ALTASCIENCES

A RANDOMIZED, DOUBLE-BLIND, ACTIVE- AND PLACEBO-CONTROLLED, 5-WAY CROSSOVER STUDY TO DETERMINE THE ABUSE POTENTIAL OF ORALLY ADMINISTERED GABAPENTIN ENACARBIL IMMEDIATE RELEASE CAPSULES IN HEALTHY, NONDEPENDENT, RECREATIONAL DRUG USERS WITH SEDATIVE EXPERIENCE

Protocol Number:	AR26.3031.1
Altasciences Project Number:	ABO-P1-904
Investigational Product:	Gabapentin Enacarbil Immediate Release Capsules
Phase of Development:	Not applicable
Sponsor:	Arbor Pharmaceuticals, LLC 6 Concourse Parkway, Suite 1800 Atlanta, GA 30328 USA

ClinicalTrials.gov: NCT06097676

COMPLIANCE

The study will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Council for Harmonisation and all applicable federal and local regulations.

Protocol Version		Date
3.0	**(Amendment 02)**	**09AUG2021**

PROTOCOL AMENDMENT 02 – SUMMARY OF CHANGES

Description of Change Made	Section/Location	Rationale
Added continuous monitoring of oxygen saturation from 1 hour before up to 6 hours after drug administration in the Qualification Phase.	Table 1 (Schedule of Activities)	Requested by the Institutional Review Board (IRB).

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STUDY SYNOPSIS

Name of Sponsor/Company:	Arbor Pharmaceuticals, LLC
Name of Product:	Gabapentin enacarbil immediate release capsules (GE-IR)
Title of Study:	A Randomized, Double-Blind, Active- and Placebo-Controlled, 5-Way Crossover Study to Determine the Abuse Potential of Orally Administered Gabapentin Enacarbil Immediate Release Capsules in Healthy, Nondependent, Recreational Drug Users with Sedative Experience
Study Development Phase:	Not applicable
Objectives:	**Primary Objective:** To evaluate the abuse potential of single oral doses of GE-IR relative to alprazolam and placebo, when administered to nondependent recreational drug users with sedative drug use experience. **Secondary Objectives:** To evaluate the pharmacokinetics (PK) of gabapentin from GE-IR when administered to nondependent, recreational drug users with sedative drug use experience. To evaluate the effects on safety and tolerability of single oral doses of GE-IR relative to alprazolam and placebo, when administered to nondependent, recreational drug users with sedative drug use experience.
Endpoints:	**Pharmacodynamic (PD) Endpoints:** The primary endpoint of this study will be maximum (peak) effect (E_{max}) over 24 hours for Drug Liking ("at this moment"), assessed on a bipolar (0 to 100 points) visual analog scale (VAS). Key Secondary PD endpoints will be: • Overall Drug Liking VAS (E_{max}) • Take Drug Again VAS (E_{max}) • High VAS (E_{max}) Non-Key Secondary PD endpoints will be: Balance of Effects • Drug Liking VAS (time of maximum effect [TE_{max}], minimum effect [E_{min}], time of minimum effect [TE_{min}], and time-averaged area under the effect-time curve [TA_AUE]) Positive Effects • High VAS (TE_{max}, and TA_AUE) • Good Effects VAS (E_{max}, TE_{max}, and TA_AUE) Negative Effects • Bad Effects VAS (E_{max}, TE_{max}, and TA_AUE)

	Other Subjective Effects • Any Effects VAS (E_{max}, TE_{max}, and TA_AUE) • Feeling Drunk VAS (E_{max}, TE_{max}, and TA_AUE) • Drowsiness/Alertness VAS (E_{min}, TE_{min}, and time-averaged area over the effect-time curve [TA_AOE]) • Relaxation/Agitation (E_{min}, TE_{min}, and TA_AOE) • Addiction Research Center Inventory (ARCI) Morphine-Benzedrine Group (MBG) Scale (E_{max}, TE_{max}, and TA_AUE) • ARCI Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) Scale (E_{max}, TE_{max}, and TA_AUE) Observer Assessments • Modified Observer's Assessment of Alertness/Sedation (MOAA/S) (E_{min}, CFB_{min}, and TA_AOE) **Pharmacokinetic Endpoints:** Pharmacokinetic parameters of GE-IR include maximum observed concentration (C_{max}), time of maximum observed concentration (T_{max}), time of last measurable observed concentration (T_{last}), and area under the curve from time 0 to the last measurable observed concentration (AUC_{0-T}). **Safety Endpoints:** Endpoints will include a summary of the incidence of adverse events (AEs), serious adverse events (SAEs), as well as descriptive summary and statistics of the safety parameters. Safety parameters will include clinical laboratory values, vital signs (i.e., systolic and diastolic blood pressure, pulse rate, respiratory rate, oral temperature, oxygen saturation [SpO_2]), continuous SpO_2 monitoring, continuous End Tidal CO_2 monitoring, electrocardiograms (ECGs), Columbia Suicide Severity Rating Scale (C-SSRS), and physical examination findings.
Study Product, Dose, and Mode of Administration (proposed):	**Gabapentin Enacarbil Immediate Release (GE-IR) Capsules** Manufacturer: Arbor Pharmaceuticals, LLC Mode of administration: Doses of GE-IR capsules including 200 mg (1 × 200 mg capsule), 450 mg (2 × 225 mg capsules) and 700 mg (3 × 233.3 mg capsules) will be administered orally according to the randomization schedule during the Treatment phase.
Active Control, Dose, and Mode of Administration:	**Over-encapsulated Xanax (alprazolam) 1 mg tablets** Manufacturer: Pfizer, Inc. Mode of administration: Single doses of 2 mg alprazolam (2 × 1 mg tablets over-encapsulated in one Swedish Orange Opaque AAEL-DB capsule) will be administered orally according to the randomization schedule during the Qualification and Treatment phases.
Placebo, Dose, and Mode of Administration:	**Placebo-to-match GE-IR capsules** Manufacturer: Arbor Pharmaceuticals, LLC Mode of administration: Single doses of placebo-to-match GE-IR (233.3 mg

	over-encapsulated placebo) capsule in one Swedish Orange Opaque AAEL-DB capsule) capsule(s) will be administered orally according to the randomization schedule during the Treatment phase. **Over-encapsulated placebo-to-match alprazolam** Mode of administration: Single doses of placebo-to-match alprazolam (2 × over-encapsulated placebo tablets in one Swedish Orange Opaque AAEL-DB capsule) will be administered orally according to the randomization schedule during the Qualification and Treatment phases.
Study Design:	This study will be a randomized, double-blind, active- and placebo-controlled, 5-way crossover study to determine the abuse potential of GE-IR relative to alprazolam and placebo, in nondependent, recreational drug users with sedative drug use experience. This study will consist of 3 phases: screening, qualification and treatment.
Duration of Treatment and Subject Confinement:	Duration of clinical trial (per subject): Screening: Day -30 to Day -2 Qualification phase: Subjects will be confined to the clinical site from Day -1 until Day 4. A minimum 3-day washout will be required between the last dose in the Qualification phase and the first dose of the Treatment phase. Treatment phase: Subjects will be confined to the clinical site from Treatment phase Day -1 until Day 14. Total study duration: up to approximately 49 days (including screening)
Study Population:	Healthy, male and female nondependent, recreational drug users with sedative drug experience, aged 18 to 55 years.
Planned Number of Subjects:	Approximately 60 subjects will be randomized into the Treatment phase, such that approximately 48 subjects complete the Treatment phase of the study.
Bioanalysis:	Gabapentin plasma concentrations will be measured by a validated bioanalytical method.
Pharmacodynamic Analysis:	For each PD endpoint, descriptive statistics by treatment and paired difference, and inferential analysis using a mixed-effects model, a paired t-test or the sign test, as appropriate, will be performed.
Pharmacokinetic Analysis:	PK analyses will be performed by non-compartmental analysis (NCA) and C_{max}, T_{max}, T_{last}, and AUC_{0-T} will be estimated for gabapentin. The PK analysis will be further detailed in the statistical analysis plan (SAP).
Statistical Analysis:	The PD and PK statistical analyses are discussed in sections 8.5 and 8.5.2.2, respectively, and will be fully detailed in the SAP.
Safety Analysis:	The safety analysis is discussed in section 8.7 and will be fully detailed in the SAP.

Table 1. Schedule of Activities

	Screening	Qualification					3-Day Washout Treatment Phase[p]															Early Termination (ET)
Day	**-30 to -2**	**-1**	**1**	**2**	**3**	**4**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
Subject Review																						
Informed consent[a]	X																					
Demographics	X																					
Inclusion/exclusion criteria review	X	X					X[b]															
Medical history	X																					
Medication & recreational drug use history	X	X					X															
C-SSRS[c]	X	X				X[p]	X[p]														X	X
Study restrictions review		X				X[p]	X[p]														X	X
Safety																						
Physical examination	X	X[d]				X[d, p]	X[d]														X[d]	X[d]
Height, weight & body mass index (BMI)	X																					
Pregnancy test[e]	X	X					X[p]														X	X
Urine drug and alcohol screen	X	X					X[p]															
COVID-19 test[t]		X					X[p]															
Clinical laboratory evaluations	X	X				X[p]	X														X	X
Follicle stimulating hormone (FSH)[f]	X																					
Serology[g]	X																					

	Screening	Qualification					3-Day Washout Treatment Phase[p]															Early Termination (ET)
Day	**-30 to -2**	**-1**	**1**	**2**	**3**	**4**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
Vital signs[h]	X	X	X	X	X	X	X[p]	X	X		X	X		X	X		X	X		X	X	X
12-lead electrocardiogram (ECG)	X	X					X[p]														X	X
Continuous oxygen saturation [u]			X		X																	
Continuous and spot respiratory rate[i]								X			X			X			X			X		
Continuous & Spot pulse oximetry[i]								X			X			X			X			X		
Continuous & Spot End Tidal CO_2[i]								X			X			X			X			X		
Concomitant medications[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events (AEs)[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacodynamics (PD)																						
Training session[l]		X					X[p]															
Subjective measures[m]			X	X	X	X		X	X		X	X		X	X		X	X		X	X	
MOAA/S[n]			X		X			X			X			X			X			X		
Pharmacokinetics (PK)																						
PK blood samples[o]								X	X		X	X		X	X		X	X		X	X	
Study Administration	X																					
Admission[p]		X					X[p]															
Randomization[q]		X					X															
Study drug administration			X[r]		X[r]			X[s]			X[s]			X[s]			X[s]			X[s]		

	Screening	Qualification					3-Day Washout Treatment Phase[p]															Early Termination (ET)
Day	**-30 to -2**	**-1**	**1**	**2**	**3**	**4**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
Discharge						X[p]															X	X

ARCI= Addiction Research Center Inventory, C-SSRS= Columbia Suicide Severity Rating Scale, DSM-IV= Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition, ECG= electrocardiogram, $EtCO_2$ = End Tidal CO_2, MOAA/S= Modified Observer's Assessment of Alertness/Sedation, VAS= visual analog scale
When timepoints coincide, procedures should be carried out in the following order, with the following windows: (1) vital signs (±15 minutes), (2) VAS/PD (±15 minutes), (3) PK blood sampling (±5 minutes), (5) MOAA/S should be administered immediately after the completion of all other PD measures when scheduling occurs at the same time (±15 minutes or 30 minutes).

[a] The latest version must be signed as soon as possible at the subject's next scheduled visit.
[b] Review of qualification criteria (section 4.3).
[c] Use "Baseline/screening version" of C-SSRS evaluation at screening visit. Use "Since last visit version of C-SSRS" evaluation at Day 14/ET, and if discharged between the Qualification and Treatment phases. Additional C-SSRS evaluations may be done at the investigator's discretion.
[d] Symptom directed physical examination. Additional physical examinations may be done at the investigator's discretion.
[e] Serum pregnancy test at Screening. Urine pregnancy test on each admission to the Qualification phase and; if applicable, Treatment phase; and at Day 14/ET.
[f] Women who are reported to be postmenopausal only.
[g] Serology screening as described in APPENDIX 6.
[h] Blood pressure, pulse rate, oxygen saturation (SpO_2) and respiratory rate. Measured and documented at screening; each admission to the Qualification phase and Treatment phase; and within 1 hour prior to and approximately 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24 hours following each study drug administration. Oral temperature required at screening and at check-in (Day -1) of the Qualification phase and, if applicable, upon re-admission to the Treatment Phase.
[i] Oxygen saturation (SpO_2), $EtCO_2$, and respiratory rate will be monitored continuously up to 1 hour prior to each study drug administration and will continue for up to 6 hours following each drug administration, or longer if deemed medically necessary. $EtCO_2$ will be documented within 1 hour prior to each dose administration and approximately 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours following each study drug administration.
[j] Medications taken within 30 days prior to screening and throughout the duration of study participation will be recorded.
[k] Adverse events will be collected on an ongoing basis from the time of first study drug administration in Qualification phase throughout the duration of study participation. Serious adverse events (SAEs) will be reported from the time of signing informed consent through the duration of study participation. Other conditions reported between the time of signing informed consent and first study drug administration in the Qualification phase will be recorded as medical history.

[l] Additional training sessions may be conducted as needed. Training will be conducted on Day -1 of the Qualification Phase and, if applicable, upon re-admission to the Treatment Phase.

[m] Subjective measures will be evaluated as follows:

Category	Evaluations	Phase	Timepoints
Drug-specific VAS	Drug Liking, Good Drug Effects, Bad Drug Effects, and Any Drug Effects	Qualification phase	approximately 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose
		Treatment phase	approximately 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, and 24 hours postdose
	Overall Drug Liking and Take Drug Again	Qualification and treatment phases	approximately 12 and 24 hours postdose
Other VAS	High, Feeling Drunk, Relaxation/Agitation, and Drowsiness/Alertness	Qualification phase	within 1 hour prior to and approximately 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose
		Treatment phase	within 1 hour prior to and approximately 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, and 24 hours postdose
ARCI Scales	Morphine-Benzedrine Group (MBG) and Pentobarbital–Chlorpromazine–Alcohol Group (PCAG)	Qualification phase	within 1 hour prior to and approximately 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose
		Treatment phase	within 1 hour prior to and approximately 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, and 24 hours postdose

[n] Conducted during the Qualification and Treatment phases within 1 hour prior to dosing and approximately (±15 minutes) at 0.5, 1, 1.5, 2 hours postdose and approximately (±30 minutes) at 3, 4, and 6 hours postdose.

[o] Blood samples will be collected as indicated in Table 4. When clinical activities are scheduled to occur at the same time, pharmacodynamic data collection (vital signs then subjective measures) is to be prioritized, followed by PK blood sampling.

[p] If subjects are discharged between the Qualification and Treatment phases, noted discharge procedures will be performed on Day 4 of the Qualification phase and noted re-admission procedures will be performed again on Day -1 of the Treatment phase. A minimum 3-day washout will be required between the last dose in the Qualification phase and the first dose of the Treatment phase.

[q] Randomization will be performed for Qualification phase only on Day -1 of the Qualification phase then, subjects who meet qualification criteria will be randomized for the Treatment phase on Day -1 of the Treatment phase.

[r] Subjects administered 2 mg alprazolam or placebo according to randomization with a minimum of 48 hours between doses during the Qualification phase.

[s] Subjects administered 200 mg GE-IR, 450 mg GE-IR, 700 mg GE-IR, or GE-IR placebo, and 2 mg alprazolam or alprazolam placebo (section 3.2) according to randomization with a minimum washout period of 3 days between doses.

[t] Covid-19 testing will be performed prior to admission for the Qualification Phase and, if applicable, upon re-admission for the Treatment Phase.

[u] Oxygen saturation (SpO_2) will be monitored continuously from 1 hour prior to each drug administration (alprazolam or placebo) and will continue for up to 6 hours following each drug administration, or longer if deemed medically necessary.

INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

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1 INTRODUCTION

1.1 Background

Gabapentin enacarbil is a transported prodrug of gabapentin designed and engineered to be stable in gastrointestinal contents and to be actively absorbed after oral dosing. It converts to gabapentin rapidly by non-specific carboxylesterase primarily in enterocytes and to a lesser extent in the liver upon absorption. The concentration of intact prodrug in blood is transient and ≤2% of the corresponding gabapentin level. As a prodrug of gabapentin, its therapeutic effects in restless legs syndrome (RLS) and postherpetic neuralgia (PHN) are attributable to gabapentin.

Gabapentin prevents pain-related responses in several models of neuropathic pain in rats and mice (e.g., spinal nerve ligation models, spinal cord injury model, and acute herpes zoster infection model). Gabapentin also decreases pain-related responses after peripheral inflammation (carrageenan footpad test, late phase of formalin test), but does not alter immediate pain-related behaviors (rat tail flick test, formalin footpad acute phase). The relevance of these models to human pain is not known.

Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but has no effect on GABA binding, uptake, or degradation. Gabapentin enacarbil 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 gabapentin enacarbil in RLS and PHN is unknown.

1.2 Study Rationale

Horizant is formulated as an extended-release (ER) formulation of gabapentin enacarbil. The primary purpose of this study is to evaluate the abuse potential of gabapentin enacarbil immediate-release (GE-IR), the active moiety in Horizant in comparison to placebo and an active control with known abuse potential (i.e., alprazolam).

Gabapentin does not exhibit affinity for benzodiazepine, opiate (mu, delta, or kappa), or cannabinoid 1 receptor sites, however, a small number of post-marketing cases report gabapentin misuse and abuse.[1] These individuals were taking higher-than-recommended doses of gabapentin for unapproved uses. Most of the individuals described in these reports had a history of poly-substance abuse or used gabapentin to relieve symptoms of withdrawal from other substances.

The Arbor drug safety database through November 2020 contained 728 reports categorized under drug abuse. Of these, 16 (2.2%) were attributed to Horizant, 452 (62%) to gabapentin, 242 (33.2%) to Regnite (gabapentin enacarbil reports in Japan), and 20 (2.7%) to gabapentin enacarbil (6 of these are specified as ER in the narrative). Of the 16 Horizant cases, the most frequently reported were intentional product misuse and use issue cases (n=9, 56%). These cases involved consumers who reported independently adjusting their dose to manage their symptoms/tolerability. This includes 6 who decreased the dose, 1 who increased the dose, and 2 with unspecified changes. This was followed in frequency by overdose (n=4, 25%). The

overdose cases involved reports of feeling "out of sorts", jittery, dizzy, and sleepy after taking 1200 mg; short-term memory loss after increasing the dose from 1200 mg to 1800 mg; and sedation after taking 600 mg instead of 300 mg. The fourth overdose case involved a male who took several pills to treat pain while golfing and was hospitalized after being found unconscious. Two cases of Horizant-related abuse involved accidental overdose (n=2). One was associated with a suspected drug interaction that increased the side effects of her seizure medication. The second accidental overdose resulted in death. An autopsy and investigation deemed the cause to be combined toxicity of multiple drugs (including Percocet, Xanax, alcohol and medical marijuana). Dependence (n=1) was reported by a male with a history of addiction to narcotics. After an unknown duration of taking Horizant for an unreported indication, he reported addiction issues. No further information was received. Horizant reports from the American Association Poison Control Centers National Poison Data System Annual Report are included.

The Regnite cases involved similar events, with intentional product misuse and use issue cases accounting for a larger majority of cases (95%).

Gabapentin abuse cases were different, however. The most common event was toxicity to various agents with (93.8%, 424/452). Of the 424 cases that involved toxicity to various agents, more specificity was provided in 173 of the cases. These 173 cases included cardiorespiratory arrest (n=73), accidental overdose (n=51), drug abuse (n=37), overdose (n=5), intentional product misuse (n=6), and intentional overdose (n=1). Gabapentin enacarbil was reported in 19 cases related to abuse. Aside from toxicity to various agents, the most frequently reported term was intentional product misuse (n=21; including the 6 report also involving toxicity to various agents). The remaining reports involved the same terms previously listed and were reported no more than 5 times each. Of the gabapentin reports, 65% involved intentional product misuse or use issues. The remaining terms, consistent with other products, were reported no more than 4 times each.

In addition, the Food and Drug Administration's Adverse Event Reporting System (FAERS) from October 2012 to December 2016 reportedly contained 634 gabapentinoid abuse-related reports (10.2% of all adverse drug event [ADE] reports). Of these, abuse was associated with 5.7% of total reports for gabapentin ADEs (576 of 10,038) compared to 10.2% of total reports for pregabalin ADEs (58 of 571). The abuse-related proportional reporting rate of pregabalin to gabapentin is 1.77. Abuse was more common relative to the total ADEs reported with pregabalin than gabapentin.[2]

Regardless of reported abuse, drugs that affect the central nervous system (CNS), are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects are required to undergo assessments related to their abuse potential.[3, 4] Horizant, a CNS -active drug, is currently approved for use in humans as a treatment for moderate to severe primary RLS and PHN; however, its abuse potential has not been formally evaluated.

This study is a randomized, double-blind, active- and placebo-controlled, 5-way crossover design, aimed to assess the abuse potential, safety, and PK of Horizant compared with an active control and placebo in healthy, nondependent, recreational sedative drug users. The overall design is consistent with United States (US) Food and Drug Administration (FDA) guidelines for human abuse potential (HAP) assessment.[4, 5]

Because of inter-individual variability in subjective responses, HAP studies are typically conducted as double-blind crossover studies including the investigational drug and active control, as well as placebo. The active control should be a controlled drug, ideally from the same pharmacological class as the study drug, which has measurable abuse liability established through experimental studies and epidemiological data, such that it will produce a significant, dose-dependent increase on measures of subjective effects. The active control provides evidence of the sensitivity of the methodology and the validity of the study.[6, 7] Therefore, based on the observed clinical effects to date, the sedative (benzodiazepine) class was considered the most appropriate pharmacologic class for an active control in this study. A placebo- control is also included to control and account for expectancy effects.

Alprazolam, the active control selected for this study, is a benzodiazepine that is widely known to be abused and has been repeatedly demonstrated to show positive effects on common measures of abuse potential in clinical investigations. Historically, alprazolam has been 1 of the most frequently used positive controls in human abuse potential studies evaluating sedative effects and has previously been found to have higher reinforcing effects compared to diazepam in a drug choice test.[33] Alprazolam has been used as an active control in several recent studies at doses ranging between 1.5 and 3.0 mg.[8, 9, 10, 11] An intermediate dose of 2.0 mg was selected as this is the common dose that is used for qualification phases in human abuse potential studies and reliably produces significant increases on subjective measures of drug effects (including Drug Liking), can be safely administered, and does not impose significant sedation that would limit the collection of study measures. In recent studies, alprazolam has been shown to maintain study validity on the measure of Drug Liking under the new statistical testing requirements outlined in the 2017 FDA guidance for industry.[4] Therefore, alprazolam was chosen as a positive control that can also reliably maintain study validity.

A double-blind Qualification phase has been included in this study design as an enrichment procedure to ensure that subjects who meet the drug use history criteria can also distinguish the subjective effects of the active control (i.e., alprazolam) from placebo. The pharmacologic qualification procedure provides more objective confirmation of drug use history, ensures that subjects can respond appropriately in a clinical setting, and reduces the chance of a false positive response to placebo. The washout between treatments in the Qualification phase is consistent with previous studies of this type, and the duration of pharmacodynamic (PD) effects associated with alprazolam has been shown to have returned to baseline by 24 hours postdose.[8, 9, 10, 11]

In clinical studies conducted to date, adverse events (AEs) of sedation, somnolence, and dizziness have been the most commonly reported in both healthy subject and patient studies of Horizant. Thus, subjects will be healthy individuals with previous nontherapeutic (recreational) experience with sedative drugs. These subjects represent the population at greatest risk for abuse of the drug and can provide meaningful ratings of the drug experiences with a lower risk of false negative results; therefore, they are the population with the most face validity.

In addition to the requirement that subjects are “history qualified” (i.e., history of recreational sedative drug use), subjects will also be required to pass a pharmacologic qualification (see above). In an abuse potential study, a negative result with a non-drug-using population can be considered inconclusive, since these subjects often do not like the effects of drugs that are readily abused by substance users.[4, 7]

The mean $T_{½}$ of alprazolam is 11.2 hours. The minimum 3-day washout interval between the Qualification phase and Treatment phase is considered sufficient given the PD effects associated with alprazolam return to baseline by 24 hours postdose, as stated above. . [23] Given the $T_{½}$ of gabapentin when receiving GE-IR (4.38 - 5.47 hours) by oral administration, the minimum 3-day interval between dosing during the treatment periods will ensure sufficient washout of GE-IR and alprazolam.

Based on the pharmacokinetic (PK) profile of gabapentin, the 24-hour assessment period following administration of study drug during the Treatment phase is sufficient to evaluate the safety and tolerability and to capture the profile of pharmacodynamic (PD) effects.

The selection of subjective abuse potential measures in this study, including the use of maximum (peak) effect (E_{max}) of the "at this moment" Drug Liking visual analog scale (VAS; administered as a bipolar scale) as a primary endpoint, is consistent with regulatory guidelines.[4] Additional VAS items will measure positive, negative, and other subjective effects to assess the pharmacologic response to the study treatments. The Overall Drug Liking and Take Drug Again VAS will provide a measure of the balance of drug effects and will indicate the subject's willingness to take the drug again.

Pharmacokinetic and safety assessments suitable for evaluating risks associated with administration of doses of GE-IR will also be included.

1.3 Rationale for Dose Selection

Standard guidelines for HAP studies indicate that doses above the anticipated therapeutic dose should be tested.[4, 7, 12] The current US FDA Guidance for Industry on the assessment of abuse potential of drugs recommends including multiple doses of the study treatment in the HAP study, ranging from therapeutic to supratherapeutic.[4]

The GE-IR doses in this study will include 200 mg, 450 mg and 750 mg doses, in order to evaluate the dose response of the drug. These doses of GE-IR correspond to the C_{max} values produced by single oral doses of 600 mg, 1200 mg, and 1800 mg gabapentinin healthy individuals.

The dose of alprazolam selected (2 mg) is consistent with doses previously evaluated in human abuse potential studies.[8, 9, 10, 11] and are expected to show significant abuse-related subjective effects. Alprazolam doses up to 3 mg have been administered in human abuse potential studies, and this dose has relatively strong sedative effects; therefore, subjects who experience unarousable sedation during the Qualification phase at a dose of 2 mg will not be enrolled. The 2 mg dose is expected to demonstrate separation from placebo based on previous data with alprazolam and will ensure that subjects are able to tolerate (with respect to sedation) and respond appropriately in the Treatment phase.

All doses of study drug will be administered in the fasted state. A previous study of alprazolam demonstrated the rate of alprazolam absorption was slower after administration during fed relative to fasted conditions. In this study, the mean maximum observed plasma concentration (C_{max}) decreased approximately 25%, and time to C_{max} (T_{max}) was delayed approximately 1.5 hours when food was administered before dosing (4.0 hours [range=2.53-6.03 hours] versus 2.5 hours [range=0.75-4.01 hours]).[34]

1.4 Risk/Benefit Assessment

1.4.1 Known Potential Risks

The safety of GE-IR in doses ranging from 350 mg to 2800 mg has been evaluated in 88 healthy subjects in 2 clinical trials (single ascending dose trial [XP 006] and multiple ascending dose trial [XP 018]).

In study XP 006, dizziness was the most common AE experienced and appeared to be dose-dependent; occurring mostly at doses from 1400 to 2800 mg. Headache was also reported and did not appear related to dose level. Fatigue, nausea and vomiting tended to be reported with higher doses or higher gabapentin concentrations.

Similarly, in study XP 018, dizziness was the most common AE experienced, followed by headache, somnolence and nausea. Adverse events were mild with frequencies that were possibly dose-related.

The doses of GE-IR administered in this study are not anticipated to induce any potential risk to the subjects. Single dose studies using up to 2800 mg of GE-IR (XP 006) as mentioned above did not result in any respiratory depression or serious adverse events. The safety monitoring practices employed by this protocol are adequate to protect the subjects' safety and to detect any treatment-emergent AEs (TEAEs).

The following safety measures will be monitored continuously for signs of respiratory depression from up to 1 hour prior to dosing up to approximately 6 hours following dosing in the Treatment phase:

- end-tidal CO_2 ($EtCO_2$) monitoring
- blood oxygen saturation (SpO_2) monitoring
- respiratory rate monitoring

Safety measurements of $EtCO_2$ and O_2 saturation are the standard in monitoring respiratory function, change in oxygenation, and change in ventilation.[21, 22, 23, 24] Monitoring $EtCO_2$ has been shown to be more sensitive in detection of respiratory depression than monitoring respiratory rate and pulse oximetry alone.[25]

In the clinical setting, respiratory depression is usually described in terms of decreased respiratory rates, decreased SpO_2 levels, or elevated $EtCO_2$ levels[26] and, therefore, these measures are appropriate to monitor respiratory depression.

Additional safety measures implemented at predose and specified timepoints postdose will include the collection and documentation of AEs and vital signs (i.e., systolic and diastolic blood pressure, pulse rate, respiratory rate, oral temperature, SpO_2), and $EtCO_2$. Subjects will be determined as healthy for inclusion into the study based on measures of clinical laboratory testing, vital signs, medical history, C-SSRS, physical examination, and ECG.

1.4.2 Known Potential Benefits

As the study treatments are not being given to subjects to treat any symptoms or illness, there will be no direct medical benefit from participation in this trial.

2 STUDY OBJECTIVES AND ENDPOINTS

The primary and secondary objectives of the study and corresponding endpoints are:

OBJECTIVES	ENDPOINTS
Pharmacodynamic	
To evaluate the abuse potential of single oral doses of GE-IR relative to alprazolam and placebo, when administered to nondependent, recreational drug users with sedative drug use experience.	The primary endpoint of this study will be E_{max} over 24 hours for Drug Liking ("at this moment"), assessed on a bipolar (0 to 100 points) VAS. Key Secondary PD endpoints will be: • Overall Drug Liking VAS (E_{max}) • Take Drug Again VAS (E_{max}) • High VAS (E_{max}) Non-Key Secondary PD endpoints will be: Balance of Effects • Drug Liking VAS (time of maximum effect [TE_{max}], minimum effect [E_{min}], time of minimum effect [TE_{min}] and time-averaged area under the effect-time curve [TA_AUE]) Positive Effects • High VAS (TE_{max}, and TA_AUE) • Good Effects VAS (E_{max}, TE_{max}, and TA_AUE) Negative Effects • Bad Effects VAS (E_{max}, TE_{max}, and TA_AUE) Other Subjective Effects • Any Effects VAS (E_{max}, TE_{max}, and TA_AUE) • Feeling Drunk (E_{max}, TE_{max}, and TA_AUE) • Drowsiness/Alertness VAS (E_{min}, TE_{min}, and time-averaged area over the effect-time curve [TA_AOE]) • Relaxation/ Agitation VAS (E_{min}, TE_{min}, and TA_AOE) • Addiction Research Center Inventory (ARCI) Morphine-Benzedrine Group (MBG) Scale (E_{max}, TE_{max}, and TA_AUE) • ARCI Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) Scale (E_{max}, TE_{max}, and TA_AUE) Observer Assessments Modified Observer's Assessment of Alertness/Sedation (MOAA/S) (E_{min}, change from baseline to minimum effect [CFB_{min}], and TA_AOE)

OBJECTIVES	ENDPOINTS
Pharmacokinetics	
To evaluate the PK of GE-IR when administered to nondependent, recreational drug users with sedative drug use experience.	Secondary Endpoint: Pharmacokinetic parameters of GE-IR include C_{max}, T_{max}, T_{last} and area under the concentration-time curve from 0 to the last measured observable concentration (AUC_{0-T}).
Safety	
To evaluate the effects on safety and tolerability of single oral doses of GE-IR relative to alprazolam and placebo, when administered to nondependent, recreational drug users with sedative drug use experience.	Secondary endpoints will include a summary of the incidence of AEs, serious adverse events (SAEs), as well as descriptive summary and statistics of the safety parameters, which include clinical laboratory values, vital signs (i.e., systolic and diastolic blood pressure, pulse rate, respiratory rate, oral temperature, oxygen saturation [SpO_2]), continuous SpO_2 monitoring, continuous End Tidal CO_2 monitoring, electrocardiograms (ECGs), Columbia Suicide Severity Rating Scale (C-SSRS), and physical examination findings.

3 STUDY DESIGN

3.1 Overall Study Design

This study will be a randomized, double-blind, active- and placebo-controlled, 5-way crossover study to determine the abuse potential of GE-IR relative to alprazolam and placebo, in nondependent, recreational drug users with sedative drug use experience.

This study will consist of 3 phases: screening, qualification and treatment. The study schema is presented in Figure 1.

After a screening period of up to 30 days, eligible subjects will be admitted to the clinical research unit (CRU) and randomized (1:1) into the double-blind Qualification phase. During the Qualification phase, subjects will receive oral doses of alprazolam 2 mg (active control) and matching placebo in a randomized, double-blind, crossover manner to ensure they are able to discriminate and show positive effects of the active control in a clinical setting and to demonstrate that they are able to tolerate the administered dose. Two doses in the Qualification phase will be separated by 48 hours.

Subjects will be encouraged to remain in the CRU but may be discharged between the Qualification phase and Treatment phase, if necessary. A minimum 3-day washout will be required between the last dose in the Qualification phase and the first dose of the Treatment phase. Appropriate discharge and re-admission procedures are noted in Table 1.

The Treatment phase is a randomized, double-blind, active- and placebo-controlled 5-way crossover design. Subjects will be randomized to 1 of the 10 pre-specified treatment sequences in which they will receive the following 5 treatments in a crossover manner (1 per treatment period) and blinded fashion:

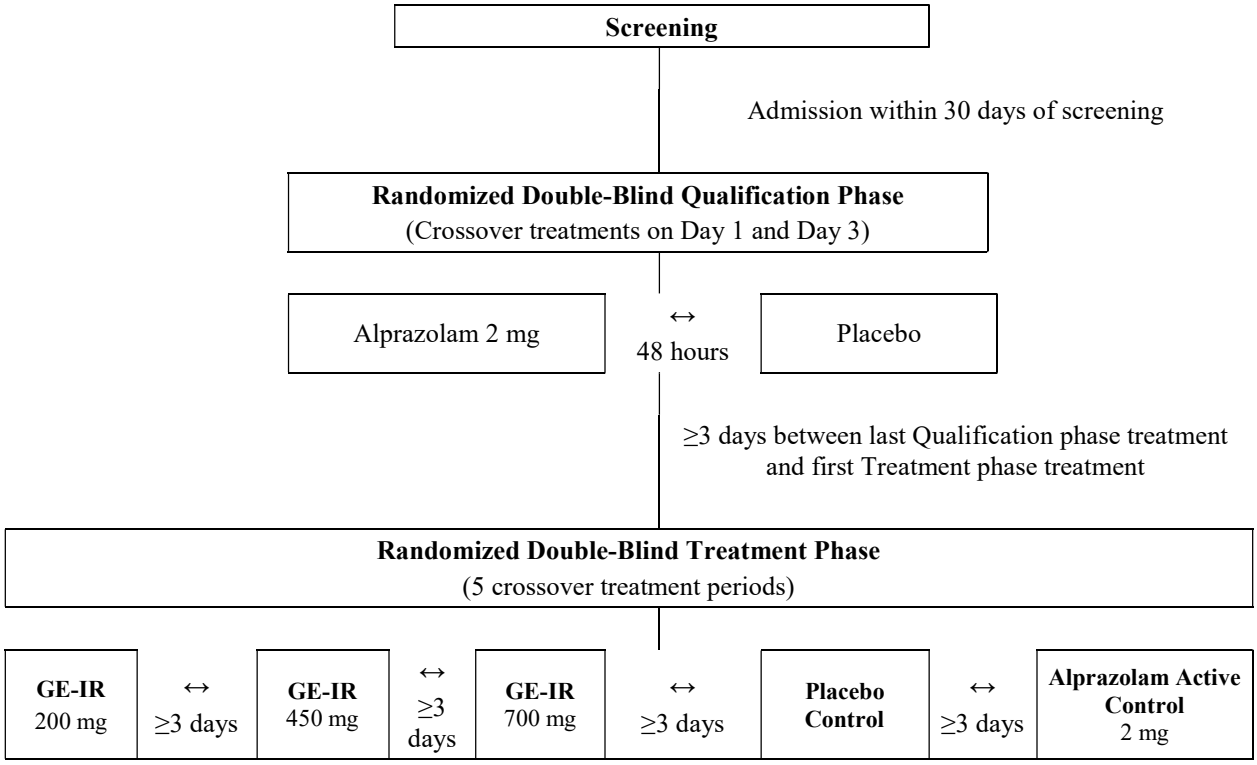
- Placebo
- Alprazolam 2 mg (active control)
- GE-IR 200 mg
- GE-IR 450 mg
- GE-IR 700 mg

Each study drug administration will be separated by at least 3 days. Drug administration will occur on the first day of each treatment period followed by PD, PK, and safety assessments for up to 24 hours postdose. Subjects will be discharged from the investigational site approximately 24 hours after the final dose if deemed medically stable for discharge by an investigator.

Study assessments will be performed at the timepoints outlined in the Schedule of Activities (Table 1).

The maximum duration of subject participation will be approximately 49 days, including screening.

Figure 1. Study Schema



Note: the sequence of treatments shown is for illustration of the overall design and does not necessarily represent an actual treatment sequence. Refer to Table 3 for all treatment sequences. A minimum 3-day washout will be required between the last dose in the Qualification phase and the first dose of the Treatment phase.

3.2 Study Treatments

The following treatments will be administered with approximately 240 mL of room temperature water in the morning under fasted conditions during the Qualification phase:

- **Placebo:** A single dose of placebo to match alprazolam (2 lactose 100 mg tablets over-encapsulated in one Swedish Orange Opaque AAEL-DB capsule) will be administered orally.
- **Active Control:** A single 2 mg dose of alprazolam (2 × 1 mg tablets over-encapsulated in one Swedish Orange Opaque AAEL-DB capsule) will be administered orally.

The following treatments will be administered with approximately 240 mL of room temperature water in the morning under fasted conditions during the Treatment phase:

- **Placebo:** Three placebo capsules to match GE-IR + 1 placebo capsule to match alprazolam [2 × over-encapsulated placebo tablets in one Swedish Orange Opaque AAEL-DB capsule] will be administered orally.
- **Active Control:** A single 2 mg dose of over-encapsulated alprazolam (2 × 1 mg tablets over-encapsulated in one Swedish Orange Opaque AAEL-DB capsule) + 3 placebo capsules to match GE-IR will be administered orally.
- **A single 200 mg dose of GE-IR** (1 × 200 mg immediate-release [IR] capsule + 2 placebo capsules to match GE-IR capsule + 1 placebo capsule to match alprazolam [2 × 1 mg placebo tablets over-encapsulated in one Swedish Orange Opaque AAEL-DB capsule]) will be administered orally.
- **A single 450 mg dose of GE-IR** (2 × 225 mg immediate-release [IR] capsule + 1 placebo capsule to match GE-IR capsule + 1 placebo capsule to match alprazolam [2 × over-encapsulated placebo tablets in one Swedish Orange Opaque AAEL-DB capsule]) will be administered orally.
- **A single 700 mg dose of GE-IR** (3 × 233.3 mg immediate-release [IR] capsules + 1 placebo capsule to match to alprazolam [2 × over-encapsulated placebo tablets in one Swedish Orange Opaque AAEL-DB capsule]) will be administered orally.

4 SUBJECT POPULATION

Subjects who meet all the inclusion criteria and none of the exclusion criteria at the screening visit may be eligible for participation in this study. Continued eligibility will be assessed upon admission to the clinical site, prior to the first study drug administration.

Screen failures are defined as subjects who consent to participate in the clinical trial but are not subsequently randomly assigned to treatment in the Qualification phase. Subjects who enter the Qualification phase and fail to qualify for the Treatment phase will be considered qualification failures.

4.1 Inclusion Criteria

Subjects must meet all of the following criteria to be enrolled:

1. Provision of signed and dated informed consent form (ICF),

2. Stated willingness to comply with all study procedures and availability for the duration of the study,

3. Male or female, between 18 and 55 years of age, inclusive,

4. Current nondependent, recreational drug user who has used sedative drugs for recreational (nontherapeutic) purposes (i.e., for psychoactive effects) at least 10 times in the subject's lifetime and at least once in the 12 weeks before screening,

5. Body mass index (BMI) within 18.0 kg/m^2 to 36.0 kg/m^2, inclusive,

6. If female, meets 1 of the following criteria:

   a) If of childbearing potential agrees to use 1 of the accepted contraceptive regimens from at least 30 days prior to the first study drug administration, during the study, and for at least 30 days after the last dose of the study drug. An acceptable method of contraception includes 1 of the following:

      - Abstinence from heterosexual intercourse,
      - Hormonal contraceptives (birth control pills, injectable/implantable/insertable hormonal birth control products, transdermal patch),
      - Intrauterine device (IUD; with or without hormones),

   Or

   b) If of childbearing potential agrees to use a double barrier method (e.g., condom and spermicide) during the study and for at least 30 days after the last dose of study drug.

   Or

   c) If of non-childbearing potential, defined as surgically sterile (i.e., has undergone complete hysterectomy, bilateral oophorectomy, or tubal ligation) or is in a postmenopausal state (i.e., at least 1 year without menses without an alternative medical condition and confirmed follicle stimulating hormone (FSH) ≥ 40 mIU/mL prior to the first study drug administration),

7. If male and engaging in sexual activity that has the risk of pregnancy must agree to use a double barrier method (e.g., condom and spermicide) and agree to not donate sperm during the study and for at least 90 days after the last dose of the study medication, a male who has a pregnant partner shall be excluded,

8. Healthy, as determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital signs or clinical laboratory (including hematology, clinical chemistry, urinalysis, and serology [screening visit only]) at screening visit and admission, as applicable, in the opinion of an investigator,

9. Negative Covid-19 test prior to each admission, as applicable.

4.2 Exclusion Criteria

Subjects meeting the following criteria will be excluded from participation:

1. History of significant hepatic, renal, cardiovascular, pulmonary, hematologic, neurological, psychiatric, gastrointestinal, endocrine, immunologic, ophthalmologic, or dermatologic disease of any etiology (including infections),

2. Presence or history of significant gastrointestinal, liver or kidney disease, or surgery that may affect drug bioavailability with the exception that cholecystectomy is permitted at the discretion of an investigator,

3. Presence of any significant respiratory illness or presence or history of chronic respiratory disease (e.g., upper respiratory illness, sleep apnea, emphysema, asthma) at screening (subjects with acute respiratory illness may be rescheduled upon resolution at the discretion of an investigator),

4. Personal or family history (first degree relatives) of allergy, hypersensitivity, or drug rash with eosinophilia and systemic symptoms (DRESS) syndrome to gabapentin enacarbil, gabapentin or any drug product including anti-convulsants (e.g., alprazolam, carbamazepine) or related drugs (e.g., other benzodiazepines) or known excipients of any of the drug products in this study (e.g., lactose),

5. History of sensitivity to or poor tolerance of gabapentin enacarbil, gabapentin, pregabalin, or alprazolam,

6. Female who is lactating at screening,

7. Female who is pregnant according to the pregnancy test at screening or prior to the first study drug administration or planning to become pregnant within 30 days following the last study drug administration,

8. History of substance or alcohol dependence (excluding nicotine and caffeine) within the past 2 years, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), and/or subject has been in a drug or alcohol rehabilitation program within the last 2 years,

9. Subjects with positive UDS results at screening and admission will be assessed for inclusion at the discretion of an Investigator. If tetrahydrocannabinol (THC) is positive at admission to the Qualification phase and Treatment phase, as applicable, a cannabis intoxication evaluation will be done by an investigator and subjects may be permitted to continue in the study, rescheduled, or discontinued at the discretion of an investigator. Other positive test results should be reviewed to determine if the subject may be rescheduled, in the opinion of the investigator,

10. Is a heavy smoker (>20 cigarettes per day or nicotine-equivalent) and/or is unable to abstain from smoking or unable to abstain from the use of prohibited nicotine-containing products for at least 1 hour before and 6 hours after study drug administration (including e-cigarettes, pipes, cigars, chewing tobacco, nicotine topical patches, nicotine gum, or nicotine lozenges),

11. Regularly consumes excessive amounts of caffeine or xanthines within 30 days prior to screening, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, or other caffeinated beverages per day,

12. History of suicidal ideation within 24 months or suicidal behaviour within 2 years of screening, showing suicidal tendency as per the Columbia Suicide Severity Rating Scale (C-SSRS) administered at screening (APPENDIX 7), or is currently at risk of suicide in the opinion of an investigator,

13. Presence of clinically significant ECG abnormalities at the screening visit, as defined by medical judgment, NOTE: QT corrected according to Fridericia's formula (QTcF) interval of >450 msec in male subjects or >470 msec in female subjects will be exclusionary. The ECG may be repeated once for confirmatory purposes if the initial value obtained exceeds the limits specified,

14. Has creatinine clearance ≤60 ml/min as calculated by the Cockcroft-Gault equation,

15. Any history of tuberculosis,

16. Positive screening results to human immunodeficiency virus (HIV) 1 and 2 antibodies, hepatitis B virus surface antigen (HBsAg) or hepatitis C virus antibody (HCV Ab) tests,

17. Intake of an investigational product (IP) within 30 days or 5 times the half-life (whichever is longer) prior to screening,

18. Use of any prescription drugs (with the exception of hormonal contraceptives or hormone replacement therapy) in the 30 days prior to the first study drug administration, that in the opinion of an investigator would put into question the status of the subject as healthy,

19. Use of over-the-counter (OTC) products (including herbal preparations and supplements) within 7 days prior to the first study drug administration, with the exception of ibuprofen or acetaminophen,

20. Donation of plasma in the 7 days prior to screening,

21. Blood donation (excluding plasma) of approximately 500 mL of blood in the 56 days prior to screening,

22. Is, in the opinion of an investigator or designee, considered unsuitable or unlikely to comply with the study protocol for any reason,

23. Poor venous access at screening, as judged by an investigator.

4.3 Qualification Criteria for Treatment Phase

Subjects must meet the following criteria to be considered eligible for enrollment in the Treatment phase of the study:

1. Peak score in response to alprazolam 2 mg greater than that of placebo on Drug Liking VAS (difference of at least 15 points), with a peak score of at least 65 points for alprazolam.

2. Acceptable placebo response based on Drug Liking VAS (peak score between 40 and 60 points, inclusive).

3. Acceptable overall responses to alprazolam and placebo on the subjective measures, as judged by an investigator or designee.

4. Able to tolerate the 2 mg dose of alprazolam, as judged by an investigator, including no episodes of vomiting during the first 3 hours postdose. Subjects with unarousable sedation within the first 4 hours postdose will not be eligible for the Treatment phase.

5. General behavior suggests that the subject could successfully complete the study, as judged by the investigational site staff. On a case-by-case basis, otherwise eligible subjects who appear to have difficulty differentiating between bipolar and unipolar VAS (e.g., making errors such as selecting 50 as neutral for a unipolar scale) or difficulty distinguishing between "at this moment" and "next-day" measures during the Qualification phase may be permitted into the Treatment phase, and will undergo additional training on the difference between the scale types. Additional training sessions will be documented in source files.

4.4 Withdrawal Criteria

4.4.1 Before First Treatment Administration

Before the first treatment administration, inclusion/exclusion criteria will govern the subjects to be dosed. Subjects withdrawn before first treatment administration will not be followed up and will not undergo ET assessments. Other safety assessments may be performed if required.

Subjects are free to withdraw their consent to participate in the study at any time, without prejudice. The reason for their withdrawal or for deciding to end their participation will be documented.

4.4.2 After First Treatment Administration

Subjects may, at any time, voluntarily withdraw from the study or be removed from the study at the discretion of an investigator or sponsor. An investigator may withdraw a subject at any time if it is determined that continuing the study would result in a significant safety risk to the subject or if their behavior is deleterious to the study environment.

If such withdrawal occurs, or if the subject fails to return for visits, an investigator should determine the primary reason for a subject's premature withdrawal from the study and record the reason in the subject's study documents.

Attempts should be made to have such subjects complete the ET assessments. ET assessments should be performed as soon as possible after the last study treatment administration.

The blind may be broken only in emergency situations, where knowledge of the treatment that the subject received is necessary for safety management (section 5.2.4)

Details of reasons for removal of subjects will be recorded, reported to the sponsor and documented in the clinical study report (CSR).

For subjects who are lost to follow-up (i.e., those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), an investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject (e.g., dates of telephone calls, registered letters).

4.5 Lifestyle and/or Dietary Requirements

- Subjects will be prohibited from consuming food or beverages containing grapefruit, pomelo, pomegranate, star fruit, Seville orange, poppy seeds, and quinine (i.e., tonic water) for 7 days prior to the first study treatment and throughout the study.
- Subjects will be prohibited from consuming alcohol for 48 hours prior to each study visit and from recreational drug use from screening and throughout the study. In case of any doubt, a test for alcohol and/or a drug screen may be performed if requested by an investigator. If a subject presents with a positive alcohol test or drug screen at any visit after the screening visit, the subject may be rescheduled at the discretion of an investigator. If THC is positive at check-in, a cannabis intoxication evaluation will be done by an investigator, and inclusion will be at the investigator's discretion.
- Subjects will be prohibited from consuming food or beverages containing xanthines (i.e., tea, coffee, cola drinks, energy drinks or chocolate) for 24 hours prior to the first study treatment through clinic discharge.
- Subjects will eat only the food provided by the study site during confinement at the CRU.
- Subjects will be instructed to abstain from strenuous physical activity for 48 hours prior to screening, each study treatment, and during inpatient stays at the investigational site.
- During the study, smokers will abstain from smoking for at least 1 hour prior to and until at least 6 hours after drug administration at each study period. Subjects will not be permitted to use other nicotine-containing products (including nicotine topical patches, nicotine gum, or nicotine lozenges).
- Subjects will be instructed to refrain from driving, operating machinery, or engaging in hazardous activities until they and an investigator are convinced the study drug is not impairing their judgment and/or ability to perform skilled tasks.
- Female subjects of childbearing potential will have to take appropriate measures to prevent pregnancy as described in section 4.1. It is the subject's responsibility to notify the CRU if a pregnancy occurs from the end of their study participation until 30 days after the last dose of the study drug.
- Males who are sexually active will be expected to use an acceptable contraceptive regimen and not to donate sperm from the first administration of the study drug, during the study, and until at least 90 days after the last drug administration, as described in section 4.1.

4.6 Concomitant Treatment

Except for medication or treatments specifically allowed per protocol and those which may be required to treat AEs, no other treatment or medication other than the study drugs will be allowed from screening until all study activities and evaluations have been completed.

Systemic contraceptives and hormone replacement therapy are permitted for female subjects.

Subjects will be asked about any new medications (including herbal preparations and supplements) taken between screening and admission to the clinic, and between the Qualification

and Treatment phase, if a subject is discharged during this interim period. Information on any concomitant medications administered after consent will be collected throughout the study. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject has received the study treatment must be listed in the subject case report form (CRF) and related conditions (e.g., AEs) documented. The drug name and dose taken will be noted. An investigator and/or the sponsor will decide whether the subject will be permitted to remain in the study, depending on the drug used, the time of drug intake, etc.

5 STUDY TREATMENTS

5.1 Investigational Products

GE-IR capsules will be provided by the sponsor. The lot number and the measured content of the dosage form, when available, of each formulation will be included in the final report.

5.1.1 Gabapentin Enacarbil

GE-IR capsules will be provided by Arbor Pharmaceuticals, LLC for oral administration, and will be provided in opaque capsules of a suitable size to contain all study doses in order to maintain the blind during dosing.

Placebo capsules matched to GE-IR will be supplied by the sponsor. The weight is matched to the sponsor's GE-IR capsule and the composition is the same, including excipients.

5.1.2 Alprazolam

Xanax (alprazolam) is manufactured by Pfizer, Inc. and will be supplied as 1 mg tablets. To maintain the study blind alprazolam tablets will be over-encapsulated. A single dose of alprazolam 2 mg will consist of 2 × 1 mg tablets over-encapsulated.

Placebo to match alprazolam tablets will be over-encapsulated 2 × 100 mg lactose tablets.

Over-encapsulated doses may be prepared up to 72 hours prior to dosing. Both the placebo to match alprazolam and alprazolam treatment assignments will utilize the Swedish Orange Opaque AAE-DB capsules by Capsugel for over-encapsulation, to ensure the study blind is maintained.

5.2 Investigational Product Management

5.2.1 Packaging, Labeling and Dispensing

The sponsor will be responsible for ensuring that GE-IR is manufactured in accordance with applicable current Good Manufacturing Practice (cGMP) regulations and requirements.

The study drug will be labeled according to the requirements of local law and legislation. The study drug will be dispensed according to International Council for Harmonisation (ICH) Good Clinical Practice (GCP) by the CRU's pharmacy, unless the sponsor supplies the pharmacy with pre-labeled individual dosing samples.

5.2.2 Storage and Handling

Once received, all study drugs will be stored in the CRU's pharmacy.

GE-IR capsules and placebo should be stored at 25°C with excursions between 15°C and 30°C allowed. Both placebo to match alprazolam and alprazolam should be stored between 15°C and 30°C. All study drugs should be kept in a tightly closed container, with provided desiccants, to protect from moisture. The products should not be used if expired and should not be frozen.

The CRU's pharmacy will maintain an inventory record of the study drugs received, stored (in a secure restricted area), and dispensed. Study drugs will be provided to study subjects only.

5.2.3 Method of Assigning Subjects to Treatment Groups

The designated, unblinded biostatistician will generate the separate randomization codes for the Qualification and Treatment phases with a computer program according to the study design, the number of subjects and the sequence of treatment administration. For the Qualification and Treatment phases, the random allocation of each sequence of treatment administration to each subject will be done in such a way that the study is balanced. Once generated, the randomization codes will be final and will not be modified.

Subjects who sign the ICF and are randomized but do not receive a study treatment in the Treatment phase may be replaced. Subjects who sign the ICF, are randomized and receive a study treatment in the Treatment phase, and subsequently withdraw, or are withdrawn or discontinued from the study, may be replaced.

5.2.3.1 Qualification Phase

Subjects who enter the Qualification phase will be assigned, in ascending order, a qualification randomization number to identify the sequence of their treatments (Table 2).

Table 2. Sample Qualification Phase Sequences

Treatment Sequence	Day 1	Day 3
XY	X	Y
YX	Y	X

Treatment X: Placebo
Treatment Y: Alprazolam 2 mg (active control)

A minimum 3-day washout will be required between the last dose in the Qualification phase and the first dose of the Treatment phase.

5.2.3.2 Treatment Phase

For the Treatment phase, qualified subjects will be randomized to 1 of 10 treatment sequences based on a computer-generated randomization schedule. The first dose will be administered at least 3 days after the Qualification phase. The study drug will be prepared for each subject based on their randomization code. Subjects will receive all 5 treatments in the order specified by the treatment sequence according to two 5 × 5 Williams square design (Table 3).

Table 3. Sample Treatment Phase Sequences

Treatment Sequence	Period 1	Period 2	Period 3	Period 4	Period 5
ABECD	A	B	E	C	D
BCADE	B	C	A	D	E
CDBEA	C	D	B	E	A
DECAB	D	E	C	A	B
EADBC	E	A	D	B	C
DCEBA	D	C	E	B	A
EDACB	E	D	A	C	B
AEBDC	A	E	B	D	C
BACED	B	A	C	E	D
CBDAE	C	B	D	A	E

Treatment A: Placebo
Treatment B: Alprazolam 2 mg (active control)
Treatment C: GE-IR 200 mg
Treatment D: GE-IR 450 mg
Treatment E: GE-IR 700 mg

5.2.4 Blinding

The treatment assignment will not be known by the study subjects.

Furthermore, the randomization code will not be available to investigators and clinical staff involved in the collection, monitoring, revision, or evaluation of AEs, as well as clinical staff that could have an impact on the outcome of the study, including the biostatistician and pharmacokineticist (or delegate). When all PD assessments during the Qualification phase have been completed for each cohort, the randomization will be released to allow for the evaluation of qualification criteria. For the Treatment phase, the randomization will remain blinded until all the CRFs have been approved and signed.

The preparation and/or dispensing of the products will be performed by designated personnel that are not directly involved in the clinical aspects of the trial.

The randomization code must not be broken except in emergency situations where the identification of a subject's study treatment is required by an investigator for further treatment of the subject or by the designated unblinding person(s) in the case of a suspected, unexpected SAE (SUSAR) report. Randomization information will be held by designated individual(s). The date and reason for breaking the blind must be recorded.

5.2.5 Study Drug Accountability

Complete and accurate inventory records of all study drugs will be kept. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), subject dispensing records, and returned or destroyed study product.

Drug accountability will be performed throughout the trial and at the completion of the trial.

5.3 Administration of Study Drug, Meals and Fluids

Study treatments, as described in section 3.2, will be administered in the morning. Each subject will be dosed at approximately the same time in each period, and all scheduled postdose activities and assessments will be performed relative to the time of study drug administration. The date and time of each dose will be recorded.

An oral dose of the assigned treatment will be administered to subjects with approximately 240 mL of water at ambient temperature following at least a 10-hour fast. The dose must be swallowed whole and must not be chewed or broken. After the subject indicates that the study drug has been swallowed, study personnel will inspect the oral/buccal cavity to ensure that the study drug was swallowed.

Food and fluid intake other than water will be controlled for each confinement period and for all subjects. Water will be provided as desired until at least 1-hour predose. Water will be allowed beginning at least 1 hour after the administration of the drug. No food will be allowed until at least 4 hours after each dose.

5.3.1 Treatment Compliance

The study drug(s) will be dispensed only to eligible subjects and administered under the supervision of study personnel. Treatment compliance will be verified according to the site's standard operating procedures (SOPs).

5.4 Other Protocol Restrictions

Subjects will remain seated or kept in minimal ambulatory movement in the immediate study area for at least 6 hours following drug administration, avoiding vigorous exertion. However, should AEs occur at any time, subjects may be placed in an appropriate position. During this interval subjects will be permitted, under supervision, to get up (e.g., to use the washroom facilities). Subjects will not engage in strenuous activity at any time during the confinement periods.

6 STUDY PROCEDURES

Unless otherwise stated in this protocol, the SOPs of the study facilities, which are available for all activities relevant to the quality of the study, will be followed during this study. Procedure windows, including PK/PD sample collection windows, will be documented in a separate clinical document.

An overview of the study activities for each subject is detailed in Table 1.

Pharmacodynamic data collection (vital signs then subjective measures) is to be prioritized, followed by PK blood sampling, when clinical activities are scheduled to occur at the same time.

Subjects will be confined to the clinical site from Day -1 of the Qualification phase through Day 4 of the Qualification phase. Subjects will be admitted to the clinical site on Day -1 of the Qualification phase and be dosed on Days 1 and 3. Subjects not qualifying for the Treatment phase may be discharged on Qualification Day 4 after final assessments are completed. Those subjects qualifying for the study will continue to the Treatment phase. These subjects will be encouraged to remain in the clinic, but may be discharged, if necessary, and return to the clinical site on Day -1 of the Treatment phase. A minimum 3-day washout will be required between the last dose in the Qualification phase and the first dose of the Treatment phase.

Subjects will be discharged on Day 14 of the Treatment phase.

Any deviation from protocol procedures shall be noted in the source documentation and compiled for reporting in the clinical study report.

6.1 Safety Assessments

Safety assessments will include physical examination, C-SSRS, vital signs (i.e., systolic and diastolic blood pressure, pulse rate, respiratory rate, oral temperature, SpO_2), 12-lead ECG, clinical laboratory tests, and AE monitoring. Continuous SpO_2 monitoring and continuous $EtCO_2$ will be conducted for approximately 6 hours postdose. Additional safety measurements may be performed at the discretion of an investigator for reasons related to subject safety.

An investigator will be present at the clinical site for at least the first 6 hours following each drug administration and will remain available at all times throughout the study.

6.1.1 Medical History

Medical history will be reviewed as scheduled in Table 1 and will include all queries by the medical and clinical staff related to the subject's well-being and history of relevant past medical events/experiences. Medical history will include all demographic data (age, gender, race, body weight, height, and BMI) and baseline characteristics. Smoking habits will also be recorded.

Any medical conditions occurring from the time of signing informed consent through the first dose of study treatment in the Qualification phase will be recorded as medical history. If the condition meets the criteria for an SAE it will be reported as described in section 7.6. Medical history conditions that worsen and are judged to be clinically significant will be recorded as AEs.

6.1.2 Recreational Alcohol/Drug Use

A lifetime history of all drug use, including alcohol, will be collected as scheduled in Table 1. History, including drug preference (i.e., drug of choice), frequency of use, and date of last use will be collected using reported drug names and drug class (e.g., cannabinoids, depressants, dissociative anesthetics, hallucinogens, opioids and morphine derivatives, and stimulants).

DSM-IV modules will be included as a part of the recreational drug/alcohol use history and used to screen for alcohol and substance dependence.

6.1.3 Physical Examination

A physical examination will be performed by a medically qualified and licensed individual as scheduled in Table 1.

The physical examination will include a general review of the following body systems (at minimum): general appearance, head, eyes, ears, nose and throat (HEENT), neck/thyroid, cardiovascular, respiratory, gastrointestinal, neurological, musculoskeletal/extremities, and skin.

A symptom-oriented physical exam may be conducted as indicated in Table 1, at the discretion of an investigator.

6.1.4 Vital Signs

Vital signs will be measured as scheduled in Table 1 and will include blood pressure, pulse rate, respiratory rate and SpO_2 measures at designated times.

All vital signs will be interpreted by an investigator as normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS). New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs.

Vital signs will be measured after being in supine or semi-supine position for at least 5 minutes.

6.1.4.1 Continuous and Spot Oxygen Saturation

Assessments of respiratory depression will include continuous and spot SpO_2 monitoring, as scheduled in Table 1. Spot oxygen saturation will be measured using a portable pulse oximeter placed on the subject's fingertip. Continuous oxygen saturation will be monitored through a capnography monitor.

SpO_2 will be monitored for alarms continuously up to 1 hour prior to each study drug administration and will continue for up to 6 hours following each drug administration, or longer if deemed medically necessary. In addition, respiratory rate will be recorded at nominal timepoints post dosing, as scheduled in Table 1. Any SpO_2 event that is deemed clinically significant will be reported as an AE if it meets the criteria of significance defined in section 6.1.8.

6.1.4.2 Continuous and Spot End-Tidal CO_2

Assessments of respiratory depression will include continuous and spot $EtCO_2$ through a capnography monitor, as scheduled in Table 1.

$EtCO_2$ will be monitored continuously for alarms up to 1 hour prior to each study drug administration and will continue for up to 6 hours following each drug administration, or longer if deemed medically necessary. Baseline $EtCO_2$ will be recorded within 1 hour prior to each dose administration. In addition, $EtCO_2$ will be recorded at nominal timepoints post dosing, as scheduled in Table 1. Any $EtCO_2$ event that is deemed clinically significant will be reported as an AE if it meets the criteria of significance defined in section 6.1.8.

6.1.4.3 Continuous and Spot Respiratory Rate

Assessments for respiratory depression will be monitored for alarms by continuous and spot respiratory rate as scheduled in Table 1. Spot respiratory rate will be measured by counting breaths for 1 minute. Continuous respiratory rate will be monitored through a capnography monitor.

Respiratory rate will be monitored continuously up to 1 hour prior to each study drug administration and will continue for up to 6 hours following each drug administration, or longer if deemed medically necessary. Baseline respiratory rate will be recorded within 1 hour prior to each dose administration. In addition, respiratory rate will be recorded at nominal timepoints post dosing, as scheduled in Table 1. Any respiratory rate event that is deemed clinically significant will be reported as an AE if it meets the criteria of significance defined in section 6.1.8.

6.1.5 12-Lead Electrocardiogram

A 12-lead ECG will be performed as scheduled in Table 1.

Electrocardiograms will be performed after the subject has been resting in a supine position for at least 5 minutes.

All abnormal ECGs will be interpreted by an investigator as abnormal NCS, or abnormal CS in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs.

6.1.6 Laboratory Evaluations

Laboratory evaluations will be performed as scheduled in Table 1.

The laboratory evaluations to be conducted for this study are presented in APPENDIX 6. The total blood volume for screening and safety assessments will be approximately 15 mL.

Each abnormal value will be interpreted by an investigator as abnormal NCS, or abnormal CS. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs.

Urine samples to be collected during the course of this study include pregnancy tests and drug screens as outlined in Table 1.

Additional clinical laboratory tests may be performed by the medical laboratory as part of larger standard test panels (not required for subject safety). Only test results required by the protocol and/or abnormal results will be entered in the clinical database and reported in the CSR, based on report requirements.

6.1.7 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a questionnaire designed for the assessment of suicidal ideation and behavior in adolescents and adults.

To monitor for a history of (the past 2 years/24 months to present) or the emergence during study participation of suicidal ideation and behavior, subjects will undergo C-SSRS evaluations at the timepoints indicated in Table 1.

The questionnaire must be administered by an investigator or other individual that is suitably qualified by education or training and designated. See APPENDIX 7 for a sample C-SSRS – Baseline/Screening version assessment and APPENDIX 8 for a sample C-SSRS-Since Last Visit version assessment.

If a subject becomes suicidal during the study, an investigator or medically qualified sub-investigator should provide the appropriate treatment and/or referral to the subject, and record as an AE.

6.1.8 Assessment of Respiratory Depression

Capnography alarms will be set to evaluate for respiratory depression and will include:

- An increase in $EtCO_2$ to >50 mmHg
- A reduction in O_2 saturation to <90%
- A reduction in respiratory rate to <6 breaths per minute

All alarms will be assessed for clinical significance and reported as AEs, as applicable. Supplemental oxygen will be given as medically necessary.

6.1.9 Rescue Therapy

The clinical study site is equipped with emergency equipment and supplies that correspond with the level of risk associated with this study. In case of a medical emergency or an SAE requiring medical intervention, emergency equipment and supplies will be available and will include, but may not be limited to, stocked crash carts, oxygen source, suction pump, and defibrillator. Emergency medication (e.g., flumazenil, diphenhydramine, epinephrine, methylprednisolone, ranitidine, rescue medication required for advanced cardiac life support [ACLS]) may be administered if deemed necessary by an investigator or designee. If required, subjects will be transported to a hospital.

During the Qualification and Treatment phases, the principal investigator (PI) or designee will be on-site at the time of study drug administration until at least 6 hours postdose. ACLS-certified staff will be present on site and an investigator will be readily available by telephone.

When not available on-site, the PI or designee will be on-call until the end of the study. While confined in the CRU, subjects will be supervised by staff nurses and/or paramedics. Dedicated nurses and/or paramedics will be available to monitor AEs and perform safety measures.

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication will be recorded.

6.2 Pharmacokinetic Assessments

A total of 14 blood samples will be collected following each dose in the Treatment phase for PK assessments. The complete blood sampling schedule is presented in Table 4.

Table 4. Pharmacokinetic Blood Sampling Schedule

Sample No	Nominal Time* (hours)
01	0.0
02	0.5
03	1
04	1.5
05	2
06	2.5
07	3
08	4
09	5
10	6
11	7
12	8
13	10
14	24

* Nominal times listed are relative to the time of study treatment administration.

Blood samples will be collected by direct venipuncture into a labeled tube containing the appropriate anticoagulant as specified by the bioanalytical facility. As an option to the subject, or if judged necessary by the clinical staff, blood samples may be collected using a catheter, which will be placed in the vein of the subject.

The time of PK blood sample collection will be calculated relative to the time of dose administration. The actual time of all PK blood draws will be recorded and reported for all subjects. Each subject will be dosed at the same time in each period and all activities (e.g., scales, meals) will be based on that dosing time. Blood volume required for PK assessments will be included in the total blood volume reported in the informed consent.

Gabapentin concentrations for PK assessments will be obtained through bioanalysis of the plasma derived from the blood samples drawn during this study, using a validated bioanalytical method.

6.2.1 Pharmacokinetic Sample Processing, Storage and Shipping

Blood samples for PK determination will be processed, stored, and shipped according to the sample processing instructions supplied by the bioanalytical facility. Each tube will be appropriately labeled.

6.3 Pharmacodynamic Assessments

Pharmacodynamic assessments will be performed throughout the study as outlined in Table 1.

Prior to completing the computerized PD measures, all subjects will undergo a scripted training and practice regimen. Eligible subjects who appear to have difficulty differentiating between bipolar and unipolar VAS (e.g., making errors such as selecting 50 as neutral for a unipolar scale) or difficulty distinguishing between "at this moment" and "next-day" measures during the Qualification phase will undergo additional training on the difference between the scale types. Additional training sessions will be documented in source files.

Testing conditions for PD assessments should remain as consistent as possible across treatment periods. Subjects will be monitored carefully to ensure that they are completing the PD assessments appropriately; all reasonable attempts should be made to rouse subjects who fall asleep during testing cycles. If subjects cannot complete the PD assessments in a timely manner prior to the next required procedure or timepoint due to an AE, testing will be aborted.

6.3.1 Subjective Effects

6.3.1.1 Visual Analogue Scales

All VASs will be scored on a 100-point scale, as shown in Table 5. The VASs may be administered as bipolar or unipolar scales, as appropriate, and the choice is determined by the nature of the subjective effect being measured. Bipolar scales ask about the neutrality, the direction and the intensity of a subjective opinion, whereas unipolar scales only ask about the extremity or intensity of a subjective opinion. When VASs are administered as bipolar scales, a neutral point equal to 50 is embedded within the scale (e.g., Drug Liking, Overall Drug Liking, Take Drug Again, Drowsiness/Alertness VAS). The neutral point reflects a state whereby a subject is experiencing neither negative nor positive effects (e.g., neither dislike nor like the effects of the drug) and is labeled with an anchor, such as “neither like nor dislike.” When VASs are administered as unipolar scales, anchors will be presented using text such as “Not at all” (score = 0) to “Extremely” (score = 100; e.g., Good, Bad, High, and Any Effects VASs). Unipolar scales do not include a neutral point but rather, a rating of “0” reflects the complete absence of a subjective effect while a rating of “100” reflects the maximum presence of a subjective effect (e.g., No Good Effects = 0, Extremely Good Effects = 100). Scales that refer specifically to drug (e.g., Drug Liking, Good Effects VAS, Bad Effects VAS, and Any Effects VAS) are not administered at predose.

Table 5. Visual Analog Scale (VAS) Descriptions

Scale Interpretation	Include Predose	Type of Scale	Description	Question Text	Response Anchors
Balance	No	Bipolar	Drug Liking	At this moment, my liking for this drug is	0: Strong disliking 50: Neither like nor dislike 100: Strong liking
Balance	No	Bipolar	Overall Drug Liking	Overall, my liking for this drug is	
Balance	No	Bipolar	Take Drug Again	I would take this drug again	0: Definitely would not 50: Neither would nor would not 100: Definitely would
Positive	Yes	Unipolar	High	At this moment, I am feeling high	0: Not at all 100: Extremely
Positive	No	Unipolar	Good Effects	At this moment, I feel good drug effects	
Negative	No	Unipolar	Bad Effects	At this moment, I feel bad drug effects	
Other	No	Unipolar	Any Effects	At this moment, I feel any drug effect	
Other	Yes	Unipolar	Feeling Drunk	At this moment, I am feeling drunk	
Other	Yes	Bipolar	Drowsiness/Alertness	At this moment, my mental state is	0: Very drowsy 50: Neither drowsy nor alert 100: Very alert
Other	Yes	Bipolar	Relaxation/Agitation	At this moment, my mental state is	0: Very relaxed 50: Neither relaxed nor agitated 100: Very agitated

6.3.1.2 Questionnaires

The ARCI MBG and PCAG scales will be administered as scheduled in Table 1.

The 49-item ARCI is a shortened version (49 true-false items) compiled by Martin et al.[37] from the 550-item Addiction Research Center Inventory (ARCI) originally developed by Haertzen.[38,39] This version contains 5 scales, which measure the following effects: Euphoria -- Morphine-Benzedrine Group (MBG) scale; Stimulant effects -- Amphetamine (A) scale and Benzedrine Group (BG) scale; Dysphoria -- Lysergic Acid Diethylamide (LSD) scale; and Sedation -- Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) scale. Subjects indicate their responses by selecting "False" or "True." One point is given for each response that agrees with the scoring direction on the scale (i.e., True items receive a score of 1 if the answer is "True;" no points are given when the answer is opposite to the scoring direction).

The following 2 scales will be administered:

- Pentobarbital Chlorpromazine Alcohol Group – PCAG
- Morphine Benzedrine Group – MBG

The items pertaining to the ARCI MBG and ARCI PCAG scales are presented below:

Questions Contributing to ARCI MBG & PCAG Scales	Scale	
	PCAG	MBG
1. My speech is slurred.	T	
2. I am not as active as usual.	T	
3. I have a feeling of just dragging along rather than coasting.	T	
4. I feel sluggish.	T	
5. My head feels heavy.	T	
6. I feel like avoiding people, although I usually do not feel this way.	T	
7. I feel dizzy.	T	
8. It seems harder than usual to move around.	T	
9. I am moody.	T	
10. People might say that I am a little dull today.	T	
11. I feel drowsy.	T	
12. I am full of energy.	F	
13. Today I say things in the easiest possible way.		T
14. Things around me seem more pleasing than usual.		T
15. I have a pleasant feeling in my stomach.		T
16. I feel I will lose the contentment that I have now.		T

17. I feel in complete harmony with the world and those about me.		T
18. I can completely appreciate what others are saying when I am in this mood.		T
19. I would be happy all the time if I felt as I feel now.		T
20. I feel so good that I know other people can tell it.		T
21. I feel as if something pleasant had just happened to me.		T
22. I would be happy all the time if I felt as I do now.		T
23. I feel more clear-headed than dreamy.	F	T
24. I feel as if I would be more popular with people today.		T
25. I feel a very pleasant emptiness.		T
26. My thoughts come more easily than usual.		T
27. I feel less discouraged than usual.		T
28. I am in the mood to talk about the feelings I have.		T
29. I feel more excited than dreamy.	F	
30. A thrill has gone through me one or more times since I started this test.	F	

T = True item
F = False item

Responses to individual items will be included. If one of the individual items is missing, the associated scale(s) score will not be calculated.

6.3.2 Modified Observer's Assessment of Alertness/Sedation (MOAA/S)

The MOAA/S is an observer-rated measure of alertness/sedation that is used widely in clinical research. It is based on the following 6 items, rated on a scale from 5 (not sedated) to 0 (unarousable):

The Observer's Assessment of Alertness/Sedation Scale (OAA/S) was developed to measure the level of alertness in subjects who are sedated.[36] The OAA/S is a reliable validated measure and was shown to be sensitive to different levels of sedation and is composed of 4 assessment categories that include responsiveness, speech, facial expression, and eyes. The Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) includes only the Responsiveness assessment category. It is easy and quick to administer (less than 1 minute). The subjects' level of responsiveness is measured in a 5-point Likert scale:

Responsiveness	Score
Responds readily to name spoken in normal tone	5 (Alert)
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1 (Deep Sleep)

7 ADVERSE EVENTS DOCUMENTATION

7.1 Definitions

An AE is defined as any untoward medical occurrence in a subject administered an investigational product and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal clinical laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

A suspected adverse reaction (SAR) is any AE for which there is a reasonable possibility the drug caused the AE. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Regarding marketed medicinal products, an adverse drug reaction is defined as a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

An AE may be:

- A new illness,
- Worsening of a concomitant illness,
- An effect of the study drug including comparator; it could be an abnormal clinical laboratory value as well as a significant shift from baseline within normal range which an investigator considers to be clinically important.

Surgical procedures themselves are not AEs. They are therapeutic measures for conditions that required surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the conditions(s) leading to these measures are not AEs, if the condition(s) was (were) known before the start of study treatment. In the latter case, the condition should be reported as medical history.

An SAE or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions),
- Is a congenital anomaly or birth defect,
- Is an important medical event (including development of drug dependence or drug abuse) that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above (according to medical judgment of an investigator).

7.2 Severity Assessment

All AEs will be graded as mild, moderate, or severe according to the following definitions:

Mild: Causing no limitation of usual activities; the subject may experience transient slight discomfort.

Moderate: Causing some limitation of usual activities; the subject may experience annoying discomfort.

Severe: Causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

Every effort will be made to obtain an adequate evaluation of the severity.

7.3 Causality Assessment

An investigator will determine the relationship of any AE to the study drug using the guidelines presented in Table 6.

Table 6. Adverse Event Relationship to Study Drug

Relationship to Drug	Comment
Reasonable Possibility	A temporal relationship exists between the AE onset and administration of the investigational product that cannot be readily explained by the subject's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or AE profile of the investigational product. In case of cessation or reduction of the dose the AE may abate or resolve and it may reappear upon rechallenge.
No Reasonable Possibility	Evidence exists that the AE has an etiology other than the investigational product. For SAEs, an alternative causality must be provided (e.g., preexisting condition, underlying disease, intercurrent illness, or concomitant medication).

7.4 Adverse Event Monitoring

For the purposes of this study, the monitoring period for AEs extends from the time of first study treatment administration in the Qualification phase until Day 14 of the Treatment phase. Any medical conditions occurring from the time of signing informed consent until the first dose of study treatment in the Qualification phase will be recorded as medical history. If the condition meets the criteria for an SAE it will be reported as described in section 7.6.

Subjects will be questioned on their health status prior to each study treatment and periodically thereafter, including prior to PD measurements. Open-ended questions will be asked.

During the study, all AEs spontaneously reported by the subject, observed by the clinical staff or elicited by general questioning will be recorded for all subjects and reported in the CRF.

Every effort will be made to obtain an adequate follow-up of the subjects and the final outcome. Should any subject choose to withdraw from the study, they will be advised of the safety precautions to be taken.

Any AE which remains unresolved as of the last visit will require an appropriate evaluation and follow-up until the AE has been resolved or a reasonable explanation for its persistence found, or is deemed mild and safely resolving.

It is an investigator's responsibility to ensure subjects experiencing adverse events receive appropriate follow-up, treatment where required, and that every action is well-documented.

Classification of AEs will be performed by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), version 22.0 or higher.

Concomitant medications will be coded using the World Health Organization Drug Dictionary-Enhanced (WHO-DDE March 2019 or later).

7.5 Reporting of Pregnancy

Pregnancy in a female study subject shall be reported to the sponsor within 24 hours of the knowledge of its occurrence by an investigator or delegate (for pregnancies occurring during the course of the study or up to 30 days following the end of the study). Because of the possibility the fetus/embryo could have been exposed to the study drug through the parent and for the subject's safety, the pregnancy will be followed up to determine its outcome, including spontaneous or voluntary termination, details of birth, presence or absence of any birth defects, congenital anomalies, or maternal and/or newborn complications.

The pregnancy will be recorded and reported by the clinical site to the sponsor. Pregnancy follow-up will also be properly recorded to ensure quality and completeness of the data belonging to the study drug and will include an assessment of the possible causal relation between the study drug and any pregnancy outcome. Any SAE experienced during pregnancy will be reported on an SAE Report Form.

7.6 Serious Adverse Event Reporting

The CRU will notify any SAE to the sponsor or designee, without regard to causality, within 24 hours after becoming aware of its occurrence.

If, during follow-up, any non-serious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

The initial SAE report must be as complete as possible, including details of any current illness and SAE, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the AE, laboratory values received after the report, or hospital discharge summary) must be documented. All follow-up information must be reported as soon as the relevant info is available, in the same manner as the initial report.

If an SAE occurs to a subject during this study, the SAE report and relevant medical records should be faxed at the time of the report to Arbor Safety Inbox [redacted] or scanned and emailed [redacted]. The SAE may also be reported by telephone to Arbor Drug Safety [redacted].

An SAE will be considered "unexpected" if the AE is not listed in the US product inserts (USPIs) or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected," as used in this definition, also refers to AEs that are mentioned in the USPIs as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

The CRU will determine whether any serious, unexpected, related AE must be reported to the institutional review board (IRB). If so, the event will be reported via fax or email within 15 calendar days of an investigator or staff becoming aware of the event.

The sponsor will determine whether the SAE must be reported in an expedited manner to the applicable regulatory agencies. If so, the sponsor will report the event to those agencies and to all participating investigators.

If reports of any new and unexpected AEs become available to the sponsor during the clinical portion of this study, the sponsor will advise the CRU, through its clinical investigator, of those events. If required, the sponsor will report to the applicable regulatory authorities.

8 DATA ANALYSIS AND STATISTICAL METHODS

8.1 Analysis Populations

8.1.1 Qualification Phase

8.1.1.1 Qualification Randomized Population

The Qualification Randomized population will include all subjects who are assigned a randomization number in the Qualification phase.

8.1.1.2 Qualification Safety Population

The Qualification Safety population will include all subjects who are randomized into the Qualification phase and receive at least 1 dose of either the study drug or placebo.

8.1.2 Treatment Phase

8.1.2.1 Randomized Population

The Randomized population will include all subjects who are assigned a randomization number in the Treatment phase.

8.1.2.2 Safety Population

The Safety population will include all subjects who are randomized into the Treatment phase and receive at least 1 dose of 1 of the study drugs or placebo.

8.1.2.3 Completer Population

All subjects in the Safety population who complete all 5 crossover periods in the Treatment phase of the study, and have sufficient data for evaluation of the primary endpoint (based on a blinded review of data prior to database lock) will be included in the Completer population. Subjects who do not have at least 1 observation within 2 hours of T_{max} for each treatment for Drug Liking VAS will be excluded from the Completer population.

8.1.2.4 Modified Completer Population

All subjects in the Completer population, excluding problematic subjects with unreliable responses which can alter study results, will be included in the Modified Completer population. For the Drug Liking VAS scale, the following elimination criteria will be used to define the Modified Completer population.

a) Similar E_{max} scores (within a 5-point difference) for a subject across all study treatments (including placebo)

OR

b) E_{max} for placebo > 60 AND the E_{max}(placebo) – E_{max}(positive control) ≥ 5

Criterion a) and b) will be applied to the Drug Liking VAS data on the Completer population. If no subjects are excluded when these criteria are applied, then the Modified Completer population is the same as the Completer population.

8.1.2.5 Pharmacokinetic (PK) Population

All subjects in the Safety population who receive at least 1 dose of GE-IR, and have at least 1 PK concentration after dosing will be included in the PK population.

8.2 Appropriateness of Measures

The selected PD measures will assess positive and negative subjective drug effects associated with the abuse potential of this drug. These subjective measures are consistent with guidelines for HAP studies[4] and are similar to those used in previous studies. Although data from all measures will be considered in the assessment of abuse potential, the Drug Liking VAS has been selected as the primary endpoint for practical purposes (such as calculating power and assessing qualification eligibility), as it is considered 1 of the most sensitive and face-valid measures of abuse potential.[6, 7] Overall Drug Liking VAS and Take Drug Again VAS have been selected as key secondary endpoints as they represent the subject's global assessment of the drug and have face validity for predicting continued use of a drug. High VAS has also been selected as a key secondary endpoint because it has been shown to be sensitive in capturing the positive subjective effects of test drugs. Additional secondary endpoints assess other subjective effects of the drug that may help with interpretation of the data.

Standard PK parameters will be evaluated to confirm plasma concentrations and the PK profile of GE-IR in the PK population. Standard measures of safety will be included to monitor the safety and tolerability of the GE-IR doses used in the study.

8.3 Missing Values

No imputation of missing PD or PK data will be performed.

The occurrence of missing PD data will be minimized by only including subjects who are rousable and complete PD assessments in the Qualification phase. In addition, all reasonable attempts will be made to rouse subjects for completion of the PD assessments in both the Qualification and Treatment phases. Missing PD assessments, including reasons for the missing data, will be listed by subject, and examined on a case-by-case basis to determine if these affect subject allocation (i.e., inclusion in the Modified Completer population). If for a given PD measure, the predose value is missing, calculation of CFB_{min} and TA_AOE will not be possible, and the subject will not be included in the Modified Completer population for that PD endpoint. If the actual date and/or time of a postdose PD assessment is unknown, but there is a result at that timepoint, the value will be used in descriptive statistics of treatment by timepoint summaries, and PD endpoint by treatment summaries but will be excluded from calculation of TA_AUE and TA_AOE which need actual time from dose in order to be calculated.

If the actual collection time of a postdose PK sample is unknown, but a valid concentration value has been measured, the sample will be set to missing in the PK analysis and will be presented in

listing but excluded from descriptive statistics. Unknown baseline collection times will be handled on a case-by-case basis.

Further details on handling of missing values will be provided in the Subject Allocation and Request to Break the Blind Form, and in the Statistical Analysis Plan (SAP).

8.4 Demographic Data and Other Baseline Characteristics

8.4.1 Qualification Phase

All subjects who are randomized into the qualification phase will be entered into the database. Disposition tables and listings will be presented for all subjects in the Qualification Randomized population. Demographics and baseline characteristics (sex, age, race, ethnicity, body weight, height, BMI) will be summarized for the Qualification Safety population. Qualification passes and failures will be listed separately.

8.4.2 Treatment Phase

A disposition table will be presented for all subjects randomized to the Treatment phase. Demographics and baseline characteristics (sex, age, race, ethnicity, body weight, height, BMI), recreational drug use history, alcohol use history, and smoking history will be summarized using descriptive statistics (n, mean, SD, minimum, median, and maximum for continuous variables, and the proportion of subjects for categorical variables) for the Safety population. No formal statistical comparison between the groups will be performed.

Medical history will be listed by subject. Medical history will be coded into the most recent version of MedDRA available (version 22.0 or later).

Prior and concomitant medications will be assigned a 12-digit code using the most recent version of the World Health Organization drug codes available. Prior and concomitant medications will be listed by subject.

The number of subjects in each treatment group will be presented, in addition to the number of subjects who complete each treatment period. The reasons for all post-randomization discontinuations will be tabulated and grouped by treatment and major reason. All deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management, or subject assessment will be listed.

8.5 Pharmacodynamics

8.5.1 Pharmacodynamic Endpoints

Pharmacodynamic endpoints will be evaluated as described in Table 7 and all PD data will be analyzed using the Modified Completer population.

Table 7. Pharmacodynamic Endpoints

Description	Type	Endpoints
Drug Liking	Bipolar VAS	E_{max}, E_{min}, TE_{max}, TE_{min}, and TA_AUE
Overall Drug Liking	Bipolar VAS	E_{max}
Take Drug Again	Bipolar VAS	E_{max}
High	Unipolar VAS	E_{max}, TE_{max}, and TA_AUE
Good Effects	Unipolar VAS	E_{max}, TE_{max}, and TA_AUE
Bad Effects	Unipolar VAS	E_{max}, TE_{max}, and TA_AUE
Any Effects	Unipolar VAS	E_{max}, TE_{max}, and TA_AUE
Feeling Drunk	Unipolar VAS	E_{max}, TE_{max}, and TA_AUE
Drowsiness/Alertness	Bipolar VAS	E_{min}, TE_{min}, and TA_AOE
Relaxation/Agitation	Bipolar VAS	E_{min}, TE_{min}, and TA_AOE
Addiction Research Center Inventory (ARCI) Morphine-Benzedrine Group (MBG) Scale	Questionnaire score	E_{max}, TE_{max}, and TA_AUE
ACRI Pentobarbital–Chlorpromazine–Alcohol Group (PCAG) Scale	Questionnaire score	E_{max}, TE_{max}, and TA_AUE
Modified Observer's Assessment of Alertness/Sedation (MOAA/S)	Observer's score	E_{min}, CFB_{min}, and TA_AOE

CFB_{min}= change from baseline to minimum effect, E_{max}= maximum (peak) effect, E_{min}=minimum effect, TA_AOE= time-averaged area over the effect-time curve, TA_AUE=time-averaged area under the effect-time curve, TE_{max}=time of maximum (peak) effect, TE_{min}=time of minimum effect, VAS=Visual Analog Scale

8.5.2 Pharmacodynamic Statistical Methodology

Drug Liking and Take Drug Again VAS E_{max} from the Qualification phase will be summarized by treatment and paired difference for the Modified Completer population. The data will be evaluated to confirm that an appropriate population was selected for the Treatment phase.

During the Treatment phase, PD values at each timepoint will be summarized by treatment using descriptive statistics and presented graphically. Derived endpoints will be summarized by treatment and paired difference using descriptive statistics.

8.5.2.1 Primary Analysis

Pharmacodynamic endpoints for the Treatment phase (E_{max}, E_{min}, CFB_{min}, TA_AUE and TA_AOE, as appropriate) will be analyzed using a mixed-effect model if the residuals are normally distributed. The model will include treatment, period, treatment sequence, and first-order carryover effect (where applicable) as fixed effects, and the baseline (predose) measurement as a covariate (where applicable). If the variance among treatments is homogeneous, subject will be considered a random effect; if the variance among treatments is heterogeneous, the default variance components (VC) variance structure block will be used for

each subject. Treatments for each PD endpoint will be tested for homogeneity of variance using [redacted]

After it is determined if the treatment variance is homogeneous or heterogeneous, the residuals from each mixed-effect model will be investigated for normality using the Shapiro-Wilk W test. The null and alternative hypotheses for this analysis are shown below:

H_0: distribution of residuals is normal vs. H_a: distribution of residuals is not normal

If the residuals from the mixed-effect model are normally distributed, e.g., p-value ≥ 0.05, it will be determined if carryover effects should be included.

When conducting drug abuse potential studies, Chen and Tsong[14] have recommended the inclusion of first-order carryover as a fixed effect in the mixed-effect model. The adoption of this conservative approach would address possible effects associated with the subjective nature of these studies. Carryover effects are defined as the treatment administered in the previous treatment period. As there are no carryover effects in treatment period 1, placebo will be used in this period. If the carryover effect is found to be non-significant at alpha ≥ 0.25, then the term will be dropped from the mixed-effects model. If the carryover effect is found to be significant at alpha < 0.25, it will be included in the model.

If the normality assumption of the model is satisfied, least-square means, standard errors (SEs), and 1-sided 95% or 2-sided 95% or 90% confidence intervals (CIs) for treatments and treatment differences will be derived from the mixed-effect model. P-values will be provided for the effects and the contrasts.

If the normality assumption of the model is not satisfied, the distribution of the paired difference for each contrast will be examined in terms of normality and skewness. Each paired difference will be investigated for normality using the Shapiro-Wilk W-test. If the p-value for the distribution of the paired difference is normal, that is, p-value ≥ 0.05, a paired t-test will be used.

If the paired difference is not normally distributed, that is, p-value < 0.05, the following steps will be taken to test skewness:

[redacted]

The calculation of the sign test, and the confidence interval for the median based on the sign test will exclude subjects who have zero difference in scores between the 2 treatments.[35]

8.5.2.1.1 Test Hypotheses for Primary Endpoint, Drug Liking VAS E_{max}

The primary objective of a HAP study is to provide information on the relative abuse potential of a test drug in humans.[4] The statistical analysis of a HAP study should address the following questions:

1. Does the known drug of abuse (positive control) produce reliable abuse-related responses compared to placebo (study validity)?

2. Does the test drug produce abuse-related responses that are smaller than those of the positive control?

3. Does the test drug produce abuse-related responses that are similar to placebo?

To address these issues, the following hypotheses will be tested for Drug Liking VAS E_{max} at a significance level of 0.05; 1-sided 95% confidence intervals will be used.

[redacted]

These hypotheses will be applied to the primary endpoint, Drug Liking VAS E_{max}.

Although a margin of 15 has been selected for Hypothesis 1 to ensure consistency with the Qualification phase criteria, subjects are expected to provide lower responses in the Treatment phase as compared to the Qualification phase.[19, 31] Therefore, if the difference between the positive control and placebo does not meet the recommended criterion for validity (i.e., δ_1= 15), a secondary planned analysis will be performed (refer to section 8.5.2.2) A margin of 11 points is considered appropriate for Hypothesis 3 based on an analysis of Drug Liking VAS E_{max} data.[15] Further details will be described in the SAP..

For study validity purposes, the primary endpoint, E_{max} for Drug Liking VAS, will be compared between the positive control (alprazolam 2 mg) and placebo. [redacted] If statistically significant, it will confirm the sensitivity of the study and allow for the comparison of the other pairwise comparisons shown below. The hypotheses can be expressed as follows:

[redacted]

where μ_C is the mean for the positive control, alprazolam, and μ_P is the mean for placebo, and will be applied to the following contrast:

[redacted]

To assess whether the test drug has less abuse potential than the positive control, the null hypothesis will be that the mean difference in Drug Liking E_{max} between alprazolam and GE-IR is less than or equal to 0 against the alternative hypothesis that the mean difference in Drug Liking E_{max} between alprazolam and GE-IR is greater than 0.

Comparison between the positive control, alprazolam, and the test drug, GE-IR, will be:

[redacted]

where μ_C is the mean for the positive control, alprazolam, and μ_T is the mean for the test drug, GE-IR, and will be applied to the following contrasts:

[redacted]

To assess whether the test drug, GE-IR, shows similar abuse potential to placebo, the hypothesis for the comparison will be:

[redacted]

where μ_T is the mean for the test drug, GE-IR, and μ_P is the mean for placebo, and will be applied to the following contrasts:

[redacted]

8.5.2.1.2 Test Hypotheses for Key Secondary Endpoints

The key secondary endpoints in this study will be E_{max} of Overall Drug Liking, Take Drug Again and High. For the comparisons of key secondary PD endpoints, the following hypothesis will be used to provide information on the relative abuse potential of the test drug in humans:

[redacted]

The hypothesis for comparison between the positive control, alprazolam and placebo will be:

[redacted]

where μ_C is the mean for the positive control, alprazolam, and μ_P is the mean for placebo, and will be applied to the following contrast:

[redacted]

The hypothesis for comparison between the positive comparator, alprazolam, and the test drug, GE-IR, will be:

[redacted]

where μ_C is the mean for the positive control, alprazolam, and μ_T is the mean for the test drug, GE-IR, and will be applied to the following contrasts:

[redacted]

The hypothesis for comparison between the test drug, GE-IR, and placebo will be:

[redacted]

where μ_T is the mean for the test drug, GE-IR, and μ_P is the mean for placebo, and will be applied to the following contrasts:

[redacted]

A significance level of 0.05 will be used for all 1-sided tests; 1-sided 95% confidence intervals will be presented. For 2-sided tests, a significance level of 0.1 will be used [32] with 2-sided 90% confidence intervals. No adjustments for p-values will be made to account for multiple comparisons.

8.5.2.1.3 Test Hypotheses for Non-Key Secondary Endpoints

For the comparisons of all other non-key secondary PD endpoints, the following hypothesis will be used to provide information on the relative abuse potential of the test drug in humans:

[redacted]

The hypothesis for comparison between the positive control, alprazolam and placebo will be:

[redacted]

where μ_C is the mean for the positive control, alprazolam, and μ_P is the mean for placebo, and will be applied to the following contrast:

[redacted]

The hypothesis for comparison between the positive comparator, alprazolam, and the test drug, GE-IR, will be:

[redacted]

where μ_C is the mean for the positive control, alprazolam, and μ_T is the mean for the test drug, GE-IR, and will be applied to the following contrasts:

[redacted]

The hypothesis for comparison between the test drug, GE-IR, and placebo will be:

[redacted]

where μ_T is the mean for the test drug, GE-IR, and μ_P is the mean for placebo, and will be applied to the following contrasts:

[redacted]

A significance level of 0.05 will be used for Hypotheses 1 and 2, and a significance level of 0.1 will be used for Hypothesis 3.[32] For Hypotheses 1 and 2, 2-sided 95% confidence intervals will be presented while 2-sided 90% confidence intervals will be presented for Hypothesis 3. No adjustments for p-values will be made to account for multiple comparisons.

8.5.2.2 Secondary Analysis

Although a margin of 15 has been selected for Hypothesis 1 for consistency with the Qualification phase criteria, subjects may have lower responses with alprazolam and higher responses with placebo in the Treatment phase as compared to the Qualification phase, [19,31] particularly for lower abuse potential drugs such as benzodiazepines (i.e., Schedule IV drugs). Therefore, in the case that the difference between the active control and placebo does not meet

the pre-specified criteria for validity of at least 15 points, secondary analysis will be performed. Details of the secondary analysis will be described in the SAP.

8.6 Pharmacokinetics

The PK analysis will be carried out according to Altasciences SOPs. Pharmacokinetic data handling and analysis will be further detailed in the SAP.

8.6.1 Measurements Below the Lower Limit of Quantitation

Concentration values below the lower limit of quantitation (LLOQ) associated with predose and postdose collection times will be replaced with zero for the non-compartmental analyses (NCA).

Concentration values below the LLOQ will be replaced with 0 for mean PK profile representations as well as for descriptive statistic calculations.

8.6.2 Actual Time

Analysis will be based on the actual sampling times, except for predose samples, which will always be reported as 0, regardless of time deviations.

The individual concentration/time profiles will be presented using actual sampling times whereas the mean concentration/time profiles and tables presenting summary statistics of concentration-time series will be presented using nominal sampling times.

Actual times will be listed in the report.

8.6.3 Noncompartmental Analysis (NCA)

The following configuration for the NCA analysis (with Phoenix® WinNonlin® version 8, or higher) will be used:

[redacted]

Reason for exclusion of AUC: In the case where less than 3 consecutive measurable concentrations are observed, the AUC parameters will not be estimated.

The PK parameters for gabapentin are presented in Table 8.

Table 8. Pharmacokinetic Parameters

Parameter	Definition
C_{max}	Maximum observed concentration occurring at time T_{max}
T_{max}	Time of maximum observed concentration. If the maximum observed concentration is not unique, then the first maximum is used.
AUC_{0-T}	Area under the concentration time curve from the time 0 to T_{last}.
T_{last}	Time of last measurable (positive) observed concentration

8.6.4 Pharmacokinetic Statistical Methodology

8.6.4.1 Descriptive Statistics

Descriptive statistics of the individual concentration data and derived parameters will be calculated with the build-in Phoenix® WinNonlin® platform and displayed with the same precision as received from the bioanalytical laboratory.

Precision for individual values will be display as follows:

- C_{max} and AUC will be displayed with the same precision as the raw PK concentration data
- Parameters associated with time will be displayed with 2 decimal places

Summary statistics will be displayed with the same precision as the individual values, with the exception of number of observations (N) and coefficient of variation (CV%) which will be presented with 0 and 1 decimal place, respectively.

Descriptive statistics will be calculated for concentrations at each individual timepoint and for all PK parameters. Individual concentrations, and PK parameters obtained from the NCA will be summarized per treatment group using the following descriptive statistics: N, minimum, arithmetic mean, geometric mean, median, maximum, standard deviation (SD), CV%.

8.6.4.2 Statistical Analysis

No formal statistical analysis of PK data will be performed.

8.7 Safety

8.7.1 Safety Endpoints

For the Treatment phase, safety endpoints will include a summary of the incidence of AEs, SAEs, as well as descriptive summary and statistics of the safety parameters (clinical laboratory values, vital signs [i.e., systolic and diastolic blood pressure, pulse rate, respiratory rate, oral temperature, SpO_2], continuous SpO_2 monitoring, continuous $EtCO_2$ monitoring, ECGs, C-SSRS, and physical examination findings.

8.7.2 Safety Analysis

The clinical laboratory tests and the measurements of vital signs, continuous SpO_2 and $EtCO_2$ monitoring, ECGs, C-SSRS and physical examination parameters will be used to perform the safety statistical analysis.

8.7.3 Safety Statistical Methodology

8.7.3.1 Qualification Phase

The Qualification Randomized population will be used to list all AEs occurring in the Qualification phase. Qualification passes and failures will be listed separately.

8.7.3.2 Treatment Phase

Analysis of safety assessments will be performed using the Safety population. Assessment of safety will be based on the incidence of AEs, AEs resulting in discontinuation, and SAEs by treatment. AE summaries will be provided showing the number and percentage of subjects who experienced at least 1 TEAE during the Treatment phase. TEAEs will also be tabulated by maximum severity and by maximum relationship to study drug. These summaries will be presented by body system and preferred term (Medical Dictionary for Regulatory Activities [MedDRA], version 22.0 or higher). SAEs and AEs resulting in discontinuation will be summarized separately. All AEs will be listed by subject for the Safety population.

Laboratory data collected during the Treatment phase will be summarized by the type of laboratory test and visit. Descriptive statistics (n, mean, SD, minimum, median, and maximum) and the number of subjects with laboratory test results below, within, and above normal ranges will be tabulated by visit. Abnormal findings in laboratory data will be listed.

Treatment phase vital signs (blood pressure, heart rate, respiratory rate, SpO_2) and $EtCO_2$ will be analyzed as minimum, maximum, and final postdose values since the analyses of these extremes are more meaningful than analyses of individual timepoints. Vital signs will be summarized using descriptive statistics (n, mean, SD, minimum, median, and maximum). Abnormal findings in vital signs data will be listed.

12-Lead ECG data during the Treatment phase (absolute values in heart rate and PR, QRS, QT, and QTcF intervals) will be summarized by parameter and visit using descriptive statistics (n, mean, SD, minimum, median, and maximum). Overall ECG interpretation will be summarized (normal; abnormal, non-clinically significant; and abnormal, clinically significant). Abnormal findings in ECG data will be listed.

Physical examination abnormal results will be listed by subject and visit. Baseline and since last visit scores from the C-SSRS questionnaire will be listed. No summaries will be provided.

8.8 Planned Interim Analyses

No formal interim analyses will be performed.

8.9 Determination of Sample Size

As reported in an unpublished HAP study evaluating doses of 1.5 mg and 3.0 mg of alprazolam, the mean paired difference (SD) for Drug Liking VAS E_{max} VAS between alprazolam 1.5 mg and placebo was 26.3 (18.62). For alprazolam 3.0 mg vs. placebo, the mean difference (SD) was 26.6 (17.83). A margin of 15, with a correlation of 0, and an upper-tailed test with a significance level of 0.05 results in 48 completers for the comparison of alprazolam 1.5 mg vs. placebo, and 42 completers for the comparison alprazolam 3.0 mg vs. placebo. The more conservative sample size estimate of 48 subjects will be used.

Assuming a drop-out rate of approximately 25%, and allowing for missed data and problematic subjects as defined for the Modified Completer population, approximately 60 subjects are planned for randomization into the Treatment phase in order to achieve a minimum of 48 completers (at least 4 subjects per 10 treatment sequences).

Due to potential sedative effects that may prevent subjects from completing measures and expected natural attrition, replacement subjects may be considered in order to meet the minimum number of completers, in the event that the preplanned attrition rate of 25% is surpassed.

Subjects will be consecutively randomized into the Qualification phase until the target number of 60 subjects eligible for participation in the Treatment phase is reached.

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10 APPENDIX 1: ETHICS

10.1 Institutional Review Board

This protocol and the informed consent form (ICF) will be submitted to an institutional review board (IRB) prior to initiation of the study and the study will not start until the board has approved the documents. Notification of the board's approval will be appended to the final report.

10.2 Ethical Conduct of the Study

This study will be conducted in compliance with the study protocol, the ethical principles that have their origins in the Declaration of Helsinki, the International Council for Harmonisation (ICH) Guideline E6 for Good Clinical Practice (GCP), the Food and Drug Administration (FDA) GCP Code of Federal Regulations (CFR) Title 21 (part 56), the European regulation EU 536/2014, and the Tri-Council Policy Statement (Canada).

10.3 Subject Information and Consent

Before screening activities commence, each subject will be given a copy of the ICF to read, as well as a full explanation of the purpose of the study, the procedures to be carried out, and the potential adverse events (AEs). Once this essential information is provided to the subject and an investigator or delegate has the conviction the subject understands the implications of participating in the study, and if the subject chooses to continue the screening process, they will be requested to sign and date a properly executed ICF prior to enrollment. Subjects will be assured they may withdraw from the study at any time without jeopardizing their medical care or future study participation (for which they may qualify).

Subjects will be given a signed copy of the ICF. If an amended or revised ICF is introduced during the study, each subject's further consent must be obtained.

10.4 Subject Confidentiality

Investigators and the sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations. Subjects shall be identified by a unique subject identifier on all study documents provided to the sponsor. In compliance with federal regulations/ICH GCP Guidelines, it is required an investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and IRB access to review the subject's original medical records for verification of study-related procedures and data. An investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above-named representatives without violating the subject's confidentiality.

11 APPENDIX 2: DATA COLLECTION, RETENTION, AND MONITORING

11.1 Case Report Forms

The data required by the protocol is obtained in 2 ways. Source Documents are used in the clinic as recording devices during procedures. The data will be transcribed from source into electronic data capture software (Medrio) and stored in the secure database for each subject included in a clinical trial (i.e., subjects randomized to the Qualification phase which includes qualification failures, and subjects randomized to the Treatment phase).

Data assembled outside the clinic source (i.e., clinical laboratory data, pharmacokinetic [PK] concentration data, and pharmacodynamics [PD] measures [e.g., visual analog scale (VAS) scores]), will be received from a specified external vendor via an electronic data file. The file received will be encrypted (or posted to a secure File Transfer Protocol) and will be stored in a secure folder on a server. The electronic data file(s) are independent of the Medrio electronic data capture (EDC) data during the conduct of the study.

The Medrio EDC cleaned data will be reviewed, approved and electronically signed by the principal investigator or delegate. The Medrio EDC data will be output in a case report form (CRF) format. The external data files will be output in SAS® datasets. At review cycles, tables, figures and listings will be provided in rtf format. All data will be included with the final report provided to the sponsor.

11.2 Data Management and Processing

Data Management develops documentation to define activities performed during the data management conduct of the study trial. Medrio EDC system is the tool used to conduct all data cleaning activities, monitoring activities and review/approval activities for clinic collected data and procedure data. The external data files will be reconciled (to compare the external vendor data and Medrio EDC sample collection data). Data Management activities are performed in accordance with the Data Management standard operating procedures (SOPs).

In addition to the cleaning activities, data entered in Medrio EDC will be checked for accuracy through quality control (QC) assessments. When the database data is declared to be complete and accurate; the database will be locked, and user access removed.

11.3 Quality Control and Quality Assurance

Designated personnel from the quality assurance unit(s) of the clinical, PK, PD, and statistical facilities will be responsible for maintaining quality assurance (QA) systems to ensure that the trial is conducted, and that clinical/PK/PD/statistical data is generated, documented and reported, in compliance with the protocol and the integrated addendum to International Conference on Harmonisation (ICH) E6: Guideline for Good Clinical Practice E6 (R2).

Designated personnel from each corresponding operation unit (i.e., clinical, PK, PD, and statistical facilities) will be responsible to maintain and assure the QC of all data generated and documented in compliance with the protocol and SOPs.

All parts of the bioanalytical phase of the study and all its documentation will be subject to inspection by the QA unit of the bioanalytical facility to ensure that the data are generated, documented and reported in compliance with the protocol and applicable requirements as

outlined in the Food and Drug Administration (FDA) and Organization for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice (GLP).

11.4 Record Retention

All essential documents and records will be maintained by the clinical site in accordance with, and for the period specified in the applicable regulatory requirement(s) (FDA Code of Federal Regulations [CFR] 312.57 (C)).

11.5 Monitoring of the Study

The sponsor or its representative may monitor the study in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study. The clinical site will permit trial-related monitoring, audits, institutional review board (IRB)/independent ethics committee (IEC) review, and regulatory inspection(s) by providing direct and/or virtual, where possible, access to source data/documents.

12 APPENDIX 3: ADMINISTRATIVE PROCEDURES

12.1 Liabilities

It is the sponsor's responsibility to guarantee sufficient insurance coverage should any serious events or deaths result, either directly or indirectly, from the execution of the present protocol.

12.2 Adherence to Protocol

Excluding an emergency situation in which proper treatment is required for the protection, safety and well-being of the study subjects, the study will be conducted as described in the approved protocol and performed according to International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) and the applicable regulatory requirements. Any deviation from the protocol will be recorded and explained.

If amendments to the protocol and/or amendments or revisions to the informed consent form (ICF) are required, the modifications will be documented and submitted to an institutional review board (IRB) for approval.

12.3 Statement of Investigator

The Food and Drug Administration (FDA) Form 1572, Statement of Investigator [Title 21, CFR Part 312], will be signed by the investigator, and will be kept on file.

12.4 Delegation of Investigator Duties

In the context of this protocol, the term 'an investigator' includes the Principal Investigator and any sub-investigator.

An investigator will ensure all personnel involved in the trial are adequately qualified and informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

An investigator will maintain a list of sub-investigator(s) and other appropriately qualified persons to whom he/she delegates significant trial-related duties.

Should an investigator delegate the supervision of the study drug administration to a designated person, this individual must have the appropriate professional-legal qualifications and certifications. An investigator should also ensure key staff personnel have the appropriate medical qualifications to effectively conduct or supervise any potential resuscitation procedures.

12.5 Premature Termination or Suspension of a Study

The sponsor or its representative may terminate the study at any time for scientific or corporate reasons.

If the trial is prematurely terminated or suspended for any reason, the clinical site or an investigator (or delegate) should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and should inform the regulatory authority(ies) and IRB, when required.

ALTASCIENCES

13 APPENDIX 4: PROTOCOL REVIEW AND APPROVALS

INVESTIGATOR AGREEMENT

TITLE: A Randomized, Double-Blind, Active- and Placebo-Controlled, 5-Way Crossover Study to Determine the Abuse Potential of Orally Administered Gabapentin Enacarbil Immediate Release Capsules in Healthy, Nondependent, Recreational Drug Users with Sedative Experience

I have carefully read and understood this study protocol and agree it contains all necessary information required to conduct this study. I agree to conduct the study according to this protocol and in accordance with Good Clinical Practice (GCP) and the applicable regulatory requirements.

[redacted]

[redacted]

Principal Investigator
Altasciences Clinical Kansas Inc.

REPRESENTATIVE OF ARBOR

TITLE: A Randomized, Double-Blind, Active- and Placebo-Controlled, 5-Way Crossover Study to Determine the Abuse Potential of Orally Administered Gabapentin Enacarbil Immediate Release Capsules in Healthy, Nondependent, Recreational Drug Users with Sedative Experience

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

[redacted]

[redacted]

Date (yyyy/mm/dd)

Arbor Pharmaceuticals, LLC

14 APPENDIX 5: LIST OF ABBREVIATIONS

Ab	Antigen/antibody
ACLS	Advanced cardiac life support
ADE	Adverse drug event
AE	Adverse event
ALT	Alanine aminotransferase
AOE	Area under the effect-time curve
ARCI	Addiction Research Center Inventory
AST	Aspartate aminotransferase
AUC_{0-T}	Area under the concentration-time curve from 0 to the last measured observable concentration
AUE	Area under the effect-time curve
BMI	Body mass index
BUN	Blood urea nitrogen
CFB_{min}	Change from baseline to minimum effect
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practice
CI	Confidence interval
C_{max}	Maximum concentration
CNS	Central nervous system
CRF	Case report form
CRU	Clinical research unit
CS	Clinically significant
CSR	Clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Coefficient of variation
DRESS	Drug rash with eosinophilia and systemic symptoms
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
ECG	Electrocardiogram
EDC	Electronic data capture
E_{max}	Maximum (peak) effect
E_{min}	Minimum effect
ER	Extended-release

ET	Early termination
$EtCO_2$	End Tidal CO_2
FAERS	Food and Drug Administration Adverse Event Reporting System
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
GE-IR	Gabapentin Enacarbil Immediate Release
GLP	Good Laboratory Practice
HBsAg	Hepatitis B Virus Surface Antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IP	Investigational product
IRB	Institutional review board
IU	International unit
IUD	Intrauterine device
kg	Kilogram
LLOQ	Lower Limit of Quantitation
MBG	Morphine-Benzedrine Group
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
N	Number of observations
NCA	Noncompartmental analysis
NCS	Not clinically significant
OECD	Organization for Economic Co-operation and Development
OTC	Over-the-counter
PCAG	Pentobarbital–Chlorpromazine–Alcohol Group
PD	Pharmacodynamic

pH	The logarithm, on the base 10, of the reciprocal of the hydrogen ion concentration
PHN	Postherpetic neuralgia
PI	Principal investigator
PK	Pharmacokinetic
PT	Preferred term
QA	Quality assurance
QC	Quality control
QTcF	QT interval corrected for heart rate using Fridericia's formula
RLS	Restless legs syndrome
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Suspected adverse reaction
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
SpO_2	Oxygen saturation
SUSAR	Suspected, unexpected SAE
$T_{½}$	Elimination half-life
TEAE	Treatment-emergent adverse event
TE_{max}	Time of maximum (peak) effect
TE_{min}	Time of minimum effect
THC	Tetrahydrocannabinol
T_{last}	Last measured observable concentration
T_{max}	Time of maximum concentration
US	United States
USPI	United States Product Insert
VAS	Visual analog scale
WHO-DDE	World Health Organization Drug Dictionary-Enhanced

15 APPENDIX 6: CLINICAL LABORATORY EVALUATIONS

Clinical Laboratory Test Panel	Description
General biochemistry:	Sodium, potassium, chloride, glucose, blood urea nitrogen (BUN), creatinine, bilirubin total, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and albumin
Endocrinology:	Follicle stimulating hormone (FSH; for female subjects)
Hematology:	White cell count with differential (absolute values of neutrophil, lymphocyte, monocyte, eosinophil, and basophil), red cell count, hemoglobin, hematocrit, mean corpuscular volume (MCV), and platelet count
Serology[1]:	Human immunodeficiency virus (HIV) antigen/antibody (Ag/Ab) Combo, Hepatitis B (HBsAg (B)) and Hepatitis C (HCV (C))
Urinalysis:	Color, clarity, specific gravity, pH, leukocyte, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen. Microscopic examination will only be performed if the dipstick test is outside of the reference range for leukocyte, blood, nitrite or protein
Urine drug screen:	Alcohol, amphetamines, barbiturates, cannabinoids, cocaine, opiates, benzodiazepines, and phencyclidine
Urine OR serum pregnancy test:	To be performed for all female subjects

[1] Screening visit only.

16 APPENDIX 7: COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) – BASELINE/SCREENING VERSION

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***) Past X Months - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past _ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

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17 APPENDIX 8: COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) –SINCE LAST VISIT VERSION

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐
If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?
Yes ☐ No ☐
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: ____ _____
Type # (1-5) ***Description of Ideation***

Most Severe

Frequency ____
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

Duration ____
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

Controllability ____
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

Deterrents ____
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

Reasons for Ideation ____
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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