaglutide in sterile water with disodium phosphate and propylene glycol and phenol for conservation (pH 8.15): The weekly dose will be 2.4 mg for the rest of the inclusion period (week 18-26) (see Table 2).

3.9.1.2 PLACEBO

The placebo will be supplied for as pre-filled saline syringes (BD PosiFlush™, BD Worldwide) containing 3 ml each. Needles are bought separately.

3.9.2 DRUG STORAGE

Semaglutide and placebo will be stored appropriately, including temperature logs.

3.9.3 DOSAGE, ADMINISTRATION AND POTENTIAL SIDE EFFECTS OF THE INVESTIGATIONAL DRUG

3.9.3.1 SEMAGLUTIDE

Semaglutide will be administered once weekly subcutaneously by an unblinded personnel, following the manufacturer's instructions. Semaglutide can be injected subcutaneously in the abdomen, thigh, or upper arm. The initial dose is 0.25 mg once weekly, and the titration will follow the table beneath until up-titration to maximal tolerable doses (the minimum tolerable dose must be 0.5 mg once weekly to continue in the trial) (Table 2). The most common side effects are transient nausea, diarrhoea, constipation, and vomiting (more details are discussed in the section about ethical considerations).

	week 1 - 4	**week 5 - 8**	**week 9 - 12**	**week 13 - 16**	**Week 17 - 26**
Semaglutide	0.25 mg	0.5 mg	1 mg	1.7 mg	2.4 mg

Table 2: Schedule of up-titration until maximum tolerable dose. The minimum tolerable dose must be 0.5 mg once weekly.

3.9.3.2 PLACEBO

The placebo will be administered in the same way and volume as semaglutide. The only expected side effect is soreness/stinging at the injection site.

3.9.4 DRUG ACCOUNTABILITY AND COMPLIANCE

One investigator will be responsible for drug accountability. For each patient treated, the batch number of the pen/placebo pen will be documented. After verification of the drug accountability, proper destruction of the pens, according to guidelines of Region H will be ensured.

4 PARTICIPANT SELECTION

4.1 NUMBER OF PATIENTS AND TARGET POPULATION

One hundred and eight patients diagnosed with alcohol use disorder and comorbid obesity (BMI ≥30 kg/m^2).

4.2 RECRUITMENT OF PATIENTS

Patients will be recruited from general practitioners in *Region Hovedstaden*, relevant hospital units in *Region Hovedstaden* and associated social nurses. Local employment centres, citizen service centres and libraries

will be asked to have our recruitment folder and poster on their noticeboard. Patients will also be recruited through the webpage "www.alkoholforskning.dk", where patients can download the written information, and through www.forsoegsperson.dk and www.forskningnu.dk. At the first contact (phone or email), an information meeting will be scheduled, and the patient will be informed about his/her right to bring a friend or adviser. The meeting will be conducted by a medical doctor associated with the research project. Information about study participation and interventions, risks, and disadvantages will be given in a confidential conversation based on the written information, and the patient will have the opportunity to ask questions. The informal conversation will take place in a closed office at the research site at Psychiatric Centre Copenhagen, Frederiksberg Hospital. After oral and written information is presented, a consideration time of two days will be offered before the written consent is obtained. If the patient wants to participate and has an alcohol breath test below 0.5 per mille, the consent of participation will be signed, and an appointment for the screening session will be planned. If the patient needs treatment for alcohol withdrawal symptoms, they will be referred to their general practitioner, local alcohol outpatient clinic or hospital.

4.2.1 INCLUSION CRITERIA

- Informed oral and written consent
- Diagnosed with alcohol dependence according to the criteria of the International Classification of Diseases 10 (ICD-10), and diagnosed with alcohol use disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)
- Alcohol use disorder identification test (AUDIT) score >15
- Body mass index (BMI) above or equal to 30 kg/m^2
- Age 18 - 70 years (both included)
- Heavy alcohol drinking defined as more than 6 days with alcohol consumption over 4 units (48 g alcohol) for women and 5 units (60 g alcohol) for men during a consecutive 30-day period, within 40 days prior to baseline evaluation, measured by the TLFB method. The 30-day period will be the 30 consecutive days with the biggest alcohol intake (most heavy drinking days *and* the largest amount of total alcohol) out of the 40 days.

4.2.2 EXCLUSION CRITERIA

- Severe psychiatric disease, defined as a diagnosis of schizophrenia, paranoid psychosis, bipolar disorder or mental retardation
- A history of delirium tremens or alcohol withdrawal seizures
- No serious withdrawal symptoms at inclusion (a score higher than 9 on the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar)) at baseline examinations
- Present or former neurological disease, including traumatic brain injury
- Type 1 diabetes, type 2 diabetes in poor glycaemic control (defined as HbA1c ≥48 mmol/l or fasting plasma glucose above 7.0 mmol/l at inclusion)
- Females of childbearing potential who are pregnant, breast-feeding or have the intention of becoming pregnant within the next 9 months (26 weeks plus two months after discontinuation of semaglutide), or are not using contraceptives (during the whole study period) considered as highly effective (combined (oestrogen and progestogen containing) hormonal contraception associated with inhibi-

tion of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable) intrauterine device – IUD, IUS, bilateral tubal occlusion, vasectomised partner, sexual abstinence)[99]

- Pregnancy (serum human chorionic gonadotropin (hCG) > 3 U/L at inclusion)
- Impaired hepatic function (liver transaminases >3 times the upper limit)
- Impaired renal function (eGFR < 50 ml/min and/or plasma creatinine >150 µmol/l)
- Impaired pancreatic function (any history of acute or chronic pancreatitis and/or amylase > 2 times upper limit)
- Former medullary thyroid carcinoma (MTC) and/or family history with MTC and/or Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
- 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 >110 mmHg)
- Concomitant pharmacotherapy against alcohol use disorder, i.e., disulfiram, naltrexone, acamprosate, or nalmefene, since the first of the 30 drinking days registered for inclusion at the TLFB-schedule.
- Receiving any investigational drug within the last three months
- Use of weight-lowering pharmacotherapy within the preceding 3 months
- Any other active substance use defined as a DUDIT-score >1 (except nicotine)
- Hypersensitivity to the active substance or any of the excipients
- Only for patients undergoing brain scans:
    - Contraindications for undergoing an MRI scan (magnetic implants, pacemaker, claustrophobia, etc.)
- Unable to speak and/or understand Danish
- Any condition that the investigator feels would interfere with trial participation

4.2.3 WITHDRAWAL CRITERIA

- The subject may withdraw at will at any time
- Any condition that the investigator feels would interfere with continued trial participation. For example, in case of a serious adverse event that requires discontinuation or withdrawal from the study, or abnormal laboratory values that require discontinuation according to the exclusion criteria.
- Failure to maintain a present level of compliance with clinical trial medication, i.e., if the patient misses more than three consecutive injections or more than five injections in total.
- Development of an allergic reaction to the active substance or any of the excipients.

Completion or trial termination for any reason will be fully documented in the case report form (CRF). Patients can withdraw from the trial at any time without providing reason(s) for withdrawal and without prejudice to further treatment in *Region Hovedstaden*. The reason for withdrawal may be a withdrawal of consent, treatment failure, adverse event, pregnancy discovered during the trial, or significant worsening in alcohol consumption levels. The reason(s) will be recorded in the CRF. Data from dropouts will be included in the data processing. Patients withdrawing from the trial who has been included for more than 12 weeks and

has not started concomitant treatment will be encouraged to go through the same final evaluations as patients completing the trial according to the protocol with a special focus on safety. The aim is to record data the same way for patients who complete the trial. Otherwise, data will be recorded as consented by the patient. Extraordinary events that prevent the study from being carried through will interrupt the study for all included patients, who will be informed about the decision and the causes of study closure.

5 ASSESSMENT OF SAFETY

5.1 ADVERSE EVENT (AE) AND ADVERSE REACTION (AR)

AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. An AE can 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. The investigators are responsible for the causality assessment of AEs. All events occurring after the subject has signed the study consent form and until five weeks after treatment has ended will be reported as an AE. AR is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. At week 2, 4, 6, 8, 10, 12, 16, 20, 24, and 26, possible AEs/ARs will be documented in the CRF. The patients will at inclusion, receive a phone number with 24-hour service and be asked to call in case of any adverse events or reactions or case of any doubt. All reported AEs/ARs will be followed until resolved as clinically required. As far as possible, all AEs/ARs must be described by their duration (start, and stop date), severity (mild, moderate, or severe – if severe, see next section), relationship to treatment evaluated by investigator the investigator (yes, uncertain, no – if relation classified as AR). The need for other specific therapy concerning the event will also be registered. The onset of AE/ARs will be classified relative to the stage of drug infusion.

5.2 SERIOUS ADVERSE EVENT (SAE) AND SERIOUS ADVERSE REACTIONS (SAR)

SAE, i.e., any untoward severe or unfavourable medical occurrence in a research study participant, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to the research. SAR, i.e., a reasonable causal relationship exists between the drug or the experiment and the untoward effect. The event/reaction is regarded as serious in case of any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/congenital disability. 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. Complications occurring during hospitalisation are AEs and SAEs if they cause prolongation of the current hospitalisation. Hospitalisation for elective treatment of a pre-existing non-worsening condition is not considered an AE.

The investigators will as soon as possible – and within 24 hours – report any SAE and SAR to sponsor, whether or not considered related to the study drug (for the period of inclusion until ten weeks after study termination). Although not SAEs, all pregnancies occurring during the study will be reported using the SAE reporting

procedures. The investigator will not wait to receive additional information to fully document the event before notifying an SAE, although additional information may be requested. Where applicable, data from relevant laboratory results, hospital records, and autopsy reports will be obtained. The investigators will submit follow-up reports until the SAE or SUSAR is resolved or in the case of permanent impairment until the SAE or SUSAR stabilises. The sponsor will report all SAE and SARs to the Ethics committees (IECs) and the Danish medical agency once a year, together with a report on the safety of the study patients via EudraVigilance. Details of SAEs and SARs will be registered on the adverse event pages in the CRF. The patients will be instructed to contact the investigator group as soon as possible in case of any events or reactions within 5 weeks after the last treatment, and all included patients will be contacted by telephone five weeks after last visit, to evaluate if any events, i.e., AE/AR/SAE/SAR/SUSAR has happened since the last injection. All reported contacts will be followed up until resolved as clinically required. Instances of death, congenital abnormality, or an event that is of such clinical concern as to influence the overall assessment of safety will be reported if there is any suspected link to the study. All SAEs and SARs will be reported to the Danish medical agency at the end of the study via CTIS.

5.3 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR)

The reference document to evaluate possible SUSARs is the semaglutide EPAR product information from the EMA.[98] All unexpected serious adverse reactions will immediately be reported by the sponsor to the Danish Medical Agency via EudraVigilance. SUSARs that result in death or are life-threatening will be reported to the Danish medical agency at the latest seven days after the sponsor has been notified about it. After reporting the SUSAR, the sponsor will provide the Danish Medical Agency all further relevant information on the course of the case within eight 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 the sponsor has been notified about the SUSAR. If the yearly report has any comments, we will take responsibility for the consequences and change the procedures related to the research project.

6 STATISTICAL EVALUATION

6.1 STATISTICAL ANALYSES

All statistical analyses will be performed with treatment groups still blinded, and the statistical analysis plan (SAP) will be uploaded to ClinicalTrials.gov before the start. Statistical analyses will be performed using "R Studio" software (version 3.6.0).[104] Adherence to the intervention will be defined by no more than three missed consecutive injections or six missed injections in total during the 26 weeks. Adherence to the intervention will be presented as a table of the distribution of percentage of weeks with study medication/placebo in the treatment period. Protocol deviations will be presented in a table divided into the categories: study procedure, eligibility, and randomisation. Protocol deviations regarding "lost to follow up" and "withdrawal" will be summarised in the section named this. All analyses will be performed after the intention-to-treat principle, e.g., all included patients who are randomised and receives at least one dose of the trial compound (semaglutide or placebo) will be included. There will be no replacement of patients dropping out, but all patients who discontinue the intervention and have been included for at least 12 weeks will be encouraged to participate in a premature week 26 follow-up, including brain scans, at the time of withdrawal. Withdrawal data will be presented in a Kaplan-Meyer survival curve. For patients who prematurely discontinue treatment

but do not withdraw, all collected data will be included in the final analyses. Data from patients screened but not randomised to treatment will not be presented in any tables or listings except for the CONSORT flowchart. Safety data will be collected during the 26 weeks of inclusion and up until 5 weeks after trial termination for all individuals, i.e., contacted by telephone by the investigators. Data will be 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.

6.1.1 Descriptive statistics

Continuous data will be summarised with the number of observations, mean, standard deviation, minimum, median, and maximum. Categorical data will be summarised with numbers and percentages.

6.1.2 Primary and secondary endpoints

Continuous outcomes will be analysed with an ANOVA adjusted for baseline until the last observational endpoint. No adjustments for covariates will be performed. DUDIT data will be analysed with a censored regression model due to zero-inflated values. Due to a potential high dropout rate in alcohol intervention trials (see section 6.2 regarding the justification of sample-size),[59,105] missing data will be imputed with the use of multiple imputations in the mice package[106] in R software version 3.6.0[104], method = "pmm" (predictive mean matching), and the number of imputed datasets =100. To test if the results with the imputed values are correct, the sensitivity analysis in section 6.1.3 will be performed.

6.1.3 Sensitivity analysis

For the outcomes of heavy drinking days, total alcohol intake, and days without alcohol consumption, we assume the dropout is caused by a relapse in alcohol intake, and therefore we will impute the values of the missing week-26 data with a) the baseline values, and b) half the baseline values. If we assume the missing data are missing not at random (MNAR), a per protocol (PP) analysis will be performed.

6.2 Justification of sample size incl. power calculation

The power is based on the primary endpoint, i.e., change in heavy drinking days. No other studies have investigated the effects of semaglutide in patients with alcohol use disorder. The sample size calculation is based on the alcohol study by Bogenschutz et al.,[107] investigating psilocybin-assisted psychotherapy as a novel treatment of AUD. They reported a reduction in the total number of heavy drinking days of 46.77% in the intervention group and 25% in the placebo group. With a power of 90%, an alpha of 5%, and an estimated SD of 26.44, we will need 64 patients, with 32 patients in each treatment group. Large drop-out rates are often observed in AUD intervention trials with attrition rates ranging between 10% and 35%.[105] In our last clinical trial investigation the GLP-1 receptor agonist exenatide, the attrition rate was 54.3%.[59] We assume that the drop-out rate will be smaller in this clinical trial due to fewer side effects with semaglutide than exenatide, and due to the large amount of therapy sessions. We anticipate a 40% dropout rate, making the total sample size 108, with 54 patients in each treatment group, all included at one research site (Psychiatric Centre Copenhagen, Frederiksberg Hospital).

The fMRI sample size is based on previous studies showing that a sample size of about 12 to 14 subjects per group has sufficient power to obtain significant group activations as well as group differences in studies on cue reactivity.[17] Due to previous experiences,[59] where only 22 out of 62 individuals were rescanned after 26

weeks of treatment, the estimated dropout is 65%. To ensure power in case of technical challenges or a larger-than-expected dropout rate, we wish to include 70 patients (35 in each group) in the brain-imaging part of the study.

7 DATA MANAGEMENT

All patients will receive a study number when entering the study. The sponsor-investigator is responsible for keeping a list separately for all randomised patients containing patient numbers, full names, and civil registration numbers. Investigators will prepare a list of individuals who were screened for participation but were not randomised and the reason for non-eligibility. The patients will be informed orally and in writing that all results will be stored in a secure database with limited access (REDCap) and analysed anonymised in a statistical software program according to national laws, as applicable, and that patient confidentiality will be maintained. All data obtained during the study will be documented in the individual electronic CRF (REDCap). All data, except informed consent forms and results from MRS/fMRI scans, will be directly keyed in REDCap. The reasons for any missing data must be logged in REDCap. Corrections on paper forms (scan results) should be made legibly, dated, and initialled. The electronic database REDCap, source data, source documents, protocol and amendments, drug accountability forms, correspondence, patient identification list, informed consent forms, and other essential GCP documents will be retained for at least ten years after the part is completed at the study site. Patient data will be entered continuously into the database REDCap by the investigators. MRS data will be analysed by Professor Graeme Mason, Yale University, US, as he is a specialist in this field, and has been collaborating with our research group on several projects regarding MRS data. The MRS data will be pseudonymised, and the data will be transferred via a secure server. The data will only be analysed for this specific project, and no transfer of data to a third parti will take place. Professor Graeme Mason will not have any contacts with patients included, only the raw MRS-data. No other foreign collaborators (Nora D. Volkow, Helene Benveniste and George Koob) will have access to the raw data, but will supervise on the protocol, trial setup, and the interpretation of the final research findings. No foreign collaborators will have contact with any of the included patients or have a medical responsibility hereof.

7.1 ADMINISTRATIVE PROCEDURES

7.1.1 INSURANCE

The investigators ensure that the patient's participation in the study is covered by insurance via the hospital.

7.2 ETHICS COMMITTEE (EC)

Before initiation of participant recruitment, the study protocol will be submitted to www.ClinicalTrials.gov and approved by the Ethics committee of the Capital Region of Denmark/the Danish National Board of Health (EU CT NUMBER: 2023-503371-25-00), and the Danish Data Protection Agency (P-2023-187). The trial will be conducted in accordance with the declaration of Helsinki II and with national laws and regulations for clinical research. The sponsor 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 will file all correspondence and notify the ethics committees and regulatory authorities when the study is completed.

7.2.1 ETHICAL CONSIDERATIONS

AUD is a major public health problem in Europe and the United States.[108,109] It is also underdiagnosed, undertreated,[110] and when alcohol abstinent, more than 2/3 of patients in abstinence-oriented treatment will relapse within the first year.[5] This study will be the first of its kind, evaluating the GLP-1RA semaglutide as a possible new pharmacotherapeutic treatment for patients diagnosed with AUD and comorbid obesity. GLP-1-based therapy was introduced to the market for treating type 2 diabetes in 2006 and obesity in 2014. Very common adverse reactions to semaglutide are mild to moderate transient gastrointestinal symptoms (nausea, constipation, and diarrhoea). Common adverse reactions are dizziness, dyspepsia, flatulence, abdominal distension, gastritis, gallstones, vomiting, abdominal pain, constipation, gastro-oesophageal reflux, an increase in pancreatic enzymes, and weight reduction (Table 3). The EMA and FDA have recently evaluated a causal association between incretin-based drugs and pancreatitis or pancreatic cancer. At the moment, the FDA and the EMA have not concluded this causal relationship. To minimise any possible risk, all patients with a history of acute or chronic pancreatitis will be excluded from the study. The patients participating in the study will have blood samples performed regularly during the study period and will be evaluated by a gastroenterologist specialist if their amylase levels are more than 3-fold the normal upper limit or in case of clinical symptoms (acute upper abdominal pain). In our previous GLP-1 alcohol study, no patients reported acute pancreatitis or an elevation of pancreatic enzymes above upper limits.[59] The patients will receive thorough verbal and written information about the risk of developing the reported adverse events. Verbal and written informed consent will be obtained from the subjects before participation in accordance with current rules. It will be emphasised in the declaration of consent that participation in the study is voluntary and that patients may withdraw 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, *Region Hovedstaden.*

The study is associated with minimal discomfort for the participating patients comprising blood sample collection and weekly subcutaneous injections. Some patients may experience minor discomfort when the needle penetrates the skin when collecting blood. A total of five blood samples, i.e., a total of 200 ml, will be drawn in the study period, which is considered safe. The main part of the blood samples taken by the investigators during the study period, will be analysed within a few hours by the department of Clinical Biochemistry at *Region Hovedstaden,* and destroyed immediately afterwards according to their guidelines. The samples will be transported to the department by the investigators.

An investigational trial-biobank with the purpose of determining a) the blood phosphatidylethanol (PEth) concentration as a biomarker for alcohol consumption for the last four weeks, b) proteomic analysis, and 3) semaglutide concentrations to evaluate if the patients had the correct semaglutide plasma levels will be created. In this investigational trial biobank, five ml of blood will be stored at weeks 0, 6, 12, 20, and 26 for the PEth analysis, and 3mL serum- and plasma from week 0 and 26 will be stored at the research site, in a locked freezer in a locked room until analyses are performed, as soon as the study is ended. The stored samples will be pseudo-anonymised, i.e., labelled with the participant's study number and the time of the sample, i.e., visit number. All analyses will be performed within Denmark, and the Danish Data Protection Agency will be notified as soon as a collaboration-agreements of analysing the samples has been made. When ready for analysis, i.e., all samples are collected and the trial is ended, the samples will be transported at -20 degrees, by a professional transportation company. All samples in the investigational trial-biobank will be destroyed after the final analysis at the end of the study, and latest on 31.07.27. Only personnel/investigators involved in the study, will have access to the samples.

The purpose of the biobank of future research (unspecified use) is to gain new knowledge about alcohol use disorder, consequences of the disease, and hopefully improve treatment. The patients will be asked to give separate written consent to store the samples in the biobank of future research. At week 0 and 26, a blood sample (20 ml fullblood) will be stored for a maximum of ten years. All samples will be stored in -80 degrees freezer in a locked room, at the investigational site until analyses are performed or the samples are destroyed according to clinical guidelines. All samples will be pseudo anonymised i.e., labelled with the participant's study number and the time of the sample, i.e., visit number. All related patient data (trial identification number, cpr.nr, name and diagnose) is stored in REDCap. Only personnel involved in this project, will have access to the samples. Analysing samples from this biobank will require new approval from the Danish Data Protection Agency and Ethical committee.

Based on the low risk for serious side effects and the safety procedures made to minimise these, participating countered with the possible benefits for this group of patients, we find this study ethically justifiable to perform.

Very common (> 10%)	Nausea, diarrhoea, constipation, fatigue. Hypoglycemia*. These are mainly seen during dose escalation and usually go away over time
Common (1-10%)	Dizziness, dyspepsia, flatulence, abdominal distension, gastritis, gallstones, vomiting, abdominal pain, constipation, gastro-oesophagal reflux, an increase of pancreatic enzymes, and weight decrease.
Uncommon (0,1-1%)	Increased heart rate, acute pancreatitis, injection site reactions.
Rare (0,01-0,1%)	Anaphylaxis
Unknown frequency	

Table 3: Adverse reactions of semaglutide.[98]

**In combination with sulphonylurea with or without metformin, i.e., not a risk in this group of patients.*

7.3 PATIENT INFORMED CONSENT

Informed written consent will be obtained from each subject before any trial-related activities.

7.4 FINANCIAL COMPENSATION TO THE PARTICIPANTS

No financial compensation will be given to the patients.

7.5 REGULATORY AFFAIRS

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

7.6 TRIAL MONITORING AND TRIAL AUDITS AND INSPECTIONS

Before the start of the study, the sponsor will ensure that the investigators are familiar with the protocol, CRFs, and other study documents and procedures. The GCP unit of Copenhagen University will monitor the trial. The clinical trial will be conducted in compliance with the protocol, according to ICH E6: Good Clinical

Practice: Consolidated guideline, CHMP/ICH/135/95, and national guidelines, including the Regulation (EU) No 536/2014. The trial can be subjected to a quality audit. The patients will be informed in writing about possible audits and/or inspections. The audit and/or inspection might be performed by the hospital's institutional review board/ethics committee or regulatory authority. In these cases, the relevant part of the patient records will be required and reviewed.

7.7 FINANCING

The study is initialised by Anders Fink-Jensen, MD DMSc, Professor, Psychiatric Center Copenhagen, Frederiksberg. The Mental Health Services, *Region Hovedstaden,* has supported the study (postdoc position) with DKK 2,093,000. The Novo Nordisk Foundation has supported operating expenses with DKK 5,465,567. The manufacturer of semaglutide, Novo Nordisk A/S, has no financial interest or involvement in this project. See the budget in appendix 2.

8 CONFIDENTIALITY AND COMMUNICATION OF RESULTS

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. One or more manuscripts will be prepared for publication in high impact international scientific journals. All results, i.e., positive, negative, and inconclusive results, will be published. The published international guidelines for authorship (International Committee of Medical Journal Editors, 1997) will be adhered to for both Danish and foreign collaborators, 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 finalised. As soon as possible and no later than one year after the trial has ended, the trial results will be submitted to the CTIS portal. Subsequently, data will be published on clinicaltrialsregister.eu. The results from the study will be presented as posters or oral presentations at national and/or international conferences.

9 APPENDIX 1: VISITS AND TIMELINE

	Screening	Baseline MRS/fMRI	Therapy, randomization, and initiation of treatment (0.25 mg)		Assesment, therapy and titration to 0.5 mg		Therapy and titration to 1 mg		Assesment, therapy and titration to 1.7 mg	Assesment, therapy and titration to 2.4 mg	Therapy and assesment		Follow-up & MRS/fMRI	Safety phonecall
Week	-1	-1	0	2	4	6	8	10	12	16	20	24	26	31
Blood pressure, pulse	X					X			X		X		X	
Blood sampling	X					X			X		X		X	
Urine sampling	X												X	
Weight	X					X	X		X	X	X		X	
Height	X													
Waist-circumference	X					X	X		X	X	X		X	
AUDIT questionnaire	X												X	
TLFB questionnaire	X					X			X		X		X	
DUDIT questionnaire	X												X	
CIWA-Ar score	X													
WHOQOL-BREF	X								X				X	
Psychosocial information	X												X	
MDI questionnaire	X												X	
PACS questionnaire	X								X				X	
Fagerströms questionnaire	X					X			X		X		X	
Drug titration			X		X		X		X	X				
Adverse event assessment				X	X	X	X	X	X	X	X	X	X	X
Cognitive behavioural therapy			X	X	X	X	X	X	X	X	X	X		
MRS/fMRI + urine toxicology screening (n=70)		X											X	

10 APPENDIX 2: BUDGET

The SEMA-ALCO study - budget from Baseline until EOT (2023-2027)				
Operating expenses (screening)				
Post	**Details**	**Price pr unit (DKK)**	**Quantity**	**Total (DKK)**
MRS/fMRI scans		5000	70	350.000
Blood samples, urine analysis	Safety	600	100	60.000
PEth blood samples		95	100	9.500
Inflammatory biomarkers		400	100	40.000
Supplies	Utensils (e.g. cannulas, syringes, tubes, storage boxes, etc)			10.000
Operating expenses (randomised controlled trial, after randomisation)				
Post	**Details**	**Price pr unit (DKK)**	**Quantity**	**Total (DKK)**
MRS/fMRI scans		5000	70	350.000
Blood samples, urine analysis	Safety	600	100	60.000
PEth blood samples		95	100x4	38.000
Inflammatory biomarkers		400	100	40.000
Supplies	Utensils (e.g. cannulas, syringes, tubes, storage boxes, etc)			10.000
Salary throughout the study				
Post	**Details**	**Price pr unit (DKK)**	**Quantity**	**Total (DKK)**
Post-doc/study coordinator (Mette Kruse Klausen MD)	Full time, 4.5 year	3.084.480	1	3.084.480
Project nurse trained in addiction therapy (TBD)	Full time, 3 years	1.401.012	1	1.401.012
Project nurse trained in addiction therapy (TBD)	Full time, 2 years	934.008	1	934.008
Research Fellow (TBD)	Full time, 1 year	120.000	3	360.000
Statistician (TBD)				100.000
Study drug				
Semaglutide				482.067
Other				
Post		**Price pr unit (DKK)**	**Quantity**	**Total (DKK)**
Publication fee (Protocol publication, baseline paper + 2-3 original papers)				80.000
Approvals from authorities				9.500
Computers		6000	5	30.000
Presentations at conferences (travel and registration)				60.000
Travel expenses (patients)				50.000
Total amount (from baseline until end of trial)				7.558.567
Already covered: Novo Nordisk Foundation - Investigator Initiated Clinical Trials 2022 (Anders Fink-Jensen)				5.465.567
Already covered: 3 years postdoc salary, Mette Kruse Klausen				2.093.000
Total amount left				**0**

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