The Effects of Exenatide, a GLP-1 Agonist, on Alcohol Self-Administration in Heavy Drinkers

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1 List of Abbreviations

Abbreviation	Abbreviation definition
ABV	Alcohol By Volume
AE	Adverse Events
AUD	Alcohol Use Disorder
AUQ	Alcohol Urge Questionnaire
BAC	Blood Alcohol Concentration
BAL	Blood Alcohol Level
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CIWA	Clinical Institute Withdrawal Assessment
CIWA-AR	Clinical Institute Withdrawal Assessment for Alcohol–Revised
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
DSMP	Data Safety Monitoring Plan
ECG	Electrocardiogram
GFR	Glomerular Filtration Rate
GLP-1	Glucose-Dependent Insulinotropic Peptide
GLP1-R	Glucagon-Like Peptide-1 Receptor
MINI	Mini International Neuropsychiatric Interview
mRNA	Messenger Ribonucleic Acid
NTS	Nucleus of the Solitary Tract
OCDS	Obsessive Compulsive Drinking Scale
SAE	Serious Adverse Events
SDU	Standard Drink Units
SNP	Single Nucleotide Polymorphisms
SSL	Secure Sockets Layer
TLFB	Time-Line Follow-Back
VAS	Visual Analogue Scale

2 Protocol Summary

Title:	The Effects of Exenatide, a GLP-1 Agonist, on Alcohol Self-Administration in Heavy Drinkers
Population:	The present study will involve 72 men and women aged 21 to 55 who exceed safe levels of drinking. Women and minorities who meet the study criteria will be eligible to participate. No vulnerable populations are being targeted for inclusion in this study
Intervention:	We propose to undertake a double-blind, randomized, placebo-controlled, crossover design trial that will test the effect of exenatide on alcohol self-administration and craving following a priming dose of alcohol. Subjects will receive either a 5 mcg dose of immediate release exenatide or a sham injection 30 minutes prior to completing a drinking challenge. Subjects will receive alcohol in the laboratory. Subjects will be presented with a priming drink mixed to raise their BAL 0.03 g/dl. Subjects will be presented with eight drinks, each mixed to raise their BAL 0.0125g/dl over a two-hour period. They will be told that they can either consume the desired number of drinks over the following 60 minutes or they will receive the equivalent in a cash reward. Subjects will serve as their own controls. The intervention will be repeated with a Sham injection/exenatide after a washout period.
Objectives:	The specific objective of this study is to test the effects of exenatide on alcohol self-administration and craving among heavy drinkers. This medication is a promising candidate that has unique actions on GLP-1 receptor systems that have been implicated in the regulation of alcohol consumption. Testing the effects of exenatide on drinking is a compelling opportunity that is consistent with the mission of NIAAA to evaluate the efficacy of re-purposed compounds with novel mechanisms that have the potential to treat AUD. If successful, this study could lead to a phase II randomized controlled trial to test exenatide as a treatment for AUD.
Design/Methodology:	This is a double-blind, randomized, placebo-controlled, crossover design trial that will test the effect of exenatide on alcohol self-administration and craving following a priming dose of alcohol. An established human laboratory self-administration procedure will be followed. Each subject will complete up to 4 clinic visits over a period of up to 38 days of participation. Study participation is comprised of a baseline assessment, alcohol self administration Trial 1, and alcohol self administration Trial 2. The volume of alcohol consumed during alcohol challenge trials 1 and 2 will be used to test the effect of exenatide on alcohol consumption. Craving measures (AUQ and VAS) collected during the self-administration trials will be used to test the effect of exenatide on alcohol craving.
Total Study Duration:	The entire study will take 24 months to complete.

Subject Participation Duration:	Each subject's length of participation will be up to 38 days.

3 Background/Rationale & Purpose

3.1 Background Information

Current models of care for treating Alcohol Use Disorder (AUD) include both behavioral therapies and pharmacotherapy[1]. Although pharmacotherapy for AUD in the US has been available since 1948 when disulfiram was approved, options for treatment are limited as there are only four medications which have been approved by the FDA for treating AUD. Disulfiram, naltrexone, acamprosate, and long-acting naltrexone have all shown promise as agents to treat AUD[2] but no single medication has proven to be effective across the heterogeneous groups of people with AUD[3]. Movement towards models of personalized care and pharmacogenetic treatment matching[4-5] hold some promise for improving AUD treatment outcomes, but the limited number of unique mechanisms of action of the currently approved drugs presents a challenge to implementing this model of care. Unfortunately, few novel compounds to treat AUD progress to phase II trials, and developing novel compounds is both costly and time-consuming[6]. One pathway of drug development efforts has been focused on re-purposing FDA approved medications that have promising mechanistic effects[7] and some success has been achieved in using this strategy with anticonvulsants[8]. Identification of additional drugs with unique mechanisms of action that are found to reduce alcohol consumption could expand the treatment options and further the goal of personalized care for AUD. The overarching goal of our research is to identify agents with unique mechanisms that hold promise for treating AUD. The specific objective of this study is to determine whether exenatide, a GLP-1 receptor agonist that is FDA-approved for treating diabetes, has effects on alcohol craving and consumption.

Alcohol Use Disorder as a national health problem

More than 16 million adults suffer from Alcohol Use Disorder (AUD) in the United States[8.] The economic burden of this is estimated to be 249 billion dollars and approximately 88,000 Americans die from alcohol-related causes each year[9]. Untreated AUD is associated with an increased risk of accidents, injuries, suicide, and worsening of other health comorbidities[10] and it is the fourth most preventable cause of death in the US[9]. Treating addiction more effectively has become a priority of national importance and the Surgeon General has urged researchers to undertake testing of new treatments to combat addiction[11]. The present study is intended to answer the call for accelerating drug development for AUD by exploring the potential to re-purpose an existing drug as a treatment for AUD[6-7].

Rationale for developing exenatide as an agent to treat AUD

GLP-1 is an endogenous peptide that regulates blood glucose by decreasing the rate of gastric emptying, promoting pancreatic beta cell activity if blood glucose levels are elevated, reducing glucagon release, and producing satiety for food[13]. Peptides that share structural similarities to GLP-1 have been synthesized including exenatide (synthetic Exendin-4) and liraglutide that are resistant to the GLP-1 metabolizing enzyme dipeptidyl peptidase IV[13-14]. There is now substantial preclinical evidence that these GLP-1 agonists can attenuate behaviors that model both the consumption and seeking of several commonly abused substances including alcohol[7-8,10-11], cocaine[15], and nicotine[16]. Consistent with the idea that GLP-1 agonists are acting on overlapping pathways that regulate both food and drug intake, these compounds have been found to attenuate the reinforcing actions of food[6,17-18]. Both Exendin-4 and liraglutide have been shown to reduce alcohol consumption by rodents[7,8-11]. The administration of these drugs attenuates alcohol-induced place preference[7,10] indicating that they reduce the rewarding effects of alcohol. Treatment with Exendin-4 blocks increases in

alcohol intake following periods of alcohol deprivation, suggesting that this drug may decrease the likelihood of relapse during periods of abstinence[19]. Exendin-4 induced reductions in alcohol consumption were not observed in mutant mice who were missing central nervous system GLP-1 receptors, providing some evidence that the effects of this drug on alcohol consumption are specifically mediated by brain GLP-1 receptors[11]. These effects in rodents may involve GLP-1 agonist attenuation of alcohol-induced release of mesolimbic dopamine, which is implicated in regulating the rewarding effects of alcohol[7,10].

The primary goal of this study is to determine whether findings from rodent studies of the inhibitory effects of GLP-1 agonists on behaviors related to alcohol consumption will translate into similar results in heavy drinking humans. In this proposed study we will examine the effects of the GLP-1 agonist exenatide on alcohol self-administration and cravings among heavy drinkers. Exenatide binds to the human GPL-1 receptor with an affinity equivalent to that of human GLP-1 peptide[20-21]. This medication is approved for use in type 2 diabetes to help normalize blood glucose levels and has been tested in non-diabetic patients as a medication for the treatment of Parkinson's disease[22]. It should also be noted that the GLP-1 agonist liraglutide has received FDA approval as a medication for the promotion of weight loss[23].

At present, the most direct evidence implicating involvement of GLP-1 receptor systems in the regulation of alcohol consumption in humans is the finding that significant associations exist between select *GLP1-R* single nucleotide polymorphisms (SNP) and the occurrence of AUD[24]. Suchankova et al. found that social drinkers who had the 168Ser/Ser variant for the rs6923761 SNP for the GLP-R1 gene consumed more alcohol in a self-administration task than subjects with the other variants of this SNP.

In the human brain, GLP-1 positive neurons have been found in the medullary tissue that contain the nucleus of the solitary tract (NTS)[25]. This may be of significance because in rodents the NTS projects to key areas implicated in mediating food and alcohol reward including the ventral tegmental area and the nucleus accumbens[26-29]. GLP-1 receptor mRNA has been detected in mesolimbic regions of the primate (Rhesus monkey) brain[30]. These findings suggest that exenatide may influence alcohol consumption in primates and, therefore possibly humans by acting through pathways that regulate drinking that are connected to the NTS. More evidence, however, is needed regarding the localization of GLP-1 neuron pathways within the human brain to support this hypothesis.

GLP-1 receptors, thus far, have been demonstrated to be present in several areas of the human brain including the hypothalamus, caudate-putamen, globus pallidus, temporal cortex, frontal cortex, parietal lobe, and orbitofrontal cortex[31-32]. Evidence concerning the functional consequences of acute administration of GLP-1 agonists, such as exenatide, on regional human brain activity has been presented in a few imaging studies. Injection of a 5 mcg dose of exenatide resulted in an increase in regional cerebral glucose metabolism in prediabetic subjects following glucose ingestion. This increase occurred in the overall mean in the collective regions that regulate glucose homeostasis (including frontal lobes, limbic system, insula, and putamen) and in those associated areas associated with food reward systems (including the orbital frontal cortex and anterior cingulate)[33]. The acute intravenous administration of exenatide to obese subjects was found by one group of investigators to reduce the activation of brain structures including the amygdala, insula, orbitofrontal cortex, and putamen that were produced by the presentation of food related cues[34-35]. Other investigators have found that exenatide administration decreased the activation of brain structures (including the amygdala, insula, hippocampus, and frontal cortex) during food cue exposure in healthy obese subjects, but had no effect on these structures in lean subjects[36]. These findings suggest that the acute administration of exenatide has effects on brain regions that have been shown to be associated with responses to alcohol cues (amygdala, temporal cortex, insula, anterior cingulate)[37-39] and alcohol administration (amygdala, anterior cingulate; insula, orbital frontal

cortex, putamen) in social and heavy drinkers[40-41]. Given the demonstrated effects of exenatide on regional brain function associated with both food and alcohol reward, we expect that this drug will modulate alcohol craving and consumption.

This study will be conducted in compliance with the protocol, applicable regulatory requirements, and BMC/BU Medical Campus Human Research Protection policies and procedures.

3.2 Rationale and Purpose

This proposal holds significant innovation as there is strong evidence that medications that act as agonists at the GLP-1 receptor decrease alcohol consumption and its rewarding effects. There are currently no published clinical studies concerning the effects of GLP-1 agonists on alcohol consumption. This proposed study answers the call for accelerating the development of medications for AUD by testing a commercially-available and well-tolerated agent at a fraction of the cost of developing novel therapies. Currently there is one placebo controlled double-blind study of the effects of sustained release formulation of exenatide on alcohol consumption by alcohol dependent subjects (NCT03232112).

4 Objectives

4.1 Study Objectives

The specific objective of this proposal is to determine whether the GLP-1 agonist exenatide has effects on alcohol consumption and craving that identify it as a candidate medication for the treatment of AUD. This medication, which is approved by the FDA for the treatment of Type 2 diabetes, has been shown in preclinical studies to be a promising candidate as an AUD treatment medication because of its actions on GLP-1 receptor systems. These systems have been implicated in the regulation of alcohol consumption[7-11]. Testing the effects of exenatide on drinking is a compelling opportunity that is consistent with the mission of NIAAA to evaluate the efficacy of re-purposed compounds with novel mechanisms that have the potential to treat AUD. If successful, this study would provide proof of concept that the administration of a GLP-1 agonist could reduce alcohol consumption in human subjects, and thereby provide support for the conduct of phase II randomized controlled trials to test one or more of the many currently FDA approved GLP-1 agonists as a treatment for AUD.

4.2 Study Outcome Measures

4.2.1 Primary Outcome Measures

The primary outcomes are alcohol consumption and cravings during the alcohol self-administration trials. Drinking volume during the alcohol self-administration will be measured to evaluate the effects of exenatide vs. sham injection on the rate of alcohol consumption after a priming drink. Alcohol craving will be measured using the Visual Analog Scale (VAS) and the Alcohol Urge Questionnaire (AUQ)[30] during the exenatide self-administration trial. These self-report measures of craving will be used to evaluate the effect of exenatide on craving vs. placebo.

4.2.2 Secondary Outcome Measures

A secondary aim of the present study is to examine the effects of exenatide on the absorption of

alcohol in a sample of heavy drinkers. It is hypothesized that areas under the breath alcohol concentration curves in heavy drinkers obtained during the first 40 minutes after ingestion of the priming drink of alcohol will be significantly lower in subjects when they receive exenatide as compared to when they are given sham injections. Another secondary goal of this study will be to determine whether blood glucose levels enter into the hypoglycemic range in any of the study subjects receiving the combination of alcohol and exenatide. It is hypothesized that the proportion of subjects with post-trial blood glucose levels in the hypoglycemic range will not differ significantly between the sham injection and exenatide treatment trials.

5 Study Design

This is a double-blind, randomized, placebo-controlled, crossover design trial that will test the effect of exenatide on alcohol self-administration and craving following a priming dose of alcohol. An established human laboratory self-administration procedure will be followed[30]. The O'Malley self-administration procedure entails the administration of a priming drink followed by the presentation of four drinks on a tray which subjects may drink, or receive compensation for the drinks not consumed. After one hour the first tray of drinks is removed and subjects are then given the opportunity to consume a second tray of drinks. Confirmation of the validity of this approach as a method for screening for medications to treat AUD include the finding that pre-treatment with naltrexone, which is an approved medication for treating AUD, significantly reduced alcohol consumption when the O'Malley self-administration procedure was used[36]. Using this procedure, our group has found that the anticonvulsant zonisamide reduces alcohol consumption in non-treatment seeking social drinkers[34]. We later confirmed that the administration of zonisamide decreases alcohol consumption in subjects with AUD in a double-blind randomized clinical trial[23] as have other investigators[34]. Testing exenatide using O'Malley's self-administration procedure is the next logical step in drug development following positive findings that exenatide reduces drinking in animal models. The human laboratory-based alcohol self-administration procedure is a cost effective and time-efficient method for testing novel drug candidates for AUD treatment[6].

Subjects: Heavy-drinking subjects will be enrolled to increase the potential generalizability of these findings to a clinical AUD population. Subjects will be recruited through advertising, study flyers, internet postings, by community recruiters, and an established subject registry at Boston Medical Center. Interested subjects will be screened by telephone to determine initial eligibility prior to the baseline assessment.

Community Recruiters: Two to three community recruiters will be hired to display/distribute approved study recruitment materials for a trial period of 2-3 months. The estimated payment for this service will be $50-100 per month but this may be increased to meet market conditions for this recruitment service. After a period of 2-3 months recruiter services may be "renewed" for an additional 2-3 months. Additional recruiters may be hired to display or distribute approved recruitment materials as needed to increase the rate of recruitment. Recruiting services may be utilized until recruitment goals have been met.

6 Potential Risks and Benefits

6.1 Risks

To minimize the risk of adverse health events we will instruct subjects to contact study staff with any questions or concerns about changes in health effects after initiating study medication/placebo. Trained medical staff will evaluate any reported adverse effects and make a clinical determination about management. Subjects will be given a wallet card that includes a phone number with 24/7 coverage for medical emergencies.

C) Potential Risks

Risks of study medication

The following adverse reactions were observed in subjects treated with 10-20 mcg of exenatide per day. The package insert for the exenatide immediate release formulations lists the incidence of the following adverse reactions versus placebo as follows for patients receiving monotherapy with exenatide in diabetic subjects: Nausea (8% versus 0%), Vomiting (4% vs 0%), and dyspepsia (3% versus 0%)[56]. Between one and two percent of Type II diabetic subjects receiving exenatide monotherapy experienced decreased appetite, diarrhea and/or dizziness. Type II diabetic subjects receiving combined therapy of exenatide with metformin (and/or sulfonylureas) experienced a higher incidence of adverse effects than did subjects receiving exenatide monotherapy. The incidence of adverse effects in patients receiving exenatide in combination with metformin or sulfonylurea versus those treated with placebo and these antidiabetic agents is shown in table 3.

Table 3. Combination therapy vs. placebo

Adverse effect	Placebo	Combination Therapy
Nausea	18%	44%
Vomiting	4%	13%
Diarrhea	6%	13%
Feeling jittery	4%	9%
Dizziness	6%	9%
Headache	6%	9%
Dyspepsia	3%	6%
Asthenia	2%	4%
Gastric Reflux	1%	3%
Hyperhidrosis	1%	3%

There is a warning that post-marketing data indicate that acute pancreatitis including necrotizing pancreatitis and hemorrhagic pancreatitis (fatal and non-fatal) have occurred in association with exenatide administration. A precaution exists stating that there is an increased risk of hypoglycemia occurring in patients taking exenatide in combination with sulfonylureas. The administration of pharmacologic doses of GLP-1 were not found to increase the incidence of occurrence of hypoglycemia in fasting healthy subjects[57]. Exenatide may produce nausea and vomiting that can be problematic in patients with impaired renal function. This drug was not well tolerated in patients with end-stage renal disease who were undergoing dialysis. It is advised that exenatide be used with caution in patients with severe renal impairment. Some reports of allergic reactions have been reported during post-approval use of exenatide including injection-site reactions, generalized pruritus and/or urticaria, macular or papular rash, angioedema, anaphylactic reaction.

In a study of the effects of monotherapy with exenatide 10 mcg twice daily over a period of 24 weeks, 10% of subjects experienced nausea vs 0% of those who received placebo. Three percent of subjects vomited vs. 0% of those who received placebo[58]. In one study 65% of healthy subjects developed nausea following injection of 10 mcg dose exenatide when they were allowed to eat a standardized meal 60 minutes after the administration of this drug[59]. In a dose ranging study of exenatide monotherapy with type-2 diabetics, nausea was reported by 13% of subjects receiving .1 mcg/kg dose, 0% of subjects receiving .2 mcg/kg dose, 29% of subjects receiving .3 mcg/kg dose, 60% of subjects receiving .4 mcg/kg dose, and 14% of subjects receiving placebo[60]. There is a warning that thyroid C-cell tumors have been observed to occur in female rats receiving extended release treatment with exenatide. Also, exenatide has produced developmental toxicity when administered to pregnant rats.

Risks of Phlebotomy, medication injection, and pinprick for blood glucose test
These procedures may cause pain, bruising, lightheadedness, fainting and on rare occasions, infection.

Risks of alcohol self-administration
There is a potential risk of increased alcohol consumption following the alcohol self-administration experiment, but studies of subjects who have completed the alcohol self-administration procedure indicate that this is rare. Social drinkers who completed an alcohol self-administration study were not found to have increased risk for problem drinking 6 weeks after completing the self-administration study[61]. Similar results were found for alcohol dependent subjects 3 months after participation in a study testing the effects of naltrexone on alcohol self-administration[62]. Young social adult drinkers also did not exhibit an increase in real life drinking 6 weeks after the completion of intravenous alcohol self-administration experiments[63].

Subjects may reach a level of intoxication that is uncomfortable to them. If a subject consumed all eight drinks that were available to them during the two one-hour alcohol Challenge Trials, there is a possibility that they could reach an estimated peak BAC of 0.09 to 0.13g/dl taking into account the rate of metabolism of 0.010 to 0.020 g/dl per hour[64]. This risk is unlikely to be a problem because we are recruiting subjects who routinely engage in binge drinking and have likely developed some tolerance to alcohol. The alcohol self-administration paradigm that we have chosen does not include any coercion, inducements, or pressure to consume more alcohol than subjects feel comfortable consuming. There are no experimental manipulations that would increase drinking (e.g., heavy-drinking confederate, anxiety manipulation). In fact, in this study design there are inducements for subjects to not drink beyond the initial priming dose. Subjects will receive monetary incentives for each drink that they do not consume. To reduce the risk of injury or harm after the subject has been discharged from self-administration laboratory, we will require that subjects have a plan for transportation that does not involve the subject driving. Subjects must have a BAC below 0.04 g/dl prior to discharge from the alcohol self-administration trials.

Risk of loss of confidentiality
There is some risk that health information collected as part of this study could be seen by unauthorized individuals. Every effort will be made to minimize this risk and protect subject confidentiality.

Adequacy of Protection against Risks
A) Recruitment and Informed Consent
All study procedures will be conducted at the Clinical Studies Unit at Boston Medical Center and the General Clinical Research Unit at Boston University Medical Campus. At the first screening visit a research assistant will greet the prospective subject and provide a copy of the consent form to read prior to meeting with a study physician. After reviewing the consent, candidates will meet with study physician and receive an explanation of the study purpose and requirements. If still interested after receiving an explanation of the study, the candidate will be given an opportunity to review, inquire about, and sign the study informed consent form. A consent questionnaire quiz will be administered to ensure that the subject understands the study procedures. Any incorrect answers will be reviewed until the consenting physician is satisfied that the subject comprehends the misunderstood information. Subjects' BAC will be measured immediately after signing consent to ensure that consent was given while not

intoxicated. BAC must be 0.000 when signing the informed consent document. The consenting physician will document the consent process in a progress note in the subject's source binder. Subjects who are deemed to lack decisional capacity will not be enrolled in this study.

B) Protections against Risks

Risks of study medication

To minimize the risk of adverse health events we will instruct subjects to contact study staff with any questions or concerns about changes in health effects after initiating study medication/sham injection. Trained medical staff will evaluate any reported adverse effects and make a clinical determination about continuation in the trial and referral for medical care. Subjects will be given a wallet card that includes a phone number with 24/7 coverage for medical emergencies.

Because of evidence that exenatide can adversely affect fetal development in rats, women will be excluded from study entry if they have a positive urine pregnancy test or if they are of childbearing age and are either not using appropriate methods of contraception or practicing abstinence.

Subjects will be excluded from this study who have renal impairment because of potential risks associated with the use of exenatide in patients with this problem. Subjects will be enrolled into this study only if the values for renal tests (Creatinine, BUN) are within normal limits. Given the warning concerning the association of exenatide treatment with pancreatitis, subjects will not be enrolled into this study if they have a history of pancreatitis or lipase above the upper normal limit. Subjects with a history of thyroid cancer or other thyroid disease will be excluded from this study because of studies showing that exenatide increases the risk of the occurrence of thyroid cancer in animals. Subjects taking warfarin will be excluded to minimize the risk of a drug interaction.

Diabetic patients will be excluded from this study because the use of antidiabetic medications including the sulfonylureas and metformin may increase the incidence of adverse effects associated with the use of exenatide. Of particular concern is the possibility that the use of antidiabetic agents may increase the risk of hypoglycemia occurring in individuals receiving injections of exenatide. Finally, the administration of exenatide to a diabetic patient would be a therapeutic intervention that should occur only in coordination their other health care providers.

The effects of the interaction of GLP-1 agonists and alcohol on blood glucose levels has not been adequately studied in humans. The administration of exenatide will decrease plasma glucagon in Type 2 diabetic patients and also may increase insulin release if blood glucose levels are elevated[13]. In fasting elderly Type 2 diabetic patients receiving the antidiabetic sulfonylurea glyburide, alcohol ingestion produced a greater decrease in blood glucose levels than did placebo[65]. Also, ethanol has also been shown to inhibit gluconeogenesis in Type 2 diabetes, although it did not produce alterations in total liver glucose output[12]. The consumption of alcohol in healthy subjects receiving the sulfonylurea glipizide did not result in a greater reduction in glucose blood levels than when this drug was taken alone, but did prolong the length of time during these reductions occurred[66]. As a precaution against subjects experiencing hypoglycemia in this study, alcoholic drinks will be administered to subjects with a sugary mixer (e.g. juice, soda). As a protection for the risk of allergic reaction, injections will be preformed in the GCRU.

Risks of Phlebotomy

To minimize the risk of pain, bruising, lightheadedness, fainting, and on rare occasions, infection from a blood draw, we will used trained phlebotomists.

Risks of alcohol self-administration

To minimize the risk of subjects reaching a level of intoxication that is uncomfortable to them,

we will remind subjects that they can discontinue study participation at any time. Subjects will be monitored during the course of the study, both through direct assessment with study staff and by observation through a video camera in the alcohol laboratory. Medical staff will evaluate subjects and may make a determination to halt study participation if the subject becomes too behaviorally impaired or if there are emergent safety issues. Subjects who have a BAC greater than 0.04 g/dl or who appear to be too behaviorally impaired to leave our research center will be asked to remain in the clinic until their intoxication is reduced to a level that it is safe to discharge them from the research laboratory.

Risk of loss of confidentiality

There is some risk that health information collected as part of this study could be seen by unauthorized individuals. Every effort will be made to minimize this risk and protect subject confidentiality. Electronic data will be housed in the REDCap data management system. REDCap is protected via Secure Sockets Layer (SSL) encryption that provides access restriction options. Exported data from REDCap will be stored on a secure password-protected server behind the BMC firewall. Source and CRF binders will be stored in a double-locked area that is accessible to only study staff. Subjects will be assigned a study identification number and this will be used to code any forms that do not require the subject's direct identifiers (e.g., consent form, laboratory results, and contact information). A linking key that associates study ID with direct identifiers will be stored in a double-locked cabinet accessible to only by study team members. Data will be stored on a password-protected computer accessible only to the study team. All study staff will receive appropriate training for the protection of human subjects (NIH Protecting Human Research Participants). Study records that include direct identifiers will be destroyed in accordance with the institutional policy at Boston Medical Center. A certificate of confidentiality will be used to protect subjects from compelled disclosure under court order or subpoena.

Protection of vulnerable populations

Women who are pregnant should not be exposed to exenatide[13]. Women who are pregnant, who think they may be pregnant, or who are trying to conceive will be excluded from the study. Women of childbearing age will complete a urine pregnancy test upon entry into the study and will be excluded for a positive finding. Women of childbearing potential must agree to use a barrier (diaphragm or condom with spermicide), oral contraceptives, non-ferrous intrauterine contraceptive system, levonorgestrel implant, medroxyprogesterone acetate contraceptive injection, surgical sterilization, or complete abstinence from sexual intercourse. Prisoners will not be enrolled in this study. Due to the potential risk to children and the minimum legal drinking age in the United States, children will not be included in this study.

Monitoring for suicidality risk

We will screen for suicidality using the Columbia-Suicide Severity Rating Scale and the MINI Neuropsychiatric Interview. Subjects with a MINI suicidality score greater than 8 (low risk) will be excluded. Subjects who report any active suicidal thoughts or behavior as measured the C-SSRS will be excluded from participation. In addition to excluding active suicidality, the MINI will be used to rule out subjects who have psychiatric conditions that may increase the risk of the occurrence of suicidal thoughts or behavior (e.g., major depression, bipolar disorder). Assessment and scoring of suicide rating scales will be conducted in real-time while the subject is present. Suicidality will be assessed by trained clinical staff including study MDs, a psychologist, a nurse, and a

mental health counselor. If subjects are found to be at risk for self harm, study staff will work with the subject to develop a safety plan that could include escorting the subject to the BMC ED or calling BEST.

Incidental findings

There is a possibility for clinically significant abnormal findings on the ECG and blood laboratory tests. Clinically significant abnormal findings will be communicated to study subjects with a recommendation to follow-up with primary care or specialized care.

6.2 Potential Benefits

There is no potential direct benefit to participation in this study. This study presents a very strong potential for benefit to science. Drug development for treating AUD is costly and few pharmaceutical companies are testing novel compounds as agents to treat AUD. Re-purposing compounds with FDA approval for other indications is the most promising route for rapid and cost-effective development of medications to treat AUD. This study will bridge the gap in drug development by providing a test of exenatide to see if it may be a candidate drug for treating AUD. If successful, this could lead to the expansion of pharmacotherapy options to treat AUD and a broadening of our understanding of the mechanistic approach to treating AUD.

6.3 Analysis of Risks in Relation to Benefits

Given that exenatide has FDA approval for another indication and is well-tolerated in other populations, the risk of this medication to human subjects has been established through pre- and post-marketing data. With the protections we have in place for all the potential risks in this study, we believe the risks of this study are well minimized. The study holds significant promise for informing new models of care given the novel mechanism of exenatide. We believe the risk/benefit ratio is favorable.

7 Study Subject Selection

7.1 Subject Inclusion Criteria

Subject Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. 21-55 years of age.
2. Able to verify age with a state or federal picture ID.
3. Exceeds safe weekly drinking limits (14 SDUs for women or 21 SDUs for men per week)
4. Reports at least one episode of binge drinking (>3 SDUs for women, >4 SDUs for men) an average of once per week in the four weeks prior to baseline screening.
5. Meets DSM-5 criteria for mild alcohol use disorder or greater severity.

7.2 Subject Exclusion
7.3 Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

An individual who meets any of the following criteria will be excluded from participation in this

study:
1. Seeking treatment for alcohol problems.
2. Clinical Institute Withdrawal Assessment at ≥10
3. DSM-5 diagnosis of current major depression, bipolar disorder, schizophrenia, bulimia/anorexia, dementia, or a substance use disorder other than alcohol, nicotine, marijuana or caffeine.
4. If female, pregnant, nursing, have plans to become pregnant.
5. If female, does not agree to use an accepted form of birth control.
6. Has a medical contraindication to the use of exenatide.
7. Has medical or mental condition for which further alcohol exposure at the planned dose range would be contraindicated.
8. Current risk of suicidality (MINI suicidality score greater than 8 (low risk) or Yes to the ideation question #4 of the C-SSRS).
9. BMI is less than 18 or greater than or equal to 30.
10. History of diabetes.
11. Baseline hemoglobin A1c ≥ 6.5%
12. Baseline nonfasting glucose >200
13. Significantly elevated serum lipase levels.
14. Impaired renal function (GFR <80 mL/min).
15. Pancreatitis, gastroparesis or other severe gastrointestinal disease.
16. Has had gastric bypass surgery
17. Subject is currently taking warfarin.
18. Has received alcohol counseling or other non-pharmacologic intervention to treat AUD in the past 90 days.
19. Has taken medications that are used to treat AUD in the past 90 days.
20. Subjects with a history of thyroid cancer or other thyroid disease.
21. Has urine toxicology results positive for cocaine, opioids, amphetamines, buprenorphine, methadone, or methamphetamines.
22. Prior history of anaphylaxis or angioedema with another GLP-1 receptor agonist.
23. Prior use of exenatide
24. Liver function values AST or ALT are twice the normal limit
25. Unable to comfortably abstain from nicotine for a period of 8 hours.
26. Has COPD, history of solid organ transplant, sickle cell disease, severe heart disease or other health condition for which exposure to COVID-19 represents an unreasonable risk as determined by the study staff physician using accepted COVID-19 guidance (e.g. Centers for Disease Control, etc.).
27. Subject has prior history of Drug-induced thrombocytopenia

8 Study Intervention

Study Medication

Study medication will be purchased by the BMC Investigational Pharmacy Service. Medication will be administered using a 250mcg/mL, 5mcg/dose, 60 doses/pen, 1.2mL prefilled pen. Subjects will receive either a 5 mcg dose of immediate release exenatide or a sham injection. The 5mcg dose of exenatide is approved as the first dose to be administered to patients at the start of their treatment with this drug for FDA-approved indications. The sham injection will be a needle stick insulin syringes with pre-affixed needles as a sham syringe. No fluid will be injected as a protection for maintaining the blind. Note that the volume of fluid injected for a 5mcg dose is only 0.02ml. We do not expect that subjects will sense this volume of fluid (or lack thereof) during the injection. Subjects will be shielded from seeing the injection to maintain the blind. The individual who administers medication will not participate in subject evaluation to maintain

the study blind. The study medication will be administered subcutaneously 30 minutes prior to the priming dose of alcohol.

Dosing
Subjects will receive either a 5 mcg dose of immediate release exenatide or a sham injection on both alcohol challenge days.

Medication Storage
Medication will be stored in the Investigational Pharmacy under refrigerated conditions and may be stored at room temperature for up to 30-days following dispensing. Medication will be stored in a secured area until the time that medication is needed for study subjects. Stability and expiry will be monitored by IPS according to the labelling of the medication from the manufacturer.

Randomization
Study randomization will be performed by IPS using a stratified block randomization procedure. The study statistician will provide IPS with a randomization log. On the day of randomization, study staff will provide IPS with a randomization number based on the stratifying variable (heavy vs very heavy drinking) and IPS will determine the order of drug vs. sham exposure based on the randomization log.

Medication Labeling
The study number will be preprinted on each injection pen. The label will include the drug name the subject number, storage conditions, the 24/7 phone number of the clinical site, and places to record the subject number and the date dispensed. Additional fields may be added to this label to meet any regulatory requirements as determined by IPS.

Medication Blinding/unblinding
Study medication will not be blinded. Medication will be administered by GCRUstaff who are not part of study staff who perform data collection. The Study PI and study staff will be blinded to study medication. The PI and study physician(s) will make the decision to un-blind the identity of the study medication in the event that the study blind needs to be broken to make medical decisions regarding subject treatment.

Medication accountability
The site principal investigator (PI) or designated study personnel will maintain a log of all study medication and record of dispensing of all medication to the subject.

9 Study Procedures

Study Overview: Each subject will complete 3 clinic visits over a period of up to 28 days of participation. Study participation is comprised of a baseline assessment, alcohol challenge Trial #1, and alcohol challenge Trial #2.

Baseline assessment: Prior to the visit, subjects will complete a COVID-19 symptom screening questionnaire following standard of care procedures. If the subject does not complete the screening questionnaire before arriving in clinic, study staff will administer the questionnaire outside of the clinic at a 6-foot distance. If the subject answers ‘yes’ to any question about known COVID symptoms, their in-clinic visit will be cancelled and they will be advised to contact their PCP and/or get tested at a testing center. Consenting subjects will undergo a general medical screen, physical examination, and electrocardiogram. Drinking will be assessed using

the Time-Line Follow-Back (TLFB)[45], and alcohol withdrawal using the Clinical Institute Withdrawal Assessment (CIWA)[46]. Exclusionary mental health conditions will be assessed using the MINI Neuropsychiatric Interview for DSM-5[47]. Subjects will undergo laboratory testing that includes liver and renal function tests, glucose, serum lipase, complete blood count, urine toxicology and a urine pregnancy test for women of child bearing potential.

Study randomization: Subjects will be randomized to a crossover sequence of drug exposure. Subjects will be assigned to one of two groups, with one group receiving exenatide in the alcohol challenge Trial #1 and the other receiving exenatide prior in the alcohol challenge Trial #2. Randomization of subjects will be accomplished using a stratified randomization procedure that will allow for between-group balance for drinking status (heavy vs. very heavy). Heavy drinking is defined as ≥ 21 and < 35 standard drinks per week for men, and ≥ 14 and < 28 standard drinks per week for women. Very heavy drinking is defined as ≥ 35 standard drinks per week for men, and ≥ 28 standard drinks per week for women. This stratified randomization will minimize the possibility that the order of study drug administration seems to influence outcomes when order effects are actually related to differences in severity of drinking between the two groups of subjects who are receiving the study medication in a different order. On the day of randomization, subjects will undergo an alcohol breath test, urine drug screening, assessment of concomitant medications, and the TLFB. Subjects who have purposefully abstained from drinking and achieved 14 days of abstinence prior to the challenge will be discontinued from participation for ethical reasons[49].

Alcohol Challenge Trials 1 & 2: Subjects will return to the laboratory within 14 days of the baseline assessment to complete the alcohol Challenge Trial #1. Prior to the visit, subjects will complete a COVID-19 symptom screening questionnaire following standard of care procedures. If the subject does not complete the screening questionnaire before arriving in clinic, study staff will administer the questionnaire outside of the clinic at a 6-foot distance. If the subject answers 'yes' to any question about known COVID symptoms, their in-clinic visit will be cancelled and they will be advised to contact their PCP and/or get tested at a testing center. Concomitant medications, urine drug screening, Blood Alcohol Concentration (BAC) will be assessed to determine eligibility to proceed with the challenge. A BAC reading of 0.000 is required at each visit to continue with the study procedures. For safety reasons, subjects will be asked to arrange transportation plans that does not include driving themselves home.

Subjects will receive either a 5 mcg dose of immediate release exenatide or a sham injection. The 5mcg dose of exenatide is approved as the first dose to be administered to patients at the start of their treatment with this drug for FDA-approved indications. The sham injection will be a needle stick insulin syringes with pre-affixed needles as a sham syringe. Note that the volume of fluid injected for a 5mcg dose is only 0.02ml. We do not expect that subjects will sense this volume of fluid (or lack thereof) during the injection. Subjects will be shielded from seeing the injection to maintain the blind. The individual who administers medication will not participate in subject evaluation to maintain the study blind. The study medication will be administered subcutaneously 30 minutes prior to the priming dose of alcohol. Peak plasma concentrations of exenatide injected as 5 mcg dose are seen at about 90-120 minutes after subcutaneous administration of this drug and its terminal half-life is 2.4 hours[13,50]. A 5 mcg dose of exenatide injected prior to the administration of oral glucose was found to enhance cerebral glucose metabolic rate in brain regions implicated in the regulation of appetite and food reward among subjects with impaired glucose metabolism[33]. These effects were observed 90 minutes after the administration exenatide. The 5 mcg dose of exenatide was found to prevent elevation in blood glucose levels and the rate of glucose absorption after the administration of oral glucose[33].

The priming drink will be given no more than 30 minutes after study drug is administered (see Figure 2 for alcohol challenge timeline). Subjects will have five minutes to consume a single priming dose of alcohol. After a 40-minute observation period, subjects will begin the alcohol self-administration Blocks 1 and 2. The alcohol self-administration trials will be conducted in a human laboratory designed to simulate a typical living room. The human laboratory is a room furnished with a lounge chair, side table, and television which allows access to popular streaming entertainment (e.g., Netflix, YouTube). A small unobtrusive camera is in the room to allow for monitoring and video recording without study staff being present.

Figure 2: Alcohol Self-Administration Procedure

Study drug	**Priming Dose**	**Absorption**	**Self-Administration**
Study drug administered 30 minutes prior to priming dose	5 minutes Drink mixed to achieve BAC= 0.03g/dl	40 minutes BAC measured in 10-minute intervals	**Blocks 1 & 2** 60 minutes each 4 drinks per block Each drink mixed to raise BAC 0.0125 g/dl

Priming dose. Subjects will be given a priming drink designed to increase the subject's blood alcohol level (BAL) to 0.03g/dl, using the alcohol of their choice that is 24% Alcohol By Volume (ABV) or greater. Drinks will be mixed with a sugary mixer (3:1 Mixer:Alcohol) to preclude the occurrence of hypoglycemia. The volume of alcohol will be calculated using an online tool developed by UW-Madison (http://dionysus.psych.wisc.edu/WebCMS/baccalc.htm) based on a formula described by Watson[51]. The subjects will be asked to drink the priming drink over a period of 5 minutes. The purpose of the priming drink is to normalize drinking in the laboratory.

Absorption period. Subjects will be observed for 40 minutes following the priming dose of alcohol. This period will provide ample time for subjects to reach the target BAC. Breathalyzer readings will be completed at 10 minutes intervals.

Alcohol self-administration Blocks 1 and 2. In each of the alcohol self-administration Blocks, subjects will be presented with four drinks, each mixed to raise their BAC by 0.0125g/dl. They will be told that they can either consume the desired number of drinks over the following 60 minutes, or they will receive the equivalent dollar amount of the cost of each drink ($3.00) they did not consume. At the end of each 1-hour session the drinks will be removed and the volume of alcohol remaining will be measured with a graduated cylinder. Cravings will be assessed using the AUQ and VAS every 30 min during the self-administration blocks. BAC levels will be obtained at the end of the Block 2 session as will blood glucose levels. Blood glucose levels will be measured at the end of Block 2 using a glucometer and blood obtained from a pinprick sample. If the subject is found to be hypoglycemic (glucose < 70 mg/dL), staff will give the subject orange juice and re-test in 30 minutes. If the subject is found to be hyperglycemic (glucose > 300 mg/dl), staff will escort the subject to the BMC emergency department for evaluation. At the end of this session subjects will also be asked to rate their experience of nausea using a visual analog scale developed to assess nausea in in an emergency department[52]. Subjects will be assessed for safety prior to subjects leaving the laboratory. Subjects will not be released until their BAC is below 0.04 g/dl and they are not behaviorally impaired.

There will be a 7-14 day washout period between alcohol Challenge Trial #1 and Trial #2. Based on the known half-life of exenatide, all of the medication will be cleared within 2 days. The washout may extend up to 14 days to provide flexibility in scheduling of Trial #2. After the second alcohol self-administration trial has been completed subjects will receive a copy of the

NIAAA publication *Rethinking Drinking*[48] and will be encouraged to review rethinking drinking materials online. Subjects will be compensated up to $448 for completion of all study activities. Subjects will receive a reimbursement of $50 for the screening visit, $150 for alcohol Challenge Trial #1, $150 for alcohol Challenge Trial #2. Subjects will receive a $50 bonus for completing both alcohol Challenge Trials. Subjects may receive up to $48 dollars in payments for drinks not consumed during the two alcohol self-administration Trials. Subjects who report no recreational drug use other than marijuana at the time of phone screening but then test positive for recreational drug use other than marijuana at the first in-clinic visit will not be reimbursed. Subjects will be informed of this policy at the time of telephone screening. This measure is in place to prevent subjects from lying about no recreational drug use in order to receive compensation for a single visit in this study.

10 Assessment of Safety and Data Safety Monitoring Plan (DSMP)

10.1 Definitions

The following definitions will be used in the assessment of safety:

Adverse Event (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Serious Adverse Event (SAE) is any adverse event that

(1) results in death;
(2) is life-threatening;
(3) results in inpatient hospitalization or prolongation of existing hospitalization;
(4) results in a persistent or significant disability/incapacity;
(5) results in a congenital anomaly/birth defect; or
(6) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Life-threatening means that the event places the subject at immediate risk of death from the event as it occurred.

Unanticipated Problem is defined as an event, experience or outcome that meets **all three** of the following criteria:

- is unexpected; AND
- is related or possibly related to participation in the research; AND
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research

Unexpected means the nature, severity, or frequency of the event is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

10.2 Safety Review

Both the risks listed in Section 6.1 and unknown risks will be monitored as follows:

Adverse events will be monitored from the time of study enrollment until the end of participation. Adverse events will be monitored by medical staff using the "adverse events" CRF. Adverse event monitoring will be conducted at each study visit from the time of consent. Subjects will be given a wallet card with a 24/7 telephone number in the event that there are adverse effects which the subject would like to consult with medical staff prior to the next scheduled visit. Adverse events will be assessed if at any point in the study a subject uses this 24/7 emergency phone contact. If a subject has an ongoing SAE or unanticipated problem at the time that the subject completes all study procedures, Adverse Event assessment will continue until satisfactory resolution (either resolved or stabilized and is not expected to resolve in the near term) of the event or problem.

For each recorded AE or SAE, the study MD staff or study nurse will assess expectedness based on the known published side effect profile for exenatide. The study MD staff or study nurse will also assess severity based on the following criteria:

Mild:	An event that is usually transient, requiring no special treatment, and does not generally interfere with the subject's daily activities.
Moderate:	An event that interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject. The event is usually ameliorated with additional specific therapeutic intervention.
Severe:	An event that interrupts usual activities of daily living or significantly affects clinical status. The event poses a significant risk of harm to the subject and hospitalization may be required, and typically requires intensive therapeutic intervention.
Life-threatening	An event that puts the subject into imminent risk of death without intervention.

The study MD staff or study nurse will assess AE/SAE relationship to the investigational product based on the following criteria:

Unrelated:	The subject did not receive the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is not reasonable, or there is another obvious cause of the AE/SAE.

Unlikely: There is evidence of exposure to the investigational product or there is another more likely cause of the AE/SAE.

Possible: There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, but the AE/SAE could have been due to another equally likely cause.

Probable: There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, and the AE/SAE is more likely explained by the investigational product than by any other cause.

Definite There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, the AE/SAE is more likely explained by the investigational product than by any other cause, and the AE/SAE shows a pattern consistent with previous knowledge of the investigational product or investigational product class.

10.3 Reporting Plans

The Principal Investigator at BMC/BU Medical Campus will report Unanticipated Problems, safety monitors' reports, and Adverse Events to the BMC/BU Medical Center IRB in accordance with IRB policies:

- Unanticipated Problems occurring at BMC/BU Medical Campus involving a fatal or life-threatening event will be reported to the IRB within 2 days of the investigator learning of the event.
- Unanticipated Problems occurring at BMC/BU Medical Campus not involving a fatal or life-threatening event will be reported to the IRB within 7 days of the investigator learning of the event.
- Reports from safety monitors with recommended changes will be reported to the IRB within 7 days of the investigator receiving the report.
- Adverse Events (including Serious Adverse Events) will be reported in summary at the time of continuing review, along with a statement that the pattern of adverse events, in total, does not suggest that the research places subjects or others at a greater risk of harm than was previously known.
- Reports from safety monitors with no recommended changes will be reported to the IRB at the time of continuing review.

10.4 Stopping Rules

There are no interim analyses planned that would allow for a determination of futility or overwhelming benefit. Study enrollment will be suspended under the following circumstances:

1. Serious Adverse Events. Study enrollment will be suspended in the event of a single serious adverse event that is determined to be unexpected and at least possibly related. If suspended, study recruitment will not continue until a determination has been made about whether the known risks of participation have changed and the BU Medical Campus/Boston Medical

Center IRB has made a finding that the risk/benefit ratio remains favorable given the possible newly identified risk.

2. Risk of intoxication. Subject recruitment will also be suspended if more than one subject of the first ten subjects enrolled is discontinued by the investigator due to intoxication during the alcohol self administration trial. Due to differences in alcohol tolerance, BAL is not a reliable measure of subjects potentially posing a safety risk. Study staff will make a subjective determination of risk based on the subject's behavior. After 10 subjects have been enrolled, the trial will be suspended if there are more than 10% of subjects whose participation has been halted by the study team due to concerns about physical safety because of intoxication during the alcohol self-administration trial. If suspended for this reason, the study team will consider design changes to reduce the likelihood of this as a potential risk to study subjects. Recruitment would resume when the BU Medical Campus/Boston Medical Center IRB has made a determination that proposed changes to the study design have an acceptable risk/benefit ratio.

11 Data Handling and Record Keeping

11.1 Confidentiality

All staff will be fully trained in the procedures for protection confidential health information. To maintain subject confidentiality, study data will be coded on CRFs that are identified by a subject number only. Source records with identifying information and CRFs will be stored in double-locked space with access only by authorized staff. Data stored in the REDcap system have strong protections including file encryption and password access. Subject information will not be released without written permission. Upon approval of the study by an IRB, an application will be filed with NIAAA for a Certificate of Confidentiality.

11.2 Source Documents

Source documents in this study include:
Laboratory test results
Photocopies of the urine drug screening test result
ECG tracings
Subject locator form
Subject contact form

Data generated by the methods described in the protocol will be recorded in the subjects' source binder. Data may be transcribed legibly on CRFs for each subject or directly inputted into an electronic system or any combination thereof.

11.3 Case Report Forms

The study case report form (CRF) will be the primary data collection instrument for the study. All data requested on the CRF will be recorded. All missing data will be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, a written explanation will be included to detail why the data was not recorded. If the item is not applicable to the individual case, a notation will be made. All entries on will be printed legibly in black ink.

If any entry error has been made, to correct such an error, a single straight line will be drawn through the incorrect entry and the correct data will be entered closely to the original data. All such changes will be initialed and dated. There will be no erasures or white-out on CRFs. For clarification of illegible or uncertain entries, the clarification will be printed near the item, then initialed and dated. Electronic CRFs in the REDcap system will include an audit trail.

The CRFs that will be used in this study are:
Demographics
Concomitant Medications
Adverse Events
Birth Control Assessment
Urine Drug Screening
Vital Signs
Blood Alcohol Level
Laboratory summary sheet
Time-line Follow-back
Pregnancy test
Birth control assessment
Medical History
Blood Glucose
Nausea VAS
Physical Examination
MINI diagnoses summary
Medication Compliance log
Eligibility
ECG
C-SSRS
CIWA-AR
OCDS
AUQ
VAS

11.4 Study Records Retention
Study records will be retained for at least seven years after completion of the study.

12 Statistical Plan

12.1 Study Hypotheses and Planned Analyses

For our primary outcomes, data from subjects who experience moderate to severe nausea during the alcohol self-administration trials will be excluded from our statistical analysis. Although the dosing chosen for this study minimizes the potential for nausea as a medication side effect, this may occur in some subjects. These subjects will be excluded from analyses as medication-induced nausea could confound the drinking outcomes. The presence of nausea will be established by a rating greater than 30 on a VAS scale that rates nausea from no nausea to unbearable nausea[53].

Hypothesis	**Proposed Analyses**
1. Subjects will consume less alcohol during an alcohol Challenge Trial when receiving exenatide	The volume of alcohol consumed during alcohol challenge trials 1 and 2 will be used to test the effect of exenatide on alcohol consumption. We will use a mixed

compared to when they receive a sham injection.	models repeated measures approach to test for differences between alcohol consumption between the exenatide and sham injection self-administration trials[54-55]. This data will be divided into first and second-hour blocks of self-administration. Within-subject factors for this analysis will include Treatment and Time Block. Trial order will be used as covariate in these analyses to allow evaluation as to whether the order of treatments had a significant effect on the outcome. Appropriate covariance structures will be determined using Akaike's information criteria to evaluate the best model fit. Results analysis will be examined for both treatment effects and the Treatment x Time Block interaction results.
2. Subjects will report lower levels of craving as measured by the Visual Analog Scale (VAS) and the Alcohol Urge questionnaire (AUQ) during the exenatide Challenge Trial compared to the sham injection Challenge Trial.	Craving measures (AUQ and VAS) collected at 30-minute intervals during the self-administration trials will be used to test the effect of exenatide on alcohol craving. A mixed models approach will be used to test for differences in craving between the exenatide and sham injection Challenge Trials. Within-subject factors for this analysis will include Treatment and Time Block. Trial order will be used as covariate in these analyses to allow evaluation as to whether the order of treatments has a significant effect on the outcome.
Hypothesis 3: Areas under the breath alcohol concentration curves (AUC's) in heavy drinkers obtained during the first 40 minutes after ingestion of the priming drink of alcohol will be significantly lower in subjects when they receive exenatide as compared to when they are given sham injections	AUC's for BAC obtained using data obtained during the 40-minute absorption period will be compared between Challenge Trials using a repeated measures mixed models approach. In addition, individual BAC values obtained at 10-minute intervals after alcohol ingestion of the priming drink also will be compared between the sham injection and exenatide treatment trials using a repeated measures mixed models approach. A significant time x trial interaction value also will be taken to indicate a significant between trial difference in the rates of alcohol absorption.
Hypothesis 4. The proportion of subjects with post-trial blood glucose levels in the hypoglycemic range will not differ significantly between the sham injection and exenatide trials.	The proportion of subjects with blood glucose values below 50 mg/dl will be compared within subjects using the McNemar's test. We hypothesize that there will be no difference in blood glucose levels between the alcohol Challenge Trials.

12.2 Sample Size Determination

A group size of 28 completers was selected for use in this study based on an assumed effect size of 0.7 suggested by similar alcohol self-administration studies with amount consumed as the primary outcome[42,44]. This effect size is in the range we found for the anticonvulsant zonisamide used in a similar alcohol self-administration study[43]. The sample size for this study is based on an estimated reduction of 1.5 standard drinks with an estimated standard deviation (2.1) of the between Challenge Trial differences in alcohol self-administration, with an effect size

of this magnitude (i.e. 0.7). This requires a sample size of 28 to allow for detection of a significant within-subject difference in alcohol consumption with an alpha value of 0.01 and power value of 0.81. Based on an estimated 15-20% rate of non-completion for randomized subjects, we anticipate randomizing 36 subjects to achieve a sample of 28 completers. Given our experience with recruiting AUD populations into clinical trials, we expect a screening exclusion rate of roughly 50%. Approximately 72 subjects will be consented and screened in clinic to yield a sample of 36 eligible subjects.

Given that this a laboratory based experiment we do not plan to conduct any planned interim analyses in this study.

13 Ethics/Protection of Human Subjects

This study is to be conducted according to applicable US federal regulations and institutional policies (which are based in federal regulations, guidance, and ICH Good Clinical Practice guidelines).

This protocol and any amendments will be submitted to the Boston Medical Center and Boston University Medical Campus IRB, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator. A copy of the initial IRB approval letter will be provided to the sponsor before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB. The consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. Consent will be documented as required by the IRB.

14 Literature References

REFERENCES

1. Treatment for alcohol problems: Finding and getting help [homepage on the Internet]. National Institutes of Health. 2014. https://pubs.niaaa.nih.gov/publications/treatment/treatment.htm.
2. Zindel LR, Kranzler HR. Pharmacotherapy of alcohol use disorders: Seventy-five years of progress. *J Stud Alcohol Drugs Suppl.* 2014; 75 Suppl 17: 79-88. PMCID: PMC4453501.
3. Litten RZ, Ryan ML, Falk DE, Reilly M, Fertig JB, Koob GF. Heterogeneity of alcohol use disorder: Understanding mechanisms to advance personalized treatment. *Alcohol Clin Exp Res.* 2015 April 01; 39(4): 579-584.
4. Engel J.A., Jerlhag E. Role of appetite-regulating peptides in the pathophysiology of addiction: Implications for pharmacotherapy. CNS Drugs. 2014;28:875–886
5. India A. Reddy GS, Aurelio Gallia. Moving beyond energy homeostasis: new roles for glucagon-like peptide-1 in food and drug reward. Neurochemistry International. 2014;73:49-55.
6. Skibicka KP. The central GLP-1: implications for food and drug reward. *Frontiers in Neuroscience.* 2013;7(181).
7. Daniel Vallöf PM, Giancarlo Colombo, Minja Mandrapa, Julia Winsa Jörnulf, Emil Egecioglu, Jörgen A. Engel, Elisabet Jerlhag. The glucagon-like peptide 1 receptor agonist liraglutide attenuates the reinforcing properties of alcohol in rodents. Addiction Biology. 2016;21(2):422–437.
8. Rozita H. Shirazi SLD, and Karolina P. Skibicka. Gut peptide GLP-1 and its analogue, Exendin-4, decrease alcohol intake and reward. PLoS One. 2013;8(4).
9. Gunnar Sorensen SBC, Morgane Thomsen. Effects of the GLP-1 agonist Exendin-4 on intravenous ethanol self-administration in mice. *Alcoholism, clinical and experimental research.* 2016; 40(10):2247-2252.
10. Emil Egecioglu PS, Ida Fredriksson, Kristin Feltmann, Jorgen A. Engel, Elisabet Jerlhag. The glucagon-like peptide 1 analogue Exendin-4 attenuates alcohol mediated behaviors in rodents. *Psychoneuroendocrinology.* 2013;38:1259-1270.
11. Sunil Sirohi JDS, Randy J.Seeley, Stephen C.Benoit, Jon F.Davis. Central & peripheral glucagon-like peptide-1 receptor signaling differentially regulate addictive behaviors. Physiology and Behavior. 2016;161:140-144.
12. Ilpo Puhakainen VAK, Hannele Yki-Järvinen. No Reduction in Total Hepatic Glucose Output by Inhibition of Gluconeogenesis With Ethanol in NIDDM Patients. Diabetes. 1991;40(10):1319-1327.
13. Keating GM. Exenatide. Drugs, 2005; 65:1681-1692
14. Madsbad S. Review of head-to-head comparisons of glucagon-like peptide-1 receptor agonists. Diabetes, Obesity & Metabolism. 2016;18(4):317-322.
15. Gunnar Sorensen IAR, Pia Weikop, Devon L. Graham, Gregg D. Stanwood, Gitta Wortwein, Aurelio Galli, and Anders Fink-Jensen. The glucagon-like peptide-1 (GLP-1) receptor agonist exendin-4 reduces cocaine self-administration in mice. *Physiology & Behavior.* 2015;149:262-268.
16. Emil Egecioglu JAE, Elisabet Jerlhag. The Glucagon-Like Peptide 1 Analogue Exendin-4 Attenuates the Nicotine-Induced Locomotor Stimulation, Accumbal Dopamine Release, Conditioned Place Preference as well as the Expression of Locomotor Sensitization in Mice. PLoS One. 2013;8(10).

17. Kimberly A. Bernosky-Smith DB, Stanger, Alexandria J. Trujillo, Luke R. Mitchell, Rodrigo A. Espana, Caroline E. Bass. The GLP agonist exendin-4 attenuates self-administration of sweetened fat on fixed and progressive ratio schedules of reinforcement. *Pharmacology, biochemistry, and behavior.* 2016;142(48-55).
18. Lene Jessen BAA, Jonathan L. Hassel, Kyle J. Roy, Eric P. Smith, Todd M. Greer, Stephen C. Woods, Randy J. Seeley, and David A. D'Alessio. Suppression of food intake by glucagon-like peptide-1 receptor agonists: Relative potencies and role of dipeptidyl peptidase-4. *Endocrinology.* 2012;153(12):5735–5745.
19. Morgane Thomsen DD, Gitta Wörtwein, Pia Weikop, Emil Egecioglu, Elisabet Jerlhag, Anders Fink-Jensen, Anna Molander. The glucagon-like peptide 1 receptor agonist Exendin-4 decreases relapse-like drinking in socially housed mice. Pharmacology Biochemistry and Behavior. 2017;160:14-20.
20. Mann RJ, Nasr NE, Sinfield JK, Paci E, Donnelly D. The major determinant of exendin-4/glucagon-like peptide 1 differential affinity at the rat glucagon-like peptide 1 receptor N-terminal domain is a hydrogen bond from SER-32 of exendin-4. British journal of pharmacology. 2010;160(8):1973–84.
21. Ulrich Werner GH, Andreas W. Herling, Werner Kramer. Pharmacological profile of lixisenatide: A new GLP-1 receptor agonist for the treatment of type 2 diabetes. Regulatory Peptides. 2010;164:58-64.
22. Dilan Athauda KM, Simon S. Skene, Martha Bajwa-Joseph, Dawn Letchford, Kashfia Chowdhury, Steve Hibbert, Natalia Budnik, Vrach, Luca Zampedri, John Dickson, Yazhou Li, Iciar Aviles-Olmos, Thomas T Warner, Patricia Limousin, Andrew J Lees, Nigel H. Greig, Susan Tebbs, Thomas Foltynie. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. The Lancet. 2017;390:1664–1675.
23. Nova Nordisk. Saxenda Liraglutide Injection 3 mg. 2017
24. P Suchankova JY, ML Schwandt, BL Stangl, EC Caparelli, R Momenan, E Jerlhag, CA Hodgkinson, M Egil, MF Lopez, HC Becker, D Goldman, M Heiilig, VA Ramchandani, L Leggio. The glucagon-like peptide-1 receptor as a potential treatment target in alcohol use disorder: evidence from human genetic association studies and a mouse model of alcohol dependence. *Translational Psychiatry* 2015;5.
25. Huiyuan Zheng LC, Linda Rinaman. Distribution of glucagon-like peptide 1-immunopositive neurons in human caudal medulla. *Brain Structure and Function.* 2015;220(2):1213-1219.
26. Matthew R. Hayes KPS, Harvey J. Grill. Caudal brainstem processing is sufficient for behavioral, sympathetic, and parasympathetic responses driven by peripheral and hindbrain glucagon-like-peptide-1 receptor stimulation. Endocrinology. 2008;149(8):4059–4068.
27. Alhadeff AL. MB, Zimmer DJ, Turner CA, Reiner DJ, Schmidt HD, Grill HJ, Hayes MR. Endogenous glucagon-like peptide-1 receptor signaling in the nucleus tractus solitarius is required for food intake control. *Neuropsychopharmacology* 2017;42(7):1471-1479.
28. Alhadeff AL. RL, Hayes MR. GLP-1 neurons in the nucleus of the solitary tract project directly to the ventral tegmental area and nucleus accumbens to control for food intake. *Endocrinology.* 2012;153(2):647-658.
29. Amanda M. Dossat NL, Kristen Kay, and Diana L. Williams. Glucagon-Like Peptide 1 Receptors in Nucleus Accumbens Affect Food Intake. Journal of Neuroscience. 2012;31(41):14453–14457.
30. Heppner MK, Anna Secher, Sarah Juel Paulsen, Rikley Buckingham, Charles Pyke, Lotte B. Knudsen, Niels Vrang, Kevin L. Grive. Expression and distribution of glucagon-like peptide-1 receptor mRNA, protein, and binding in the male nonhuman primate

(macaca mulatta) brain. *Endocrinology.* 2015;156(1):255-267.
31. Elvira Alvarez MDM, Isabel Roncero, Julie A. Chowen, Beatriz Garcia-Cuartero, Juan D. Gispert, Carmen Sanz, Patricia Vazquez, Antonio Maldonade, Javier De Caceres, Manuel Desco, Miguel Angel Pozo, Enrique Blazquez. The expression of GLP-1 receptor mRNA and protein allows the effect of GLP-1 on glucose metabolism in the human hypothalamus and brainstem. *Journal of Neurochemistry* 2005;92(798-806).
32. Farr OM. SM, Tsoukas MA., Dincer F., Thakkar B., Sahin-Efe A., Filippaios A., Bowers J., Srnka A., Gavrieli A, Ko BJ., Liakou C., Kanyuch N., Tseleni-Balafouta S., Mantzoros CS. GLP-1 receptors exist in the parietal cortex, hypothalamus and medulla of human brains and the GLP-1 analogue liraglutide alters brain activity related to highly desirable food cues in individuals with diabetes: a crossover, randomized, placebo-controlled trial. . *Diabetologia.* 2016;59:954-965.
33. Giuseppe Daniele PI, Marjorie Molina-Carrion, Jack Lancaster, Demetrio Ciociaro, Eugenio Cersosimo, Devjit Tripathy, Curtis Triplitt, Peter Fox, Nicolas Musi, Ralph DeFronzo and Amalia Gastaldelli. Exenatide Regulates Cerebral Glucose Metabolism in Brain Areas Associated With Glucose Homeostasis and Reward System. Diabetes. 2015;64(10):3406-3412.
34. Liselotte van Bloemendaal RGI, Jennifer S. ten Kulve, Frederik Barkhof, Robert J. Konrad, Madeleine L. Drent, Dick J. Veltman, Michaela Diamant. GLP-1 Receptor Activation Modulates Appetite- and Reward-Related Brain Areas in Humans. Diabetes. 2014;62(12):4186-4196.
35. Liselotte van Bloemendaal DJ, Veltman, Jennifer S. ten Kulve, Madeleine L. Drent, Frederik Barkhof, Michaela Diamant, Richard G. IJzerman. Emotional eating is associated with increased brain responses to food-cues and reduced sensitivity to GLP-1 receptor activation. *Obesity, biology, and integrated physiology.* 2015;23(10):2075-2082.
36. Roy Eldor GD, Claudia Huerta, Mariam Al-Atrash, John Adams, Ralph DeFronzo, Timothy Duong, John Lancaster, Mahmoud Zirie, Amin Jayyousi, Muhammad Andul-Ghani. Discordance between central (brain) and pancreatic action of exenatide in lean and obese subjects. *Diabetes Care.* 2016;39:1804-1810.
37. Alecia Dager BMA, Michael C. Stevens, Carmen Pulido, Rivkah Rosen, Rachel E. Jiantonio-Kelly, Jason-Flor Sisante, Sarah A. Raskin, Howard Tennen, Carol S. Austad, Rebecca M. Wood, Carolyn R. Fallahi, Godfrey D. Pearlson. Influence of Alcohol Use and Family History of Alcoholism on Neural Response to Alcohol Cues in College Drinkers. Alcoholism: Clinical and Experimental Research. 2013;37:E161-E171.
38. Niklas Ihssen WMC, Alison Wiggett, Javad Salehi Fadardi, David E. J. Linden. Differentiating Heavy from Light Drinkers by Neural Responses to Visual Alcohol Cues and Other Motivational Stimuli. Cerebral Cortex. 2011;21(6,1):1408–1415.
39. Kelly E. Courtney DGG, Lara A. Ray. The effect of alcohol priming on neural markers of alcohol cue-reactivity *The American Journal of Drug and Alcohol Abuse.* 2015;41(4):300-308.
40. Michael Marxen GG, Daniel Schwarz, Eva Mennigen, Maximilian Pilhatsch, Ulrich S. Zimmermann, Matthias Guenther, Michael N Smolka. Acute effects of alcohol on brain perfusion monitored with arterial spin labeling magnetic resonance imaging in young adults. Journal of Cerebral Blood Flow and Metabolism. 2014;34(3):472–479.
41. Nicole M. Strang EDC, Vijay A. Ramchandani, Ariel Graff-Guerrero, Isabelle Boileau, Christian S. Hendershot. Dose-dependent effects of intravenous alcohol administration on cerebral blood flow in young adults. Psychopharmacology. 2015;232(4):733-744.
42. O'Malley SS, Krishnan-Sarin S, Farren C, Sinha R, Kreek MJ. Naltrexone decreases craving and alcohol self-administration in alcohol-dependent subjects and activates the

hypothalamo-pituitary-adrenocortical axis. *Psychopharmacology (Berl).* 2002 February 01; 160(1): 19-29.
43. Sarid-Segal O, Knapp CM, Burch W, Richardson MA, Bahtia S, DeQuattro K, Afshar M, Richambault C, Sickels L, Devine E, Ciraulo DA. The anticonvulsant zonisamide reduces ethanol self-administration by risky drinkers. *Am J Drug Alcohol Abuse.* 2009; 35(5): 316-319. PMCID: PMC4028067.
44. Arias AJ, Feinn R, Oncken C, Covault J, Kranzler HR. Placebo-controlled trial of zonisamide for the treatment of alcohol dependence. *J Clin Psychopharmacol.* 2010 June 01; 30(3): 318-322. PMCID: PMC3157084.
45. Sobell LC, Sobell MB. Timeline followback: A technique for assessing self-reported alcohol consumption. In: Litten RZ, Allen JP, editors. Measuring alcohol consumption: psychosocial and biochemical methods. Totowa, NJ: Humana Press; 1992. p. 41-72.
46. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: The revised clinical institute withdrawal assessment for alcohol scale (CIWA-ar). *Br J Addict.* 1989 November 01; 84(11): 1353-1357.
47. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The mini-international neuropsychiatric interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry.* 1998; 59 Suppl 20: 57.
48. Rethinking drinking [homepage on the Internet]. Bethesda, MD: NIH publication. 2009. Available from: https://www.rethinkingdrinking.niaaa.nih.gov/.
49. Administering Alcohol in Human Studies- recommended council guidelines on ethyl alcohol administration in human experimentation [homepage on the Internet]. National Institutes of Health. 2005. Available from: https://www.niaaa.nih.gov/Resources/ResearchResources/job22.htm.
50. Kothare PA1, Linnebjerg H, Isaka Y, Uenaka K, Yamamura A, Yeo KP, de la Peña A, Teng CH, Mace K, Fineman M, Shigeta H, Sakata Y, Irie S. 10.1177/0091270008323750. Pharmacokinetics, pharmacodynamics, tolerability, and safety of exenatide in Japanese patients with type 2 diabetes mellitus. J Clin Pharmacol. 2008 Dec;48(12):1389-99.
51. Watson PE, Watson ID, Batt RD. Prediction of blood alcohol concentrations in human subjects. updating the widmark equation. *J Stud Alcohol.* 1981 July 01; 42(7): 547-556.
52. Robert Meek A-MK, Xue Feng Hu. Use of the Visual Analog Scale to Rate and Monitor Severity of Nausea in the Emergency Department. Academic Emergency Medicine. 2009;16(12):1304-1310.
53. Boogaerts JG, Vanacker E, Seidel L, Albert A, Bardiau FM. Assessment of postoperative nausea using a visual analogue scale. Acta Anaesthesiol Scand. 2000;44:470–474.
54. Chow SC, Liu JP. Design and analysis of bioavailability and bioequivalence studies. New York: Marcel Dekker; 1999.
55. Senn S. Cross-over trials in clinical research, 2nd edition. West Sussex, England: John Wiley & Sons Ltd; 2002.
56. BYETTA (exenatide) injection. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2015.
57. Susanne Lerche BB, Jorgen Rungby, Hans E. Botker, Niels Moller, Anders Rodell, Bo Martin Bibby, Jens J. Holst, Ole Schmitz, Albert Gjedde. Glucagon-like peptide-1 inhibits blood-brain glucose transfer in humans. *Diabetes.* 2008;57(2):325-331.
58. Thomas J. Moretto DRM, Terry D. Ridge, Leigh A. MacConell, Ted Okerson, Anne M. Wolka, Robert G. Brodows. Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naive patients with type 2 diabetes: a randomized, double-blind, placebo-controlled parallel-group study. *Clinical Therapeutics.* 2008;30(8):1448-1460.

59. Pinelli N.R. JA, Smith Z., Abouhassan A., Ayar C., Jaber N.A., Clarke A.W., Commissaris R.L., Jaber L.A. Effect of administration time of exenatide on satiety responses, blood glucose, and adverse events in healthy volunteers. Journal of Clinical Pharmacology 2011;51(2):165-172.
60. Orville G. Kolterman DDK, Larry Shen, James A. Ruggles, Loretta L. Nielsen, Mark S. Fineman, Alain D. Baron. Pharmacokinetics, pharmacodynamics, and safe of exenatide in patients with type 2 diabetes mellitus. *American Journal of Health-System Pharmacy.* 2005;62(2):173-181.
61. Pratt WM, Davidson D. Does participation in an alcohol administration study increase risk for excessive drinking? *Alcohol.* 2005 November 01; 37(3): 135-141.
62. Sinha R, Krishnan-Sarin S, Farren C, O'Malley S. Naturalistic follow-up of drinking behavior following participation in an alcohol administration study. *J Subst Abuse Treat.* 1999 September 01; 17(1-2): 159-162.
63. Sommer C, Seipt C, Spreer M, Blumke T, Markovic A, Junger E, Plawecki MH, Zimmermann US. Laboratory alcohol self-administration experiments do not increase subsequent real-life drinking in young adult social drinkers. *Alcohol Clin Exp Res.* 2015 June 01; 39(6): 1057-1063. PMCID: PMC4452407.
64. Cederbaum AI. ALCOHOL METABOLISM. Clinics in liver disease. 2012;16(4):667-685. doi:10.1016/j.cld.2012.08.002.
65. M. R. Burge TMZ, T. A. Sobhy, A. G. Rassam, D. S .Schade. Low-dose ethanol predisposes elderly fasted patients with type 2 diabetes to sulfonylurea-induced low blood glucose. Diabetes. 1999;22(12):2037-2043.
66. Svend G Hartling OKF, Marie-Louise Wegmann, Elisabeth Wåhlin-Boll, Arne Melander. Interaction of Ethanol and Glipizide in Humans. Diabetes. 1987;10(6):683-686.

15. Appendix A: Schedule of Events

	Baseline (May be split over 2 visits)	Randomization & Trial1	Trial 2
Clinic Visit #	**0**	**1**	**2**
COVID-19 Screening Questionnaire (pre-visit)	**X**	**X**	**X**
Informed Consent	**X**		
Urine Drug Screen[A]	**X**	**X**	**X**
Locator Form	**X**		
Demographics	**X**		
Medical History	**X**		
Physical Exam	**X**		
MINI V 6.0	**X**		
CBC w Diff AST, ALT, GGT, Tbili, BUN, Ca, CO2, Cl, Cr, G K, Na, Triglycerides, Serum lipase, Ha1c	**X**		
Vital Signs, weight, Blood Alcohol Level[b, c]	**X**	**X**	**X**
ECG	**X**		
Prior and Concomitant Meds	**X**	**X**	**X**
CIWA-AR	**X**	**X**	**X**
Eligibility Checklist		**X**	
Confirm Eligibility to continue		**X**	**X**
Urine Pregnancy Test	**X**	**X**	**X**
Birth control assessment	**X**	**X**	**X**
AEs	**X**	**X**	**X**
C-SSRS	**X**	**X**	**X**
Treatment Referral			**X**
TLFB (28 day at baseline)	**X**	**X**	**X**
Alcohol Craving VAS[c]		**X**	**X**
OCDS[c]	**X**	**X**	**X**
AUQ[c]		**X**	**X**
Nausea VAS		**X**	**X**

	Baseline (May be split over 2 visits)	**Randomization & Trial1**	**Trial 2**
Clinic Visit #	**0**	**1**	**2**
Blood Glucose (at end of block2)		**X**	**X**

A) Test for opioids, cocaine, amphetamines, methamphetamine, tetrahydrocannabinol (THC), barbiturates, oxycodone, buprenorphine, methadone and benzodiazepines, and alcohol (Ethyl Glucuronide)
B) if the baseline visit is split between two days, vitals, breathalyzer, and weight are to be taken at each visit.
c) See Table 2 for specific administration times

Items highlighted in blue will be performed in-clinic remote. The study staff and subject will connect through video call while located in separate rooms in the Clinical Studies Unit to avoid unnecessary face-to-face contact. Forms that must be filled out by the subject will be left on a clipboard in the exam room to be occupied by the subject, and study staff will instruct subjects to fill out the forms. Forms filled out by study staff through interviewing the subject will be kept in the study staff's room. The COVID-19 screening questionnaire will be administered before the subject arrives for their in-clinic visit.

Items highlighted in yellow will be performed with social distancing. The study staff and subject will be located in the same room, but will maintain a 6-foot distance and both persons will wear PPE at all times.

Items highlighted in green require direct contact between study staff and subject. Contact will be limited to minimum necessary and PPE will be worn at all times by both study staff and subject.

16. Appendix B: Schedule of assessments during drinking lab

	Pre-challenge	Observation	Self-admin Block1	Self-admin Block2
Assessment				
BAC	**Prior to drug admin**	**Every 10 minutes**	**Every 30 minutes**	**Every 30 minutes**
VAS-Alcohol Craving	**Prior to drug admin**	**Every 10 minutes**	**Every 30 minutes**	**Every 30 minutes**
AUQ	**Prior to drug admin**	**At end of observation**	**Every 30 minutes**	**Every 30 minutes**
OCDS	**Prior to drug admin**	**None**	**None**	**None**
VAS-Nausea			**End of block**	**End of block**