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Randomized, Double Blind, Placebo-Controlled Trial of the Safety and Efficacy of HORIZANT® (Gabapentin Enacarbil) Extended-Release Tablets for the Treatment of Alcohol Use Disorder

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STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CRF Part 46, 21 CFR Part 50, 21 CFR Part 56 and 21 CFR Part 312)
- International Conference on Harmonisation (ICH) E6

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

1. Protocol Synopsis

Name of Sponsor/Company: National Institute on Alcohol Abuse and Alcoholism (NIAAA)	
Name of Investigational Product: HORIZANT® Extended-Release Tablets	
Name of Active Ingredient: Gabapentin enacarbil	
Protocol Number: NCIG-006	
Study Title: Randomized, Double Blind, Placebo-Controlled Trial of the Safety and Efficacy of HORIZANT® (Gabapentin Enacarbil) Extended-Release Tablets for the Treatment of Alcohol Use Disorder	
NIAAA Principal Investigator: Raye Litten, Ph.D.	
Study Centers: 10 sites in the United States	
Study Period: Estimated date first subject enrolled: May 2015 Estimated date last subject completed: October 2016	**Phase of Development:** 2
Objectives: **Primary:** The primary objective of the study is to compare the efficacy of HORIZANT (gabapentin enacarbil) Extended-Release Tablets 600 mg twice daily (BID) with matched placebo on the primary alcohol consumption outcome endpoint, percentage of subjects with no heavy drinking days (PSNHDD) during the last 4 weeks of treatment, among patients with Alcohol Use Disorder (AUD). **Secondary:** Secondary objectives are separated into two categories: key secondary objectives and supportive secondary objectives. The key secondary objective is to compare HORIZANT to placebo on the percentage of subjects abstinent from alcohol during the last 4 weeks of treatment. The supportive secondary study objectives are to assess other treatment benefits including: reduction in other alcohol consumption endpoints, alcohol-related craving and consequences, mood, sleep quality, smoking quantity and frequency, and safety.	
Methodology: This study is a double-blind, randomized, placebo-controlled, parallel group, multi-site study designed to assess the efficacy of HORIZANT Extended-Release Tablets compared with placebo to reduce drinking in 346 subjects (173 in each group) who report 4 or more Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5™) symptoms of AUD and who meet the drinking criteria outlined hereafter. This study will be conducted at 10 clinical sites. If eligible for the study, subjects will be randomized using a stratified permuted block randomization procedure with "clinical site" as the stratification variable in an approximate 1:1 ratio (targeting 173 subjects per group) to receive either HORIZANT Extended-Release Tablets or placebo for 26 weeks (1 week escalation; 24 weeks maintenance; 1 week taper). Subjects will be seen in the clinic at screening, at randomization and 11 other times during the study. During the Week 1 dose escalation period (midway through the week) and during the maintenance period (Weeks 2 to 25), subjects will be contacted once per week by telephone at non-clinic visit weeks to encourage study drug compliance and to assess withdrawal, adverse events (AEs), and concomitant medications. A final follow-up telephone interview will occur during Weeks 28 to 29 (1 to 2 weeks after the end of dosing).	
Number of Subjects (Planned): 346	
Main Inclusion/Exclusion Criteria: Subjects will be male and female at least 21 years of age with 4 or more DSM-5™ symptoms of AUD. They must also be seeking treatment for alcohol dependence and if male, report drinking an average of 28 drinks per week or if female report drinking an average of 21 drinks per week and at least one heavy drinking day per week for the 28-day period prior to consent, and be abstinent for the 3 consecutive days prior to the day of randomization. A "heavy drinking day" is 4 or more drinks per drinking day for women and 5 or more drinks per drinking day for men.	

Investigational Product, Dosage and Mode of Administration:

Dose titration, maintenance and taper will occur as scheduled below. The target maintenance dose of HORIZANT Extended-Release Tablets is 600 mg BID. Subjects in the placebo group will take the equivalent number of placebo tablets.

Study Period	Time Period	AM Dose (# of tablets)	PM Dose (# of tablets)
Titration	Week 1, Days 1-3	600 mg (1)	None
Titration	Week 1, Days 4-7	600 mg (1)	600 mg (1)
Maintenance	Weeks 2-25	600 mg (1)	600 mg (1)
Taper	Week 26	600 mg (1)	None

Reference Therapy, Dosage and Mode of Administration: Identically debossed placebo tablets will be administered according to the same schedule as HORIZANT Extended-Release Tablets.

Duration of Study: Each subject will participate in the study for up to approximately 30 weeks, including up to 2 weeks of screening, 26 weeks of treatment, one follow-up visit after completing treatment, and a final telephone contact 1 to 2 weeks after completing treatment.

Criteria for Evaluation:

Primary: The primary outcome measure examines the hypothesis that HORIZANT Extended-Release Tablets will increase the PSNHDD compared to placebo during the last 4 weeks of the maintenance period (Study Weeks 22-25). A "heavy drinking day" is 4 or more drinks per drinking day for women and 5 or more drinks per drinking day for men. Drinking data will be collected by the Timeline Followback (TLFB) method. If during the last 4 weeks of the maintenance period of the study, the subject does not come back for clinic visits or provide TLFB data but agrees to telephone contact, then the subject will be asked if there were any heavy drinking days during the final study period. These data will be used to determine the primary efficacy endpoint when TLFB data are missing, otherwise the data will be imputed as having a heavy drinking day during this period.

Secondary: Secondary efficacy endpoints will also be analyzed over the last 4 weeks of treatment.

1. Percentage of subjects abstinent from alcohol (key secondary endpoint)
2. Percentage of subjects with a World Health Organization (WHO) drinking risk category decrease of:
    a. at least 1-level
    b. at least 2-levels
3. Percentage of days abstinent per week
4. Percentage of heavy drinking days per week
5. Weekly mean number of drinks per week
6. Weekly mean drinks per drinking day
7. Cigarettes smoked per week among smokers
8. Alcohol craving score [Alcohol Craving Scale – Short Form (ACQ-SR-R)]
9. Alcohol related consequences (ImBIBe) score
10. Pittsburg Sleep Quality Index (PSQI) score
11. Beck Anxiety Inventory (BAI) score
12. Beck Depression Inventory Scale – II (BDI-II) score

Safety Endpoints Safety endpoints will be evaluated over the entire treatment and follow-up periods.

1. Vital signs
2. Blood chemistries
3. Urine drug screen results
4. Blood alcohol concentration (BAC) by breathalyzer
5. AEs
6. Electrocardiogram (ECG) results

7. Clinical Institute of Withdrawal – Alcohol Revised (CIWA-AR) scores
8. Profile of Moods States (POMS) scores
9. Frequency of subjects with suicidal ideation at any time during the treatment period –Columbia-Suicide Severity Rating Scale (C-SSRS)

Compliance: Self report of compliance with investigational products and gabapentin plasma levels.

Pharmacokinetics (PK): A population PK/pharmacodynamics (PD) analysis will be performed using gabapentin plasma levels determined from blood samples collected at Weeks 12, 20, and 24 from subjects in the HORIZANT Extended-Release Tablets group. Blood will be collected from all subjects at different times at each PK visit (pre-dose and up to 12 hours post dose).

Exploratory Analysis: An exploratory analysis of the primary and secondary efficacy endpoints will test treatment effects over varying time intervals (e.g., weekly, monthly, and by grace periods) and by the use of imputation; in addition, these endpoints will be analyzed within the evaluable population. The MINI AUD number of symptoms, blood phosphatidylethanol (PEth) levels, and abstinence from cigarette smoking will also be tested as endpoints. Potential moderators of the treatment effect will be tested using the primary endpoint, PSNHDD.

Statistical Methods (Data Analysis):

Analysis Populations:

Modified intention-to-treat (mITT) Analysis Set: The mITT set is defined as subjects randomized to participate in the study who took at least one dose of investigational product.

Evaluable Analysis Set: The evaluable analysis set is defined as those subjects randomized to the study who took at least 80% of the per-protocol prescribed dose of tablets during the maintenance period (Weeks 2-25) and did not have a major protocol violation.

The primary and secondary efficacy analyses will be conducted on both the mITT and evaluable analysis sets. Exploratory analyses will be performed on the mITT analysis set, unless otherwise specified. Safety analyses will be conducted on the mITT analysis set.

Analysis of the Primary Efficacy Endpoint:

The primary analysis will be conducted via a fully covaried logistical regression of the PSNHDD during Study Weeks 22 to 25 (last 4 weeks of the maintenance period) on the mITT population. The model includes treatment group, clinical site, pre-randomization drinking goal (abstinence versus not abstinent), and baseline percent heavy drinking days as covariates. Subjects with any missing drinking data during Weeks 22 to 25 will be considered heavy drinkers. Treatment group differences will be tested for significance using the Wald statistic and will be considered statistically significant at a two-tailed $p < 0.05$.

Analysis of the Key Secondary Endpoint:

The key secondary endpoint is the percentage of subjects abstinent during Weeks 22 through 25 on the mITT population. The analysis will be performed using a fully covaried logistic regression that includes treatment group, clinical site, pre-randomization drinking goal (abstinence versus not abstinent), and baseline percent days abstinent as covariates; however, fewer covariates may be included given a limited number of observed events. Subjects with any missing drinking data during Weeks 22 to 25 will be considered non-abstinent. Statistical significance will be evaluated if and only if the primary endpoint (PSNHDD) is statistically significant ($p<0.05$). The testing procedure utilizes serial gate keeping methodology (Dmitrienko and Tamhane 2009). If statistical significance for the primary endpoint of PSNHDD is met then the Wald statistic from the fully covaried logistic regression will be used to test treatment differences in the percentage of subjects abstinent with statistical significance identified with a two-tailed p-value below 0.05.

Analysis of the Supportive Secondary Endpoints:

Secondary endpoints will compare the HORIZANT Extended-Release Tablets group with the placebo group using mixed-effects models. Covariates for continuous secondary efficacy endpoints include the baseline equivalent of the endpoint, clinical site, treatment, time and the treatment by time interaction. Additional covariates for the secondary efficacy endpoints may include baseline characteristics with a theoretical and/or empirical basis for a relationship with a particular secondary endpoint. In general, every continuous secondary efficacy endpoint is analyzed using a repeated measures mixed effects model where subjects are random effects; factors and covariates are fixed effects. The overall least squares means and least square means for each time point along with the 95% confidence intervals will be presented for the untransformed endpoint only, while two-tailed p-values and Cohen's d will be presented for both the untransformed and transformed data. Inference and Cohen's d will be based upon the results using

appropriately transformed data. Percent subjects with a WHO 1-level decrease in alcohol consumption and a WHO 2-level decrease in alcohol consumption will be analyzed via a fully covaried logistic regression of the endpoint measured during the last 4 weeks of the maintenance period. No imputation will be used for the analysis of secondary endpoints.

PK Analyses: Population PK/PD analyses will be conducted under a separate population PK/PD SAP.

Safety Analyses:

The severity, frequency, and relationship of AEs to investigational product will be presented by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT) grouping. Listings of each individual AE including start date, stop date, severity, relationship, outcome, and duration will be provided. Clinical chemistry, urine drug screen results, pregnancy test results, and BAC results, will be reported as summary statistics. Vital signs will be presented as summary statistics and change from baseline. The proportions of ECG results considered clinically significant will also be provided. CIWA-AR scores will be analyzed in a manner similar to the efficacy endpoints: mixed effects models with and without baseline characteristics. In addition, change from baseline (shift tables) will also be presented for clinical chemistry data. The numbers and proportion of subjects who reported CIWA-AR scores ≥ 10 at any time after the start of dosing will be presented.

Compliance and Retention Analyses:

Medication compliance, defined as the amount of investigational product taken as a proportion of the total amount prescribed per protocol, will be evaluated for the HORIZANT Extended-Release Tablets and placebo groups. Self-reported compliance with HORIZANT Extended-Release Tablets will be compared against plasma samples collected at Weeks 12, 20, and 24 having detectable levels of gabapentin when drug exposure was reported. Average amounts of investigational product taken overall and weekly will be reported for the HORIZANT Extended-Release Tablets and placebo groups. The research participation rate, defined as percentage of subjects with complete drinking data, will be compared between treatment groups. In addition, the percentage of subjects discontinuing medication or early withdrawal from the study and a listing of these reasons for discontinuation will be provided.

Baseline Descriptive Statistics:

Summaries of the characteristics of the subjects in each of the study groups at baseline will be prepared for both the mITT and evaluable analysis sets. Baseline characteristics will be compared between the HORIZANT Extended-Release Tablets and placebo groups using appropriate statistical methods.

2. Table of Contents, List of Tables, and List of Figures

Table of Contents

List of Tables

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3. List of Abbreviations and Definition of Terms

Abbreviation	Definition
5-HT	Serotonin
AA	Alcoholics anonymous
ACQ-SR-R	Alcohol Craving Scale – Short Form
AE	Adverse event
AEDs	Antiepileptic drugs
ALT	Alanine aminotransferase
ASI	Addition severity index.
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
AUD	Alcohol Use Disorder
BAC	Blood alcohol concentration
BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory-II
BID	Twice daily
BIS	Barratt Impulsiveness Scale
CAP	College of American Pathologists
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Act
CYP 450	Cytochrome P450
CI	Confidence interval
CIWA-AR	Clinical Institute Withdrawal Assessment for Alcohol-revised
CrCl	Creatinine clearance
C-SSRS	Columbia-Suicide Severity Rating Scale
$C_{ss,avg}$	Concentration at steady state average
C_{max}	Maximum concentration
$C_{ss,max}$	Concentration at steady state maximum
eCRF	Electronic Case Report Form
CTCAE	Common terminology criteria for adverse events
dL	Deciliter
DNA	Deoxyribonucleic acid
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EDMS	Electronic data management system
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EOS	End of study

Abbreviation	Definition
F	Fahrenheit
FDA	Food and Drug Administration
g	Gram
GABA	Gamma aminobutyric acid
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HIPAA	Health Insurance Portability Accountability Act
hr	Hour
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IWRS	Interactive web response system
L	Liter
LC–MS/MS	liquid chromatography–mass spectrometry/mass spectrometry
MAOI	Monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
MCT-1	Monocarboxylate transporter-1
mg	Milligram
µg	Microgram
min	Minutes
MINI	MINI Neuropsychiatric Interview
mITT	Modified intention-to-treat
mL	Milliliter
mm	Millimeter
mmol	Millimole
NIAAA	National Institutes on Alcohol Abuse and Alcoholism
OTC	Over-the-counter
oz	Ounce
PD	Pharmacodynamic
PEth	Phosphatidylethanol
PI	Principal Investigator
PK	Pharmacokinetic
POMS	Profile of Mood State
PSNHDD	Percentage of subjects with no heavy drinking days
PSQI	Pittsburg Sleep Quality Index
PT	Preferred Term
QTcF	QT interval with Fridericia's correction
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDU	Standard drinking unit

Abbreviation	Definition
SOC	System Organ Class
SOS	Secular organizations for sobriety
SNRI	Serotonin-norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
$T_{1/2}$	Terminal elimination half-life
THC	Tetrahydrocannabinol
TLFB	Timeline followback
T_{max}	Time to maximum plasma concentration
ULN	Upper limit of normal
US	United States
WHO	World Health Organization

4. Introduction

4.1. Alcohol Use Disorder

Alcohol use disorder (AUD) (alcohol dependence and abuse) affects 76 million adults world-wide, including 18 million Americans, and is responsible for a myriad of medical, psychological, social, economic and personal problems (Litten et al-2012). Tragically, more than 2.5 million individuals including 80,000 Americans die each year from alcohol-related events. The total economic cost to society is a staggering $224 billion each year in the United States (US) (NIAAA-2014).

4.2. Current Treatments for Alcohol Use Disorder

Pharmacologic treatment of AUD has mostly focused on altering the reinforcing effects of alcohol use. Medication development has focused on several neurotransmitter systems that interact with the corticomesolimbic dopamine pathway, which can mediate reinforcement. Many available or promising compounds appear to act by modulating the function of opioids, glutamate (with or without gamma aminobutyric acid, GABA), and serotonin (5-HT) (Heilig and Egli-2006).

During the past decade, advances have been made in medications development. Currently, there are four medications approved by the US Food and Drug Administration (FDA) to treat alcohol dependence: disulfiram, oral naltrexone, long-acting injectable (depot) naltrexone, and acamprosate. Last year, nalmefene was approved by the European Medicines Agency (EMA) to treat alcohol dependence. The indications and efficacy of the drugs for the treatment of alcohol dependence is shown in Table 1.

Table 1: Drugs Approved in the US or European Union for Alcohol Dependence

Drug Name	Target Receptor	Putative Mechanism of Action	Randomized Controlled Trial Design	Outcomes	Reference
Oral naltrexone (Revia, Depade)	μ-opioid antagonist	Reduce positive reinforcement of drinking and increase unpleasant effects	Meta analysis of 50 randomized trials of 7793 subjects	Compared with placebo relative risk was 0.8 (95% CI[a] 0.76-0.90)	Rasner et al-2010
Oral naltrexone (Revia, Depade)	μ-opioid antagonist	Reduce positive reinforcement of drinking and increase unpleasant effects	Meta analysis of 53 randomized trials of 9120 subjects	Numbers needed to prevent return to any drinking was 20 (95% CI, 11 to 500), risk difference -0.05% (95% CI[a] -0.10 to -0.002)	Jonas et al-2014

Table 1: Drugs Approved in the US or European Union for Alcohol Dependence (Continued)

Drug Name	Target Receptor	Putative Mechanism of Action	Randomized Controlled Trial Design	Outcomes	Reference
Depot naltrexone (Vivitrol)	μ-opioid antagonist	Reduce positive reinforcement of drinking and increase unpleasant effects	Randomized placebo controlled trial of two doses of depot naltrexone in 624 subjects	Vivitrol had a 25% greater reduction in rate of heavy drinking days after 24 weeks (relative risk 0.75, 95% CI 0.60 to 0.94)	Garbutt et al-2005
Disulfiram (Antabuse)	Inhibits aldehyde dehydrogenase and prevents the metabolism of alcohol's primary metabolite, acetaldehyde	Maintain abstinence (leads to adverse effects when given with alcohol)	Only effective when given under regular supervision. Randomized trial vs naltrexone or acomprosate over 12 weeks	Patients taking disulfiram experienced a greater reduction in heavy drinking days and average weekly consumption, and a longer time to first drink	Laaksonen et al-2008
Acamprosate (Campral)	Glutamate system and the gamma-aminobutyric acid system	Prevent relapse – should be given when abstinence is achieved.	Meta analysis	Compared with placebo, relative risk was 0.84, (95% CI 0.71-0.91)	Rasner et al-2008
Nalmefene (Selincro)	Opioid antagonist (all 3 subtypes of receptors)	Reduce positive reinforcement of drinking	Meta analysis of two randomized placebo controlled trials of 403 subjects over 28 weeks	Reduction in relapse rate compared with placebo relative risk 0.62 (95% CI 0.41-0.93)	Srisurapanont & Jarusuraisin-2005

[a] CI=confidence interval.

As these medications do not work for everyone or in all situations, additional research is vital to develop more efficacious and safe medications to treat AUD.

4.3. HORIZANT (Gabapentin Enacarbil) Extended-Release Tablets

Gabapentin is a GABA analog that was originally developed to treat epilepsy (Neurontin®) and more recently has been approved for the treatment of postherpetic neuralgia (Neurontin and Gralise®). HORIZANT Extended-Release Tablets is an actively transported prodrug of gabapentin that undergoes rapid post absorption hydrolysis to gabapentin that was designed to produce dose proportional gabapentin blood level exposure. HORIZANT Extended-Release Tablets is approved for the treatment of moderate-to-severe primary Restless Legs Syndrome in adults and management of postherpetic neuralgia in adults. HORIZANT overcomes some of the limitations of oral gabapentin including highly variable and dose dependent bioavailability among patients and fluctuations in gabapentin blood levels over 24 hours.

4.3.1. Rationale for Studying HORIZANT Extended-Release Tablets

Recent research findings have shown gabapentin to be a promising medication to treat alcohol dependence. Mason et al (2014) conducted a 12-week, double-blind, placebo-controlled randomized trial of gabapentin (900 mg or 1800 mg/day) in 150 alcohol dependent patients. Gabapentin significantly improved rates of abstinence and no heavy drinking as well as alleviated relapse-related symptoms of insomnia, dysphoria, and alcohol craving. Patients treated with gabapentin exhibited no serious adverse events (SAEs) with a favorable safety profile. The results of this randomized controlled trial are supported by the following earlier studies.

Mason et al (2009) demonstrated in a human laboratory paradigm that gabapentin (1200 mg/day) was effective in reducing alcohol craving and improving measures of sleep quality. Gabapentin was also effective in reducing alcohol withdrawal symptoms (Myrick et al- 2009). In addition, several single-site clinical trials have also yielded promising results for gabapentin in treating alcohol dependence. In a small clinical trial, Brower et al (2008) reported that gabapentin (1500 mg/day) significantly delayed the onset to heavy drinking and improved the symptoms of insomnia in alcohol dependent patients. Furieri and Nakamura-Palacios (2007) conducted a double-blind, placebo-controlled trial of gabapentin (600 mg/day) in 60 alcohol dependent patients and found gabapentin effective in reducing alcohol consumption and alcohol craving. Anton et al (2009) reported that a combination of gabapentin (1200 mg/day) and flumazenil was efficacious in increasing percent days abstinent and time to first heavy drinking in alcohol dependent patients with pretreatment alcohol withdrawal symptoms. In another clinical trial, Anton et al (2011) found that the addition of gabapentin (1200 mg/day) to naltrexone improved drinking outcomes over naltrexone alone. With these positive efficacy and safety results from the single site studies above, gabapentin is now ready to be tested in a multi-site clinical trial. HORIZANT Extended-Release Tablets was selected over other oral gabapentin products due to more uniform bioavailability, faster time to titrating to full therapeutic dose, and less fluctuating gabapentin blood levels with twice daily administration.

4.3.2. HORIZANT Extended-Release Tablets Pharmacodynamics

Gabapentin is structurally related to the neurotransmitter GABA but has no effect on GABA binding, uptake, or degradation. HORIZANT Extended-Release Tablets and gabapentin have been tested in radioligand binding assays, and neither exhibited affinity for a number of other common receptor, ion channel, or transporter proteins. In vitro studies have shown that gabapentin binds with high affinity to the α2δ subunit of voltage-activated calcium channels; however, the relationship of this binding to the therapeutic effects of HORIZANT Extended-Release Tablets in Restless Legs Syndrome and postherpetic neuralgia is unknown.

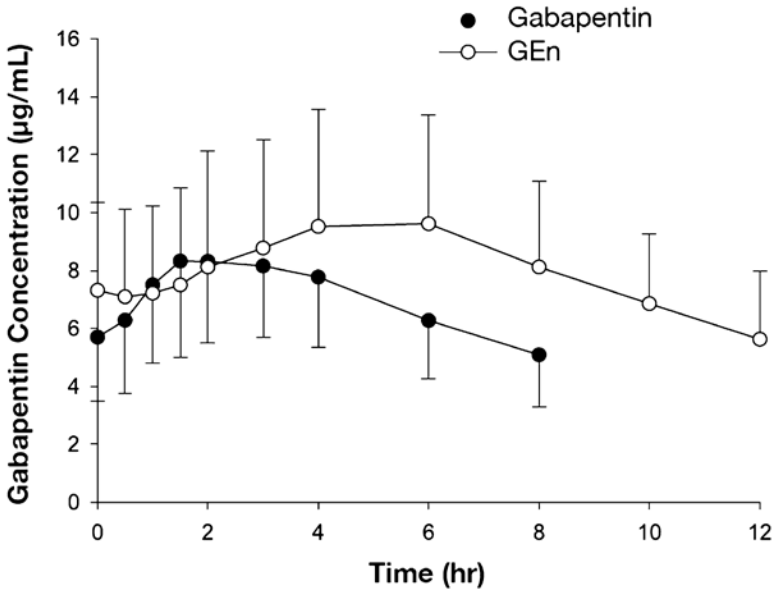
4.3.3. Pharmacokinetics and Metabolism

Gabapentin pharmacokinetic (PK) parameters were compared within the same postherpetic neuralgia patients taking gabapentin and HORIZANT Extended-Release Tablets by Backonja et al (2011). As shown in Table 2 and Figure 1, average steady-state gabapentin concentrations in plasma when patients received 1468 mg-equivalents in divided doses of 1200 mg tablets twice daily of HORIZANT Extended-Release Tablets were increased 17% when compared with 1800 mg of gabapentin given as 600 mg tablets 3 times per day ($p = 0.005$; paired t-test).

Table 2: Pharmacokinetics of Gabapentin in Postherpetic Neuralgia Patients Taking Gabapentin and HORIZANT Extended-Release Tablets

	Treatment	
PK Parameter	**Gabapentin (N=42)**	**HORIZANT Extended-Release Tablets (N=42)**
Gabapentin equivalent dose	1,800 mg	1,248 mg
$C_{ss,avg}$ µg/mL	6.93 (2.25)	8.10 (2.91)
F, %	43.3 (19.8)	76.8 (26.4)
$AUC_{(0-24)}$, µg·h/mL	166 (54.1)	194 (69.9)
$C_{ss,\ max}$ µg/mL	9.07 (3.00)	11.00 (3.99)
T_{max}, hours	2.31 (1.13)	4.63 (2.45)
$T_{1/2}$, hours	7.23 (3.22)	7.37 (2.97)

Figure 1: Comparison of Gabapentin Concentrations in Patients Dosed with Gabapentin and HORIZANT Extended-Release Tablets



Legend: Data are mean ± SD steady-state concentrations of gabapentin in plasma of 42 patients with postherpetic neuralgia after repeated dosing of either gabapentin (600 mg three times daily) or HORIZANT Extended-Release Tablets (1,200 mg twice daily). GEn = gabapentin enacarbil. From Backonja et al (2011).

For subjects with postherpetic neuralgia taking HORIZANT Extended-Release Tablets 600 mg twice daily, the estimated steady state mean C_{max} was 5.35 µg/mL, mean $AUC_{(0-24)}$ was approximately 109 µg*hr/mL, mean C_{min} was 3.63 µg/mL, and mean peak trough ratio was 1.5 (HORIZANT Extended-Release Tablets Product Label).

Absorption: The pathway for absorption of HORIZANT Extended-Release Tablets is believed to include active transport via a proton-linked monocarboxylate transporter, MCT-1. This transporter is expressed at high levels in the intestinal tract and is not saturated by administration of high doses of HORIZANT Extended-Release Tablets. Mean bioavailability of gabapentin

(based on urinary recovery of gabapentin) for HORIZANT Extended-Release Tablets in the fed state is about 75%. Bioavailability under fasting conditions has been estimated by gabapentin urinary recovery to be 42% to 65%. In a food effect study, the exposure of gabapentin increased by 24%, 34%, and 44% with low, moderate, and high fat meals, respectively. The T_{max} of gabapentin after administration of 600 mg of HORIZANT Extended-Release Tablets was 5.0 hours in fasted subjects and 7.3 hours in fed subjects. Steady state is reached in 2 days with daily administration.

Metabolism: Neither HORIZANT Extended-Release Tablets nor gabapentin are substrates, inhibitors, or inducers of the major cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4). HORIZANT Extended-Release Tablets is neither a substrate nor an inhibitor of P-glycoprotein *in vitro*.

4.3.4. Drug Interactions

Alcohol: Gabapentin enacarbil is released faster from HORIZANT Extended-Release Tablets in the presence of alcohol. This was determined in an in vitro dissolution study which was conducted to evaluate the impact of ethanol (5, 10, 20, and 40%) on the extended-release characteristics of HORIZANT Extended-Release Tablets. The in vitro study showed that about 63% of the total gabapentin dose was released at 1 hour at the highest alcohol level (40%), and about 43% of total drug was released at 1 hour with 5% alcohol. Ethanol causes a more rapid release of gabapentin enacarbil from the Extended-Release Tablets that may increase the risk for AEs associated with HORIZANT Extended-Release Tablets. Based on this data, consumption of alcohol is not recommended when taking HORIZANT Extended-Release Tablets.

Morphine: HORIZANT Extended-Release Tablets taken in conjunction with morphine causes increased somnolence/ sedation, dizziness, and nausea when compared with either drug alone. This was determined via the administration of a single 600 mg dose of HORIZANT Extended-Release Tablets 2 hours after a single 60 mg dose of extended-release morphine sulfate in 18 subjects and was associated with increased somnolence/sedation, dizziness and nausea for the combination compared to HORIZANT Extended-Release Tablets or morphine alone as measured by the visual analog scale. No changes in C_{max} and AUC of gabapentin, morphine or its active metabolite morphine-6-glucuronide were observed.

4.3.5. Contraindicated Medications

No medications are contraindicated in patients taking HORIZANT Extended-Release Tablets.

4.3.6. Warnings and Precautions for Subjects Taking HORIZANT Extended-Release Tablets

HORIZANT Extended-Release Tablets is not recommended for patients who are required to sleep during the daytime and remain awake at night.

Driving impairment: Patients should be warned not to drive until they have gained sufficient experience with HORIZANT Extended-Release Tablets to assess whether it will impair their ability to drive.

Somnolence/sedation and dizziness: HORIZANT Extended-Release Tablets may impair the patient's ability to operate complex machinery.

Suicidal thoughts or behaviors: HORIZANT Extended-Release Tablets is a prodrug of gabapentin, an antiepileptic drug. Antiepileptic drugs increase the risk of suicidal thoughts or behaviors. Subjects will be monitored for suicidal thoughts or behaviors in this study.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): This is also known as multiorgan hypersensitivity and has been reported in patients taking antiepileptic drugs, including gabapentin. HORIZANT Extended-Release Tablets is a prodrug of gabapentin, and therefore carries this risk.

4.3.7. Clinical Studies of Gabapentin in Alcohol Use Disorder

Three randomized double-blind placebo controlled trials have evaluated the effects of gabapentin on heavy alcohol drinking in alcohol dependent subjects.

In the study by Brower et al (2008), 21 subjects with a diagnosis of alcohol dependence and insomnia underwent a 1-2 week single-blind placebo lead-in period, a 6-week randomized double-blind, parallel group period of gabapentin (1500 mg/day) vs placebo, then were followed by a 6-week post trial follow-up visit. The primary drinking outcome variable was survival in days to first episode of heavy drinking. Heavy drinking was defined as more than 4 standard drinks in a day for women and more than 5 standard drinks in a day for men, or presenting to any study visit with a blood alcohol level > .08% as measured by breathalyzer. Altogether, among the gabapentin group, 3 (30.0%) of 10 were categorized as having relapsed to heavy drinking during the 6-week trial vs 9 (81.8%) of 11 in the placebo group (Fisher's exact test, p = 0.03). A survival analysis of time to heavy drinking by treatment group revealed a statistically significant difference (log rank p= 0.03) favoring the gabapentin group. Insomnia improved in both treatment groups during the medication phase, but gabapentin had no differential effects on sleep as measured by either subjective report or polysomnography.

Furieri and Nakamura-Palacios (2007) conducted a double-blind, placebo-controlled trial of gabapentin in 60 alcohol dependent Brazilian males who received 7 days of diazepam for acute withdrawal then were randomized to gabapentin (600 mg/day) or placebo for 28 days. The gabapentin group showed a significant reduction in both number of drinks per day and mean percentage of heavy drinking days (p = 0.02 for both), and an increase in the percentage of days of abstinence (p = 0.008), compared to the placebo group. Additionally, some improvement in obsessive-compulsive symptoms was noted in both groups after the treatment, but it resulted in a more pronounced decrease in automaticity of drinking and aspects of craving in the gabapentin group than in the placebo group.

Mason et al (2014) conducted a 12-week, double-blind, placebo-controlled randomized trial of gabapentin (900 mg or 1800 mg/day) in 150 alcohol dependent patients who had to be abstinent for 3 days prior to randomization. The co-primary endpoints were rates of complete abstinence and no heavy drinking days over the 12-week period. A heavy drinking day was defined as 4 or more drinks per day for women and 5 or more drinks per day for men. Gabapentin significantly improved rates of abstinence and no heavy drinking in a dose dependent manner. The rate of sustained abstinence was 4.1% (95% CI, 1.1%-13.7%) in the placebo group, 11.1% (95% CI, 5.2%-22.2%) in the 900 mg group, and 17.0% (95% CI, 8.9%-30.1%) in the 1800 mg group. The no heavy drinking rate was 22.5% (95% CI, 13.6%-37.2%) in the placebo group, 29.6% (95% CI, 19.1%-42.8%) in the 900 mg group, and 44.7% (95% CI, 31.4%-58.8%) in the 1800 mg group. Gabapentin also had a significant linear dose effect on reduction in log-transformed

gamma-glutamyl transferase (GGT) values (p = 0.02). Beneficial effects included alleviation of relapse-related symptoms including insomnia [Pittsburg Sleep Quality Index total score: gabapentin 1800 mg vs placebo: -1.5 (95% CI, -2.1 to -0.8); $p < .001$), dysphoria [Beck Depression Inventory – II (BDI-II)], gabapentin 1800 mg vs placebo: -1.1 (95% CI, -2.0 to -0.3); p = 0.01), and alcohol craving (ACQ-SR-R: gabapentin1800 mg vs placebo: -6.8 (95% CI,-1.5 to -12.1); p = 0.01]. Subjects reported experiencing sleep disturbance and related daytime dysfunction that significantly improved with gabapentin relative to placebo. No evidence of drug substitution or misuse of gabapentin was detected.

4.3.8. Safety of HORIZANT Extended-Release Tablets in Clinical Studies of Restless Legs Syndrome

The safety of HORIZANT Extended-Release Tablets in doses ranging from 600 to 2,400 mg has been evaluated in 515 patients with restless leg syndrome in 3 double-blind, placebo-controlled, 12-week clinical trials. The 600-mg dose was studied in 2 of the 3 studies. Eleven out of 163 (7%) patients treated with 600 mg of HORIZANT Extended-Release Tablets discontinued treatment due to adverse reactions compared with 10 of the 245 (4%) patients who received placebo. The most commonly observed adverse reactions (≥5% and at least 2 times the rate of placebo) in these trials for the 600-mg BID dose of HORIZANT Extended-Release Tablets were somnolence/sedation (27%) and dizziness (22%).

4.3.9. Safety of HORIZANT Extended-Release Tablets in Clinical Studies of Postherpetic Neuralgia

The safety of HORIZANT Extended-Release Tablets in doses ranging from 1,200 to 3,600 mg has been evaluated in 417 patients with postherpetic neuralgia in 3 clinical studies. The principal study evaluating the efficacy and safety of HORIZANT Extended-Release Tablets in the management of postherpetic neuralgia was a 12-week, double-blind, multicenter study comparing 1,200 mg/day, 2,400 mg/day and 3,600 mg/day to placebo. Six out of 107 (6%) patients treated with 1,200 mg of HORIZANT Extended-Release Tablets discontinued treatment due to AEs compared with 12 of the 95 (13%) patients who received placebo.

During the 12-week, controlled study in patients with postherpetic neuralgia, somnolence was reported in 10% of patients treated with 1,200 mg of HORIZANT Extended-Release Tablets per day compared with 8% of patients receiving placebo. Fatigue/asthenia was reported in 6% of patients treated with 1,200 mg of HORIZANT Extended-Release Tablets per day compared with 1% of patients receiving placebo. In those patients treated with 1,200 mg of HORIZANT Extended-Release Tablets per day who reported somnolence (10%), the somnolence persisted during treatment in about 27%. In the remaining patients, symptoms resolved within 4 to 5 weeks. Dizziness was reported in 17% of patients receiving 1,200 mg of HORIZANT Extended-Release Tablets per day compared with 15% of patients receiving placebo. In those patients treated with 1,200 mg of HORIZANT Extended-Release Tablets per day who reported dizziness, symptoms persisted during treatment in about 6%.

Somnolence led to withdrawal in <1% of patients receiving 1,200 mg of HORIZANT Extended-Release Tablets per day compared with 2% of patients receiving placebo. Dizziness led to withdrawal in 2% of patients receiving 1,200 mg of HORIZANT Extended-Release Tablets per day compared with 3% of patients receiving placebo.

4.3.10. Subjects with Renal Impairment

Gabapentin is known to be almost exclusively excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Subjects with abnormal creatinine clearance will be excluded for this study, and creatinine will be monitored monthly during treatment.

4.3.11. Risk of Suicidal Thoughts or Behaviors in Patients Taking Antiepileptic Drugs

HORIZANT Extended-Release Tablets is a prodrug of gabapentin, an antiepileptic drug (AED). AEDs increase the risk of suicidal thoughts or behaviors in patients taking these drugs for any indication. Because HORIZANT Extended-Release Tablets is a prodrug of gabapentin, HORIZANT Extended-Release Tablets also increases this risk.

Pooled analyses of 199 placebo-controlled clinical trials (monotherapy and adjunctive therapy) of 11 different AEDs showed that patients randomized to 1 of the AEDs had approximately twice the risk (adjusted relative risk 1.8, 95% CI: 1.2, 2.7) of suicidal thinking or behavior compared with patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared with 0.24% among 16,029 placebo-treated patients, representing an increase of approximately 1 case of suicidal thinking or behavior for every 530 patients treated. There were 4 suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effects on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as 1 week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed.

4.3.12. Drug Reaction with Eosinophilia and Systemic Symptoms

DRESS, also known as multiorgan hypersensitivity, has been reported in patients taking antiepileptic drugs, including gabapentin. HORIZANT Extended-Release Tablets is a prodrug of gabapentin, and therefore carries this risk. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved.

It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. HORIZANT Extended-Release Tablets should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

4.3.13. Overdose Information

The highest single dose of HORIZANT Extended-Release Tablets administered to date is 6,000 mg in healthy subjects. At this supratherapeutic dose there were no SAEs. The incidence of central nervous system adverse reactions, particularly dizziness and somnolence/ sedation, is increased with doses greater than 600 mg daily.

In the event of an overdose, the patient should be treated supportively with appropriate monitoring as necessary. Gabapentin derived from HORIZANT Extended-Release Tablets can be removed from plasma by hemodialysis. The mean percentage of gabapentin recovered following hemodialysis in patients with end-stage renal disease was 29% (expressed as a proportion of the gabapentin released from HORIZANT Extended-Release Tablets). Further management should be as clinically indicated or as recommended by a poison control center.

4.3.14. HORIZANT Extended-Release Tablets in Pregnant Women

HORIZANT Extended-Release Tablets is considered a Pregnancy Category C drug and should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus. There are no adequate and well-controlled studies with HORIZANT Extended-Release Tablets in pregnant women. In nonclinical studies in rat and rabbits, administration of HORIZANT Extended-Release Tablets was developmentally toxic when administered to pregnant animals at doses and gabapentin exposures greater than those used clinically.

4.3.15. Summary of Safety in Restless Legs Syndrome and Postherpetic Neuralgia

In all controlled and uncontrolled trials across various patient populations with Restless Legs Syndrome or postherpetic neuralgia, more than 2,300 patients have received HORIZANT Extended-Release Tablets orally in daily doses ranging from 600 to 3,600 mg. The most commonly observed adverse reactions in 12-week studies of patients with Restless Legs Syndrome (≥2% of patients and numerically greater than placebo) in trials for the 1200-mg total daily dose of HORIZANT Extended-Release Tablets were somnolence/sedation (27% vs 6% for placebo), dizziness (22% vs 4% for placebo), and headache (15% vs 11%). Adverse reactions reported in these studies in <2% of patients treated with 600 mg of HORIZANT Extended-Release Tablets and numerically greater than placebo were balance disorder, blurred vision, disorientation, feeling drunk, lethargy, and vertigo. Eleven out of 163 (7%) patients treated with 600 mg of HORIZANT Extended-Release Tablets discontinued treatment due to adverse reactions compared with 10 of the 245 (4%) patients who received placebo.

In studies of HORIZANT Extended-Release Tablets for the treatment of postherpetic neuralgia (600 mg BID), 6 out of 107 (6%) patients treated with HORIZANT Extended-Release Tablets discontinued treatment due to AEs compared with 12 of the 95 (13%) patients who received placebo. The most commonly observed adverse reactions (≥2% and numerically greater than placebo) in this trial for the 1,200 mg dose of HORIZANT Extended-Release Tablets compared with placebo were dizziness (17% vs 15%), somnolence (10% vs 8%), and headache (10% vs 9%). The following adverse reactions were also reported as ≥2% at 2,400 mg/day and/or 3,600 mg/day and appeared to be dose-related but were <2% at 1,200 mg/day: balance disorder, confusional state, depression, dry mouth, flatulence, increased appetite, irritability, and vertigo. Dizziness, somnolence, fatigue, and insomnia appeared to show a dose relationship.

In the randomized controlled trial of 150 alcohol dependent subjects receiving 900 mg (54 subjects) or 1800 mg of gabapentin per day (47 subjects) or placebo (49 subjects), gabapentin was well tolerated, with no deaths and no drug-related SAEs (Mason et al-2014). Nine participants discontinued the study due to AEs. Of these, 5 were rated as drug related by blinded study physicians: 2 complaints of headache (900 mg), 2 complaints of fatigue (1 in the 900-mg group and 1 in the 1800-mg group), and 1 complaint of euphoria and feeling "on speed" (placebo group). No differences were found among groups in type of AEs with10% or more of the sample complaining of fatigue (23%), insomnia (18%), and headache (14%). Groups also were similar in the number and severity of AEs reported.

At a dose of 6,000 mg, HORIZANT Extended-Release Tablets does not prolong QTc to a clinically relevant extent.

4.3.16. Rationale for Selection of Doses for this Study

The recommended dose of HORIZANT Extended-Release Tablets in the product label is 600 mg once daily for the treatment of moderate-to-severe primary Restless Legs Syndrome in adults and 600 mg BID for the management of postherpetic neuralgia in adults. In contrast, the recommended dose of Neurontin (immediate release gabapentin) for the treatment of postherpetic neuralgia is 1800 mg per day given as 3 daily divided doses of 600 mg (Neurontin Product Insert). Based on the product prescribing information, the proportion of postherpetic neuralgia patients responding at the recommended doses of HORIZANT Extended-Release Tablets and Neurontin were similar. Higher doses of Neurontin or HORIZANT Extended-Release Tablets were not more effective in treating postherpetic neuralgia, suggesting that both recommended dose regimens achieved essentially equivalent maximum levels of efficacy. The systemic exposure to gabapentin at the recommended HORIZANT dose in postherpetic neuralgia is approximately 20 to 30% lower than that from the recommended dose of Neurontin. However, HORIZANT Extended-Release Tablets achieves a similar level of efficacy to Neurontin despite this lower systemic exposure, presumably as a result of its more sustained plasma profile.

In the Phase 2 randomized controlled trial in alcohol dependent patients reported by Mason et al (2014), two doses of the immediate release form of gabapentin were studied (900 mg per day and 1800 mg per day). There was a dose dependent efficacy response with 1800 mg per day favoring the higher response. Therefore, based on the optimal dose of 1800 mg of immediate release gabapentin in the treatment of alcohol dependence and the fact that 600 mg BID HORIZANT Extended-Release Tablets produces equivalent efficacy to 1800 mg gabapentin in postherpetic neuralgia, a dose of 600 mg BID of HORIZANT Extended-Release Tablets was selected for evaluation in this study.

4.4. Discussion of the Study Design

The primary efficacy endpoint for this study is PSNHDD during the last 4 weeks of the maintenance period. We propose a grace period of 5 months and a responder analysis during the last 4 weeks (month 6) because of the highly variable baseline amounts and unstable drinking patterns observed during alcohol trials during the initial months of the treatment period. Several studies have indicated that drinking patterns over the first 3 months are not stable or representative of future experience when reported at 6 months. For example, in the Project MATCH study, Zweben and Cisler (2003) reported that 47% of the subjects experienced

abstinence or moderate drinking without problems at the three month follow-up interval, but decreased to 38% at the six month follow-up and 29% at the one year follow-up interval, indicating that subjects were returning to heavy drinking and alcohol-related problems over time.

Recently, using patients with alcohol use disorders from Kaiser Permanente, Kline-Simon et al (2013; 2014) reported that compared with heavy drinkers, abstinent or low-risk drinkers at 6 months post-treatment (looking back at the 1 month period before the 6 month follow-up) were more likely to be abstinent or low-risk drinkers at 12 months post-treatment. Moreover, compared to heavy drinkers, abstinent and low-risk drinkers at 6 months were similarly associated with lower 12-month psychiatric severity and family/social problem severity. Furthermore, abstainers and low-risk drinkers had lower inpatient (hospitalization) treatment utilization over the next 5 years compared to that of heavy drinkers. Heavy drinkers had increased emergency department and inpatient costs during this period. Based on this data, we chose a 5-month grace period with the primary analysis being conducted during Month 6 of the treatment period as a clinically meaningful primary outcome. Treatment effects during earlier months will be explored.

In the analysis by Kline-Simon and Weisner (2014), three month post-treatment was compared to 6 month post-treatment in predicting consequences at 12 months (see Table 3 and Table 4). Compared with the heavy drinkers, the abstinent and low-risk drinkers at 6 months post-treatment had improved social/family and employment consequences at 12 months post-treatment, whereas in the 3 month post-treatment group, the psychosocial outcomes did not differ among the abstinent, low-risk, and heavy drinking groups at 12 month post-treatment.

The drinking pattern appears to be more stable at 6 months than 3 months, thus more representative of the patient's drinking pattern going forward in time. The responder analysis was selected for month 6 because of this stable period in the 4 weeks prior to Month 6. Months 4 and 5 were not selected because the available data supported the last 4 weeks of the treatment period.

Table 3: Normative Status on ASI Severity Scores at Twelve-Months by Three-Month Drinking Status

		Abstinence (n=294)	Low-risk Drinking (n=47)	Heavy Drinking (n=53)	p-Value
Alcohol (%)	ASI[a] ≤ Norm	76.2	42.6	28.3	<0.0001
Medical (%)	ASI ≤ Norm	61.2	59.6	58.5	ns[b]
Psychiatric (%)	ASI ≤ Norm	45.9	44.7	34.0	ns
Social/Family (%)	ASI ≤ Median	66.3	59.6	50.9	ns
Employment (%)	ASI ≤ Median	59.5	48.9	43.4	ns

[a] ASI=addition severity index.
[b] ns = not significant.

Table 4: ASI Severity Scores at Twelve Months by Six-Month Drinking Status

		Abstinence (N=660)	Low-risk drinking (N=137)	Heavy drinking (N=198)	p-value
Alcohol (%)	ASI[a] ≤ Norm	80.3	51.8	31.3	<0.0001
Medical (%)	ASI ≤ Norm	65.2	73.7	67.2	ns
Psychiatric (%)	ASI ≤ Norm	58.6	62.0	53.5	ns
Social/family (%)	ASI ≤ Median	68.0	65.7	48.5	0.0003
Employment (%)	ASI ≤ Median	55.2	54.0	41.4	0.0070

[a] Addiction Severity Index (ASI) score values: Alcohol Norm = 0.11; Medical Norm = 0.24; Psychiatric Norm = 0.03; Social/Family Median = 0; Employment Median = 0.19; (Normed to the general population on ASI scores (Weisner et al-2000); Median based on full sample scores). Six month data relies on the 4 week period prior to this time point.

5. Study Objectives

5.1. Primary Objective

The primary objective of this study is to compare the efficacy of HORIZANT Extended-Release Tablets 600 mg BID compared with matched placebo on the primary alcohol consumption outcome endpoint, PSNHDD during the last 4 weeks of the maintenance phase, among subjects with AUD. PSNHDD will also be analyzed during other time periods (i.e., the last 8, 12, 16, 20, and 24 weeks of the maintenance period) in exploratory analyses.

5.2. Secondary Objective

Secondary objectives are separated into two categories: key secondary objectives and supportive secondary objectives. The key secondary objective is to compare HORIZANT to placebo on the percentage of subjects abstinent from alcohol during the last 4 weeks of treatment. The supportive secondary study objectives are to assess other treatment benefits, including: reduction in other alcohol consumption endpoints, alcohol-related craving and consequences, mood, smoking, sleep quality, safety, and tolerability.

6. Investigational Plan

This study is a double-blind, randomized, placebo-controlled, parallel group, multi-site study designed to assess the efficacy of HORIZANT Extended-Release Tablets compared with placebo to reduce drinking in 346 subjects (173 in each group) who report 4 or more Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5™) symptoms of AUD and who meet the drinking criteria outlined hereafter. This study will be conducted at 10 clinical sites. If eligible for the study, subjects will be randomized using a stratified permuted block randomization procedure with "clinical site" as the stratification variable in an approximate 1:1 ratio (targeting 173 subjects per group) to receive either HORIZANT Extended-Release Tablets or placebo for 26 weeks (1 week escalation; 24 weeks maintenance; 1 week taper).

Subjects will be seen in the clinic at screening, at randomization and 11 other times during the study. During the Week 1 dose escalation period (midway through the week) and during the maintenance period (Weeks 2 to 25), subjects will be contacted once per week by telephone at non-clinic visit weeks to encourage study drug compliance and to assess withdrawal, AEs, and concomitant medications. A final follow-up telephone interview will occur during Weeks 28 to 29 (1 to 2 weeks after the end of dosing).

An overview of the study design is provided in Figure 2. Study assessments and procedures will be performed at the visits and time points outlined in the Schedule of Assessments (Table 5).

Figure 2: Overview of Study Design

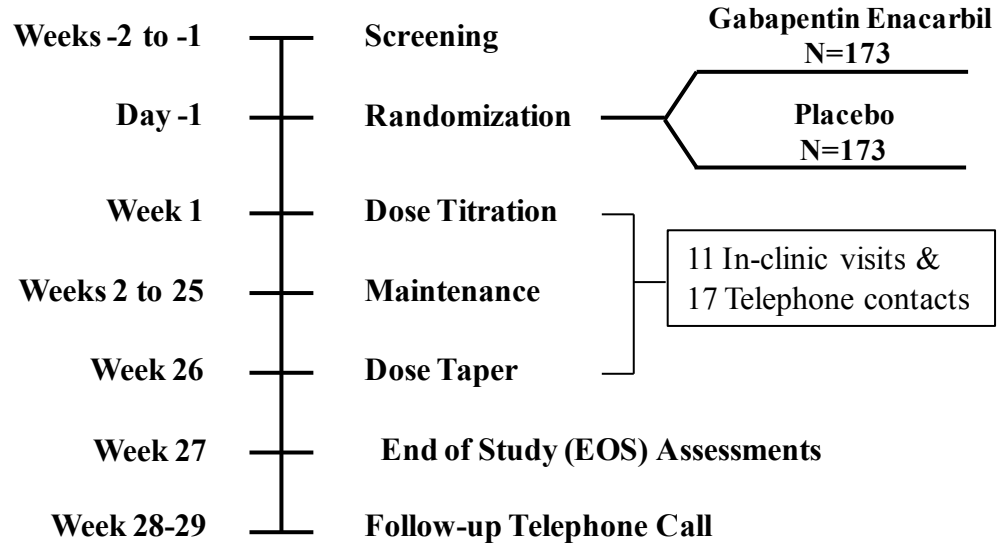


Table 5: Schedule of Assessments

	Screen		Ti-trate	Maintenance																		Taper		Safety Follow-up
Clinic Visit #	**0**	**1**		**2**		**3**		**4**		**5**		**6**		**7**		**8**		**9**		**10**		**11**	**12**	
Study Week	**-2 to -1**	**Day -1**	**1**	**2**	**Mid week 2 & 3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13 - 15**	**16**	**17-19**	**20**	**21-23**	**24**	**25**	**26**	**EOS[a] /27**	**28-29**
Informed Consent	X																							
Alcohol Breathalyzer	X	X		X		X		X		X		X		X		X		X		X		X	X	
Urine Drug Screen[b]	X	X		X		X		X		X		X		X		X		X		X		X	X	
Locator Form	X																							
Demographics	X																							
Medical History	X	X																						
Physical Exam	X	X																					X	
MINI V 7.0	X																					X[c]		
Clinical Chemistry[d]	X					X				X				X		X		X		X		X	X	
Vital Signs[e]	X	X				X				X				X		X		X		X		X	X	
ECG	X																						X	
Prior and Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CIWA-AR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Eligibility Checklist	X	X																						
Blood for DNA Genomics Testing[f]		X																						
Blood for RNA Expression Testing		X																		X				
Blood for PK/Medication Compliance[g]														X				X		X				
Blood spot for PEth		X																				X		
Drug compliance/ accountability				X		X		X		X		X		X		X		X		X		X	X	
Pregnancy Test + birth control	X	X				X				X				X		X		X		X			X	

	Screen		Ti-trate	Maintenance																		Taper		Safety Follow-up
Clinic Visit #	**0**	**1**		**2**		**3**		**4**		**5**		**6**		**7**		**8**		**9**		**10**		**11**	**12**	
Study Week	**-2 to -1**	**Day -1**	**1**	**2**	**Mid week 2 & 3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13 - 15**	**16**	**17-19**	**20**	**21-23**	**24**	**25**	**26**	**EOS[a] /27**	**28-29**
Weight	**X**															**X**							**X**	
Drinking Goal		**X**																						
AEs	**X**[h]		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
C-SSRS		**X**		**X**		**X**		**X**		**X**		**X**		**X**	**14**	**X**	18	**X**	22	**X**		**X**	X	
RANDOMIZATION		**X**																						
Brief Telephone Interview[i]			**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**			
Take Control		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**		
Exit Interview																							**X**	
Treatment Referral																							**X**	
Follow-Up Telephone Interview			**7**																					**X**
Final Subject Disposition																								**X**
Subject Reported Outcomes																								
Family History of Alcohol Problems		**X**																						
BIS		**X**																						
ImBIBe		**X**				**X**				**X**				**X**		**X**		**X**		**X**		**X**		
TLFB	**X**	**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**	**X**	
Drinking question[j]				**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**	**X**	
ACQ-SR-R		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**		
Fagerström Test for Nicotine Dependence		**X**																						
Smoking quantity/frequency		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**	**X**	
PSQI		**X**				**X**				**X**				**X**		**X**		**X**		**X**		**X**		
BAI		**X**				**X**				**X**				**X**		**X**		**X**		**X**		**X**		

	Screen		Ti-trate	Maintenance																		Taper		Safety Follow-up
Clinic Visit #	**0**	**1**		**2**		**3**		**4**		**5**		**6**		**7**		**8**		**9**		**10**		**11**	**12**	
Study Week	**-2 to -1**	**Day -1**	**1**	**2**	**Mid week 2 & 3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13 - 15**	**16**	**17-19**	**20**	**21-23**	**24**	**25**	**26**	**EOS[a] /27**	**28-29**
BDI-II		X				X				X				X		X		X		X		X		
POMS		X				X				X				X		X		X		X		X		
Other Services Used for Alcohol Use Problems		X				X				X				X		X		X		X			X	

[a] EOS=end of study. These assessments are to be done at Week 27 or if the subject discontinues early and agrees to a final clinic visit.
[b] Test for opioids, cocaine, amphetamines, methamphetamine, tetrahydrocannabinol (THC), buprenorphine, methadone or benzodiazepines.
[c] Only the AUD module is performed at Week 26.
[d] AST, ALT, total bilirubin, creatinine, GGT.
[e] Sitting blood pressure and heart rate.
[f] Only for subjects who consent to provide this sample.
[g] For each subject, blood collections should be scheduled at different times relative to the morning dose at these 3 clinic visits.
[h] Only SAEs will be reported from the time of signing informed consent until the first dose of investigational product administration. Thereafter, AEs and SAEs will be reported for the duration of the study.
[i] AEs, concomitant medications, CIWA-AR, and drug compliance reminder.
[j] Only asked to subjects who are no longer participating in clinic visits and not willing to providing TLFB drinking data.

7. Study Interventions

7.1. Investigational Products: HORIZANT Extended-Release Tablets and Placebo

HORIZANT Extended-Release Tablets, 600 mg, are white to off-white, oval-shaped tablets debossed with "GS LFG". HORIZANT Extended-Release Tablets may contain occasional black/grey spots.

Placebo tablets debossed with "GS LFG" that are identical in appearance to HORIZANT Extended-Release Tablets will also be used in this study.

Both the HORIZANT Extended-Release Tablets and placebo tablets will be provided by XenoPort Inc., Santa Clara, CA.

7.2. Investigational Product Packaging, Labeling, and Distribution of Drug Kits to Sites

Investigational products will be provided in drug kits containing 14 bottles of either HORIZANT Extended-Release Tablets or placebo in each kit. Each bottle contains 30 tablets and each kit contains a total of 420 tablets. Each subject is scheduled to receive a total of 354 tablets, thus providing a sufficient supply of tablets for the entire study for a single subject in one kit. Kits will be shipped periodically to sites during the study depending on enrollment.

The study number and a brief protocol title that does not link the subject with an alcohol research study will be preprinted on each bottle label. The label will also have a kit number, the number of tablets contained in the bottle, storage conditions, and the words "Caution: New Drug – Limited by Federal law to investigational use" and "Keep Out of Reach of Children**"**. A separate label will be supplied to affix to the bottle each time a bottle is dispensed. This label will contain the clinical site name, clinical site phone number and 24/7 emergency phone number, and places to record the subject number and the date dispensed.

7.3. Investigational Product Storage

Kits should be stored at room temperature (within the range of 59°F to 86°F) in a secured area at the clinical site.

7.4. Investigational Product Dispensing

The dispensing plan is provided in Table 6. At each visit when bottles are dispensed the appropriate number of drug diary cards will be given to the subject as well. An example of the drug card is provided in Appendix 19.1. As shown in Table 6, an extra bottle (#14) will be dispensed at Week 2 to the subject to hold at home until the end of the study in case of shortage due to scheduling conflicts or other unanticipated circumstances. Drug accountability and compliance will be performed by the clinical site at each clinic visit. The subject will be instructed to return all study bottles, including bottle #14 at the last clinic visit.

The subject will be asked to bring all bottles and the drug cards at each subsequent visit for accountability. Bottle #14 will be re-dispensed after performing accountability. The first time that investigational products are dispensed, the subject will also be given a copy of the Medication Guide for HORIZANT Extended-Release Tablets (Appendix 19.2).

Table 6: Schedule for Dispensing Study Drug Bottles

Study Visit	Study Week	Bottle #s Dispensed	# Tablets[a]	Anticipated Usage	Anticipated Return	Return for Accountability
1	Day -1[b]	Dispense #1	30	12	18	
2	2	Dispense #2 & #14	30	28	2	Bottle #1
3	4	Dispense #3 & #14	30	28	2	Bottle #2 & #14
4	6	Dispense #4 & #14	30	28	2	Bottle #3 & #14
5	8	Dispense #5 & #14	30	28	2	Bottle #4 & #14
6	10	Dispense #6 & #14	30	28	2	Bottle #5 & #14
7	12	Dispense #7, #8, & #14	60	56	4	Bottle #6 & #14
8	16	Dispense #9, #10 & #14	60	56	4	Bottle #7, #8, & #14
9	20	Dispense #11, #12 & #14	60	56	4	Bottle #9, #10 & #14
10	24	Dispense #13 & #14	30	28	2	Bottle #11, #12 & #14
11	26	Dispense #14	30	6	24	Bottle #13 & #14
12	27	none				Bottle #14
Total:			**420**	**354**	**66**	

[a] Does not include Bottle #14 tablets until Week 26.
[b] Study drug will be dispensed on the day of randomization. Subjects are expected to take the first dose of drug the following morning, Week 1, Day 1 of the study.

7.5. Investigational Product Accountability

The site principal investigator (PI) or designated study personnel will maintain a log of the receipt of all investigational products and record of dispensing of all investigational products to the subject. Investigational product for each subject will be inventoried and accounted for throughout the trial. The site PI or his/her staff will count the tablets remaining at the end of the study and record the tablet count on the appropriate drug accountability form. Subject compliance with investigational product will be assessed by comparing unused tablet count to dispensing logs and dosing records (number of tablets dispensed, number of tablets prescribed, versus the number returned). Subjects will also be asked to account for any missing tablets. If the bottle is not returned, the subject will be asked to report daily drug self-administration.

7.6. Used/Unused Investigational Product Supplies

Unused investigational products will be retained at the clinical sites pending instructions for return by the Study Coordinating Center to XenoPort.

7.7. Investigational Product Administration

Dose titration, maintenance and taper will occur as shown in Table 7. The target maintenance dose of HORIZANT Extended-Release Tablets is 600 mg BID. Subjects receiving placebo will take the same number of tablets as those prescribed for HORIZANT Extended-Release Tablets to preserve the study blind.

Table 7: Schedule of Administration of Investigational Products

Study Period	Time Period	AM Dose (# of tablets)	PM Dose (# of tablets)
Titration	Week 1, Days 1- 3	600 mg (1)	None
Titration	Week 1, Days 4-7	600 mg (1)	600 mg (1)
Maintenance	Weeks 2-25	600 mg (1)	600 mg (1)
Taper	Week 26	600 mg (1)	None

Tablets should be swallowed whole and should not be cut, crushed, or chewed. Tablets should be taken with food.

Missed Doses: Subjects will be instructed, if the dose is not taken at the recommended time, to skip this dose, and the next dose should be taken at the time of next scheduled dose; doses should never be doubled up. Subjects will be instructed to record the dose that was missed.

Dose Reduction and Discontinuation. If the subject is not tolerating the investigational product or has a medical condition requiring dose reduction or discontinuation of the investigational product, a reduction to one tablet in the evening is permitted. If discontinuation of the investigational product altogether is necessary, then if the subject was taking the investigational product twice daily, he/she should taper to one tablet per day for one week before stopping. If the subject was already taking just one tablet per day, he/she can simply discontinue unless clinically inappropriate to do so. In the event that a female subject becomes pregnant, she will be instructed to undergo the same dose reduction of investigational product as is recommended for all subjects as sudden discontinuation from 600 mg BID to zero could potentially increase the risk for withdrawal seizures.

7.8. Take Control Behavioral Platform

The behavioral platform "Take Control" will consist of a series of 11 computerized modules. Subjects will view a single module of "Take Control" at each clinic visits from Visit 1 to 11. If a visit is missed, missed modules will be reviewed at the next visit. The paper versions of the modules are not to be given to the subject to take home and must remain at the clinic. The intervention is derived from a self-help approach developed by NIAAA that provides evidence-based, field tested information for individuals with alcohol problems, and suggestions for making changes in their drinking. The NIAAA material is publically available in a NIAAA booklet entitled "Rethinking Drinking" and on a NIAAA website http://rethinkingdrinking.niaaa.nih.gov. Delivering these materials in a computerized method in this trial has the advantage of standardizing the amount of educational material received by the subject.

7.9. Concomitant Medications

Although there are no specific contraindicated medications, due to the somnolence effects of HORIZANT Extended-Release Tablets, drugs with sedative properties should be used with caution as it is assumed that sedative properties could be additive. While taking study drug, subjects may not take HORIZANT Extended-Release Tablets, gabapentin or other gabapentinoids.

For study inclusion, subjects cannot have taken any anti-convulsants, hypnotics, barbiturates, antipsychotics, psychomotor stimulants (such as methylphenidate), or benzodiazepines within 5-half lives prior to the date of randomization. In addition, if a subject is taking a medication for depression or anxiety, he or she must have been taking a stable dose in the 2-months prior to randomization and plan to continue during the study. This includes drugs such as the following:

- selective serotonin reuptake inhibitors (SSRIs)
- dual uptake inhibitors
- serotonin-norepinephrine reuptake inhibitors (SNRIs)
- tricyclic antidepressants
- monoamine oxidase inhibitors (MAOIs)
- bupropion

Pharmaceutical treatments approved for treatment of alcoholism or treatments known to be used off-label or experimentally for treatment of alcoholism are prohibited during the study. Besides HORIZANT Extended-Release Tablets, gabapentin or other gabapentinoids already not allowed during the study, the following drugs approved for the treatment of alcoholism are also prohibited:

- Oral naltrexone (Revia, Depade)
- Depot naltrexone (Vivitrol)
- Disulfiram (Antabuse)
- Acamprosate (Campral)
- Nalmefene (Selincro)

In addition, a list of prohibited drugs that are prescribed off-label or experimentally for the treatment of alcoholism will be included in the Manual of Procedures and updated during the study if new drugs are identified. Also, if a subject reports using a drug or having been prescribed a drug to treat alcoholism during the trial, they will be asked to discontinue its use.

Subjects will be instructed to check with study staff before taking any new medications or stopping current medications. Subjects will be informed that starting any new medication without consulting study staff could pose health risks and/or result in their discontinuation for the study drug.

Management of investigational products and concomitant medications during the study is at the discretion of the PI or designated medical doctor. The PI or designee may consult with the medical monitor if there are questions.

8. Study Procedures

8.1. Recruitment of Subjects

Subject recruitment methods at each site will be based on their local population; however, standard tactics will be used (i.e., flyers, newspaper advertisements, radio advertisements, and television advertisements). Local institutional review boards (IRBs) and NIAAA will approve all advertising materials used for subject recruitment. Interested candidates responding to recruitment materials by telephone will be asked to complete a standardized telephone interview that includes questions about their drinking behavior, health status, interest in participation, and availability for the entire 31 weeks of the trial. Study staff will ask these questions without revealing the entry criteria for the study. Candidates who report drinking and other information consistent with the entry criteria and appear to be available and interested in the study will meet with the investigator or designated investigational staff ideally within 14 days after the initial inquiry to start the informed consent and assessment process.

8.2. Informed Consent

At the first screening visit, candidates will meet with either the PI or his/her designee 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 approved by the local site's IRB. Subjects must have blood alcohol content (BAC) of 0.000 measured by breathalyzer when signing the informed consent document (tested shortly before or just after providing consent). Repeat measurements of BAC are permitted at the discretion of the investigator. Subjects will be given a copy of the signed informed consent form.

8.3. Selection and Withdrawal of Subjects

8.3.1. Inclusion Criteria

Subjects must meet each one of the following inclusion criteria in order to be eligible for participation in the study:

1. Be at least 21 years of age.
2. Have a current (past 12 months) DSM-5 diagnosis of AUD (4 or more symptoms) assessed using the MINI neuropsychiatric interview version 7 (moderate severity, ICD-10-CM Code F10.20 alcohol dependence, uncomplicated).
3. If male, report drinking an average of at least 28 drinks per week or if female report drinking an average of at least 21 drinks per week for the 28-day period prior to consent and for both males and females one heavy drinking day per week over the 28-day period.
4. Have a BAC by breathalyzer equal to 0.000 when s/he signed the informed consent document (either just prior to or immediately after signing consent).
5. Be abstinent (by self report) in the 3-days prior to the day of randomization and have a BAC of 0.000 by alcohol breathalyzer on the day of randomization.

6. Be seeking treatment for problems with alcohol.
7. Be able to verbalize an understanding of the consent form, able to provide written informed consent, verbalize willingness to complete study procedures, able to understand written and oral instructions in English and able to complete the questionnaires required by the protocol.
8. Agree (if the subject is female and of child bearing potential) to use at least one of the following methods of birth control, unless she is surgically sterile, partner is surgically sterile or she is postmenopausal:
    a. oral contraceptives,
    b. contraceptive sponge,
    c. patch,
    d. double barrier (diaphragm/spermicidal or condom/spermicidal),
    e. intrauterine contraceptive system,
    f. etonogestrel implant,
    g. medroxyprogesterone acetate contraceptive injection,
    h. complete abstinence from sexual intercourse, and/or
    i. hormonal vaginal contraceptive ring.
9. Be able to take oral medication and be willing to adhere to the medication regimen.
10. Complete all assessments required at screening and baseline.
11. Have a place to live in the 2 weeks prior to randomization and not be at risk that s/he will lose his/her housing by Study Week 28.
12. Not anticipate any significant problems with transportation arrangements or available time to travel to the study site by Study Week 28.
13. Not have any plans to move within Study Week 28 to a location which would make continued participation in the study impractical.
14. Not have any unresolved legal problems that could jeopardize continuation or completion of the study.
15. Provide contact information of someone, such as a family member, spouse, or significant other, who may be able to contact the subject in case of a missed clinic appointment.
16. Be someone who in the opinion of the investigator would be expected to complete the study protocol.
17. Agree to the schedule of visits, verbally acknowledge that s/he will be able to attend each scheduled visit, participate in phone visits and that s/he does not have any already scheduled events or a job that may substantially interfere with study participation.
18. If taking a medication for depression or anxiety, must have been taking a stable dose in the 2-months prior to randomization and plan to continue during the study. This includes drugs such as the following:
    - SSRIs
    - dual uptake inhibitors

- SNRIs
- tricyclic antidepressants
- MAOIs
- bupropion

8.3.2. Exclusion Criteria

Subjects will not be eligible to participate in this study if any one of the following exclusion criteria is met:

1. Have current substance use disorder for any psychoactive substance (including sedatives and hypnotics) other than alcohol and nicotine as defined by DSM-5 criteria.
2. Have a urine toxicology screen positive during screening or baseline for any of the following substances:

   a. benzodiazepines,
   b. cocaine,
   c. opioids,
   d. amphetamines,
   e. buprenorphine,
   f. methadone, and/or
   g. methamphetamines.

   Note: Testing for tetrahydrocannabinol (THC) will be included in the urine drug test; however, subjects who test positive for THC are still eligible to participate in the study unless they endorse moderate or severe substance use disorder for marijuana as indicated by DSM-5 criteria. The results for THC will be recorded for information only. If positive for opioids but recent opiate use for acute pain is reported by the subject, then the subject can be re-screened.
3. Have been hospitalized for alcohol intoxication delirium, alcohol withdrawal delirium, alcohol-induced persisting dementia or amnestic disorder, or have had an alcohol withdrawal seizure, alcohol-induced psychotic disorder with a primary diagnosis of alcohol use disorder or a history of any seizure disorder.
4. Have participated (received treatment) in any behavioral and/or pharmacological intervention research study for the treatment of alcohol problems in the past 7 years.
5. Be mandated by the court to obtain treatment for problems with alcohol.
6. Be anyone who in the opinion of the investigator could not be safely withdrawn from alcohol without medical detoxification.
7. Be currently undergoing psychotherapy by a licensed therapist or psychiatrist for alcohol problems

   NOTE: Current psychotherapy should be considered on a case-by-case basis. Psychotherapy for a disorder that may be related to the subject's use of alcohol should be exclusionary. However, shorter term focused behavioral therapy for defined problems for non-alcohol related problems may be acceptable.

8. Have undergone medical detoxification (e.g., reports using a benzodiazepine) during the screening phase (prior to randomization).
9. Have been treated with a pharmacotherapy for alcohol problems within 6 months prior to randomization.
10. Have taken any anti-convulsants, hypnotics, barbiturates, antipsychotics, psychomotor stimulants (such as methylphenidate), or benzodiazepines within 5-half lives days prior to the date of randomization.
11. Have any of the following, based on DSM-5 criteria as assessed using the MINI:
    a. Current or lifetime diagnosis of psychotic disorders
    b. Current bipolar disorder,
    c. Current major depressive episode, or
    d. Current (past 3 months) eating disorder (anorexia or bulimia).

    Note: Subjects diagnosed with psychiatric disorders not specifically excluded above may be included at the discretion of the PI as long as the concurrent treatment for the comorbid psychiatric condition does not compromise the study integrity by virtue of its type, duration, or intensity.
12. Have any of the following:
    a. attempted suicide past year,
    b. current (past year) suicide behavior disorder in accordance with DSM-5 criteria as assessed using the MINI (see note below about assessment of subjects diagnosed at low risk), or
    c. current (since screening MINI) suicidality risk as indicated during the conduct of the C-SSRS with concurrence after a study physician's evaluation if the response to C-SSRS questions 1 or 2 is "yes").

    Note: The MINI suicidality module rates scores of 1 to 8 as a diagnosis of low risk of suicidality. As the MINI questions that could result in a low risk score are considered inadequate to fully determine the potential suicidal risk of an individual (e.g., "Feel hopeless" and "Think that you would be better off dead or wish you were dead?" responses of "yes" dictates a score of 1 for each question), any subject who scores in the low risk category should be evaluated further by a study physician who should document whether the subject is appropriate for study inclusion based on his/her clinical judgment of the potential suicide risk of the subject. Likewise, if the subject responds "yes" to either the first two questions on the screening C-SSRS performed on the day of randomization as a final eligibility check, the subject should also evaluated by a study physician for current suicidality risk, who should document the subject's suitability for study inclusion.
13. Have moderate or serious dementia as assessed by clinical exam.
14. Be pregnant or breast-feeding or have plans to become pregnant at any time during the study.

15. Have clinically significant abnormal laboratory values, including elevation of liver enzymes (AST, ALT) 5-fold above the upper limit of normal (ULN), or bilirubin greater than 2 times the ULN.

    Note: If the subject has values of liver enzyme that are 3.0-to-4.9 fold above the ULN and bilirubin that is 1.5-to-1.9 fold above the ULN of normal, these assessments should be repeated at least a week apart and if still in this range or higher, the subject should be excluded from the study and referred to their physician for further follow-up.

16. Have abnormal calculated creatinine clearance (<60 mL/min), as calculated by Cockcroft and Gault formula (section 11.8).
17. Have a serious or unstable medical illness or any potentially life-threatening or progressive medical condition other than addiction that may compromise subject safety or study conduct.
18. Have data suggesting cirrhosis of the liver.
19. Have taken HORIZANT Extended-Release Tablets, gabapentin or other gabapentinoids during the 6 month period prior to randomization for treatment of any disorder or if ever treated with these drugs for AUD.

8.4. Eligibility Screening

After the subject signs informed consent, screening may begin. During the first screening visit (additional visits are permitted if needed), subjects will undergo the following assessments:

- Demographics and locator form
- Urine drug screen
- Medical history
- Physical examination (weight may be recorded at this visit or the randomization visit)
- MINI Version 7.0
- Clinical chemistry
- Pregnancy test for females of child bearing potential and birth control methods, if female
- Vital signs
- ECG
- TLFB for the previous 28 days
- Prior medication use
- CIWA-AR

Eligible subjects will be instructed that they must be abstinent (no alcoholic beverage consumption) for 3 days prior to the date of randomization. Subjects will be instructed that if they are taking a medication for depression or anxiety that they should continue to do so throughout the study. They will also be instructed not to take HORIZANT Extended-Release

Tablets, gabapentin or other gabapentinoids from the start of the study or during the study and that they should report any new medications they are taking at each visit or telephone contract.

The above assessments can be performed in any order except that it is recommended to perform physical examinations including vital signs prior to blood draws. If any of these assessments reveal that the subject is not eligible for the study, screening can be immediately terminated. Clinical chemistry tests may be repeated at the discretion of the investigator if the first assessment yields values outside normal laboratory limits. The eligibility checklist will be reviewed, and if the subject is still eligible after the assessments are completed at the first screening visit (or additional screening visits), the subject will be scheduled for the final eligibility baseline visit. It is recommended that hypertensive subjects be referred to their primary care physician for additional assessment and possible treatment, and then be further evaluated for study inclusion.

8.5. Baseline and Final Eligibility Assessments

If the subject is eligible after performing all the initial screening assessments, s/he will be scheduled to start the study and will come to the clinic for a final eligibility check including the following assessments:

- Alcohol breathalyzer (must have a reading of 0.0 to support abstinence)
- Urine drug screen
- Update medical history
- Update physical exam – new symptoms directed exam
- Vital signs
- Weight (if not recorded at the initial screening visit)
- CIWA-AR
- C-SSRS*
- Pregnancy test for females of child bearing potential (must be completed within 2 days of the subject being randomized and dispensed investigational product)
- Birth control methods, if female
- Prior medications update
- TLFB (must report 3 days of abstinence prior to randomization)

*Note that the MINI will be used to rule out subjects who attempted suicide in the past year and current (past year) suicidal ideation at initial screening, with the C-SSRS providing an update on current suicidal ideation since screening.

An eligibility checklist will be completed and reviewed by a study investigator and, if the subject is still eligible, he/she will complete the following baseline assessments:

- Blood for DNA genomics and RNA expression testing
- Blood spot collection for phosphatidylethanol (PEth) level determination

The subject will complete the following questionnaires electronically:

- ACQ-SR-R
- Drinking Goal
- Modified Fagerström Test for Nicotine Dependence
- Smoking Quantity Frequency Questionnaire
- PSQI
- BAI
- BDI-II
- ImBIBe
- Family History of Alcohol Problems
- Barratt Impulsiveness Scale (BIS)
- POMS
- Other Services for Alcohol Use Problems

If the subject reported drinking in the three days prior to randomization, they can be rescheduled for another randomization visit if they agree to try to stop drinking for the required period of 3 consecutive days prior to randomization. The screening period will not be extended. If the investigator determines that the subject could be a viable participant who could not for extenuating circumstances complete the screening period in 14-days, the subject can be re-screened by completing all of the screening assessments again. In this case, the subject will be assigned a new subject number.

8.6. Measures Taken to Minimize/Avoid Bias

8.6.1. Randomization (Day -1)

If eligible for the study, subjects will be randomized in an approximate 1:1 ratio to receive either HORIZANT Extended-Release Tablets or placebo using a stratified permuted block randomization procedure with "clinical site" as the stratification variable. Clinical site was chosen because both local study populations, and the investigative staff influence on the subject's drinking behaviors may differentially influence endpoints.

Centralized randomization will be performed using an interactive web response system (IWRS). The IWRS is available for randomization of subjects 24 hours/day, 7 days/week from any computer using a web browser.

If the subject is determined to be eligible, site personnel who are authorized to randomize subjects and who have completed training for the IWRS, will log onto the system and provide the pre-assigned unique subject number and the subject's date of birth. The IWRS provides the randomized group kit number and assigns the subject to one of the two interventions. If the subject is randomized and is never dispensed study drug, then the subject will be considered a randomization failure and an additional subject will be randomized with the next randomization sequence at the time he/she is randomized at that site. Likewise, if the subject was randomized

and then is determined to not be eligible for the study, and never received study drug, then another subject will be randomized such that the total numbers of subjects who were eligible, randomized, and dispensed study drug meet the enrollment goals. In the case of a subject who was eligible, randomized, and dispensed study drug but did not return for follow-up visits, this subject will not be replaced. Any subject who received study drug but was later determined to be ineligible will likewise not be replaced. The reason(s) that a subject was considered a randomization failure or screen failure will be documented in source documents and eCRFs.

8.6.2. Blinding

HORIZANT Extended-Release Tablets and placebo tablets will be identically matched in appearance and the bottle labels will not reveal the drug identity. The site investigator or designated approved study physician will make the decision to un-blind the identity of the investigational product in the event that the study blind needs to be broken to make medical decisions regarding subject treatment. If it is determined that unblinding is necessary to assess AEs or SAEs for expedited reporting, NIAAA may decide to request unblinding of a subject. Site staff or Sponsor's designee approved to un-blind the study drug will log into the IWRS to obtain the name of the investigational product to which the subject was randomized. The IWRS will automatically notify the un-blinded staff member at the Data Coordinating Center who will notify the Medical Monitor. NIAAA will be notified that an unblinding has occurred if unblinding has been performed by the investigator or medical monitor.

8.7. Interventions on Day -1 and Day 1

At study Day -1, after the subject is randomized, he/she will receive the first bottle of study drug and the instructional drug card to take home (Appendix 19.1). Site staff will explain the dosing plan to the subject (one tablet in the morning for the first 3 days, then one tablet in the morning and one in the evening for the next 4 days) and how to complete the drug card to track when tablets are taken. The subject will be instructed to take the first dose in the morning of Day 1 (expected to occur the day after the date of randomization). Subjects will be instructed to take tablets with meals and will be advised to avoid driving and operating heavy machinery, until they are aware of how the study drug affects them. The subject will watch the first module of Take Control (Day -1), will be given the schedule of visits, and the Week 2 visit will be scheduled.

Every study subject will be provided with a wallet card and instructed to carry this card that identifies the potential investigational products that s/he could be taking during the study. The card will provide the name and 24-hour phone number of the investigator (physician) at the site who can be contacted in the event of an emergency. The card will also instruct the non-study physician rendering emergency care to contact the study physician and inform him/her about the care.

If possible, clinic visits should be scheduled on the same day of the week that the subject received the first dose of study drug, but a 3-day window is allowed for conducting visits within the scheduled study week. Visits may be scheduled and conducted on any day of the week. Visits can be conducted outside of the scheduled study week, but only based upon subject request (e.g., for reasons related to patient non-compliance with the study schedule). Each subject will receive a visit schedule to take home for future reference.

8.8. Weeks 1 and 2 Safety Telephone Contact

Midway through Weeks 1 and 2 subjects will be called for a safety assessment. The call during Week 1 should ideally be the day before the subject escalates their dose to 2 pills per day. Assessments will be the same as all other telephone contacts (see section 8.10).

8.9. Maintenance Phase

During Study Weeks 2 through 25 of the maintenance phase of the study, subjects will be seen in person at the clinical site 9 times and assessed by telephone 16 times. Week 26 is dose taper and there is a final clinic visit at Week 27 at the end of dose taper.

An alcohol breathalyzer will be administered at each visit, prior to any study assessments, to determine if the subject meets the BAC requirement of a BAC ≤ 0.020 before proceeding with assessments. A urine drug test will be performed at each visit. At each of the clinic visits, subjects will meet with one or more study staff members who will systematically assess AEs since the last visit, take vital signs, administer questionnaires (CIWA-AR and C-SSRS), inquire about other medication use and assess drinking by TLFB. Clinical chemistry, pregnancy test for women of child-bearing potential and birth control methods (if female), blood for study drug compliance, and subject's weights will be collected in accordance with the schedule in Table 5. In addition, subjects will complete the battery of questionnaires in accordance with the schedule in Table 5.

Brief telephone assessments will occur weekly between in-clinic visits. The final in-clinic assessment will occur during Week 27. This visit should be scheduled after the subject takes the last dose of study drug.

Subjects will view a single module of Take Control that is expected to have a run-time of 10-15 minutes during each clinic visit. After completion of the Take Control module, a new supply of investigational product will be given and the bottle(s) from the previous period will be collected and a tablet count will be performed for accountability. Bottles with unused tablets will be returned to the subject. The dosing schedule will be reviewed and the subject will be provided instructions on how to complete the drug card to track tablet consumption. The subject will be instructed to bring the bottle(s) and drug cards with them to the next visit so the site staff can perform drug accountability (tablet counts). The subject will also be instructed to contact site staff if they are experiencing any intolerable AEs and are contemplating drug discontinuation.

Additional in-clinic visits are permitted under the protocol, if needed, due to the following circumstances: (1) the subject has concerns either about the medication or their drinking and wishes to be seen at a time other than their next scheduled in-clinic visit, or, (2) the subject has missed a visit and wishes to resume regular participation before their next scheduled visit, (3) the subject has reported some change in health, functioning, or circumstances which necessitate a visit to conduct safety assessments and evaluate the risk of continued participation in the trial, or (4) clinical laboratory measurements need to be repeated.

Subjects desiring additional counseling or professional therapy for non-crisis psychiatric matters (e.g., marital problems, work issues) should be encouraged to postpone such activity until their study participation is concluded. Attendance at self-help support groups (i.e., alcoholics anonymous) will neither be encouraged or discouraged. Any attendance at self-help support

groups will be recorded at the randomization visit and monthly in the Other Services Used for Alcohol Use Problems electronic case report form (eCRF).

8.10. Telephone Assessments

The brief telephone interview (approximately 10 minutes) will occur in accordance with the schedule in Table 5 to assess AEs, concomitant medication use and the emergence of withdrawal symptoms, to encourage the subject to continue taking investigational products, to verify that the subject is taking the prescribed dose, and to remind the subject of the next scheduled visit. A summary of the telephone script follows:

1. AEs: An open-ended question will be asked as follows: "How have you been feeling since your last clinic visit or phone contact?" If the subject reports a new AE, the resolution of an AE, or a change in the severity of an AE, ask additional questions to determine the severity and dates of occurrence or resolution.
2. CIWA-AR: Subjects will be assessed for the emergence of withdrawal symptoms using the CIWA-AR. The subject may be asked about changes in drinking status after responses to the CIWA-AR interview indicate significant withdrawal.
3. Concomitant Medications: Ask the following question: "Have you taken any new medications since you were last seen in the clinic or since our last call? If the subject responds affirmatively, record the name of the medication, the daily dose, route of administration, and reason used. If the medication is contraindicated for the study (HORIZANT Extended-Release Tablets, gabapentin or gabapentinoids), then notify a study physician, nurse practitioner, or physician assistant for follow-up with the subject.
4. Drug Compliance: Verification that the subject is taking the prescribed dose and a reminder to take investigational product and to return the bottle(s) with untaken tablets at the next visit will be made. During the Week 1 call, the subject will be reminded of the drug escalation schedule.
5. Reminders: Remind the subject of their next scheduled clinic visit, and adjust the date within the visit week if they have a conflict.

8.11. Final Clinic Visit

The final clinic visit occurs during Week 27; at which time the subject has completed taking investigational product. In addition to the assessments previously stated, subjects will have an Exit Interview assessment. The subject will be asked about their drinking for his/her impression of whether he/she was receiving active drug or placebo, if they felt that the medication helped drinking, how they would describe their experience taking the medication, if they would recommend it to a friend, if they would take it again if they needed further treatment in the future, and a question about desire to please people. The subject will be provided with a referral to a treatment program for their alcohol dependence. If a subject withdraws from the study early for any reason, the subject should be asked to return to the clinic for the conduct of all of the final clinic visit assessments.

8.12. Telephone Follow-up

Subjects will be contacted by telephone for a follow-up interview 1-to-2 weeks after the final in-clinic visit. During the telephone follow-up interview, the subject will be asked about any ongoing AEs that they may have been experiencing at the last clinic visit and any newly emerged medical conditions/AEs since that visit. To prompt reporting of new AEs, the subject will also be asked about any ongoing or new medication use.

8.13. Duration of Subject Participation

The total time period that each individual subject will participate is 31 weeks including up to 2 weeks for screening, 26 weeks of study interventions, and final safety and efficacy follow-up the week after completing treatment (Week 27), and a final safety follow-up telephone contact from 1-to-2 weeks after completion of study drug dosing.

8.14. Dose-adjustment Criteria

8.14.1. Safety Criteria for Dose Adjustment or Stopping Doses

The PI or sub-investigator will follow the protocol to identify and intervene with subjects experiencing clinical deterioration during study participation. Criteria to determine when a subject requires a higher level of care and discontinuation from the trial intervention are detailed below.

8.14.1.1. Investigational Product Dose Reduction

The daily dosage of investigational product may be reduced by the study physician for any AE determined, by the study physician, to compromise the subject's ability to maintain activities of daily living or if the subject reports undue discomfort. As the investigational products are taken twice per day, only one dose reduction can occur. If dose reduction is warranted, the subject should continue to only take the evening dose.

8.14.1.2. Investigational Product Discontinuation

Subject who will discontinue investigational products will have the dose reduced to once daily for 1 week prior to discontinuation to minimize the potential of withdrawal seizure. Subjects should continue in the study, even if withdrawn from investigational products and complete all assessments.

Pregnancy. Females who become pregnant during the course of the study will be instructed to reduce the dose to once daily for 1 week prior to discontinuation to minimize the potential of withdrawal seizure. If already on once daily dosing, females should immediately discontinue use of the investigational product. The investigator must report a pregnancy within 1 working day of the site being aware to the NIAAA Study Manager and the Medical Monitor.

Physical Illness. Subjects will need to be removed from investigational products if they have a serious illness or a disabling condition that precludes them from taking the investigational product.

Adverse Events. If the subject experiences any AEs that are considered study drug related and for which the investigator has determined that continuation of the study drug could be

detrimental to the health of the subject, then drug will be reduced for 1 week, then discontinued, or immediately discontinued as described above.

8.15. Subject Withdrawal or Discontinuation Procedures

Each subject has the right to withdraw consent and withdraw from the study at any time. In addition, the investigator may find it necessary to discontinue a subject for any reason, including the occurrence of an AE or noncompliance with the protocol.

In the event that a subject withdraws or is discontinued from the study, the reason(s) for the discontinuation from the study will be recorded and a pregnancy test (females only), body weight, vital signs measurement, ECG, clinical chemistry, C-SSRS, TLFB and an assessment of AEs will be performed as soon as possible after discontinuation from the study. Other assessments scheduled for the end of study visit will be collected if possible (Table 5). Additional blood samples for study drug measurement may be collected at the time of discontinuation from subjects who are discontinued due to AEs.

8.16. Situations Requiring Discontinuation from the Study as well as from Investigational Product

It is possible that there will be some subjects who cannot be safely managed in the clinical study even though investigational products have been discontinued. Examples are given below.

1. **Increased Drinking.** Subjects whose alcohol problem worsens, and, in the opinion of the site medical staff, require a more intense level of care than provided in the study may have investigational product suspended, and referred to more appropriate care.
2. **Psychiatric Crises.** Examples of psychiatric crises include but are not limited to the following:
   a. Acute psychosis (hallucinations, impaired reality testing, paranoid ideation, etc.) requiring medication and/or hospitalization or intensive outpatient intervention;
   b. Suicidal or homicidal ideation that results in a credible threat of violence directed at oneself or others;
   c. Hospitalization for psychiatric symptoms

   Subjects requiring more intensive treatment resulting from acute psychosis or suicidal/homicidal behavior will be referred to local treatment centers, emergency departments, or hospitalization as appropriate, but will not be provided with medication or psychotherapy by study staff.
3. **Absence from the Protocol due to Confinement in a Controlled Environment.** If a subject is confined to a controlled environment (such a hospital or jail where access to alcohol is presumably restricted) for less than 2 weeks, they can resume full participation in the trial if in the judgment of the investigator, the subject is still a good candidate for the study and continues to meet eligibility requirements. Before resuming investigational products the subject should be assessed by the study physician for appropriateness to resume the trial (e.g. any new medications or symptoms, pregnancy test, etc.). The decision to restart study drug at the full dose or titrate to the full dose will be made in the judgment of the investigator based on the subject's time off study drug and past experience with side effects with the study drug.

If a subject is in a controlled environment (such a hospital or jail where access to alcohol is presumably restricted) for 2 weeks or more, the subject will be discontinued from the study.

8.17. Study Termination Criteria

NIAAA may terminate this study prematurely, either in its entirety or at any sites, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to NIAAA in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If NIAAA terminates the study for safety reasons, NIAAA will immediately notify the investigators by telephone and subsequently provide written instructions for study termination. The FDA may stop the study at any time as well. If the FDA notifies NIAAA to stop the study, then NIAAA will notify the sites of this action.

9. Study Endpoints

9.1. Efficacy Endpoints

9.1.1. Primary Efficacy Endpoint

Self-reported daily alcohol consumption will be assessed using the TLFB method from 28 days before signing informed consent until the last study visit or contact. The primary efficacy endpoint examines the hypothesis that HORIZANT Extended-Release Tablets will increase the PSNHDD compared to placebo during the last 4 weeks of maintenance period of treatment (Study Weeks 22-25). A "heavy drinking day" is 4 or more drinks per drinking day for women and 5 or more drinks per drinking day for men. PSNHDD will also be analyzed during other time periods (i.e., the last 8, 12, 16, 20, and 24 weeks of the maintenance period) in exploratory analyses.

9.1.2. Secondary Efficacy Endpoints

Secondary endpoints will be analyzed over the last 4 weeks of the maintenance phase of treatment.

1. Percentage of subjects abstinent from alcohol (key secondary endpoint)
2. Percentage of subjects with a WHO drinking risk category decrease of:
    a. 1-level
    b. 2-levels
3. Percentage of days abstinent per week
4. Percentage of heavy drinking days per week
5. Weekly mean number of drinks per week
6. Weekly mean drinks per drinking day
7. Cigarettes smoked per week among smokers
8. Alcohol craving score (ACQ-SR-R)
9. Alcohol related consequences (ImBIBe) score
10. PSQI score
11. BAI score
12. BDI-II score

9.2. Safety Endpoints

Safety endpoints will be analyzed over the entire treatment and follow-up period.

1. Vital signs
2. Blood chemistries
3. BAC by breathalyzer

4. Urine drug tests
5. AEs
6. ECG results
7. CIWA-AR scores
8. POMS scores
9. Frequency of subjects with suicidal ideation at any time during the treatment period (C-SSRS)

9.3. Compliance

Compliance will be assessed by self report of compliance with investigational products and gabapentin plasma levels. Compliance will be calculated as the percentage of investigational products taken as prescribed.

9.4. Pharmacokinetics

A population PK/PD analysis will be performed using gabapentin plasma levels determined from blood samples collected at Weeks 12, 20, and 24 from subjects in the HORIZANT Extended-Release Tablets group. Blood will be collected from each subject at a different time at each PK visit (pre-dose and up to 12 hours post-dose). A total of three samples per subject will be taken over 3 sampling visits. Times to target post-dose collections include 8 hours post-dose (expected $C_{max,ss}$) and 12 hours post-dose ($C_{min,ss}$). It is preferable not to take samples before 4 hours post-dose.

10. Safety Monitoring Plan

Safety monitoring will be conducted throughout the study; therefore safety concerns will be identified by continuous review of the data by the PI, clinic staff, clinical monitor, medical monitor, and NIAAA.

Study Safety Management: The IRB, Medical Monitor, PI, clinical monitors, NIAAA and XenoPort (or its affiliates) will review any safety concerns throughout the trial. In addition, a data and safety monitoring board (DSMB) will participate in this study. The roles of these individuals/committee are described below.

Medical Monitor: A Medical Monitor and Alternate Medical Monitor have been appointed by NIAAA for the study. The Medical Monitor will be available for making recommendations to the investigator and NIAAA on the severity of any SAEs, and the relatedness to the study interventions. The Medical Monitor will also be responsible for tracking and assessing trends in the AEs reported.

Clinical Monitors: All investigators will allow representatives of the Data Coordinating Center (Fast-Track Drugs and Biologics, LLC) staff to periodically monitor, at mutually convenient times during and after the study, all study data. These monitoring visits provide the Data Coordinating Center, NIAAA, and XenoPort with the opportunity to evaluate the progress of the study and to obtain information about potential problems. The monitors will assure that submitted data are accurate and in agreement with any paper source documentation used; verify that investigational products are properly stored and accounted for, verify that subjects' consent for study participation has been properly obtained and documented, confirm that research subjects entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by Good Clinical Practices (GCP) guidelines are appropriately filed.

Monitors will conduct a site initiation visit prior to the start of the study. At this visit, they will assure that proper study-related documentation exists, assist in training investigators and other site personnel in study procedures and GCP guidelines, confirm receipt of study supplies, and assure that acceptable facilities are available to conduct the study.

Routine monitoring visits by the Data Coordinating Center and NIAAA's representatives will be scheduled at appropriate intervals but more frequently at the beginning of the study. A monitoring visit soon after the first two subjects have been randomized is planned. At these visits, the monitors will verify that study procedures are being conducted according to the protocol guidelines, monitor eCRFs against source documents, review AEs and SAEs, and perform drug accountability. At the end of the study, they will confirm that the site has the appropriate essential documents on file, advise on storage of study records, and inspect the return and destruction records for unused investigational products.

Sponsor and XenoPort Site Visits: All investigators will allow NIAAA and XenoPort full access to study records during periodic site visits by NIAAA and XenoPort. Visits by NIAAA and XenoPort will be made for a mutually convenient time and will be scheduled in advance.

DSMB: An independent DSMB of external advisors will meet prior to the start of the study, quarterly during enrollment and follow-up and at trial end to review safety data. The Board will be blinded to subjects' actual randomized group assignments but may request at any time that the

blind be broken by the data center, if concerns arise from the blinded data. In addition to quarterly meetings, the DSMB will meet after half of the subjects (173) have been randomized to review safety data and the integrity of the study (i.e., an evaluation of the dropout rate and impact on the planned statistical analysis of the data) and make a formal recommendation to the sponsor on the continuation or early stopping of the study due to safety concerns. *Ad hoc* meetings will be convened if SAEs occur that are considered at least possibly related to the investigational product.

11. Assessment Methods

All study assessments will be performed at the visits and time points outlined in the Schedule of Assessments (Table 5); the following sections outline the details and procedures associated with the assessments. All assessments will be recorded on a source document with the exception of staff or subject completed questionnaires.

11.1. Alcohol Breathalyzer

An alcohol breathalyzer will be administered at consent, at screening, and at every in-clinic visit as a safety measure. Acceptable BAC level at consent and screening visit 2 (Day -1, the day of randomization) is equal to 0.000 and less than or equal to 0.020 for all other in-clinic visits prior to performing other assessments.

11.2. Adverse Events and Serious Adverse Events

The investigator and study site staff are responsible for the detection, documentation, classification, reporting, and follow up of events meeting the definition of an AE or SAE.

11.2.1. Adverse Event Definition

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and may not necessarily have a causal relationship with the administered treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant laboratory abnormality), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. Pre-existing conditions, diseases, or disorders are not considered AEs unless there is a change in severity or frequency.

11.2.2. Serious Adverse Events and Serious Unexpected Adverse Events Definition

An SAE is any untoward medical occurrence that meets one of the following:

- Results in death
- Is life-threatening (at the time of the event)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

A serious and unexpected AE is an SAE that is not identified in nature, intensity, or frequency in the risk information included in the Product Label for the drug.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the study subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

11.2.3. Methods/Timing for Assessing, Recording, and Analyzing Safety Endpoints

AEs will be assessed at study visits starting after the first administration of investigational product until the final follow-up visit. However, SAEs will be collected from the time of informed consent onward. General symptoms will be collected via an open ended question: "How have you been feeling since your last visit or the last time we spoke?"

AEs will be documented in the source records, and recorded on the eCRFs using accepted medical terms and/or the diagnoses that accurately characterize the event. When a diagnosis is known, the AE term recorded on the eCRF will be the diagnosis rather than a constellation of symptoms. The investigator will assess all AEs for seriousness, relationship to investigational product, and severity. When an event has not resolved by study closure, it will be documented on the AE eCRF as "ongoing".

If a woman has a positive or borderline pregnancy test after enrollment, the NIAAA Medical Monitor will be contacted and the pregnancy will be recorded as an AE. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been terminated or completed. The outcome of the pregnancy will be reported to the NIAAA Medical Monitor without delay within 24 hours of knowledge of the event if the outcome is a SAE (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by study physicians until satisfactory resolution (the event either resolved or stabilized and is not expected to resolve in the near term). AEs must be reported up to 2 weeks following completion of, or termination from investigational product administration. At the follow-up telephone contact, AEs will be recorded and followed to resolution only if they are serious, or if the study physician assesses them to be clinically significant.

11.2.4. Clinical Laboratory Abnormalities and Other Abnormal Assessments

Abnormal clinical laboratory findings (e.g., clinical chemistry) or other abnormal assessments (e.g., from vital signs or ECG), judged as clinically significant by the investigator will be recorded as AEs or SAEs, if they meet the definitions provided in Section 11.2.2. Abnormal laboratory or other findings present at baseline that significantly worsen following start of the study will be reported as AEs or SAEs. Abnormal findings present at the start of the study that do not worsen will not be reported as AEs or SAEs, unless the investigator or designee judges them as more severe than expected for the subject's condition.

11.2.5. Classification of Adverse Event Intensity and Relationship to Investigational Product

For each recorded AE or SAE, a physician- investigator must make an assessment of severity. For those AEs included in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.03), these severity criteria will apply. For those not listed in the CTCAE, the following criteria will be used:

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.

In particular, clinical chemistry severity and blood pressure increases will be graded in accordance with the CTCAE version 4.03. The severity grades for the chemistry tests used in this study and for systolic and diastolic blood pressure are provided in Appendix 19.3.

The investigator must make an assessment of 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 but 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.

11.2.6. Outcomes and Actions Taken

All unresolved AEs will be followed for a minimum of 14 days (unless the AE is an ongoing pregnancy which must be followed to conclusion) after the subject's final study visit, unless the investigator's judgment dictates otherwise, the event has resolved or stabilized prior to the 14-day period, or the subject is lost to follow-up.

Investigators are not obligated to actively seek AEs or SAEs in former study subjects that occur following the follow-up period.

For each recorded AE or SAE, the investigator must make an assessment of outcome at the time of last observation, as follows:

Fatal:	The subject died.
Resolved without Sequelae:	The AE or SAE has ended.
Resolved with Sequelae:	The AE or SAE has ended but changes are noted from baseline.
Unresolved – Ongoing:	The AE has not ended and is ongoing at the end of the reporting period (i.e., 14 days after the final Follow-up visit) and the investigator deems that further follow up is not medically required
Unknown – Lost to Follow-up:	Lost to follow-up after repeated unsuccessful attempts to contact the subject.

Actions taken with respect to investigational agents (discontinuation or not) will also be recorded. In addition, if the AE was treated (medications or other physical measures), this will also be recorded.

11.2.7. Reporting Serious Adverse Events

11.2.7.1. 24 hour Reporting Requirements (Initial Report)

Any SAE, including death due to any cause, which occurs to any subject from the time of signing consent through the final follow-up visit whether or not related to the investigational product, must be reported ***within 24 hours*** of knowledge of the event by completing the SAE eCRF. This will trigger an automatic notification of the SAE via an email communication to NIAAA and Fast-Track. Fast-Track will notify the Medical Monitors upon receipt of the notification and coordinate communications with the Medical Monitors.

11.2.7.2. 3-Day Supporting Documentation Requirements (Follow-up Report)

Written documentation for all SAEs must be received by the NIAAA Medical Monitor/Alternate within 3 days of reporting the event. Required eCRF that must be completed include the following:

- SAE eCRF (follow-up)
- Concomitant Medication eCRF
- AE eCRF

In addition, paper copies of the following may be requested

- Copies of source documents pertinent to the event (laboratory reports, ECG tracings, medical chart notes, etc.). These should be identified only by Subject number and not include any subject identification information prohibited by Health Insurance Portability Accountability Act (HIPAA).

- Any other relevant information necessary to support the investigator's judgment regarding the SAE's relatedness severity to the investigational product OR by request of the Medical Monitor/Alternate.

These paper documents may be submitted by facsimile, as email attachments, or by attaching them to the subject's eCRF casebook.

11.2.7.3. Reporting to the IRB

Unanticipated problems involving risk to subjects or others, SAEs related to participation in the study and all subject deaths should be promptly reported by phone, email, or fax to the local IRB.

Investigators are required to forward safety information provided by the sponsor's representative to the IRB.

11.3. Alcohol Craving Scale

The ACQ-SR-R contains 12-items adapted from the 47-item ACQ-NOW developed by Singleton et al (1994) to assess craving for alcohol among alcohol users in the current context (right now). There are 4 subscale scores for compulsivity, expectancy, purposefulness and emotionality and a total score. Each item has a 1 to 7 raw score (from strongly disagree to strongly agree). The sum of the raw scores for each factor are divided by 3 to yield a factor based score. Items 3, 8, and 11 are reverse keyed. A general craving index is derived by summing all items and dividing by 12. This form takes ~5 minutes to complete. This questionnaire will be completed by the subject electronically and will be both the source and eCRF.

11.4. Barratt Impulsiveness Scale

The BIS is a widely used measure of impulsiveness that includes 30 self-reported items that are scored to yield six first-order factors (attention, motor, self-control, cognitive complexity, perseverance, and cognitive instability impulsiveness) and three second-order factors (attentional, motor, and non-planning impulsiveness) (Patton et al-1995). This questionnaire will be completed by the subject electronically and will be both the source and eCRF.

11.5. Beck Anxiety Inventory

The BAI consists of 21 questions about how the subject has been feeling in the last week, expressed as common symptoms of anxiety (such as numbness and tingling, sweating not due to heat, and fear of the worst happening). This inventory was designed to minimize the overlap with depression scales (Beck et al-1988). Each question has the same set of four possible answer choices, which are arranged in columns and are answered by marking the appropriate one with a cross. These are:

Not at all. (0 points)

Mildly: It did not bother me much. (1 point)

Moderately: It was very unpleasant, but I could stand it. (2 points)

Severely: I could barely stand it. (3 points)

The BAI has a maximum score of 63. The standardized cutoffs for anxiety severity are:

0-7: minimal level of anxiety

8-15: mild anxiety

16-25: moderate anxiety

26-63: severe anxiety

This questionnaire will be completed by the subject electronically and will be both the source and eCRF.

11.6. Beck Depression Inventory – II

The BDI-II is a 21-item multiple choice questionnaire that is used for measuring the severity of depression (Beck et al-1966). Each item is scored on a scale value of 0 to 3. The standardized cutoffs for depression severity are:

0–13: minimal depression

14–19: mild depression

20–28: moderate depression

29–63: severe depression

This questionnaire will be completed by the subject electronically and will be both the source and eCRF.

11.7. Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-AR)

The CIWA-AR modified telephone version is an adaptation for telephone administration of the CIWA-AR a brief 10-item measure used to provide a quantitative index of the severity of the alcohol withdrawal syndrome (Sullivan et al-1989). The CIWA-AR has been used both in clinical and research applications and has demonstrated both reliability and validity (Sellers et al-1992, Stuppaeck et al-1994). This questionnaire will be administered by a clinical staff member and subject responses will be recorded electronically and will be both the source and eCRF.

11.8. Clinical Chemistry

Clinical laboratory tests will be performed at the clinical site's local clinical laboratory. Laboratories performing these assessments should be directly regulated by the College of American Pathologists (CAP) or Clinical Laboratory Improvement Act (CLIA) guidelines. The laboratory will need to provide a copy of current certification. All clinical laboratory data will be reviewed by the investigator for clinical significance. The total blood volume is approximately 72 mL. Additional laboratory samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure safety. Clinical chemistry tests are listed below.

- Creatinine
- Total bilirubin
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)

- Gamma glutamyl transferase (GGT)

Serum creatinine levels will be used to calculate creatinine clearance (CrCl) according to the Cockroft-Gault (1976) formula as follows:

$$\text{Males} \quad \text{CrCl (mL/min)} = \frac{(140 - \text{age in years}) \times \text{body weight in kg}}{72 \times \text{serum creatinine mg/dL}}$$

$$\text{Females} \quad \text{CrCl (mL/min)} = \frac{0.85 \times (140 - \text{age in years}) \times \text{body weight in kg}}{72 \times \text{serum creatinine mg/dL}}$$

For any laboratory test value outside the reference range that the investigator considers clinically significant:

- The investigator will repeat the test to verify the out-of-range value
- The investigator will follow the out-of-range value to a satisfactory clinical resolution
- A laboratory test value that requires a subject to be discontinued from the study or requires a subject to receive treatment will be recorded as an AE

11.9. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a 4-page form asking questions about suicidal ideation, intensity of ideation, and suicidal behavior developed by Posner and collaborators at the New York State Psychiatric Institute (Oquendo et al-2003). This scale is intended for use by trained administrators. The questions contained in the C-SSRS are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment. Training is required before administering the C-SSRS through a 30-minute interactive slide presentation followed by a question-answer session through the Columbia University Medical Center. Those completing the training are certified to administer the C-SSRS, and will receive a training certificate. As the MINI will be used to establish subject initial eligibility with respect to suicidality, the "Since Last Visit" version of the C-SSRS will be used at each clinic visit starting with Visit 1 at Week 1. At Visit 1, Week 1, this scale will be used to assess current suicidal ideation since the MINI interview. This questionnaire will be administered by a clinical staff member and subject responses will be recorded electronically and will be both the source and eCRF.

11.10. Demographics

Demographics data include the subject's age, gender, race/ethnicity, marital status, education, employment pattern, occupation, and income level. These data will be collected by site staff on a source document and entered into an eCRF.

11.11. Drinking Question

If a subject is withdrawn from the study early and is no longer participating in clinic visits or providing TLFB drinking data but is willing to be contacted by phone at the week most proximal to dropout, then they will be asked about any drinking and heavy drinking during the time since last contact. Phone calls will continue until the end of the treatment period, as deemed acceptable by the patient, to obtain data on the primary efficacy endpoint (any heavy drinking days defined as 5 drinks per day for males and 4 drinks per day for females) and on the secondary efficacy

endpoint of abstinence. The rules regarding standard drinking units (SDU) applies. This data will be recorded on a source document and eCRF. This does not apply to subjects who are willing to supply daily drinking data by the TLFB method.

11.12. ECG

A 12-lead resting ECG will be obtained. Any abnormalities will be noted and an assessment of clinical significance will be done by a study physician.

11.13. Exit Interview

At the final in-clinic visit (or by phone if the subject withdraws early), the subject will complete a questionnaire for his/her impression of whether he/she was receiving active drug or placebo, if they felt that the medication helped drinking, how they would describe their experience taking the medication, if they would recommend it to a friend, if they would take it again if they needed further treatment in the future, and a question about desire to please people. This questionnaire will be completed by the subject electronically and will be both the source and eCRF.

11.14. Fagerström Test for Nicotine Dependence

The Fagerström Test for Nicotine Dependence will be used to assess smoking status and motivation to change smoking behavior at baseline (Heatherton et al-1991). This questionnaire will be completed by the subject electronically and will be both the source and eCRF.

11.15. Cigarette Smoking Quantity-Frequency

A quantity frequency interview at baseline will include three questions to assess cigarette smoking behavior and other tobacco/nicotine containing products use during the study: 1) “Over the past week, on how many days did you smoke cigarettes?”, 2) “On the days you smoked during the past week, how many cigarettes did you smoke on average?”, and 3) “Have you used any other tobacco or nicotine containing products besides cigarettes in the past week (e.g., cigars, cigarellos, pipes, bidis, or smokeless tobacco such as pan, chewing tobacco, or snuff, or nicotine replacement therapies such as patch or gum)?”. This questionnaire will be completed by the subject electronically and will be both the source and eCRF.

11.16. Family History of Alcohol Problems

Information on family history of alcohol problems will also be collected using the Family History of Alcohol Problems. The questionnaire provides subjects with a consistent set of cues for identifying blood relatives with alcohol problems by using a family tree listing for relatives (Mann et al-1985). This questionnaire will be completed by the subject electronically and will be both the source and eCRF.

11.17. Genetic Analysis

Blood samples for genotyping and expression analysis will be collected using standard phlebotomy techniques into PAXgene tubes containing special preservatives for subsequent isolation of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Tubes will be stored frozen at < -20°C and will be shipped to a central storage facility at the end of the study for

storage prior to analysis. Details of sample collection, storage and shipping are provided in the study Manual of Operations.

One or two 4 mL tubes of whole blood sample for DNA isolation will be collected from each subject who consents to provide samples for pharmacogenetic analysis. One tube will be collected from all subjects. The second tube is optional and will only be collected from subjects who agree to have their sample analyzed for a broader range of research.

One 2.5 mL tube of blood for RNA analysis will be collected at baseline and at Week 24 at approximately the same time of day to control for circadian rhythm.

The samples will be retained while research on HORIZANT Extended-Release Tablets (or drugs of this class) continues but no longer than 20 years in cases where the subject agrees to provide the second optional sample. If the subject withdraws consent for testing or storage before the sample is shipped to the central laboratory, the site will destroy the sample. If the subject withdraws consent for testing or storage after the sample is shipped to the central laboratory, any results already obtained will be kept.

11.18. ImBIBe

ImBIBe is a 15-item questionnaire in which the subject responds on a 5-point scale responses to questions on the consequences of alcohol use. This scale was adapted from the Drinker Inventory of Consequences questionnaire based on FDA recommendations on patient reported outcomes (Miller & Tonigen-1995). This questionnaire will be completed by the subject electronically and will be both the source and eCRF.

11.19. Locator Form/Mobile Phone Contact

After signing informed consent, subjects will be asked to provide names, addresses, and phone numbers of several friends and/or family members who can be contacted if the subject cannot be located (Locator Form). This locator form will be used to assist in contacting subjects between visits and at follow-up. This form asks subjects his/her name, address, and phone number and to provide names, addresses, and phone numbers of several friends and family members who can be contacted if the subject cannot be located. This information is essential and will be collected during screening, and will be updated throughout the study as necessary. This information will remain exclusively at the site. In addition, a mobile phone provided by the clinical site will be offered to subjects who do not have a mobile phone or who do not wish to use their personal mobile phone for study related contacts. The mobile phone will only be given to subjects who are determined to be eligible and who are dispensed study drug.

11.20. Medical History

A medical history will be taken for all potential study subjects to assure medical fitness during screening. The age at which the subject started drinking alcohol regularly at least 3 times per month (age of onset) will also be collected as part of the medical history. Prior (lifetime) treatment for alcohol problems and drinking will also be collected. The answers to the following questions will be collected:

1. Number of lifetime inpatient hospitalizations (i.e. at least one overnight stay) to get help with reducing or quitting drinking.

2. Number of lifetime inpatient hospitalizations (i.e. at least one overnight stay) for illnesses, injuries, or accidents due to drinking.

3. Number of times in lifetime underwent alcohol detoxification using medication.

4. Number of lifetime outpatient visits (i.e. no overnight stay) with a health professional to get help with reducing or quitting drinking.

5. In the past year, how many alcoholics anonymous (AA), 12 Step, Save Ourselves, or similar group meetings attended for alcohol problems or drinking.

The medical history will be updated on the day planned for randomization by asking the subject if anything has changed since the initial screening interview.

11.21. MINI

The MINI (paper version 7.0) is a short structured diagnostic interview, developed jointly by psychiatrists and clinicians in the United States and Europe, for DSM-5 and ICD-10 psychiatric disorders (Sheehan et al-1998). With an administration time of approximately 15 minutes, it was designed to meet the need for a short but accurate structured psychiatric interview for multicenter clinical trials and epidemiology studies and to be used as a first step in outcome tracking in non-research clinical settings. Diagnoses recorded on the MINI will be recorded on the interview form and entered into an eCRF. The individual items of the Alcohol Use Disorders Module will be also collected on an eCRF in addition to all other diagnoses. At the last study visit, the Alcohol Use Disorders Module will be assessed again, but the initial drinking question will not be asked and the time period for which the questions apply has been revised to "the past month" instead of the past 12 months.

11.22. Other Services Used for Alcohol Use Problems

At randomization (past 4 weeks) and monthly during the study, the subject will be interviewed about attendance at group meetings [AA, 12-step programs, secular organizations for sobriety (SOS), or similar group meetings] and visits with health professionals for assistance in reducing or stopping drinking. Use of additional counseling or professional therapy for non-crisis psychiatric matters or any additional pharmacologic or non-pharmacologic treatments received will be documented. This questionnaire will be administered by a clinical staff member and subject's responses will be recorded electronically and will be both the source and eCRF.

11.23. Phosphatidylethanol Determination

Phosphatidylethanol (PEth) as a biomarker for chronic alcohol use has been reviewed recently by Viel et al-2012). PEth is formed in the blood by hydrolysis of phosphatidylcholine catalyzed by phospholipase D to phosphatidic acid that when in the presence of blood alcohol results in the production of PEth (Mueller et al-1988). In clinical studies conducted on chronic heavy drinkers, PEth was found to be detectable in blood up to 28 days after sobriety (Aradottir et al-2006; Hansson et al-1997; Hartmann et al-2007; Varga et al-1998; Wurst et al-2010; Wurst et al-2012). In 15 alcoholics following a detoxification program, the mean half-life of blood PEth was 4.0 ± 0.7 days with a range of 3.0-5.3 days (Varga et al-2000). It has been demonstrated that sex,

gender, age and body mass index do not influence the normalization rate of PEth (Wurst et al-2010). In a recent experiment during which, after three weeks of abstinence, 11 social drinkers were exposed to an amount of ethanol of 1 g/Kg for five consecutive days (daily alcohol intake ranging between 67 and 109 g/day), and then remained abstinent for 16 days, undergoing regular and scheduled blood sampling, the mean half-life of PEth ranged from 4.5 to 10.1 days in the first week and from 5.0 to 12.0 days in the second week (Gnann et al-2012).

A dried blood spot method will be used by pricking the subject's finger (after wiping with an alcohol swab) with the lancet provided in the collection kit and allowing blood to wick onto the collection card (5 total spots will be collected on the card). The card may be stored at room temperature for up to one year before assay. Cards will be sent periodically during the study to the central laboratory (United States Drug Testing Laboratories, Des Plaines, IL) for analysis.

11.24. Pittsburg Sleep Quality Index (PSQI)

The PSQI is a 19-item questionnaire with 6 subscales (subjective sleep quality, sleep latency, sleep duration, habitual sleep disturbances, use of sleep medication and day time dysfunction) (Buysse et al-1989). Each subscale is rated from 0 to 3 with the higher scores reflecting more severe sleep complaints. The addition of all the scores permits an analysis of the subject's overall sleep experience in the past 30 days. The lower the overall score, the better the person sleeps. The tool has an adequate internal reliability, validity and consistency for clinical and community samples of the various populations. This questionnaire will be completed by the subject electronically and will be both the source and eCRF.

11.25. Procedures for Monitoring Subject Compliance

11.25.1. Drug Accountability/Compliance

Drug accountability will be performed by recording the number of tablets dispensed and the number of tablets returned at clinic visits. The amount dispensed, daily dose prescribed, and amount returned will be reconciled and recorded at each visit. The drug card will be reviewed for subject reported consumption of investigational product. If the subject reports missing tablets that were not taken, these data will also be recorded and used to calculate total drug exposure. If the investigational product bottle was not returned, then the subject's self-report of drug taken will be reported. If the study drug was discontinued, the reason for discontinuation will also be recorded.

11.25.2. Gabapentin Plasma Levels

Blood samples for determining plasma levels of gabapentin to assess for drug compliance and to perform population PK/PD analysis will be collected according to the schedule in Table 5. Blood will be collected in one 8 mL K_3EDTA tube and placed on ice. The tube will be centrifuged and plasma collected, aliquoted, and frozen at ≤ - 20°C until shipment to PPD laboratories for analysis. Gabapentin levels will be determined using a validated liquid chromatography–mass spectrometry/mass spectrometry (LC–MS/MS) method. The LC–MS/MS method was validated for gabapentin in plasma over the range 80-10,000 ng/mL. The lower limit of quantitation is 80 ng/mL. The details for collection, centrifugation, aliquoting, storage and shipment of samples to the central laboratory are provided in the Manual of Procedures. If a subject has discontinued

investigational product for at least two days, then blood for PK determination does not need to be collected.

11.26. Profile of Mood State (POMS)

The POMS measures dimensions of affect or mood (McNair and Heuchert-2005). It consists of 65 adjectives to which the subject responds according to a 5-point scale ranging from "not at all" to "extremely." Six subscale scores will be computed for items grouped as follows: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion=Bewilderment. A total mood disturbance score will also be computed which consists of the sum of the 5 of the six subscale scores (the Vigor-Activity score is not included). This questionnaire will be completed by the subject electronically and will be both the source and eCRF.

11.27. Pregnancy Test and Birth Control Record

An FDA approved rapid result urine pregnancy test will be used (i.e., dipstick test), unless the site IRB requires a blood-based assay. If applicable, subjects will be asked to sign a release of information form for study personnel to access medical records to obtain information regarding the outcome of a pregnancy that occurred during the study.

The Birth Control Assessment is designed to determine a female subject's compliance with the birth control specifications detailed in the inclusion criteria.

11.28. Prior and Concomitant Medications

All medications taken by the subject 2-months prior to the start of screening, during the screening period, and through the final follow-up contact will be recorded. All medications reported by the subject will be recorded on a source document and eCRF.

11.29. Physical Examination

A physical examination of the oral cavity, head, eyes, ears, nose, and throat, cardiovascular system, lungs, abdomen, extremities, skin, neuropsychiatric mental status and sensory/motor status, musculoskeletal system and general appearance will be performed during screening. The physical exam will be updated on the day planned for randomization by querying the subject about any physical changes since the screening examination. Weight (kg) will be collected per the schedule in Table 5. A symptom directed physical examination will be performed, as applicable, at other visits if the subject reports any problems. Abnormal findings will be reported as AEs, if appropriate.

11.30. Screen Failures Documentation

To document the reason that a subject who consented to the study was not randomized, the Enrollment and Eligibility Checklist eCRFs will be completed for these subjects.

11.31. Subject Disposition

A subject disposition eCRF will be completed for all subjects who are randomized to the study and who are dispensed investigational product. This eCRF will be used to record the following

data as applicable: 1) completion status of the subject at the end of their participation and if they were discontinued early, and reason for early discontinuation.

Completion status is as follows:

1. Subject completed full study (i.e., telephone contact was made at the Weeks 28 to 29 follow-up).
2. Subject completed the full intervention phase of the study (i.e., subject came to Week 27 clinic visit).
3. Subject was withdrawn prior to the Week 27 visit (reasons for early withdrawal are to be specified).
4. If the subject discontinued study medications.

Even if the subject had investigational product suspended for any reason but attended clinic visits, the above definitions still apply.

In addition, if the subject was confined and/or incarcerated at any time during the study, the dates of confinement and/or incarceration will be collected.

11.32. Drinking Goal

The Thoughts About Abstinence Scale developed by Marlatt et al (1988) for smoking was adapted for drinking and items for a drinking goal, and confidence and motivation to meet the selected goal have been included. The resultant assessment, named Drinking Goal, is a 3-item questionnaire completed by the subject and will be both the source and eCRF.

11.33. TLFB Interview

Drinking behavior will be assessed using the TLFB methodology (Sobell & Sobell-1992). The TLFB is a semi-structured interview that provides estimates of the daily quantity of alcohol consumption during specified time periods. It uses a calendar prompt and a number of other memory aids (e.g., holidays, payday, and other personally relevant dates) to facilitate accurate recall of drinking or other drug use during the target period. The procedure has been widely used in clinical and research contexts. It has demonstrated adequate levels of reliability and validity when administered as an in-person interview, over the telephone, and when administered via computer (Carey-1997, Sobell et al-1988, Sobell et al-1996). After consent is signed, the TLFB interview will be performed for the 28-day period prior to signing consent. Thereafter, the interview will be for the previous days between the last assessment and the day prior to the day of the assessment. It is estimated that a 28-day TLFB assessment will take 20 minutes to complete. In the event of missed visits, collection of missed drinking data at the following visit is required.

If a subject requests to withdraw from the study but agrees to continued telephone contact to assess drinking, the TLFB will be performed over the phone for the duration of the study at a frequency acceptable to the study subject and site staff.

An Excel spreadsheet customized for use in this study will be used for double data entry by clinical site staff to collect the TLFB drinking data. This spreadsheet contains a calculator to

determine standard drink units (SDUs). This spreadsheet will be reviewed, compared with source documents and collected by study monitors for upload into the main study database.

Drinking days are defined as the number of days in which the subject reported any alcohol consumption (i.e., > 0 standard drinking units [SDUs]). A standard drink contains approximately 0.6 fluid ounces (oz) of pure alcohol. The data given by the subjects on amount and type of alcoholic beverage(s) consumed will be converted to SDUs. Standard drink unit definitions are provided in Table 8.

Table 8: Standard Drink Unit Definitions

For Beer (~ 5% alcohol), the approximate number of SDUs in: • 12 oz = 1.0 • 16 oz = 1.3 • 22 oz = 2.0 • 40 oz = 3.3 For malt liquor (~ 7% alcohol), the approximate number of SDUs in**:** • 12 oz = 1.4 • 16 oz = 1.9 • 22 oz = 2.6 • 40 oz = 4.7
For table wine (~ 12% alcohol), the approximate number of SDUs in: • 750 mL bottle = 25oz = 5.0 • 5 oz glass = 1.0 • 10 oz glass = 2.0
For 80 proof spirits (~ 40% alcohol), or hard liquor, the approximate number of SDUs in: • 1.5 oz (mixed drink) = 1.0 • 16 oz (pint) = 11.0 • 25 oz (a fifth) = 17.0 • 1.75 L (59 oz) = 39.0

11.34. World Health Organization Drinking Risk Categorical Scale

The WHO has developed a drinking risk categorical scale that can be used in a responder analysis approach to assess clinically relevant decreases in alcohol consumption (Aubin et al-2015). Two dichotomous endpoints will be analyzed: WHO 1-level and WHO 2-level decrease in alcohol consumption. The WHO 1- and 2-level decrease endpoints are the percentage of subjects experiencing at least 1- and 2-level decrease in WHO levels of alcohol consumption, respectively, from the level at baseline (the period including the 28 days before screening) to the level during the last 4 weeks of the maintenance phase (Study Weeks 22-25).

The WHO levels of average alcohol consumption per day are as follows:

	Males	**Females**
Low Risk	1 to 40g	1 to 20g
Medium Risk	41 to 60g	21 to 40g
High Risk	61 to 100g	41 to 60g
Very High Risk	101+g	61+g

where 14g = 1 SDU (WHO-2000). In computing the WHO alcohol consumption level, average drinks per day will be used, computed as the sum of all drinks in the 28 day period divided by the number of days with non-missing drinking data in that period. Abstinent subjects will be included in a separate "Abstinent" category. A subject must have at least 1 week of data during the last 4 weeks of the maintenance phase to be considered non-missing.

11.35. Urine Drug Screen

An FDA cleared, CLIA waived urine drug test card will be used to assess candidates for recent use of opioids, cocaine, amphetamines, methamphetamine, THC, buprenorphine, methadone or benzodiazepines. During screening subjects must be negative for all substances except THC and in special cases opioids. If positive for opioids but recent opiate use for acute pain is reported by the subject, then the subject can be re-screened. If positive for these drugs at other times during the study, the subject will not be removed from the study but should be asked about medication use and possibly re-evaluate their medical history for substance abuse.

11.36. Vital Signs

Vital signs to be assessed include sitting blood pressure and pulse rate (after sitting for at least 3 minutes).

12. Statistical Methods and Determination of Sample Size

12.1. Statistical and Analytical Plans

Complete details of the statistical analyses to be performed will be documented in a SAP, which will be completed prior to locking and unblinding the study data. This document will include more detail of analysis populations, summary strategies, and any amendments to the proposed analyses listed here, if necessary. Any changes to the SAP will be outlined in the final study report.

12.2. Statistical Hypotheses

Primary Efficacy Endpoint: It is hypothesized that HORIZANT Extended-Release Tablets, as compared to placebo will increase the PSNHDD during Study Weeks 22 to 25 (last 4 weeks of the maintenance period (where a heavy drinking day is defined as 5 or more drinks per drinking day for men, 4 or more drinks per drinking day for women). This hypothesis will be explored using other time periods in exploratory analyses.

Secondary Efficacy Endpoints:

Over the last 4 weeks of the maintenance period, it is hypothesized that the HORIZANT Extended-Release Tablets group, as compared to the placebo group, will:

1. Increase the percentage of subjects abstinent from alcohol (key secondary endpoint)
2. Increase the percentage of subjects with a WHO drinking risk category decrease of:
    a. 1-level
    b. 2-levels
3. Increase the percentage of days abstinent per week
4. Decrease the percentage of heavy drinking days per week
5. Decease the weekly mean number of drinks per week
6. Decrease the weekly mean drinks per drinking day
7. Decrease the cigarettes smoked per week among smokers
8. Decrease the alcohol craving score (ACQ-SR-R) per visit
9. Decrease the alcohol related consequences (ImBIBe) score per visit
10. Decrease PSQI score
11. Decrease the BAI score
12. Decrease the BDI-II score

12.3. Analysis Populations

The study analysis populations will consist of the following:

Modified Intention-to-Treat (mITT) Analysis Set: The mITT set is defined as subjects randomized to participate in the study who took at least one dose of investigational product.

Evaluable Analysis Set: The evaluable analysis set is defined as those subjects randomized to the study who took at least 80% of the prescribed dose of tablets during the maintenance period (Weeks 2 - 25) and did not have a major protocol violation.

The primary and secondary efficacy endpoints will be analyzed on both the mITT and evaluable analysis sets. Exploratory analyses will be performed on the mITT analysis set, unless otherwise specified. Safety analyses will be conducted on the mITT analysis set.

12.4. Description of Statistical Methods

12.4.1. General Approach

For descriptive purposes, dichotomous and categorical variables will be presented as number of observations and percentages; continuous variables will be given as means, standard deviations (SD), median, minimum (min) and maximum (max). Statistical tests will be two-tailed at a 0.05 Type I error rate. P-values for the primary and secondary endpoints of < 0.05 will be considered statistically significant. Covariates will be pre-specified in the SAP. Endpoint data will also be screened for outliers and skewness. Appropriate non-parametric tests will be used to compare treatment groups on continuous baseline characteristics that are not normally distributed. Continuous endpoint data that are not normally distributed will be transformed. Cohen's d will be used to calculate the effect size for means and Cohen's h will be used to calculate the effect size for proportions. Odds ratios will be provided for all dichotomous outcomes and converted to Cohen's d where appropriate. Descriptive statistics – mean, SD, median, min and max – of all endpoint data will be provided for each assessment point or summarized at each week for drinking endpoints. All data will be presented in listings.

12.4.2. Analysis Addressing the Primary Efficacy Endpoint

The primary analysis will be conducted via a fully covaried logistic regression analysis of the PSNHDD during Study Weeks 22 to 25 (last 4 weeks of the maintenance period on the mITT population). The model includes treatment group, clinical site, pre-randomization drinking goal (abstinence versus not abstinent), and baseline percent heavy drinking days (in the 28-day period prior to the date that the subject signed the informed consent form). Exploratory analyses will examine other timeframes beyond the last 4 weeks. A two-tailed p-value < 0.05 will be considered statistically significant. The primary analysis will use all mITT subjects and will employ imputation for missing drinking data such that any subject with any missing drinking data during the evaluation period for this endpoint will be imputed as a subject with a heavy drinking day.

Prior to the subject dropping out of the study, every attempt will be made to continue to collect TLFB data; however, if the subject does not want to participate in the collection of the TLFB they will be asked to participate in a periodic follow-up phone call to collect a summary of drinking information. If the subject agrees to be contacted then they will be asked about any drinking and heavy drinking during the time since last contact. Phone calls will continue until the end of the treatment period, as deemed acceptable by the patient. The two questions cover whether the subject had any heavy drinking days or drinking days during the period covered. This summary drinking data will be used for the primary endpoint when TLFB data are not available. If the subject does not agree to participate with phone contact, thus no summary drinking data nor TLFB data is available, then imputation as indicated above will be used. An

analysis of PSNHDD without imputation for missing data will be performed as an exploratory analysis.

12.4.3. Secondary Efficacy Endpoints Analysis

12.4.3.1. Key Secondary Endpoint: Percentage of Subjects Abstinent from Alcohol

Percentage of subjects abstinent during Weeks 22 to 25 is the key secondary endpoint. Covariates for percentage of subjects abstinent will be the same as those for the primary endpoint PSNHDD as described in Section 9.4.2. Fewer covariates for the logistic regression may be used depending upon the number of events. If the number of events permits the inclusion of a baseline drinking covariate, the percentage of days abstinent will be used as the covariate for the percent subjects abstinent endpoint. The testing procedure utilizes the serial gate keeping methodology (Dmitrienko and Tamhane-2009). The key secondary endpoint can only be evaluated for statistical significance after the primary endpoint has been identified as statistically significant. In this situation, percentage of subjects abstinent will be evaluated using the Wald statistic from the logistic regression model at $p<0.05$ after PSNHDD is found to have $p<0.05$. If PSNHDD is not statistically significant at the 0.05 level then no significance testing of percentage of subjects abstinent will be performed. This analysis will be performed on mITT subjects with no imputation for missing data. However, if drinking data are missing by TLFB, but the subject reports any drinking during Weeks 22 to 25 using the Drinking Question eCRF, then the subject will be considered not abstinent. An analysis of percent subjects abstinent without imputation for missing data will be performed as an exploratory analysis.

12.4.3.2. Supportive Secondary Efficacy Endpoints

Supportive secondary efficacy endpoints will also be analyzed based on data during the last 4 weeks of the maintenance period (Weeks 22 through 25), including TLFB and other questionnaire data assessed at Week 26 that reflect data collected during this period. No imputation will be done on any supportive secondary efficacy endpoint.

In general, every continuous secondary efficacy endpoint is analyzed using a repeated measures mixed effects model where subjects are random effects; factors and covariates are fixed effects.

The primary analysis model for all continuous endpoint is:

- Appropriately transformed endpoint = treatment + week + treatment*week + clinical site + baseline equivalent of endpoint + covariates

Covariates for continuous secondary efficacy endpoints include the baseline equivalent of the endpoint, clinical site, treatment, time and the treatment by time interaction. Additional covariates for the secondary efficacy endpoints may include baseline characteristics with a theoretical and/or empirical basis for a relationship with a particular secondary endpoint.

Such characteristics may include, but are not limited to, drinking goal (total abstinence versus less than total abstinence), age, years of regular drinking (age minus age first started drinking alcohol regularly), baseline alcohol craving scale total score. Prior to the unblinding of the data, matrices of correlations between these baseline characteristics and each of the secondary efficacy endpoints, pooled across blinded treatment assignment, will be produced (using Pearson for continuous variables, Spearman for categorical outcomes). Selection of baseline variables to

include as covariates in the models will be based on consideration of the following criteria: at least modest correlation with outcome (i.e., $r \geq 0.20$), and clinical expertise. Each endpoint may have a unique set of covariates. Care is taken to only select a limited number of covariates such that the models are not over fitted.

This primary model will also be applied to the untransformed endpoint.

Results based on the primary analysis model and the model of the untransformed endpoint will be presented in tabular form. The overall least squares means and least square means for each time point along with the 95% confidence intervals will be presented for the untransformed endpoint only, while two-tailed p-values and Cohen's d will be presented for both the untransformed and transformed data. Inference and Cohen's d will be based upon the results using appropriately transformed data.

Analysis of the dichotomous secondary drinking endpoints, percent subjects with a WHO 1- and 2-level decrease in alcohol consumption (Aubin et al-2015), will be conducted via a fully covaried logistic regression model and contingency table. Covariates for the logistic regression model will be selected using a similar approach as that used for the primary endpoint PSNHDD as described in Section 9.4.2. Fewer covariates for the logistic regression may be used depending upon the number of observed events. No baseline drinking covariate will be employed for the endpoints, as these endpoints already adjust for baseline drinking in their calculation.

Covariates for both of these endpoints will be pre-specified in the SAP.

Analyses of supportive secondary endpoints with imputation for missing data will be performed as exploratory analyses.

12.4.4. Safety Analyses

AEs will be coded using the most recent version of the MedDRA and will be grouped by SOC and PT designation. The severity, frequency, and relationship of AEs to investigational product will be presented by SOC and PT groupings. Listings of each individual AE including start date, stop date, severity, relationship, outcome, and duration will be provided. Each AE (based on PT) will be counted once only for a given study subject. If the same AE occurred on multiple occasions, the highest severity will be assumed. Thus, study subjects are not counted multiple times in a given numerator in the calculation of frequencies for a specific AE. C-SSRS reports of suicidality or suicidal ideation will be reported as AEs and analyzed as AEs if the investigator determines after an interview with the subject that the responses are consistent with suicidal ideation or attempt.

Chemistry data, urine drug screen results, pregnancy test results, and alcohol breathalyzer results, will be reported as summary statistics. Vital signs will be presented as summary statistics and change from baseline. The proportions of ECG results considered abnormal and clinically significant will also be provided. CIWA-AR scores will be analyzed similar to the efficacy endpoints: mixed effects models with and without baseline characteristics. In addition, change from baseline (shift tables) will also be presented for clinical laboratory data. The numbers and proportion of subjects who reported CIWA-AR scores ≥ 10 at any time after the start of dosing will be presented.

12.4.5. Compliance and Retention Analyses

Medication compliance, defined as the amount of investigational product taken as a proportion of the total amount prescribed per protocol, will be evaluated for the HORIZANT Extended-Release Tablets and placebo groups. Self-reported compliance with HORIZANT Extended-Release Tablets will be compared against plasma samples having detectable levels of gabapentin. Average amounts of investigational product taken will be reported for the HORIZANT Extended-Release Tablets and placebo groups. The research participation rate, defined as percentage of subjects with complete drinking data, will be compared between treatment groups. Average amounts of investigational product taken will be reported on a weekly basis and across the entire trial duration. In addition, the percentage of subjects discontinuing medication and a listing of the reasons for discontinuation will be provided. Weekly days of attendance at self-help meetings or other professional service providers to help reduce/quit drinking will be presented as summary statistics by treatment group.

12.4.6. PK Analysis

Plasma levels of gabapentin will be presented as descriptive statistics including mean, SD, coefficient of variation, geometric mean, minimum and maximum levels and mean ± SD will be presented graphically over time. Population PK analyses will be conducted in accordance with a separate PK/PD SAP.

12.4.7. Baseline Descriptive Statistics

Summaries of the characteristics of the subjects in each of the study groups at baseline will be prepared for the mITT, safety, and evaluable analysis sets. Baseline characteristics will be compared between the HORIZANT Extended-Release Tablets and placebo groups using appropriate statistical methods. A summary will be prepared to show dropouts/retention over time in each group, along with the reason for early termination. The number of missing observations will be presented between groups.

12.4.8. Exploratory Analyses

Exploratory analyses of the continuous secondary drinking endpoints, and the WHO 1- and 2-risk level decrease in alcohol consumption endpoints, will employ a multiple imputation method for handling missing weekly drinking data for the mITT population (Hopke et al-2001, Rubin-1976, Rubin-1996, Schafer-1997). Multiple imputation replaces each missing value with a set of "m" plausible values that represent the uncertainty about the right value to impute. The imputation model will include a limited set of variables likely to be associated with missingness on the primary endpoint, excluding treatment assignment. The variables may include but are not limited to site, time and baseline alcohol use. Specification of the variables used in the multiple imputation models will be provided in the SAP.

Analysis of abstinence from alcohol will not employ imputation for missing drinking data.

The percentage of subjects abstinent from smoking will be analyzed only among subjects who smoked at baseline. Analysis will include two treatment time periods of interest: during the last 4 weeks of the maintenance period and over the entire maintenance period. All analyses of this endpoint will be conducted on both a nonimputed and imputed endpoint using the same modeling methods as other dichotomous secondary endpoints. Imputation will proceed such that

any subject with any missing cigarettes per week data during the evaluation periods for this endpoint will be imputed as a smoker.

Blood PEth levels at Week 26 will be compared between treatment groups using analysis of covariance with treatment group, clinical site, and baseline blood PEth level. The proportion of positive samples [a test result > 8 ng/mL - the lower limit of quantitation (LLOQ) of the test] at Week 26 data will be modeled using logistic regression with treatment group, clinical site, and baseline level as covariates provided there are sufficient observed events.

The MINI AUD number of symptoms (identifiers) at Week 26 (covering the last 4 weeks of the maintenance period) will be compared between the treatment groups using analysis of covariance.

Primary and secondary efficacy endpoints will be compared between treatment groups over the entire maintenance period using the same analytic methods described above for these endpoints; in addition, these endpoints will be analyzed with and without imputation. The PSNHDD, percent subjects abstinent from alcohol, and the WHO 1- and 2- risk level decrease endpoints will be analyzed on a weekly and monthly basis; and cumulatively over Weeks 18-25 (last 8 weeks), Weeks 14-25 (last 12 weeks), and over Weeks 10-25 (last 16 weeks).

A number of variables will be tested as potential moderators of the medication treatment effect on the imputed PSNHDD endpoint over the last 4 weeks of the maintenance period (primary endpoint). The potential moderator variables that will be examined include measures suggestive of alcohol withdrawal (i.e., withdrawal question on the MINI for alcohol use disorder, BAI, BDI-II, PSQI total score, POMS total and subscales, ACQ-SR-R total score, and number of days abstinent prior to randomization), severity of alcohol use disorder (i.e., drinks per week [28 days prescreen], years of regular drinking), reducer status (change in baseline drinks per day), alcohol-related treatment goal (total abstinence vs. less than total abstinence), BIS score, and baseline smoking status.

12.4.9. Adjustment for Covariates

Covariates used in logistic regression and mixed effects models are described in section 12.4.2 and 12.4.3.

12.4.10. Interim Analyses and Data Monitoring

No interim analyses are planned for this study.

12.4.11. Multiple Comparison/Multiplicity

The primary endpoint and key secondary endpoint use the serial gate keeping methodology (Dmitrienko and Tamhane 2009) to maintain a family-wise Type I error of 0.05. This process requires an ordering of the hypotheses; namely, that the primary hypothesis for PSNHDD is evaluated first, followed conditionally by the key secondary hypothesis for percentage of subjects abstinent. This procedure requires that the primary hypothesis be rejected at $p<0.05$ then the hypothesis for the key secondary endpoint may be evaluated. If the primary hypothesis is not rejected then there is no test for the key secondary hypothesis. The serial gate keeping methodology indicates that if the primary hypothesis is rejected then the entire alpha (0.05, two-

sided) is available for the key secondary hypothesis. As such, the key secondary endpoint of percentage of subjects abstinent is evaluated at $p<0.05$ (two-sided) for statistical significance.

12.4.12. Tabulation of Individual Response Data

Individual subject data will be listed by measure and time point.

12.5. Determination of Sample Size

The sample size was based on a conservative approach to the results of the randomized, placebo-controlled trial reported by Mason et al (2014). Mason et al (2014) found an effect size for PSNHDD of odds ratio = 2.8 (Cohen's h = 0.48). However, this study was a single site trial and single site trials are known to have greater effect sizes than multi-site trials (Feinn and Kranzler-2005). Taking a conservative approach, we assumed a smaller effect size for the current multi-site trial, an odds ratio = 2.5; (Cohen's h=.34, that occurs given a placebo PSNHDD during Study Weeks 22-25 of 13% and an active study drug PSNHDD of 27%). To achieve 91% power for this trial, given a two-tailed alpha of 0.05, then a sample size of 173 per group (346 total) is needed (Fleiss et al-2003). The estimates of 13% and 27% for placebo and gabapentin, respectively, assumes 15% of the randomized subjects in each treatment group will dropout prior to or during the last 4 weeks of the Maintenance Period, and consequently, these dropouts will be imputed as subjects with heavy drinking days (i.e., treatment failures).

13. Quality Control and Quality Assurance

This study will be conducted under International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines and all applicable regulatory requirements.

Actions to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers; the review of protocol procedures with the investigator and study personnel prior to study start; the design of suitable source documents with appropriate instructions for use; the internal audit of source data according to GCP and internal procedures to ensure their accuracy, completeness, and verifiability; as well as the periodic site monitoring by the Sponsor's representatives (clinical monitors of Fast-Track Drugs & Biologics, LLC). Written instructions will be provided for collection, preparation, and shipment of blood and plasma samples. Clinical monitors will review source documents and eCRFs for accuracy and completeness during on-site monitoring visits; any discrepancies will be resolved with the investigator, as appropriate.

Significant and/or repeated noncompliance will be investigated and remedial action instituted when appropriate. Failure to comply with remedial actions may result in study site termination and regulatory authority notification.

13.1. Study Monitoring

Study monitoring will be the responsibility of designated clinical monitors of Fast-Track. Monitors will assure compliance with the clinical protocol and ICH GCPs, human subject's protection, drug accountability, maintenance of the site regulatory file, and conformance of eCRF data with source documents. Monitoring visits by clinical monitors will be scheduled to take place at the initiation of the study, during the study at appropriate intervals, and after the last subject has completed the study. A report of monitoring observations will be provided to the PI (for corrective actions) and the Sponsor.

13.2. Audits and Inspections

Authorized representatives of the Sponsor, the FDA, and the IRB may visit the site to perform audits or inspections, including source data verification. The purpose of the audit or inspection is to systematically and independently examine all study related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines, and any applicable regulatory requirements.

The PI should contact the Sponsor's representative and Fast-Track if contacted by a regulatory agency about an inspection.

14. Ethics

14.1. Ethics Review

The study will be conducted under a protocol reviewed by the local site's IRB; the study is to be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the study will ensure that the hazards do not outweigh the potential benefits; the results to be reported will be accurate; subjects will give their informed consent and will be competent to do so and not under duress; and all study staff will comply with the ethical principles in 21 Code of Federal Regulations (CFR) Part 50 and the Belmont Principles.

14.1.1. Review/Approval of Study Protocol

The study may not begin until the IND has been submitted to the FDA and the 30-day waiting period has expired without notification by FDA to the Sponsor of any clinical hold issues. NIAAA will be the study Sponsor. The site must obtain written approval from the appropriate IRB to conduct the study before study initiation. NIAAA will issue a formal authorization letter for the study to be initiated at the site. Progress reports will be submitted to the IRB by the Investigator at the frequency requested by the site's IRB.

14.1.2. Protocol Modifications

All necessary protocol changes will be submitted in writing as protocol amendments to the IRB by the site PI for approval prior to implementation. NIAAA will submit all protocol amendments to the FDA.

14.1.3. Protocol Deviation Reporting Procedures

All subject-specific deviations from the protocol are to be documented. The PI or designee will be responsible for identifying and reporting all deviations, which are occurrences involving a procedure that did not follow the study protocol. Any protocol deviation that adversely affects the safety or rights of a subject or scientific integrity of the study is considered a major deviation and will be reported immediately to the NIAAA Project Manager and the local site's IRB.

14.2. Ethical Conduct of the Study

This study will be conducted in accordance with all applicable Federal human research protections requirements and the Belmont Principles of respect for persons, beneficence, and justice.

The procedures set out in this study are designed to ensure that the sponsor's representative and all study personnel abide by the principles of the ICH GCP Guideline and the Code of Federal Regulations (CFR). The PI confirms this by signing this study protocol and Form FDA 1572.

14.2.1. Confidentiality

14.2.1.1. Confidentiality of Data

Particular attention is drawn to the regulations promulgated by the FDA under the Freedom of Information Act providing, in part, that proprietary information furnished to clinical investigators and IRBs will be kept confidential by the FDA only if maintained in confidence by the clinical investigator and IRB.

By signing this protocol the investigator affirms to NIAAA that information furnished to the investigator by NIAAA will be maintained in confidence and such information will be divulged to the IRB or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

14.2.1.2. Confidentiality of Subject Records

To maintain subject confidentiality, all laboratory specimens, eCRFs, reports and other records will be identified by a subject number only. Research and clinical records will be stored in a locked cabinet. Only research staff, NIAAA program officials, Fast-Track Drugs & Biologics clinical monitors, and XenoPort representatives will have access to the records. Subject information will not be released without written permission, except as necessary for monitoring by representatives of NIAAA. Upon approval of the study by an IRB, an application will be filed with NIAAA for a Certificate of Confidentiality. The use and procedure for applying for a Certificate of Confidentiality are provided in Appendix 19.4.

By signing the protocol the investigator agrees that within local regulatory restrictions and ethical considerations, NIAAA or any regulatory agency may consult and/or copy study documents in order to verify eCRF data.

14.2.2. Compensation for Participation

Subjects will be compensated for travel expenses and for time contributed to this research study in the form of cash or vouchers. Compensation will be provided in increasing amounts with each subject visit and is detailed in the informed consent form.

14.2.3. Written Informed Consent

The informed consent process and document will be reviewed and approved by the IRB and sponsor's representative prior to initiation of the study. The consent document contains a full explanation of the possible risks, advantages, and alternate treatment options, and availability of treatment in the case of injury, in accordance with 21 CFR Part 50. The consent document indicates that by signature, the subject, permits access to relevant medical records by the sponsor's representative and by representatives of the FDA. The sponsor's representative will submit a copy of the initial IRB- and sponsor's representative-approved consent form to the FDA and will maintain copies of revised consent documents that have been reviewed and approved by the site's IRB.

A written informed consent document, in compliance with 21 CFR Part 50, 32 CFR Part 219, and the Belmont Principles, and HIPAA Authorization will be signed by the subject before any study-related procedures are initiated for each subject.

All potential subjects for the study will be given a current copy of the Informed Consent Form to read. All aspects of the study and informed consent will be explained in lay language to the subject by either the investigator, or a medically trained designee. Any subject who is unable to demonstrate understanding of the information contained in the informed consent will be excluded from study participation.

All study subjects will be given a copy of the signed informed consent.

14.2.4. Delegation of Responsibilities and Adequate Resources

The PI should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study.

The term "investigator" used throughout this protocol refers to the PI and/or qualified subinvestigators. The PI may delegate responsibilities to other study site personnel. The PI shall delegate tasks only to individuals qualified by education, training, and experience to perform the delegated tasks. The PI shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The PI is responsible for ensuring all delegated staff has been properly trained on the protocol and their assigned study responsibilities. A delegation log identifying all delegated duties and the individual to whom they have been delegated will be maintained at the study site.

14.2.5. Financial Disclosure

Clinical investigators are required to provide financial disclosure information for the submission of certification or disclosure statements required under 21 CFR § 54. As defined in 21 CFR § 54.2, a clinical investigator is a listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects. The term also includes the spouse and each dependent child of the investigator. In addition, investigators must promptly update financial disclosure information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

15. Data Handling and Record Keeping

Source documents include but are not limited to original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, laboratory results, data recorded in automated instruments, and pharmacy records, etc. This study will use an electronic data management system (EDMS) (Merge eClinicalOS) and eCRFs. Data will be transcribed from source documentation into web-based eCRFs. Only questionnaire data will be entered directly into eCRF (i.e., without prior written or electronic record of data). Paper copies of the eCRFs will be provided in the event that the site cannot access the EDMS at the time the questionnaire is being completed. The transcribed data will be consistent with the source documents or the discrepancies will be explained.

Clinical monitors will review all source records and compare them to the data entered into the eCRF. All entries, corrections, and alterations will be made by the investigator or other authorized study personnel. Any errors identified during monitoring will have a query posted by monitor for site staff to address. The EDMS system maintains a full audit trail of data entry, data corrections, and data queries.

15.1. Subject Identification and Confidentiality

Subjects will be identified on eCRFs by a unique subject number. No personal identifier will be used in any publication or communication used to support this research study. The subject number will be used if it becomes necessary to identify data specific to a single subject. The Sponsor's representative and designated clinical monitors of Fast-Track, the IRB, and the FDA are eligible to review medical and research records related to this study as a part of their responsibility to protect human subjects in clinical research. Personal identifiers will be removed from photocopied or electronic medical and research records.

15.2. Inspection of Records

The sponsor's representative or designee will be allowed to visit the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, investigational product stocks, drug accountability records, subject charts, study source documents, and other records relative to study conduct.

Subjects' health information is used to report results of research to the sponsor's representative and Federal regulators and may be reviewed during study audits for compliance with study plans, regulations, and research policies. The consent document indicates that by signature, the subject permits access to relevant medical records by the sponsor's representative, XenoPort representatives, and by representatives of the FDA.

Upon a subject's termination from the trial, completed eCRFs will be ready and available for on-site review by the sponsor's representative at scheduled monitoring visits.

15.3. Retention of Records

The investigator is responsible for creating and/or maintaining all study documentation required by Title 21 Code of Federal Regulations (21CFR) Parts 50, 54, 56, and 312, ICH E6 section 8, as well as any other documentation defined in the protocol. The investigator must provide key

documents to the Sponsor prior to start of the study. A complete list of required regulatory documents will be provided in the study Manual of Procedures.

Federal and local regulations require that the investigator retain a copy of all regulatory documents and records that support the data for this study for whichever of the following is the longest period of time:

- A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study drug for the purposes that were the subject of the investigation; or
- A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of, an application for a research or marketing permit for the study drug for the purposes that were the subject of the investigation.

The Sponsor will notify investigators once one of the above 2 timeframes has been satisfied.

If the investigation does not result in the submission of the data in support of, or as part of, an application for a research or marketing permit, records must be retained for a period of 2 years following notification by the Sponsor that the entire clinical investigation (not merely the investigator's portion) is completed, terminated, or discontinued or 2 years following withdrawal of the Investigational New Drug application/Clinical Trial Authorization or request for marketing approval (New Drug Application/Marketing Authorization Application).

If the investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consultation with the Sponsor.

15.4. Trial Registration

As the IND holder and Sponsor, NIAAA will register the trial on the National Library of Medicine's Clinical Trials Registry on the world wide web at http://www.clinicaltrials.gov.

16. Publication Policy

Review of manuscripts resulting from this study or from data generated during this study must occur according to the NIAAA Publications Policy prior to submission for publication. Authorship shall be consistent with NIAAA policies.

17. Protocol Signature Page

NIAAA REPRESENTATIVES

Typed Name	Signature	Date
Raye Z. Litten, Ph.D. NIAAA PI	_____	_____
Joanne Fertig, Ph.D. NIAAA Investigator	_____	_____
Daniel E. Falk, Ph.D. NIAAA Investigator	_____	_____
Megan Ryan, MBA, CCRP NIAAA Project Manager	_____	_____

MEDICAL MONITOR

Roberta Kahn, M.D.	_____	_____

INVESTIGATORS

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment with the IRB approval. I also agree to report all information or data in accordance with the protocol, and in particular I agree to report any serious adverse experiences as defined in section 11.2.7 of this protocol.

Typed Name	Signature	Date
_____	_____	_____
_____	_____	_____

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19. Appendices

19.1. Example Drug Card

ID Number:_____

Study Week (circle one): 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 24, 25, 26

First day tablets were taken:_____
mm/dd/yy

# of morning tablets to take:_____

# of evening tablets to take:_____

Record tablet/time taken each day below:

Day	# Tabs taken in morning	Time	# Tabs taken in evening	Time
1				
2				
3				
4				
5				
6				
7				

19.2. Medication Guide to Be Given to Subjects

19.3. Common Terminology Criteria for Adverse Events for Clinical Laboratory and Blood Pressure Elevation Adverse Events

The following are the toxicity grades for which grading criteria are provided by the CTCAE (Version 4.03) for chemistry tests performed in this study and for elevated blood pressure measurements.

Table 9: CTCAE Criteria for Clinical Laboratory and Blood Pressure Elevation Adverse Events

Analyte	Grade 1	Grade 2	Grade 3	Grade 4
Blood Chemistries				
ALT elevated	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
AST elevated	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Total bilirubin elevated (bilirubinemia)	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN
Gamma glutamyl transferase (GGT) elevated	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Creatinine elevated	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN
Hypertension	Pre-hypertension (systolic BP 120 - 139 mmHg or diastolic BP 80 - 89 mmHg)	Stage 1 hypertension (systolic BP 140 - 159 mmHg or diastolic BP 90 - 99 mmHg); medical intervention indicated; recurrent or persistent (24 hrs); symptomatic increase by >20 mmHg (diastolic) or to >140/90 mmHg if previously WNL; monotherapy indicated	Stage 2 hypertension (systolic BP≥160 mmHg or diastolic BP ≥100 mmHg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated

19.4. Certificate of Confidentiality

The only people who will know the identity of the subjects are members of the research team including authorized staff responsible for oversight of the study at the local IRB, authorized representatives of the FDA, and representatives of NIAAA including Fast-Track Drugs & Biologics, LLC, and NIAAA's collaborator, XenoPort Inc. No information about the subjects, or provided by the subjects during the research, will be disclosed to others without the subjects' written permission, except if necessary to protect subjects' rights or welfare.

When the results of the research are published or discussed in conferences, no information will be included that would reveal subjects' identity. Authorized representatives of the FDA, NIAAA, and XenoPort Inc. may need to review records of individual subjects periodically. As a result, they may know subjects' names, but they are bound by rules of confidentiality not to reveal their identity to others. The results of this study including laboratory results and clinical information collected during this study will be submitted to the FDA and may be used for research purposes. The results of this study may be published but will not personally identify any subjects. All records will be kept in locked storage locations that will be accessible only to authorized study personnel.

The clinical sites, XenoPort Inc., and Fast-Track Drugs & Biologics, LLC will apply for a Certificate of Confidentiality electronically through the following website:

https://www.nichd.nih.gov/health/clinicalresearch/cccert/default.aspx?ic=NIAAA

This Certificate of Confidentiality helps researchers protect the privacy of subjects in health research projects against compulsory legal demands (e.g., court orders and subpoenas) that seek the names or other identifying characteristics of research subjects. The certificate was developed to protect against the involuntary release of personally identified research information of a sensitive nature sought through any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. This authority was granted under the Comprehensive Drug Abuse Prevention and Control Act of 1970, Public Law No. 91-513, Section 3(a).

This certificate is necessary for investigators to avoid being required to involuntarily disclose personally identifiable research information about individual study subjects. Under this statute:

"The Secretary [of the Department of Health and Human Services] may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, and on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals" (Public Health Service Act 301 (d), 42 U. S. C. 241 (d), as amended by Public Law No. 100-607, Section 163 (November 4, 1988))."

Accordingly, this special privacy protection can be granted only to research (i.e., a systematic investigation, designed to develop or contribute to generalizable knowledge). It is granted only when the research is of a sensitive nature where the protection is judged necessary to achieve the research objectives.

The study subjects should be informed that a Certificate is in effect, and be given a fair and clear explanation of the protection it affords, including the limitations and exceptions. This information will be included in the informed consent. Please see below some suggested wording:

"If you decide to take part in this research study, you will be required to give us information about substance use. A Certificate of Confidentiality (CoC) issued by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) which is part of the National Institutes of Health (NIH). NIH is governed by a part of the federal government called the Department of Health and Human Services (DHHS) has been granted for this study. This Certificate, however, does not imply that the Secretary, DHHS, approves or disapproves of the project.

The CoC is issued to protect the investigators on this study from being forced to tell people that are not connected with this study about your participation in this study, even under a subpoena. This protection, however, is not absolute. The protection offered by the CoC does not stop us from voluntarily reporting information about suspected or known sexual, physical, or other abuse of a child or older person, or a subject's threats of violence to self or others.

If any member of the research team is given such information, he or she will make a report to the appropriate authorities. Individuals who participate as research subjects in the specified research project are protected permanently during any time the Certificate is in effect - even if the subject gave the researcher data before the Certificate is issued. Also, because this research is sponsored by NIAAA, staff from NIAAA and other DHHS agencies may review records that identify you but only for the purposes of audit for quality and accuracy or program evaluation.

Even when a CoC is in place, you must still continue to actively protect your own privacy. If you voluntarily give your written consent to anyone to receive information about your participation in the research or freely volunteer information to anyone other than the study staff that you are a research subject in this study, then we may not use the CoC to withhold this information."

Study subjects will be notified that a Certificate has expired if they are recruited to the study after the expiration date of the Certificate and an extension of the Certificate's coverage has not been granted.

If the research scope of a project covered by a Certificate should change substantially, the PI will request an amendment to the Certificate; however, the NIAAA Certificate Coordinator may require a new Certificate depending on the extent of the change in scope. An extension of coverage must be requested if the research extends beyond the expiration date of the original Certificate, as research information collected after the expiration of a Certificate is not protected from compelled release.

A Certificate of Confidentiality is a legal defense against a subpoena or court order, and is to be used by the researcher to resist disclosure. The researcher should seek legal counsel from his or her institution if legal action is brought to release personally identifying information protected by a certificate. The Office of General Counsel for DHHS is willing to discuss the regulations with the researcher's attorney.