A RANDOMIZED, DOUBLE-BLIND, ACTIVE- AND PLACEBO-CONTROLLED, 6-WAY CROSSOVER STUDY TO EVALUATE THE ABUSE POTENTIAL OF ORALLY ADMINISTERED GABAPENTIN ENACARBIL IMMEDIATE RELEASE CAPSULES TAKEN ALONE AND IN COMBINATION WITH OXYCODONE IN HEALTHY, NONDEPENDENT, RECREATIONAL OPIOID USERS

Protocol Number:	AR26.3031.2
Altasciences Project Number:	ABO-P4-292
Investigational Product:	Gabapentin Enacarbil Immediate Release Capsules
Phase of Development:	Not applicable
Sponsor:	Arbor Pharmaceuticals, LLC [redacted]
NCT	06247488

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
2.0 (Amendment 01)	**August 13, 2021**

PROTOCOL AMENDMENT 01 – SUMMARY OF CHANGES

Description of Change Made	Section/Location	Rationale
Modified the primary objectives to remove the evaluation of abuse potential for single oral doses of GE-IR taken *alone*.	• Synopsis (Primary Objectives) • Section 2 (Study Objectives and Endpoints)	Added as per FDA recommendation.
Added appropriateness of including High VAS as a key secondary endpoint	Section 8.2 (Appropriateness of Measures)	Added High VAS for completeness.
Added "in addition to the option "RANDOM SUBJECT;"	Section 8.5.2.1 (Primary Analysis)	Added clarification, as per FDA recommendation.
Added sentences clarifying that Hypotheses 3 and 4 will be removed. Removed Hypotheses 3 and 4, and any references to them for the primary endpoint.	Section 8.5.2.1 (Primary Analysis), Test Hypotheses for Primary Endpoint, Drug Liking VAS E_{max})	Added as per FDA recommendation: the primary objective is pertaining to the combination drug of GE-IR and OXY20 rather than GE-IR alone.
Removed Hypotheses 3 and 4, and any references to them for key secondary endpoints	Section 8.5.2.1 (Primary Analysis), Test Hypotheses for Key Secondary Endpoints	Added as per FDA recommendation: the primary objective is pertaining to the combination drug of GE-IR and OXY20 rather than GE-IR alone.
Removed Hypotheses 3 and 4, and any references to them for non-key secondary endpoints	Section 8.5.2.1 (Primary Analysis), Test Hypotheses for Non-Key Secondary Endpoints	Added as per FDA recommendation: the primary objective is pertaining to the combination drug of GE-IR and OXY20 rather than GE-IR alone.
Removed reference for "Chen L. Statistical Considerations on Pharmacodynamic Assessment of Human Abuse Potential Studies. CCALC/CSS, October 11, 2018", as it contains information regarding the alpha level for 2 sided-tests which will no longer be done as Hypotheses 3 and 4 have been removed.	Section 9 (References)	Reference no longer needed.

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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, 6-Way Crossover Study to Evaluate the Abuse Potential of Orally Administered Gabapentin Enacarbil Immediate Release Capsules Taken Alone and in Combination with Oxycodone in Healthy, Nondependent, Recreational Opioid Users
Study Development Phase:	Not applicable
Objectives:	**Primary Objectives:** To evaluate the abuse potential of single oral doses of GE-IR taken in combination with an opioid active control (oxycodone) in healthy, nondependent, recreational opioid users **Secondary Objectives:** To evaluate the pharmacokinetics (PK) of gabapentin from GE-IR when administered alone or in combination with oxycodone in healthy nondependent, recreational opioid users To evaluate the effects on safety and tolerability of single oral doses of GE-IR taken alone or in combination with oxycodone, compared to placebo and oxycodone alone, in healthy nondependent, recreational opioid users
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 (minimum effect [E_{min}], time of maximum effect [TE_{max}], time of minimum effect [TE_{min}], and time-averaged area under the effect-time curve [TA_AUE]) Positive Effects • Good Effects VAS (E_{max}, TE_{max}, and TA_AUE) • High 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 area over the effect-time curve [TA_AUE]) • Relaxation/Agitation (E_{min}, TE_{min}, and TA_AUE) • 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_AUE) **Pharmacokinetic Endpoints:** Pharmacokinetic parameters of gabapentin include maximum observed concentration (C_{max}), time of occurrence of C_{max} (T_{max}), area under the curve from time 0 to the last measureable observed concentration (AUC_{0-t}), and area under the curve from time 0 to infinity (AUC_{0-inf}). **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, electrocardiograms (ECGs), Columbia Suicide Severity Rating Scale (C-SSRS), and physical examination findings.
Study Product, Doses, and Mode of Administration (proposed):	**Gabapentin Enacarbil Immediate Release (GE-IR) Capsules** Manufacturer: Arbor Pharmaceuticals, LLC Mode of administration: Doses of GE-IR 200 mg and 450 mg will be administered orally according to the randomization schedule during the treatment phase.
GE-IR 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 will be administered orally according to the randomization schedule during the treatment phase.
Active Control, Dose, and Mode of Administration:	**Oxycodone 10 mg immediate-release (IR) tablets** Dose: Over-encapsulated oxycodone 20 mg; administered as 2 × 10 mg tablets Mode of administration: Single doses of oxycodone 20 mg will be administered orally alone or in combination with GE-IR, according to the randomization

	schedule, during the qualification and treatment phases, respectively.
Oxycodone Placebo, Dose, and Mode of Administration:	**Placebo-to-match oxycodone** Over-encapsulated placebo tablets to match oxycodone IR tablets Mode of administration: Single doses of placebo-to-match oxycodone tablets will be administered orally alone or in combination with GE-IR, according to the randomization schedule, during the qualification and treatment phases, respectively.
Naloxone, Dose and Mode of Administration:	**Naloxone HCl solution for intravenous (i.v.) injection, 0.4 mg/mL** Mode of administration: Naloxone HCl will be administered as i.v. bolus injections in single ascending doses of 0.2 mg (Step 1) and 0.6 mg (Step 2) during the qualification phase.
Study Design:	This study will be a randomized, double-blind, active- and placebo-controlled, 6-way crossover study to evaluate the abuse potential, PK, safety and tolerability of GE-IR co-administered with oxycodone relative to GE-IR alone, oxycodone, and placebo, in nondependent, recreational opioid users. This study will consist of 4 phases: screening, qualification, treatment, and follow-up.
Duration of Treatment and Subject Confinement:	Duration of clinical trial (per subject): Screening: Day -30 to Day -2 (up to 28 days) Treatment period (qualification, treatment, and follow-up phases): Subjects will be confined to the clinical site from Day -1 of the qualification phase until Day 17of the treatment phase and will return to the clinical site for a follow-up visit 7 days after the last dose of study drug (Day 23 ±2 days). Total study duration: up to 59 days (including screening)
Study Population:	Healthy, male and female nondependent, recreational opioid users, aged 18 to 55 years.
Planned Number of Subjects:	Approximately 66 subjects will be randomized into the treatment phase, such that at least 54 subjects complete the treatment phase of the study.
Bioanalysis:	Gabapentin and oxycodone plasma concentrations will be measured by validated bioanalytical methods.
Pharmacokinetic Analysis:	Pharmacokinetic analyses will be performed by non-compartmental analysis (NCA) and C_{max}, T_{max}, AUC_{0-t}, and AUC_{0-inf} will be estimated for gabapentin and oxycodone. 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 8.6, 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 Phase[a]				Treatment Phase																		Early Termination (ET)/ Follow-Up Visit[b]
Day	**-30 to -2**	**-1**	**1**	**2**	**3**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**23±2**
Subject Review																								
Informed consent[c]	X																							
Demographics	X																							
Inclusion/exclusion criteria review	X	X				X[d]																		
Medical history	X																							
Medication & recreational drug use history	X	X				X																		
C-SSRS[e]	X	X			X[f]	X[f]																	X	X
Study restrictions review		X			X[f]	X[f]																	X	X
Safety																								
Physical examination	X	X[g]			X[f, g]	X[f,g]																	X[g]	X[g]
Height, weight & body mass index (BMI)	X																							
Pregnancy test[h]	X	X				X[f]																	X	X
Urine drug and alcohol screen	X	X				X[f]																		
COVID-19 test[v]		X				X[f]																		
Clinical laboratory evaluations	X	X			X[f]	X																	X	X
Follicle stimulating hormone (FSH)[i]	X																							
Serology[j]	X																							

	Screening	Qualification Phase[a]				Treatment Phase																		Early Termination (ET)/ Follow-Up Visit[b]
Day	**-30 to -2**	**-1**	**1**	**2**	**3**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**23±2**
Vital signs[k]	X	X	X	X	X	X[f]	X	X		X	X		X	X		X	X		X	X		X	X	X
12-lead ECG	X	X				X[f]																	X	X
Continuous respiratory rate[l]			X	X			X			X			X			X			X			X		
Continuous pulse oximetry[l]			X	X			X			X			X			X			X			X		
Continuous and Spot End Tidal CO_2[l]			X	X			X			X			X			X			X			X		
Concomitant medications[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events (AEs)[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmaco-dynamics (PD)																								
Training/practice[o]		X				X																		
Subjective measures[p]			X	X	X		X	X		X	X		X	X		X	X		X	X		X	X	
MOAA/S[q]			X	X			X			X			X			X			X			X		
Pharmacokinetics (PK)																								
PK blood samples[r]							X	X		X	X		X	X		X	X		X	X		X	X	
Study Administration																								
Admission[f]		X				X[f]																		
Naloxone challenge		X																						
COWS		X																						
Randomization[s]		X				X																		

	Screening	Qualification Phase[a]				Treatment Phase																	Early Termination (ET)/ Follow-Up Visit[b]
Day	**-30 to -2**	**-1**	**1**	**2**	**3**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**23±2**
Study treatment administration			X t	X t			X[u]			X[u]			X u			X[u]			X[u]			X[u]		
Discharge					X f																		X	

C-SSRS= Columbia Suicide Severity Rating Scale, ECG= electrocardiogram, GE-IR = Gabapentin Enacarbil Immediate Release, MOAA/S= Modified Observer's Assessment of Alertness/Sedation, COWS= Clinical Opiate Withdrawal Scale
When timepoints coincide, procedures should be carried out in the following order, with the following windows: (1) vital signs, ECG and spot $EtCO_2$ (±15 minutes), (2) VAS/PD (±15 minutes), (3) PK blood sampling (±5 minutes), (5) MOAA/S to be done at any time around the other procedures (±30 minutes).

[a] Includes naloxone challenge and qualification (oxycodone versus placebo).
[b] Early termination/follow-up visit can be performed in a window of ±2 days.
[c] The latest version must be signed prior to subject's inclusion (prior to naloxone challenge on Day -1)
[d] Review of qualification criteria (section 4.3).
[e] Baseline/screening version of C-SSRS evaluation at screening visit. Since last visit version of C-SSRS evaluation at all other visits.
[f] Subjects should remain housed at the clinical research unit (CRU) from Day -1 of the qualification phase through Day 17 of the treatment phase. Only if subjects are discharged between the qualification and treatment phases, the noted discharge procedures will be performed on Day 3 of the qualification phase and noted admission procedures will be performed again on Day -1 (treatment phase). If subjects remain housed at the CRU the noted procedures are NOT required. Time between discharge from the qualification phase and admission for the treatment phase cannot exceed 14 days.
[g] Symptom-directed physical examination.
[h] Serum pregnancy test at Screening. Urine pregnancy test at all other visits.
[i] Postmenopausal women only.
[j] Serology screening as described in APPENDIX 6~~APPENDIX 6~~.
[k] Blood pressure, pulse rate, oxygen saturation (SpO_2) and respiratory rate. Measured at screening; each admission to the qualification phase and treatment phase; 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) for the qualification and treatment phases
[l] Oxygen saturation (SpO_2) 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 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 recorded 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. Predose measurements for $EtCO_2$, SpO_2 and respiratory rate will be collected to establish an average baseline value prior to each dose.
[m] Medications taken within 30 days prior to screening and throughout the duration of study participation will be recorded.
[n] Adverse events will be collected on an ongoing basis from the time of first study treatment 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 treatment administration in the qualification phase will be recorded as medical history.

[o] Additional training sessions may be conducted as needed.
[p] 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-Bezedrine 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
*24 hour postdose timepoint relative to the first dose of the qualification phase is to be performed prior to the second dose of the qualification phase.			

[q] Conducted during the qualification and treatment phases within 1 hour prior to dosing and approximately 0.5, 1, 1.5, 2, 3, 4, and 6 hours postdose.
[r] Blood samples will be collected as indicated in Table 4~~Table 4~~. When clinical activities are scheduled to occur at the same time, pharmacodynamic data collection (vital signs, including spot $EtCO_2$, then subjective measures) is to be prioritized, followed by PK blood sampling.
[s] Randomization will be performed for qualification phase only on Day -1. Subjects who meet qualification criteria will be randomized for the treatment phase on Day -1 (treatment phase).
[t] Subjects administered 20 mg oxycodone or placebo according to randomization with a minimum of 24 hours between doses during the qualification phase.
[u] Subjects administered placebo, GE-IR 200 mg + oxycodone 20 mg, GE-IR 450 mg + oxycodone 20 mg, GE-IR 200 mg, GE-IR 450 mg, or oxycodone 20 mg (minimum washout period of at least 3 days between doses).
[v] Covid-19 test will be performed before each admission.

INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

SPONSOR'S CONTACT: [redacted]
Arbor Pharmaceuticals, LLC
[redacted]

PRINCIPAL INVESTIGATOR: [redacted]
Altasciences
[redacted]

CLINICAL RESEARCH UNIT: Altasciences
[redacted]

CLINICAL LABORATORY FACILITY: Quest Diagnostics
[redacted]

BIOANALYTICAL FACILITY: Altasciences
[redacted]

MEDICAL WRITING & SCIENTIFIC AFFAIRS: Altasciences
[redacted]

STATISTICAL FACILITY: Altasciences
[redacted]

DATA MANAGEMENT FACILITY: Altasciences
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PROJECT MANAGEMENT: Altasciences

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COGNITIVE TESTS: Cambridge Cognition

[redacted]

MONITORING: Randstad Life Sciences

[redacted]

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.

The mechanism of action by which gabapentin is efficacious in PHN is unknown but in animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli).

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

The primary purpose of this study is to evaluate the abuse potential of gabapentin enacarbil immediate-release (GE-IR), the active moiety in Horizant, taken alone and taken in combination with oxycodone, compared to that of oxycodone alone.

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 June 2019 contained 606 reports categorized under drug abuse. Of these, 13 (2.1%) were attributed to Horizant, 344 to gabapentin, and 249 to Regnite (gabapentin enacarbil reports in Japan). Of the 13 Horizant cases, the most frequently reported were intentional product misuse and use issue cases (n=6, 46%). These cases involved consumers who reported adjusting their own dose to manage their own symptoms/tolerability. This was followed in frequency by overdose (n=4, 31%). The overdose cases involved reports of

being jittery 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. The remaining 3 cases of Horizant-related abuse involved accidental overdose (n=2) and dependence (n=1) and contained limited information in each case. The Regnite cases involved similar events, with intentional product misuse and use issue cases accounting a larger majority of cases (6%).

Gabapentin abuse cases were different, however. The most common event was toxicity to various agents with (97.7%). Of the 336 cases that involved toxicity to various agents more specificity was provided in 86 of the cases. These 86 cases also included accidental overdose (n=51), drug abuse (n=21), overdose (n=8), and intentional product misuse (n=4), intentional overdose (n=1), and cardiorespiratory arrest (n=1). With the exception of toxicity to various agents, no term was reported more than 3 times. There have been no Horizant reports from the American Association Poison Control Centers National Poison Data System Annual Report.

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]

Further, per FAERS update (cumulative to June 30 2019), the proportional reporting ratio (PRR) of gabapentin versus gabapentin enacarbil abuse related events was 2.22 [calculated as (Ga/Gt)/(GEa/GEt) = (576/10038)/(55/2128)]. This indicates that the number of abuse-related events in relation to the number of reported ADEs is greater for gabapentin compared to gabapentin enacarbil.

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, 6-way crossover design, aimed to assess the abuse potential, safety, and PK of GE-IR doses when administered alone or in combination with an opioid active control (oxycodone), and compared to placebo and oxycodone intake alone, in healthy, nondependent, recreational opioid users. The overall design is consistent with United States (US) Food and Drug Administration (FDA) guidelines for human abuse potential (HAP) assessment.[4, 5]

Further, gabapentin abuse is reported both alone (i.e., without other drugs), and in conjunction with opioids to enhance the 'high' obtained from opioids.[22, 23,24] This study is thus designed with the goal of characterizing any additive or synergistic effects on the abuse potential and physiologic effects of co-administered GE-IR and opioid.

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. In this study, immediate-release (IR) oxycodone 20 mg (oral) will be administered during the qualification and treatment phases, given that this dose is used by recreational drug users, is within the range of recommended label doses, and is supported by published abuse potential studies.[27, 28] A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment as well as to minimize subject and investigator bias. Blinded treatment, including the use of double-blind and double-dummy procedures, will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

The subjects in this study will be healthy individuals with previous nontherapeutic (recreational) experience with opioids. These subjects represent the population at greater 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 opioid use), subjects will also be required to pass a pharmacologic qualification. 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]

A double-blind qualification phase has been included in the study design as an enrichment procedure to ensure that study subjects are not opioid dependent (through a naloxone challenge) and that subjects who meet the drug use history criteria can also distinguish the subjective effects of the active control (i.e., oxycodone) 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.

The 3-day washout interval between the qualification phase and treatment phase is considered sufficient to ensure complete washout of oxycodone. Given the $T_{½}$ of gabapentin when receiving GE-IR (4.38 - 5.47 hours) and oxycodone (approximately 3-5 hours)[27] following oral administration, the 3-day interval between study treatment administrations will ensure sufficient washout of GE-IR and oxycodone.

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, 13] 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 and 450 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 and1200 mg Horizant in healthy individuals.

Oxycodone is the selected positive control for this study. The dose of oxycodone selected (20 mg) will be used per the recommendations of the Food and Drug Administration (FDA) and has been well tolerated in the study population.[26, 30, 31]

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 SpO_2 are the standard in monitoring respiratory function, change in oxygenation, and change in ventilation.[38,39,40,41] Monitoring $ETCO_2$ has been shown to

be more sensitive in detection of respiratory depression than monitoring respiratory rate and pulse oximetry alone.[42]

In the clinical setting, respiratory depression is usually described in terms of decreased respiratory rates, decreased SpO_2 levels, or elevated $ETCO_2$ levels [42] 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
Primary	
To evaluate the abuse potential of single oral doses of GE-IR taken in combination with an opioid active control (oxycodone) in healthy, nondependent, recreational opioid users.	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 (minimum effect [E_{min}], time of maximum effect [TE_{max}], time of minimum effect [TE_{min}] and area under the effect-time curve [AUE]) Positive Effects • Good Effects VAS (E_{max}, TE_{max}, and TA_AUE) • High VAS (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 area over the effect-time curve [TA_AUE]) • Relaxation/Agitation VAS (E_{min}, TE_{min}, and area over the effect-time curve [TA_AUE]) • 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_AUE)

OBJECTIVES	ENDPOINTS
Secondary	
To evaluate the PK of gabapentin from GE-IR when administered alone or in combination with oxycodone in healthy nondependent, recreational opioid users.	Pharmacokinetic parameters of gabapentin include C_{max}, T_{max}, area under the curve from time 0 to the time of last measurable observed concentration (AUC_{0-t}), and area under the curve from time 0 to infinity (AUC_{0-inf})
To evaluate the effects on safety and tolerability of single oral doses of GE-IR taken alone or in combination with oxycodone, compared to placebo and oxycodone alone, in healthy nondependent, recreational opioid users.	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, 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, 6-way crossover study to evaluate the abuse potential, PK, safety and tolerability of GE-IR co-administered with oxycodone relative to GE-IR alone, oxycodone, and placebo, in nondependent, recreational opioid users

This study will consist of 4 phases: screening, qualification, treatment, and follow-up. The study schema is presented in Figure 1~~Figure 1~~.

3.1.1. Screening and Qualification Phase

After a screening period of up to 30 days, eligible subjects will be admitted to the clinical research unit (CRU) on Day -1 of the qualification phase.

A sufficient number of subjects will be screened and entered into the qualification phase to ensure that approximately 66 subjects will be randomized in the treatment phase, so that at least 54 subjects complete the study. Females will be recruited on a best-effort basis to ensure an appropriate representation of females in the study.

All subjects will complete a naloxone challenge at least 24 hours prior to the first drug administration in the qualification phase, to confirm that they are not opioid-dependent. The test will be administered in the following 2 steps:

1. Naloxone 0.2 mg will be given via intravenous (i.v.) bolus followed by a 2 to 3 mL saline flush. The subject will be observed for 1 minute after bolus administration for signs or symptoms of withdrawal.

2. If there is no evidence of withdrawal after 1 minute, naloxone 0.6 mg will be given via i.v. bolus within 5 minutes of the first administration followed by a 2 to 3 mL saline flush. The subject will be observed for an additional 5 minutes.

The naloxone doses selected for the challenge are consistent with doses commonly administered to confirm opioid nondependence. The Clinical Opiate Withdrawal Scale (COWS)[28] will be used to record any signs or symptoms of opioid withdrawal observed in step 1 (predose and 1 minute after administration) and step 2 (5 minutes after administration) of the naloxone challenge test.

Subjects who present symptoms of withdrawal during predose assessment or following administration of the naloxone challenge (i.e., COWS score ≥5, unless in the opinion of an investigator the symptoms present are not related to opioid withdrawal) will be excluded from the study and will not be eligible to enter the qualification phase.

The qualification phase will further determine whether subjects like and tolerate the effects of oxycodone, and can discriminate these from placebo; this visit will also determine if each subject is suitable for entry into and is likely to complete the treatment phase (i.e. likely to comply with the study protocol).

On Days 1 and 2 of the qualification phase, subjects will receive the following treatments in a randomized, double-dummy, crossover manner as further detailed in section 3.2:

	Day 1	**Day 2**
Sequence 1	Treatment X: Placebo	Treatment Y: Oxycodone 20 mg
Sequence 2	Treatment Y: Oxycodone 20 mg	Treatment X: Placebo

Each dose will be separated by approximately 24 hours.

Each subject must meet all of the qualification criteria (see section 4.3) to be randomized for participation in the treatment phase.

It is preferred that subjects remain confined at the CRU from the start of the qualification phase through completion of the treatment phase; however, subjects may be discharged between these phases if required. Appropriate discharge and re-admission procedures are noted in Table 1~~Table 1~~.

3.1.2. Treatment Phase and Follow-Up

The treatment phase is a randomized, double-blind, active- and placebo-controlled, 6-way crossover design in which subjects will receive the following 6 treatments in a crossover manner and blinded fashion, as further detailed in section 3.2:

- Treatment A: Placebo
- Treatment B: Oxycodone 20 mg
- Treatment C: GE-IR 200 mg + oxycodone 20 mg
- Treatment D: GE-IR 450 mg + oxycodone 20 mg

- Treatment E: GE-IR 200 mg
- Treatment F: GE-IR 450 mg

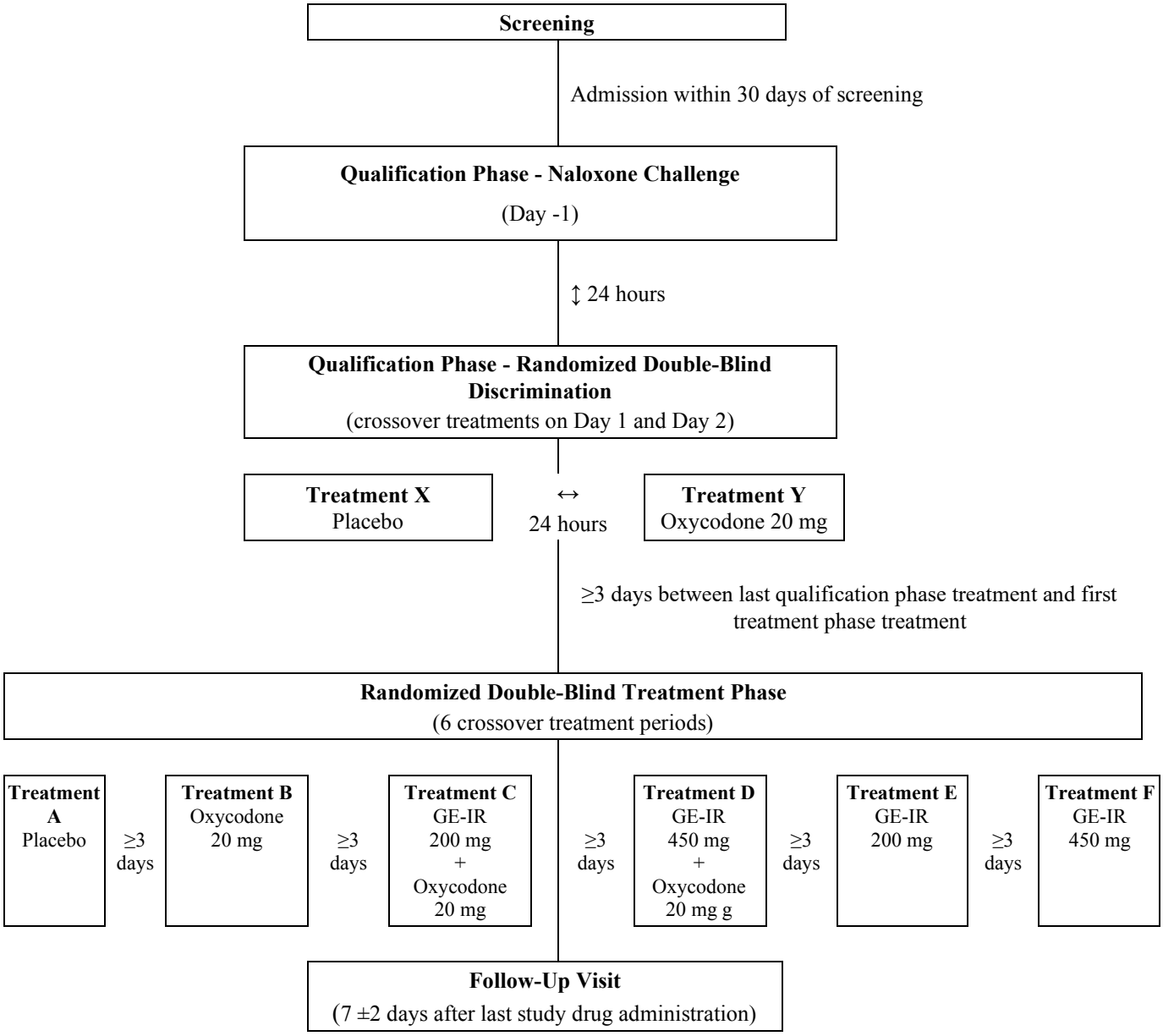
Each study treatment administration will be separated by 3 days. Drug administrations will be followed by PD, PK, and safety assessments for up to 24 hours postdose. Subjects will be discharged from the investigational site approximately 24 hours after the final dose of the treatment phase, if deemed medically stable for discharge by an investigator. A follow-up visit will occur 7 days (±2 days) following the final dose.

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

The maximum duration of subject participation, including screening, will be approximately 59 days.

Subjects who terminate the study early will perform follow-up procedures at the time of early termination (ET).

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.

3.2. Study Treatments

During the qualification phase each dose will consist of 1 capsule containing oxycodone or placebo. The following treatments will be administered orally with approximately 240 mL of room temperature water in the morning under fasted conditions:

- **Treatment X (Placebo):** 2 × placebo tablets over-encapsulated to match oxycodone
- **Treatment Y (Active Control):** 2 × 10 mg oxycodone tablets over-encapsulated

During the treatment phase, each dose will consist of 2 capsules of GE-IR and/or placebo to match GE-IR to achieve assigned dose plus 2 capsules containing oxycodone or placebo. The following treatments will be administered orally with approximately 240 mL of room temperature water in the morning under fasted conditions:

- **Treatment A (Placebo):**

  2 × placebo capsules to match GE-IR and 2 × placebo tablets over-encapsulated to match oxycodone

- **Treatment B (Active Control):**

  2 × placebo capsules to match GE-IR and 2 × 10 mg oxycodone tablets over-encapsulated

- **Treatment C (GE-IR 200 mg + Oxycodone):**

  1 × 200 mg GE-IR capsules, 1 × placebo capsules to match GE-IR, and 2 × 10 mg oxycodone tablets over-encapsulated

- **Treatment D (GE-IR 450 mg + Oxycodone):**

  2 × 225 mg GE-IR capsules and 2 × 10 mg oxycodone tablets over-encapsulated

- **Treatment E (GE-IR 200 mg):**

  1 × 200 mg GE-IR capsules, 1 × placebo capsules to match GE-IR, and 2 × placebo tablets over-encapsulated to match oxycodone

- **Treatment F (GE-IR 450 mg):**

  2 × 225 mg GE-IR capsules and 2 × placebo tablets over-encapsulated to match oxycodone

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 treatment 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 opioid user who has used opioid drugs for recreational (nontherapeutic) purposes (i.e., for psychoactive effects) at least 5 times in the subject's lifetime and at least once in the last 12 weeks,

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 treatment administration, during the study, and for at least 30 days after the last dose of the study treatment. 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), or
      - 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 treatment.

   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 treatment 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 study treatment, 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, in the opinion of an investigator.

9. Negative Covid-19 test prior to each admission.

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 naloxone, opioids (e.g., oxycodone), or related drugs 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, naloxone, or oxycodone,

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 treatment administration or planning to become pregnant within 30 days following the last study treatment 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 ever 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, 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 treatment administration (including e-cigarettes, pipes, cigars, chewing tobacco, nicotine topical patches, nicotine gum, or nicotine lozenges),

11. Is a heavy opioid user and not likely to be sensitive to a 20 mg dose of oxycodone, in the opinion of an investigator or designee,

12. 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,

13. History of suicidal ideation 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~~APPENDIX 7~~), or is currently at risk of suicide in the opinion of an investigator,

14. 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,

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

16. Any history of tuberculosis,

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

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

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

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

21. Use of a prohibited medication as specified in section 4.7,

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

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

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

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

4.3. Inclusion Criteria into Qualification Phase

Subjects must not present symptoms of withdrawal during predose assessment or following administration of the naloxone challenge (i.e., COWS score <5).

4.4. 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 of at least 65 points in response to oxycodone 20 mg and greater than that of placebo on the Drug Liking VAS (difference of at least 15 points), with a peak score of at least 65 points for oxycodone.

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

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

4. Able to tolerate the 20 mg dose of oxycodone, as judged by an investigator, including no episodes of vomiting during the first 3 hours postdose.

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.

4.5. Withdrawal Criteria

4.5.1. Before First Treatment Administration

Before the first treatment administration of the qualification phase (oxycodone or placebo), inclusion/exclusion criteria will govern the subjects to be dosed. Subjects withdrawn before first treatment administration of the qualification phase 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.

4.5.2. 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 and documented to have such subjects complete the ET assessments. Early termination 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).

4.6. 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 administration 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 until the follow-up visit. 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 his or her discretion.

- Subjects will be prohibited from consuming food or beverages containing xanthines (i.e., tea, coffee, cola drinks, energy drinks or chocolate) for 48 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 asked to abstain from strenuous physical activity for 48 hours prior to screening and prior to each admission to the CRU and during inpatient stays.
- During the study, smokers will abstain from smoking for at least 1 hour prior to and until at least 6 hours after each drug administration. Subjects will not be permitted to use other nicotine-containing products (including nicotine topical patches, nicotine gum, or nicotine lozenges).
- Subjects will be asked 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 engage in sexual activity that has a risk of pregnancy will be expected to use an acceptable contraceptive regimen and not to donate sperm from the first study treatment administration, during the study, and until at least 90 days after the last drug administration, as described in section 4.1.

4.7. Concomitant Treatment

Except for medication 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 will be collected daily while subjects are in the clinic. 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

The lot number and the measured content of each dosage formulation will be included in the final report.

5.1.1. Gabapentin Enacarbil

Gabapentin enacarbil immediate release capsules (GE-IR) 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 225 mg capsule and the composition is the same. Placebo will be filled with 225 mg of calcium phosphate dibasic dihydrate in the capsules. Patheon will take into consideration the client's request for the same opaque and simple in color capsule to encapsulate both the active and placebo strengths.

5.1.2. Oxycodone

Oxycodone IR will be supplied as 10 mg tablets, and over-encapsulated.

Placebo to match oxycodone tablets will be over-encapsulated 100 mg lactose tablets.

Both products may be obtained by the CRU and will be over-encapsulated with the same capsules (Swedish Orange Opaque AAE-DB capsules [Capsugel] or similar) to maintain study blinding.

5.2. Investigational Product Management

5.2.1. Packaging, Labeling and Dispensing

The sponsor will be responsible for ensuring that the study drug 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 contract research unit's (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.

Gabapentin enacarbil immediate release (GE-IR) capsules and placebo should be stored at 25°C with excursions between 15°C and 30°C allowed. Both placebo to match oxycodone and oxycodone 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, 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. Replacement subjects will be assigned a new randomization number equivalent to the Treatment randomization + 1000 (e.g., 3000 series).

Subjects who enter the treatment phase will be assigned a unique treatment randomization number. Subjects will be randomized to 1 of 6 treatment sequences, according to one 6 x 6 Williams Squares. The range of qualification and treatment randomization numbers may be distinct to avoid confusion (e.g., 1000 series and 2000 series).

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~~).

Table 2 Sample Qualification Phase Sequences

Treatment Sequence	Day 1	Day 2
XY	X	Y
YX	Y	X

Treatment X: Placebo
Treatment Y: Oxycodone 20 mg

5.2.3.2. Treatment Phase

For the treatment phase, qualified subjects will be randomized to 1 of 6 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 6 treatments in the order specified by the treatment sequence according to one 6 x 6 Williams Square (Table 3~~Table 3~~).

Table 3 Sample Treatment Phase Sequences

Treatment Sequence	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6
ABFCED	A	B	F	C	E	D
BCADFE	B	C	A	D	F	E
CDBEAF	C	D	B	E	A	F
DECFBA	D	E	C	F	B	A
EFDACB	E	F	D	A	C	B
FAEBDC	F	A	E	B	D	C

Treatment A: Placebo
Treatment B: Oxycodone 20 mg
Treatment C: GE-IR 200 mg + Oxycodone 20 mg
Treatment D: GE-IR 450 mg + Oxycodone 20 mg
Treatment E: GE-IR 200 mg
Treatment F: GE-IR 450 mg

5.2.4. Blinding

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

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, 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 administration 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 to the subject or to complete a SAE report. Code break envelopes containing 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 at the completion of the trial.

5.3. Study Treatment Administration, Meals and Fluids

Study treatments will be administered in the morning as described in section 3.2. The date and time of each dose will be recorded. For each subject, all scheduled postdose activities and assessments will be performed relative to the time of study treatment administration.

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. If needed, subjects may be provided additional water, in 50-mL increments, to ensure complete dose is swallowed. Any additional water given will be recorded.

Food and fluid intake other than water will be controlled for each confinement period and for all subjects.

Subjects will fast for at least 4 hours following each drug administration. Water will be provided as needed until at least 1 hour prior to dosing and will be allowed beginning at least 1 hour after each drug administration.

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 for at least 6 hours following each drug administration, avoiding both vigorous exertion and complete rest. 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.

An overview of the study activities for each subject is detailed in Table 1~~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 3 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 2. Subjects not qualifying for the treatment phase may be discharged on Qualification Day 3 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 17 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), continuous SpO_2 monitoring, continuous End Tidal CO_2, 12-lead ECG, clinical laboratory tests, and AE monitoring. 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

The medical history will be reviewed as scheduled in Table 1~~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 the ICF 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 worsening and judged to be clinically significant will be recorded as AEs.

6.1.2. Recreational Alcohol/Drug Use

A lifetime history of all drug use will be collected as scheduled in Table 1~~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 by drug class (e.g., cannabinoids, depressants, dissociative anesthetics, hallucinogens, opioids and morphine derivatives, and stimulants). A history of alcohol use will also be collected.

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~~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~~Table 1~~, at the discretion of an investigator.

6.1.4. Vital Signs

Vital signs will be measured as scheduled in Table 1~~Table 1~~ and will include spot blood pressure, pulse rate, respiratory rate and oxygen saturation (SpO_2) measures.

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~~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 continuous pulse oximeter during the Qualification phase and through a capnography monitor during the Treatment phase.

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. 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~~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~~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~~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~~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~~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~~Table 1~~.

The laboratory evaluations to be conducted for this study are presented in APPENDIX 6~~APPENDIX 6~~. Additional clinical laboratory tests may be performed by the medical laboratory as part of larger standard test panels (not required for subject safety).

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.

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 unique, simple, and short method of assessing both behavior and ideation that tracks all suicidal events and provides a summary of suicidal ideation and behavior. It assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation, and deterrents), all of which are significantly predictive of completed suicide.

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~~Table 1~~.

A trained rater will record the clinical observations on the scale, which will be used as the source document. See APPENDIX 7~~APPENDIX 7~~ for a sample C-SSRS –Baseline/Screening version assessment and APPENDIX 8~~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.

6.1.8. Assessment of Respiratory Depression

Predose measurements for $EtCO_2$, SpO_2, and respiratory rate will be collected prior to each dose in order to establish an average baseline value and calculate the threshold of absolute change for each safety assessment, as defined below:

Capnography alarms will be set to evaluate for respiratory depression, for whichever threshold is reached first for a given endpoint, and will include:

- An increase in $EtCO_2$ to >50 mmHg, or an absolute increase in $EtCO_2$ of 10 mmHg compared to baseline
- A reduction in SpO_2 to <90%, or an absolute decrease in SpO_2 of 4% compared to baseline
- A reduction in respiratory rate to <8 breaths per minute, or an absolute decrease in respiratory rate of 50% compared to baseline

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 treatment 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. Blood Volume Collected

The total blood volume for screening and safety assessments will be approximately 15 mL. Blood volume required for pharmacokinetic assessments will be included in the informed consent.

6.3. Pharmacokinetic Assessments

Blood samples will be collected for each dose in the treatment phase for PK assessments of gabapentin and oxycodone. The complete blood sampling schedule is presented in Table 4~~Table 4~~.

Table 4. Pharmacokinetic Blood Sampling Schedule (Gabapentin and Oxycodone)

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 that will be placed in the vein of the subject.

The time of PK blood sample collection will be calculated relative to the time of treatment administration. The actual time of all PK blood draws will be recorded and reported for all subjects. Each subject will be dosed at approximately the same time in each period and all activities (e.g., PK sampling, scales, meals) will be based on that dosing time.

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

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

6.3.1. 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 (e.g., analyte, sample collection time, subject identifier).

6.4. Pharmacodynamic Assessments

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

Prior to completing the computerized PD measures, all subjects will undergo a scripted training and practice session. Eligible subjects experiencing 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 practice 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 the study (i.e., qualification and treatment phases). 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 may be aborted and the reason for discontinuation of a PD assessment will be provided.

6.4.1. Subjective Effects

6.4.1.1. Visual Analogue Scales

All VAS will be scored on a 100-point scale, as shown in Table 5~~Table 5~~. The VAS 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	No	Unipolar	Good Effects	At this moment, I feel good drug effects	0: Not at all 100: Extremely
Positive	Yes	Unipolar	High	At this moment, I am feeling high	
Negative	No	Unipolar	Bad Effects	At this moment, I feel bad drug effects	
Other	No	Unipolar	Any Effects	At this moment, I can 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

6.4.1.2. Addiction Research Center Inventory (ARCI)

Martin et al. [35] have compiled a shortened version (49 true-false items) from the 550-item Addiction Research Center Inventory (ARCI) originally developed by Haertzen.[36,37] This version of the shortened ARCI contains 5 scales, which measure the following effects:

- Euphoria: Morphine-Benzedrine Group (MBG) scale
- Stimulant effects: Amphetamine (A) scale, Benzedrine Group (BG) scale
- Dysphoria: Lysergic Acid Diethylamide (LSD) scale
- Sedation: Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) scale

The ARCI MBG and PCAG scales will be administered as scheduled in Table 1~~Table 1~~. The ARCI MBG and PCAG scales are presented in APPENDIX 9~~APPENDIX 9~~ and APPENDIX 10~~APPENDIX 10~~, respectively.

6.4.2. 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.[34] 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, or
- 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, or
- 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~~.

Table 6. Adverse Event Relationship to Study Drug

Relationship to Drug	Comment
Reasonable Possibility	A temporal relationship exists between the adverse event (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 serious adverse events (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 the follow-up visit. If AEs are ongoing after the follow-up visit, attempts will be made to follow the AEs to resolution. Any medical conditions occurring from the time of signing the ICF 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.

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 is found, or it 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 23.0 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 a[redacted]or scanned and emailed to [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 or designee 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 placebo or oxycodone.

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 in the Randomized population who receive at least 1 dose of study drug (e.g. placebo, oxycodone or GE-IR).

8.1.2.3. Completer Population

All subjects in the Safety population who complete all 6 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. 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

If such subjects do not exist in the study, then the Modified Completer population is the same as the Completer population.

8.1.2.5. Pharmacokinetic (PK) Population

The PK population will include all subjects in the Safety population who receive at least 1 dose of GE-IR during the treatment phase, have evaluable PK data, and have no protocol deviations or other circumstances that would exclude them from analysis.

8.2. Appropriateness of Measures

The selected PD measures will assess positive and negative subjective drug effects associated with the abuse potential of a 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 nondependent, recreational drug users. 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 data, 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/Completer population, as

appropriate). 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/Completer population (as appropriate) 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 phase, and for qualification failures. Tables for demographic and baseline characteristics (sex, age, race, ethnicity, body weight, height, BMI) will be presented by population, and by qualification failures. Demographics and baseline characteristics for subjects who pass and who fail the qualification phase will be listed.

8.4.2. Treatment Phase

A disposition table will be presented for 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 23.0 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~~Table 7~~ and PD data will be analyzed for the Modified Completer population. 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 using descriptive statistics.

Table 7. Pharmacodynamic Endpoints

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

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

8.5.2. Pharmacodynamic Statistical Methodology

Drug Liking 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 [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 [redacted] 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 [16] 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.[32]

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 combination of the test drug and the positive comparator produce abuse-related responses that are larger than those of the positive control?

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

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

The objective of this study to assess the relationship between oxycodone and the combination of GE-IR and oxycodone therefore Questions 3 and 4 will not be addressed in this study.

To address Questions 1 and 2, the following hypotheses will be tested.

1. Validation test of the sensitivity and integrity of the study: Does the positive control (C) produce mean responses that show greater abuse potential compared to placebo (P)? This question may be expressed using the following hypothesis:

[redacted] (Hypothesis 1)

2. Does the combination drug (COMBO) produce mean responses that show more abuse potential compared to the positive control (C)?

[redacted] (Hypothesis 2)

These hypotheses will be applied to the primary endpoint, Drug Liking VAS E_{max}. For Drug Liking VAS E_{max} at a significance level of 0.05; 1-sided 95% confidence intervals will be presented for both hypotheses. For Hypothesis 2, a 2-sided 95% confidence interval will also be provided; it will provide information about the absolute difference between the combination and 20 mg dose of oxycodone.

For study validity purposes, the primary endpoint, E_{max} for Drug Liking VAS, will be compared between the positive control (oxycodone 20 mg) and placebo. The comparison will assess the null hypothesis that the mean difference in Drug Liking E_{max} between oxycodone and placebo is less than or equal to 15 against the alternative hypothesis that the mean difference in Drug Liking E_{max} between oxycodone and placebo is greater than 15. 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] (Hypothesis 1)

where μ_C is the mean for the positive control, oxycodone, and μ_P is the mean for placebo. This hypothesis will be applied to the following contrast:

[redacted]

Although a margin of 15 has been selected for Hypothesis 1 for consistency with the qualification phase criteria, subjects may have lower responses in the treatment phase as compared to the qualification phase.[21,33] Therefore, in the case that the difference between the positive control and placebo does not meet the pre-specified criteria for validity of more than [redacted] 17~~17~~ These will be included in the post-hoc analysis. Further details will be described in the SAP.

To assess whether the combination drug has more abuse potential than the positive control, the [redacted]

[redacted]

Comparison between the combination and the positive control, will be:

[redacted] (Hypothesis 2)

where μ_{COMBO} is the mean for the combination of GE-IR + the positive control, μ_C is the mean for the positive control, oxycodone, and μ_P is the mean for placebo. This hypothesis will be applied to the following contrasts:

[redacted]

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 hypotheses will be used:

Hypothesis 1: [redacted]

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

[redacted] (Hypothesis 1)

where μ_C is the mean for the positive control, oxycodone, and μ_P is the mean for placebo. This hypothesis will be applied to the following contrast:

[redacted]

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

[redacted]

where μ_{COMBO} is the mean for the combination of GE-IR + the positive control, μ_C is the mean for the positive control, oxycodone, and μ_P is the mean for placebo. This hypothesis 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 Hypothesis 2, a 2-sided 95% confidence interval will also be provided; it will provide information about the absolute difference between the combination and 20 mg dose of oxycodone.

No adjustments for p-values will be made to account for multiple comparisons.

Test Hypotheses for Non-Key Secondary Endpoints

For the comparisons of all other non-key secondary PD endpoints, the following hypotheses will be used:

Hypothesis 1[redacted]

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

[redacted] (Hypothesis 1)

where μ_C is the mean for the positive control, oxycodone, and μ_P is the mean for placebo. This hypothesis will be applied to the following contrast:

[redacted]

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

[redacted] (Hypothesis 2)

where μ_{COMBO} is the mean for the combination of GE-IR + the positive control, μ_C is the mean for the positive control, oxycodone, and μ_P is the mean for placebo. This hypothesis will be applied to the following contrasts:

[redacted]

A significance level of 0.05 will be used for Hypotheses 1 and 2. For Hypotheses 1 and 2, 2-sided 95% confidence intervals will be presented. No adjustments for p-values will be made to account for multiple comparisons.

8.5.2.2. Post-Hoc 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 oxycodone and higher responses with placebo in the treatment phase as compared to the qualification phase,[21,33] 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 do not meet the pre-specified criteria for validity of at least 15, exploratory analysis will be performed. Details of the post-hoc 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. Pharmacokinetic analyses will be performed using the PK population.

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 [redacted]

[redacted]

The PK parameters for gabapentin are presented in Table 8~~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 time 0 to the last measurable observed concentration
AUC0-inf	Area under the concentration time curve from time 0 to infinity

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 [redacted] 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, actual sampling times, 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 Treatment 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. Adverse events will be presented by body system and preferred term (MedDRA, version 23.0 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

The sample sizes are based on [redacted] 3030 which evaluated doses of 20 mg oxycodone and placebo; approximate means for oxycodone 15 mg and 30 mg were provided by the FDA.

Validation Test

For Drug Liking VAS E_{max} VAS, the mean (SD) was 54.7 (3.9) for placebo, and 68 (15.6) for oxycodone 20 mg.[30] Using the FDA recommendation of approximate means of 78 for oxycodone 15 mg, and 84 for oxycodone 30 mg, standard deviation (SD) of 15.6 for both oxycodone 15 mg and 30 mg, a margin of 15, correlation of 0, and an upper-tailed test with a significance level of 0.05, 34 completers would be needed for the comparison of oxycodone 15 mg vs. placebo, and 13 completers would be needed for the comparison of oxycodone 30 mg vs. placebo.

Primary Comparison

The primary comparison,

$$H_o: \mu_{COMBO} - \mu_C \geq \delta_2 \text{ vs. } H_a: \mu_{COMBO} - \mu_C < \delta_2 \text{ where } \delta_2 = 0.xx(\mu_C - \mu_P),$$

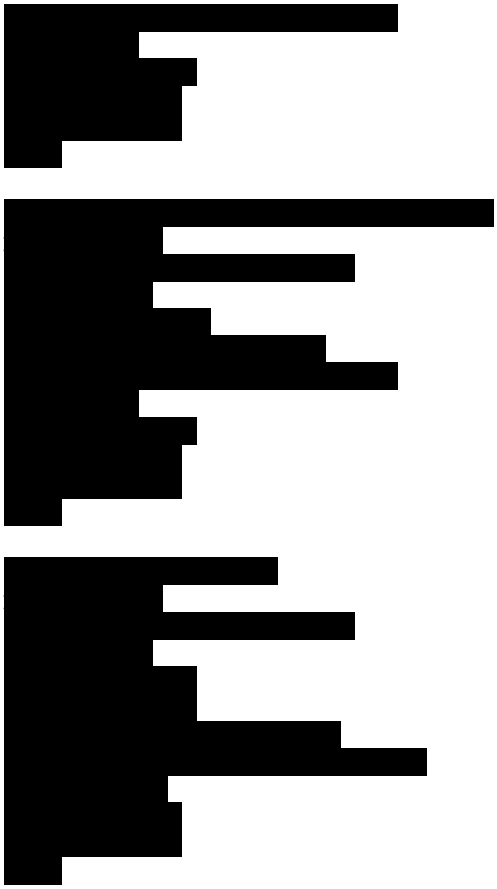
is written as a linear combination of three means as follows:

$$H_o: 1.2\mu_C - 0.2\,\mu_P - \mu_{COMBO} \leq 0 \text{ versus } H_a: 1.2\mu_C - 0.2\,\mu_P - \mu_{COMBO} > 0$$

Using the information for oxycodone 15 mg for the estimate of $1.2\mu_C - 0.2\,\mu_P$, the mean (SD) is 82.66 (18.74). The mean for oxycodone 15 mg was increased by 10% to approximate the mean for the combination drug. The mean (SD) for the combination drug is estimated to be 86 (15.6). Using a with a margin of 0, correlation of 0.9 and a upper-tailed test with a significance level of 0.05, 54 completers would be needed for the primary comparison.

Inflating the most conservative estimate of 54 completers for balanced sequences, drop-outs, and problematic subjects, approximately 66 subjects will be randomized into the treatment phase in order to ensure 54 completers.

The [redacted]



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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 is transcribed from source into an electronic data capture software [redacted]) 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). Pharmacodynamic/VAS data is electronic.

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 encrypted (or posted to a secure File Transfer Protocol) and is stored in a secure folder on a server. The electronic data file(s) are independent of the [redacted] electronic data capture (EDC) data during the conduct of the study.

[redacted] EDC cleaned data will be reviewed, approved and electronically signed by the principal investigator or delegate. [redacted] EDC data will be output in a case report form (CRF) format. The external data files will be output [redacted]. 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[redacted] 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 are reconciled (to compare the external vendor data [redacted] 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 [redacted] 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 (e.g., 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.

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 Organisation for Economic Co-operation 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 access to source data/documents and read-only access to the EDC.

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 Principal Investigator (PI), 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) when required.

13. APPENDIX 4: PROTOCOL REVIEW AND APPROVALS

TITLE: A Randomized, Double-Blind, Active- and Placebo-Controlled, 6-Way Crossover Study to Evaluate the Abuse Potential of Orally Administered Gabapentin Enacarbil Immediate Release Capsules Taken Alone and in Combination with Oxycodone in Healthy, Nondependent, Recreational Opioid Users

I have carefully read 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] _____

Principal Investigator
Altasciences Clinical Kansas Inc.

Date (yyyy/mm/dd)

TITLE: A Randomized, Double-Blind, Active- and Placebo-Controlled, 6-Way Crossover Study to Evaluate the Abuse Potential of Orally Administered Gabapentin Enacarbil Immediate Release Capsules Taken Alone and in Combination with Oxycodone in Healthy, Nondependent, Recreational Opioid Users

On behalf of the sponsor, I am aware of, and agree to comply with, all of the procedures contained within this protocol.

_____ _____

[redacted] Date (yyyy/mm/dd)

Vice President Clinical Development
Arbor Pharmaceuticals, LLC

14. APPENDIX 5: LIST OF ABBREVIATIONS

ACLS	Advanced cardiac life support
ADE	Adverse drug event
AE	Adverse event
Ab	Antigen/antibody
ALT	Alanine aminotransferase
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
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
COWS	Clinical Opiate Withdrawal Scale
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
GLP	Good Laboratory Practice
HAP	Human Abuse Potential
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HEENT	Head, eyes, ears, nose, and throat
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IP	Investigational product
IR	Immediate release
IRB	Institutional review board
IU	International unit
IUD	Intrauterine device
i.v.	Intravenous
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

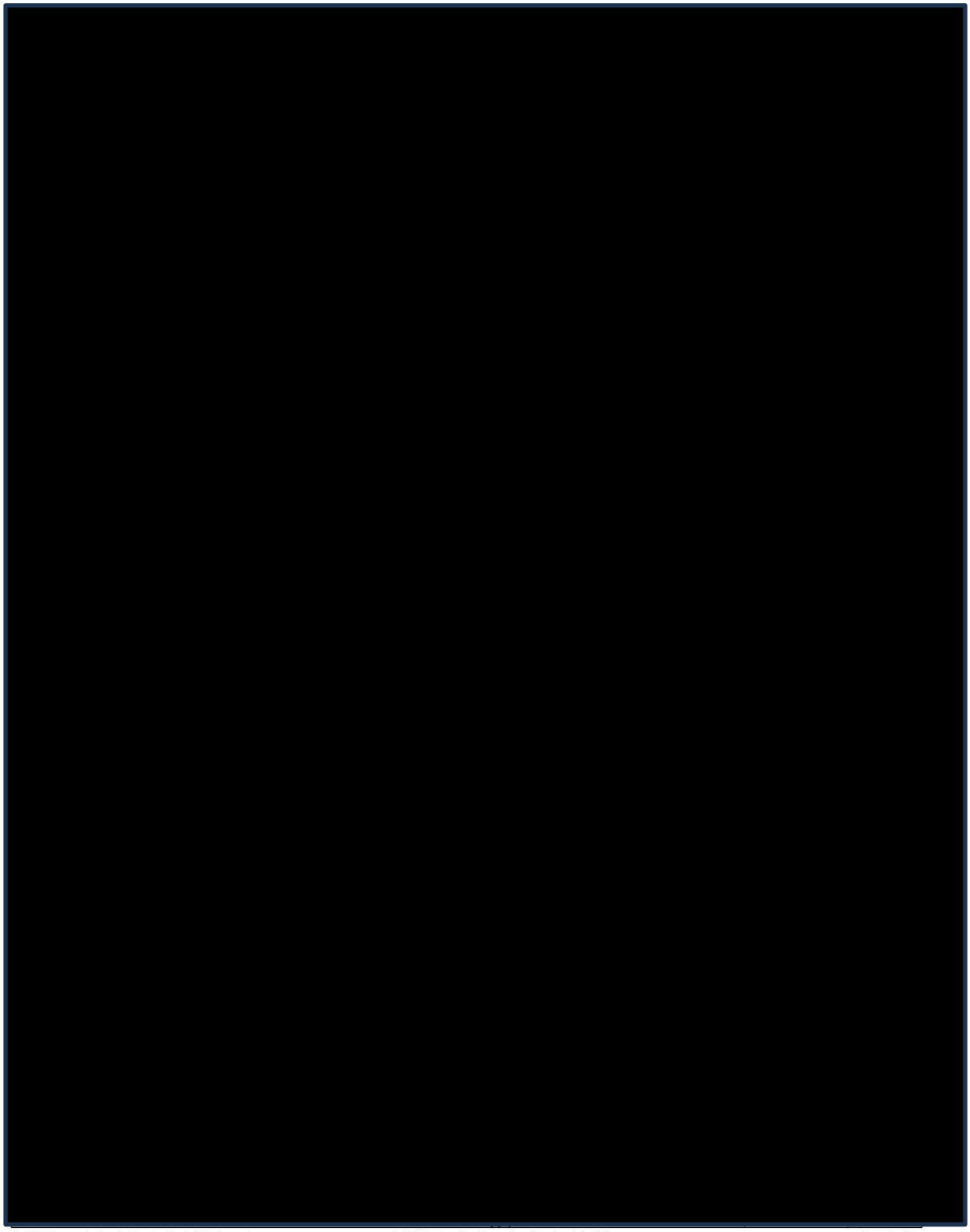
PCAG	Pentobarbital–Chlorpromazine–Alcohol Group
PD	Pharmacodynamic
pH	The logarithm, on the base 10, of the reciprocal of the hydrogen ion concentration
PHN	Postherpetic neuralgia
PI	Principal investigator
PK	Pharmacokinetic
PRR	Proportional Reporting Ratio
PT	Preferred term
QA	Quality assurance
QC	Quality 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
SpO2	Oxygen saturation
TA_AUE	Time-averaged area under the effect-time curve
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
TQTc	Thorough corrected QT
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

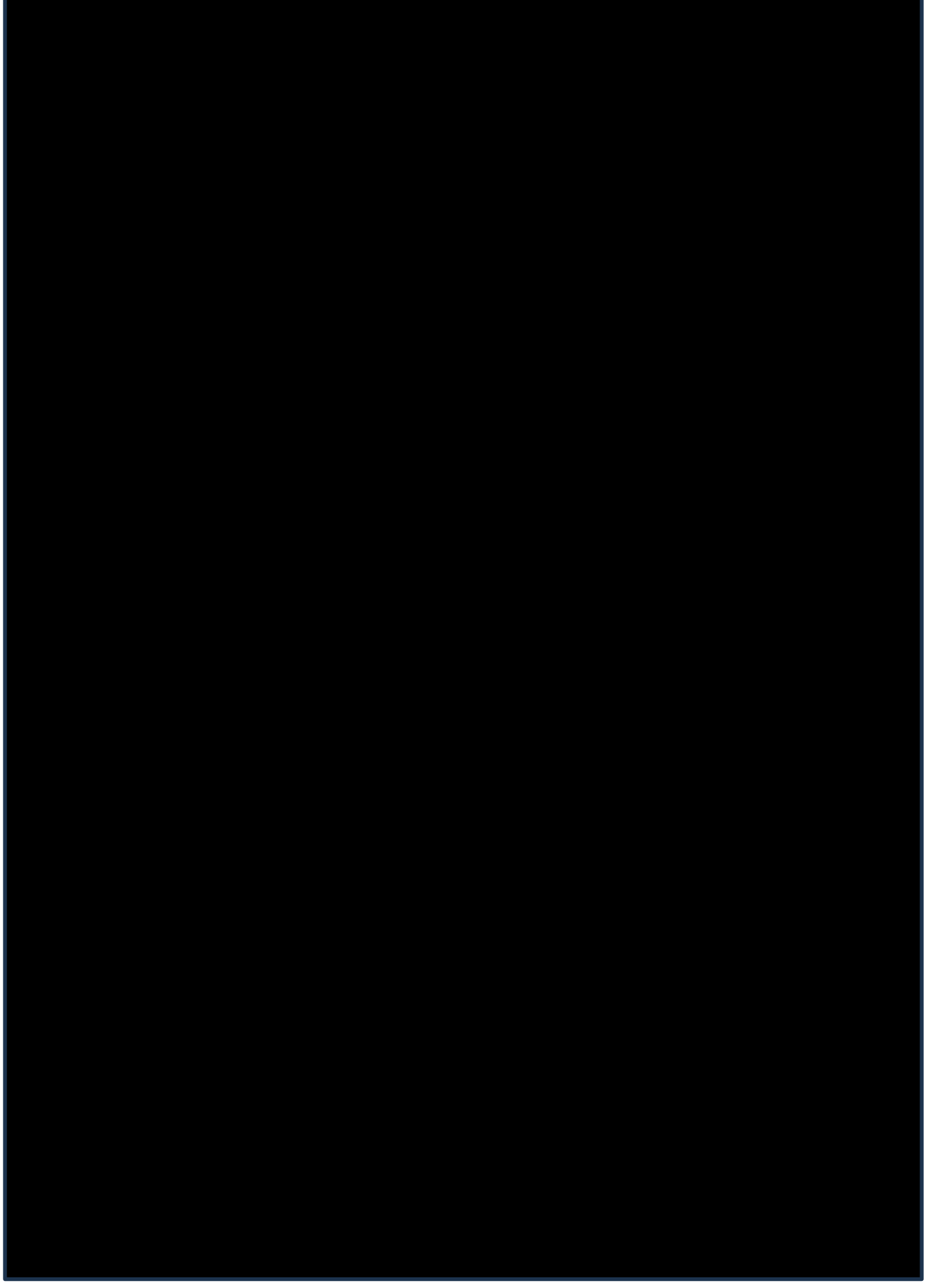
Clinical Laboratory Test Panel	Description
General biochemistry:	Sodium, potassium, chloride, glucose, blood urea nitrogen (BUN), creatinine, bilirubin total, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and albumin
Endocrinology:	Follicle stimulating hormone (FSH; for postmenopausal 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) and hepatitis C (HCV)
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



C-SSRS—Baseline/Screening (Version 1/14/09)
Page 1 of 2



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

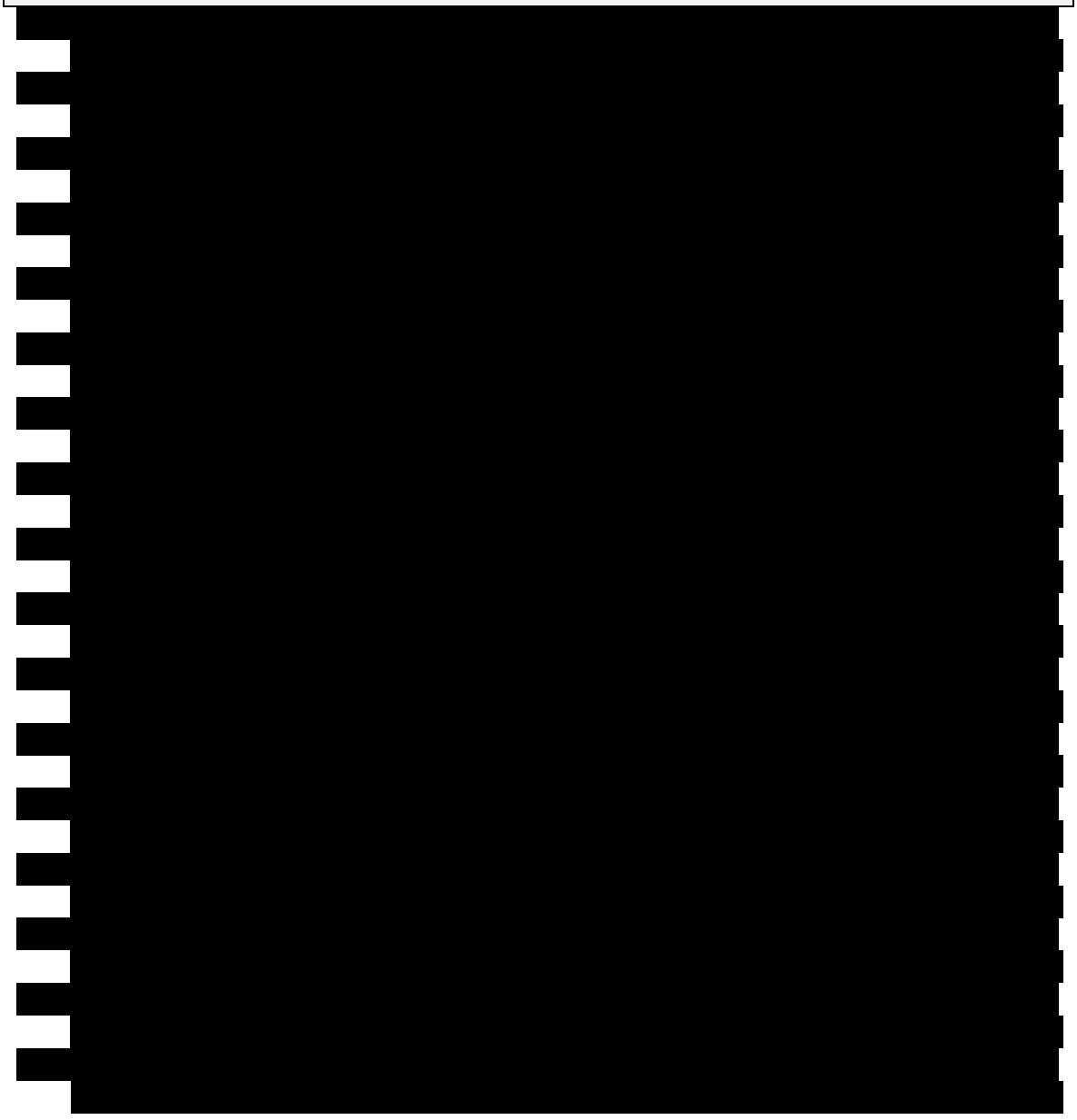
[redacted]

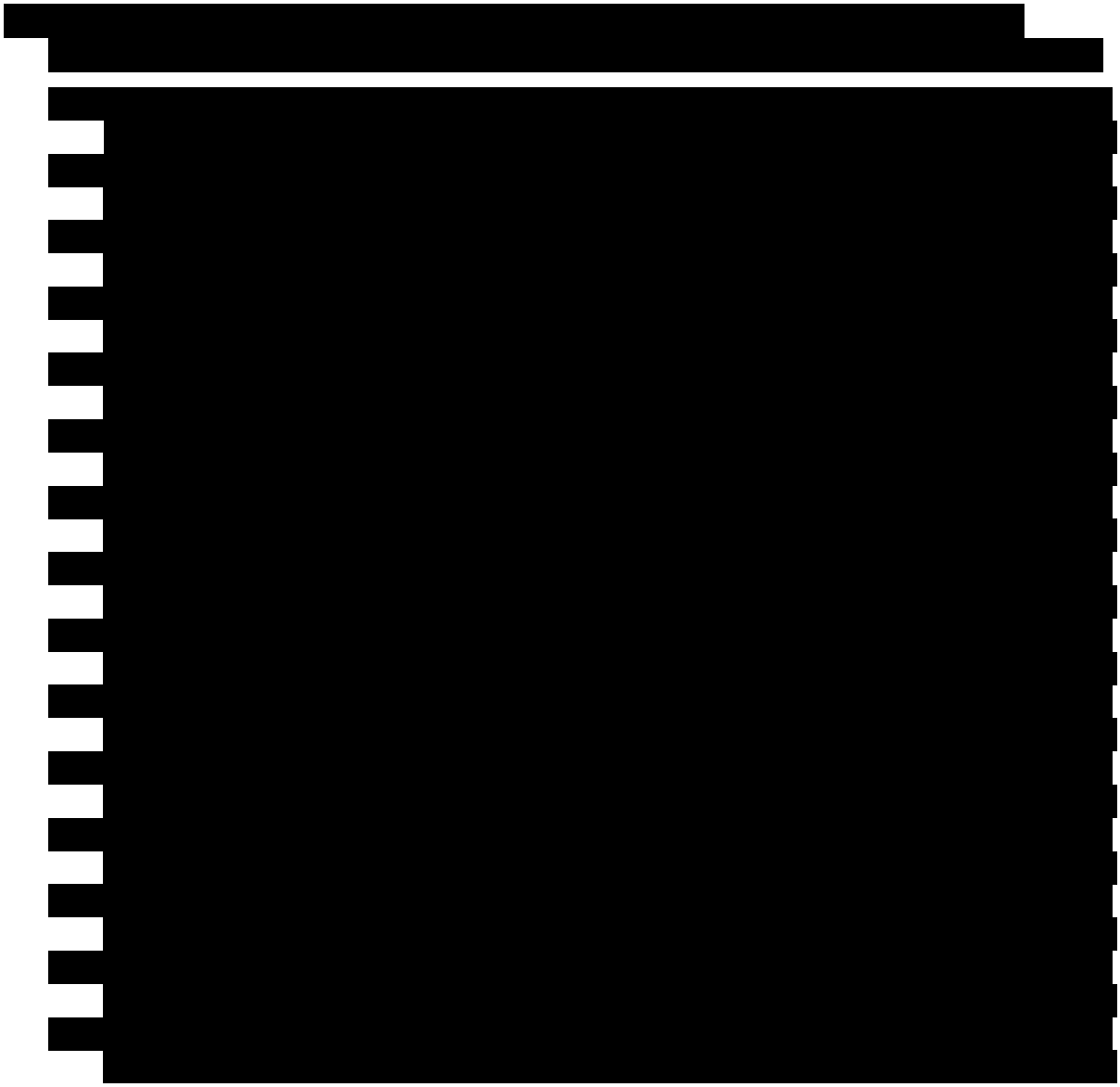
[redacted]

18. APPENDIX 9: ADDICTION RESEARCH CENTER INVENTORY (ARCI) MORPHINE-BENZEDRINE GROUP (MBG) SCALE

Instructions: Answer each question as to how you are feeling at this moment.

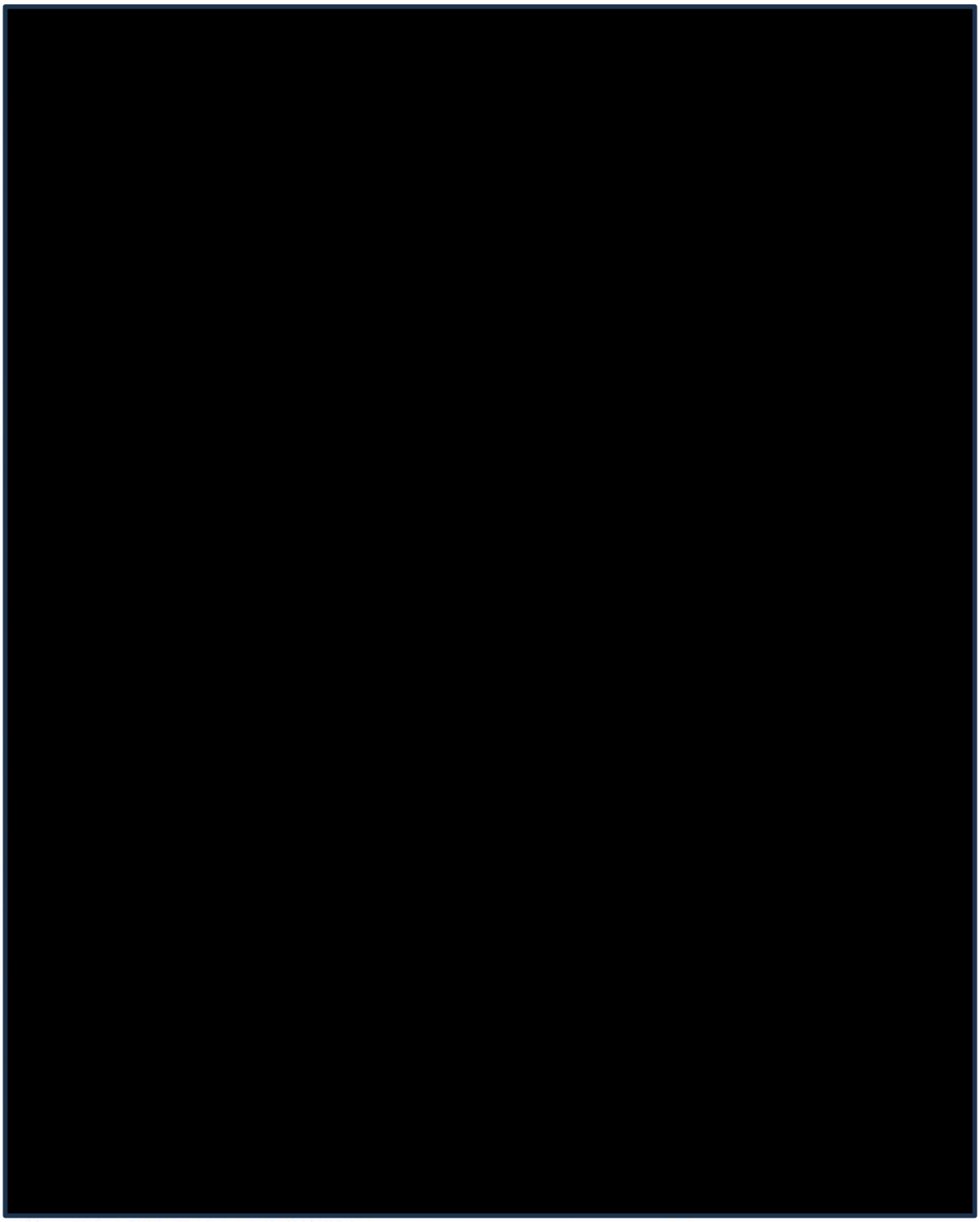
One point is given for every "true" answer to the following:





20. APPENDIX 11: CLINICAL OPIATE WITHDRAWAL SCALE (COWS)

Clinical Opiate Withdrawal Scale



This version may be copied and used clinically.

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