STATISTICAL ANALYSIS PLAN

For:

Arbor Pharmaceuticals, LLC

PROTOCOL No. AR26.3031.1

PROTOCOL VERSION: Final v3.0 (Amendment 02), 09-Aug-2021

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

Altasciences Project No. ABO-P1-904

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Prepared by:

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[redacted]

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STATISTICAL ANALYSIS PLAN APPROVAL

We have carefully read this statistical analysis plan and agree it contains the necessary information required to handle the statistical analysis of study data.

[redacted] Date

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On behalf of the Sponsor:

[redacted] Date

VERSION CONTROL

Version	Date	Author	Description of Changes
Final 1.0	16-Jan-2022	[redacted]	Not applicable

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ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ARCI	Addiction Research Center Inventory
AST	Aspartate Aminotransferase
$AUC_{0\text{-}inf}$	Area under the concentration-time curve from the time 0 extrapolated to infinity
$AUC_{0\text{-}t}$	Area under the concentration-time curve from time 0 to t h
$AUC_{0\text{-}T}$	Area under the concentration-time curve from time 0 to the last measurable observed concentration
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
C	Positive Control
CFB_{min}	Change from baseline to minimum effect (predose - postdose)
CI	Confidence Interval
C_{max}	Maximum observed concentration
CRU	Clinical Research Unit
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV%	Coefficient Of Variation Percentage
DMP	Data Management Plan
DTS	Deviation Tracking System
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
E_{max}	Maximum effect
E_{min}	Minimum effect
ER	Extended Release
$EtCO_2$	End Tidal CO_2
FSH	Follicle Stimulating Hormone
HAP	Human Abuse Potential
HBsAg (B)	Hepatitis B Virus Surface Antigen
HCV (C)	Hepatitis C Virus Antibody
HEENT	Head, Eyes, Ears, Nose, Throat
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
λ_Z	Individual estimate of the terminal elimination rate constant, calculated using log-linear regression of the terminal portions of the plasma concentration-versus-time curves

LLOQ	Lower Limit of Quantitation
ln	Natural Log
Max	Maximum
MBG	Morphine-Benzedrine Group
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary For Regulatory Activities
Min	Minimum
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
n	Number of Subjects
N	Number of Observations
NCA	Non-Compartmental Analyses
P	Placebo
PCAG	Pentobarbital-Chlorpromazine-Alcohol Group
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
SOP	Standard Operating Procedure
SpO_2	Oxygen Saturation
SUSAR	Suspected Unexpected Serious Adverse Event
T	Test Drug
$T_{1/2}$	Terminal elimination half-life
T_{last}	Time of the last measurable observed concentration
T_{max}	Time of maximum observed concentration
TA_AOE	Time-averaged area over the effect-time curve
TA_AUE	Time-averaged area under the effect-time curve
TEAE	Treatment-Emergent Adverse Event
TE_{max}	Time of maximum effect
TE_{min}	Time of minimum effect
TFLs	Tables, Figures, and Listings
UDS	Urine Drug Screen
VAS	Visual Analog Scale
VC	Variance Components
WHO-DDE	World Health Organization Drug Dictionary - Enhanced

1. INTRODUCTION

This study will be a randomized, double-blind, active- and placebo-controlled, 5-way crossover study to determine the abuse potential of GE-IR relative to alprazolam and placebo, in heatlhy, nondependent, recreational drug users with sedative drug use experience. This study will consist of 3 phases: screening, qualification and treatment.

This statistical analysis plan (SAP) provides a detailed description of the statistical methods and procedures to be implemented for the analyses of data from protocol AR26.3031.1. Pre-planning of analyses reduces the potential for bias and often reduces disputes between sponsor and the regulatory authority regarding the validity of the results. The same principles apply to supportive and/or post-hoc analyses. These analyses must be prospectively specified. (Good Review Practice: Clinical Review of Investigational New Drug Applications, December 2013).

The analyses described in the SAP are based upon the final protocol version 3.0 (Amendment 02), dated 09-Aug-2021.

2. STUDY OBJECTIVES

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

The objectives of the study and corresponding study endpoints are detailed in Table 1.

Table 1: Objectives and Related Endpoints

Objective(s)	Endpoint	Analysis
Pharmacodynamic (PD)		
To evaluate the abuse potential of single oral doses of GE-IR relative to alprazolam and placebo, when administered to nondependent recreational drug users with sedative drug use experience	The primary endpoint will be the 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).	Refer to Section 7.4.1
	Key Secondary PD endpoints will be: • Overall Drug Liking VAS (E_{max}) • Take Drug Again VAS (E_{max}) • High VAS (E_{max}) Non-Key Secondary PD endpoints will be: Balance of Effects • Drug Liking VAS (time of maximum effect [TE_{max}], minimum effect [E_{min}], time of minimum effect [TE_{min}], and time-averaged area under the effect-time curve [TA_AUE]) Positive Effects • 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 VAS (E_{max}, TE_{max}, and TA_AUE) • Drowsiness/Alertness VAS (E_{min}, TE_{min}, and time-averaged area over the effect-time curve [TA_AOE]) • Relaxation/Agitation VAS (E_{min}, TE_{min}, and TA_AOE) • Addiction Research Center Inventory	Refer to Section 7.4.2 and Section 7.4.3

Objective(s)	Endpoint	Analysis
	(ARCI) Morphine-Benzedrine Group (MBG) Scale (E_{max}, TE_{max}, and TA_AUE) • ARCI Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) Scale (E_{max}, TE_{max}, and TA_AUE) Observer Assessments • Modified Observer's Assessment of Alertness/Sedation (MOAA/S) (E_{min}, change from baseline to minimum effect [CFB_{min}], and TA_AOE)	
Pharmacokinetic (PK)		
To evaluate the PK of GE-IR when administered to nondependent, recreational drug users with sedative drug use experience	Secondary Endpoint: Pharmacokinetic parameters of GE-IR include C_{max}, T_{max}, T_{last} and area under the concentration-time curve from 0 to the last measured observable concentration (AUC_{0-T})	Refer to Section 8
Safety		
To evaluate the effects on safety and tolerability of single oral doses of GE-IR relative to alprazolam and placebo, when administered to nondependent, recreational drug users with sedative drug use experience	Secondary endpoints will include a summary of the incidence of adverse events (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.	Refer to Section 9

3. STUDY DESIGN

3.1 Overall Study Design

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

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

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

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

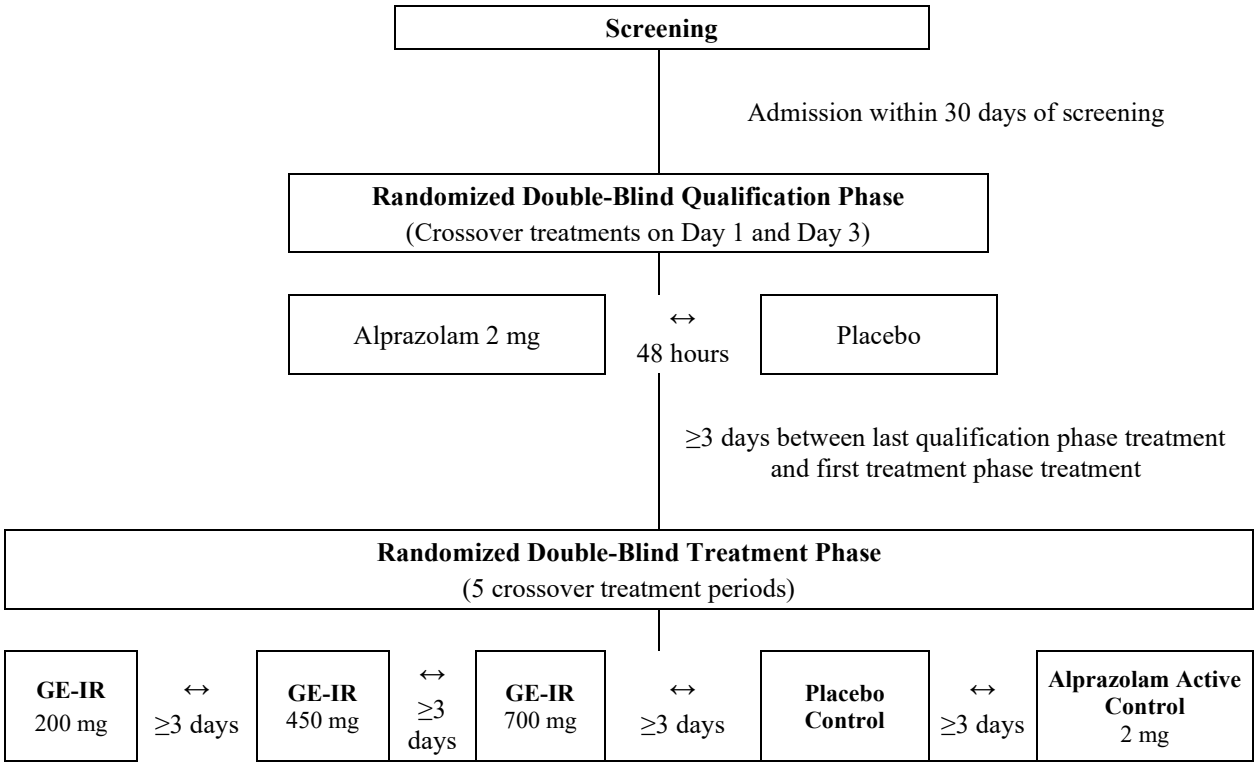
The treatment phase is a randomized, double-blind, active- and placebo-controlled 5-way crossover design. Subjects will be randomized to 1 of the 10 pre-specified treatment sequences in which they will receive the following 5 treatments in a crossover manner (1 per treatment period) in blinded fashion:

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

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

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

Figure 1: Study Schema



Note: the sequence of treatments shown is for illustration of the overall design and does not necessarily represent an actual treatment sequence. Refer to Table 2 and Table 3 for all treatment sequences. A minimum 3 day washout will be required between the last dose in the qualification phase and the first dose of the treatment phase.

3.3 Determination of Sample Size

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

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

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

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

3.4 Treatments

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

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

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

- **Placebo:** Three placebo capsules to match GE-IR + 1 placebo capsule to match alprazolam [2 × over-encapsulated placebo tablets in one size 0 opaque white capsules with no markings] will be administered orally.
- **Active Control:** A single 2 mg dose of over-encapsulated alprazolam (2 × 1 mg tablets over-encapsulated in one size 0 opaque white capsules with no markings) + 3 placebo capsules to match GE-IR will be administered orally.
- **A single 200 mg dose of GE-IR** (1 × 200 mg immediate-release [IR] capsule + 2 placebo capsules to match GE-IR capsule + 1 placebo capsule to match alprazolam [2 × 1 mg placebo tablets over-encapsulated in one size 0 opaque white capsules with no markings]) will be administered orally.
- **A single 450 mg dose of GE-IR** (2 × 225 mg immediate-release [IR] capsule + 1 placebo capsule to match GE-IR capsule + 1 placebo capsule to match alprazolam [2 × over-encapsulated placebo tablets in one size 0 opaque white capsules with no markings]) will be administered orally.
- **A single 700 mg dose of GE-IR** (3 × 233.3 mg immediate-release [IR] capsules + 1 placebo capsule to match to alprazolam [2 × over-encapsulated placebo tablets in one size 0 opaque white capsules with no markings]) will be administered orally.

3.4 Study Procedures

For complete details on the study assessments to be performed for each study period, refer to Appendix A.

3.5 Randomization and Unblinding Procedures

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

3.5.1.1 Qualification Phase

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

Table 2: Sample Qualification Phase Sequences

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

Treatment X: Placebo
Treatment Y: Alprazolam 2 mg

A minimum 3 day washout will be required between the last dose in the qualification phase and the first dose of the treatment phase.

3.5.1.2 Treatment Phase

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

Table 3: Sample Treatment Phase Sequences

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

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

3.5.2 Blinding

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

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

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

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

4. ANALYSIS POPULATIONS

4.1 Qualification Phase

4.1.1 Qualification Randomized Population

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

4.1.2 Qualification Safety Population

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

4.2 Treatment Phase

4.2.1 Randomized Population

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

4.2.2 Safety Population

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

4.2.3 Completer Population

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

4.2.4 Modified Completer Population

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

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

OR

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

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

4.2.5 Pharmacokinetic (PK) Population

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

5. STUDY SUBJECTS

5.1 Disposition

5.1.1 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 using the Qualification Randomized population.

5.1.2 Treatment Phase

Subject disposition will be summarized and listed for subjects randomized to the treatment phase using the Randomized population. Percentages will be calculated using the number of randomized subjects. Completion by population, by period, by study, and reasons for discontinuation will be included in this table.

Subject discontinuations will be summarized by last treatment prior to discontinuation during the treatment phase. Listings of subject disposition by completion/discontinuation will also be provided.

Subject exclusions from each population will be summarized and listed for each phase of the study. Randomization scheme and code will be listed for the each phase of the study.

5.2 Protocol Deviations

All protocol deviations related to study inclusion or exclusion criteria, conduct of the study, subject management, or subject assessment (including PD and PK sample processing deviations) will be listed for the qualification and randomized phases using the Qualification and Randomized populations, respectively. Information for PD and PK sampling time deviations during the treatment phase will be derived programmatically, and presented in listings.

Deviations will be collected in the clinic deviation tracking system (DTS) and presented as entered in a general protocol deviation listing.

6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

6.1 Qualification Phase

Demographics, baseline characteristics and informed consent information will be listed for the Qualification Randomized population. Demographics and baseline characteristics (sex, age, race, ethnicity, body weight, height, BMI) will be summarized separately for the Qualification Randomized and Safety populations. Subjects who did not complete the qualification phase or were not randomized into the treatment phase will also be summarized.

6.2 Treatment Phase

Demographics, baseline characteristics and informed consent information will be listed for the Qualification Randomized population. Demographics and baseline characteristics (sex, age, race, ethnicity, body weight, height, and body mass index (BMI)) will be summarized by each population in the treatment phase using descriptive statistics (number of subjects (n), mean, standard deviation (SD), minimum, median, and maximum for continuous variables, and number of subjects and the proportion of subjects for categorical variables).

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

Histories of recreational drug use, alcohol use and smoking history will be summarized for the Randomized population using descriptive statistics and listed by subject for the Qualification Randomized population.

7. PHARMACODYNAMICS ANALYSIS

Unless otherwise specified, all available PD data and analysis results will be presented for the Modified Completer population.

7.1 Pharmacodynamics Assessments

Prior to completing the computerized pharmacodynamics measures, all subjects will undergo a scripted training and practice regimen with additional training sessions as necessary.

7.1.1 Subjective Effects Visual Analogue Scales (VASs)

All VASs will be scored on a 100-point scale, as shown in Table 4. The VASs may be administered as bipolar or unipolar scales, as appropriate, and the choice is determined by the nature of the subjective effect being measured. When VASs are administered as bipolar scales, the neutral point equals 50 (e.g., Drug Liking, Overall Drug Liking, Take Drug Again, Drowsiness/Alertness and Relaxation/Agitation VAS). The neutral point will also be labeled with an anchor, such as "neither like or dislike." When VASs are administered as unipolar scales, the 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). 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 4: 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 or 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 or would not 100: Definitely would
Positive	Yes	Unipolar	High	At this moment, I am feeling high	0: Not at all 100: Extremely
Positive	No	Unipolar	Good Effects	At this moment, I feel good drug effects	
Negative	No	Unipolar	Bad Effects	At this moment, I feel bad drug effects	

Scale Interpretation	Include Predose	Type of Scale	Description	Question Text	Response Anchors
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 agitated 50: Neither agitated or relaxed 100: Very relaxed

7.1.2 Addiction Research Center Inventory (ARCI) Scales

The ARCI Morphine-Benzedrine Group (MBG) consists of a series of 17 true/false statements, and Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) scales consist of a series of 15 true/false statements. The respective questionnaires are presented in Appendix 9 and 10 of the protocol.

7.1.3 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.[1] 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)

7.2 Appropriateness of Measures

The selected PD measures will assess positive and negative subjective drug effects associated with the abuse potential of this drug. These subjective measures are consistent with guidelines for HAP studies[2] 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 one of the most sensitive and face-valid measures of abuse potential.[3,4] Overall Drug Liking VAS and Take Drug Again have been selected as key secondary endpoints as they represent the subject's global assessment of the drug, and have face validity for predicting continued use of a drug. High VAS has also been selected as a key secondary endpoint because it has been shown to be sensitive in capturing the positive subjective effects of test drugs. Additional secondary endpoints assess other subjective effects of the drug that may help with interpretation of the data.

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

7.3 Pharmacodynamics Assessment Visit Windows

Predose measures should be no more than 1 hour prior to dosing. Visit windows for VAS and ARCI should be ±15 minutes from each postdose time point. MOAA/S will be conducted during the qualification and treatment phases within 1 hour prior to dosing and approximately (±15 minutes) at 0.5, 1, 1.5, 2 hours postdose, and approximately (±30 minutes) at 3, 4, and 6 hours postdose (refer to Appendix A for more details regarding the order of administration).

7.4 Analysis of Pharmacodynamics Measures

The primary analysis of PD data will be analyzed for the Modified Completer population.

E_{max} of Drug Liking, Overall Drug Liking, Take Drug Again and High VAS from the qualification phase will be summarized by treatment and paired difference for the Modified Completer population using standard descriptive statistics. The data will be evaluated to confirm that an appropriate population was selected for the treatment phase.

During the treatment phase, PD measures at each time point will be summarized by treatment using descriptive statistics and presented graphically. Derived endpoints will be summarized by treatment and paired difference using descriptive statistics. Only descriptive statistics will be output for TE_{max} and TE_{min}. Descriptive statistics will include n, mean, standard error (SE), minimum, first quartile (Ql), median, third quartile (Q3) and maximum for all PD values and endpoints other than TE_{max} and TE_{min}. For TE_{max} and TE_{min}, minimum, Q1, median, Q3 and maximum will be output.

A mixed-effects model for a crossover study design will be used to compare the primary and secondary PD endpoints between treatments (e.g., E_{max}, E_{min}, CFB_{min}, TA_AUE and TA_AOE) with appropriate covariance-variance structure, if the residuals are normally distributed. Necessary adjustment in the model will be made for possible heteroscedasticity of variances through Kenward Roger approximation of degrees of freedom.

The model will include treatment, period, treatment sequence, and first-order carryover effect (where applicable) as fixed effects, and the baseline (predose) measurement as a covariate (where applicable).

If the variance among treatments is homogeneous, subject will be considered a random effect; if the variance among treatments is heterogeneous, the default variance components (VC) variance structure block will be used for each subject. Treatments for each PD endpoint will be tested for homogeneity of variance using the SAS procedure [redacted]

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

[redacted]

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.

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 analysis model. If the carryover effect is found to be significant at the alpha = 0.25, it will be included in the model.

The conditional residuals from the mixed-effects model will be investigated for normality using the Shapiro-Wilk W test. The following provides an example of the SAS code that will be used if the variance is homogeneous:

[redacted]

If the normality assumption of the model is satisfied, least squares means, SE, and 1-sided 95% or 2-sided 90% or 95% 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 for a PD endpoint, 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:

a) If the alternative hypothesis is upper-tailed, and skewness is [0, 0.5] then mean difference, SE, 1-sided 95% or 2-sided 90% CI, and p-value from the t-test will be output.

b) If the alternative hypothesis is upper-tailed, and skewness < 0 or skewness > 0.5 then median of the paired difference (Q1-Q3), 1-sided 95% or 2-sided 90% CI, and p-value from the sign test will be output.

c) If the alternative hypothesis is lower-tailed, and skewness is [-0.5, 0] then mean difference, SE, 1-sided 95% or 2-sided 90% CI, and p-value from the t-test will be output.

d) If the alternative hypothesis is lower-tailed, and skewness < -0.5 or skewness > 0 then median of the paired difference (Q1-Q3), 1-sided 95% or 2-sided 90% CI, and p-value from the sign test will be output.

e) If the alternative hypothesis is two-tailed, and skewness is [-0.5, 0.5] then mean difference, SE, 2-sided 95% (Hypotheses 1 and 2) or 2-sided 90% CI (Hypothesis 3), and p-value from the t-test will be output.

f) If the alternative hypothesis is two-tailed, and skewness < -0.5 or skewness > 0.5 then median of the paired difference (Q1-Q3), 2-sided 95% (Hypotheses 1 and 2) or 2-sided 90% CI (Hypothesis 3), and p-value from the sign test will be output.

The following provides an example of the SAS code that will be used for a t-test and a sign test respectively:

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

The primary objective of a HAP study is to provide information on the relative abuse potential of a test drug in humans.[2] The statistical analysis of a HAP study should address the following questions:

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

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

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

To address these issues, the following hypotheses will be tested for Drug Liking VAS E_{max} at a significance level of 0.05; 2-sided 90% confidence intervals will be used.

[redacted]

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

Although a margin of 15 has been selected for Hypothesis 1 to ensure consistency with the qualification phase criteria, subjects are expected to provide lower responses in the treatment phase as compared to the qualification phase.[6,7] Therefore, if the difference between the positive control and placebo does not meet the recommended criterion for validity (i.e., $\delta_1 = 15$), a secondary planned analysis will be performed (refer to Section 7.4.4 for more details). A margin of 11 points is considered appropriate for Hypothesis 3 based on an analysis of Drug Liking VAS E_{max} data.[8]

For study validity purposes, the primary endpoint, E_{max} for Drug Liking VAS, will be compared between the positive control (alprazolam 2 mg) and placebo. The comparison will assess the null hypothesis that the mean difference in Drug Liking E_{max} between alprazolam and placebo is less than or equal to 15 against the alternative hypothesis that the mean difference in Drug Liking E_{max} between alprazolam 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]

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

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

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

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

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

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

The following

```
PROC MIXED DATA=ADPD;
```

[redacted]

7.4.2 Test Hypotheses for Key Secondary Endpoints

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

[redacted]

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

[redacted]

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

- Treatment B: Alprazolam 2 mg vs. Treatment A: Placebo

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

[redacted]

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

[redacted]

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

[redacted]

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

[redacted]

A significance level of 0.05 will be used for Hypotheses 1 and 2, and a significance level of 0.1 will be used for Hypothesis 3.[9] For Hypotheses 1 and 2, 1-sided 95% confidence intervals will be presented while 2-sided 90% confidence intervals will be presented for Hypothesis 3.

7.4.3 Test Hypotheses for Non-Key Secondary Endpoints

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

[redacted]

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

[redacted]

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

- Treatment B: Alprazolam 2 mg vs. Treatment A: Placebo

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

[redacted]

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

[redacted]

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

[redacted]

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

[redacted]

A significance level of 0.05 will be used for Hypotheses 1 and 2, and a significance level of 0.1 will be used for Hypothesis 3.[9] For Hypotheses 1 and 2, 2-sided 95% confidence intervals will be presented while 2-sided 90% confidence intervals will be presented for Hypothesis 3.

7.4.4 Secondary Analysis

Although a margin of 15 has been selected for Hypothesis 1 for consistency with the qualification phase criteria, subjects may have lower responses with alprazolam and higher responses with placebo in the treatment phase as compared to the qualification phase,[6,7] particularly for lower abuse potential drugs such as benzodiazepines (i.e., Schedule IV drugs). Therefore, in the case that the difference between the active control and placebo does not meet the pre-specified criteria for validity of at least 15 points, Drug Liking VAS E_{max} will be explored in terms of the following criteria using descending point differences starting at 4.

[redacted]

7.4.5 Adjustment for Covariates

Baseline (pre-dose) measurement will be included as a covariate, where applicable, in the mixed effects models.

7.4.6 Adjustment for Multiple Comparison/Multiplicity

No adjustments will be made for multiple comparisons. The primary hypotheses follow a hierarchical (sequential) testing method, and all doses of GE-IR should show statistical significance in the hypothesis testing.

8. PHARMACOKINETICS ANALYSIS

8.1 Pharmacokinetic Analysis

The PK analysis will be carried out according to Altasciences standard operating procedures (SOPs).

8.1.1 Concentration Data

Plasma concentrations of gabapentin resulting from the single 200 mg, 450 mg, and 700 mg dose administration of the investigational product (GE-IR) from the treatment phase will be determined to establish the PK profile of gabapentin in healthy, nondependent, recreational drug users with sedative experience.

8.1.2 Missing Values

The lack of concentration values due to failure to collect the sample, a lost or compromised sample or due to the subject's early termination from the study will be termed "missing" in the dataset, and no imputation will be done.

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 descriptive statistics, but the concentration value will be presented in the concentration listing. Unknown baseline collection times will be handled on a case-by-case basis.

8.1.3 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 zero for mean PK profile representations as well as for descriptive statistic calculations.

8.1.4 Actual Times

The NCA will be based on the actual sampling times, except for predose samples, which will always be reported as zero, 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. Concentration profiles will be presented on both linear and semi-logarithmic scales.

Individual actual times will be listed.

8.1.5 Non-Compartmental Analysis

The PK analyses will be based on the PK population.

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

[redacted]

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

The PK parameters to be determined are defined in Table 5.

Table 5: Pharmacokinetic Parameters in Plasma

PK Parameter	Definition
C_{max} (ng/mL)	Maximum observed concentration occurring at time T_{max}
T_{max} (h)	Time of maximum observed concentration. If the maximum observed concentration is not unique, then the first maximum is used.
AUC_{0-1} (h*ng/mL),	Area under the concentration-time curve from the time 0 to 1 h
AUC_{0-2} (h*ng/mL),	Area under the concentration-time curve from the time 0 to 2 h
AUC_{0-12} (h*ng/mL),	Area under the concentration-time curve from the time 0 to 12 h
AUC_{0-24} (h*ng/mL),	Area under the concentration-time curve from the time 0 to 24 h
AUC_{0-T} (h*ng/mL),	Area under the concentration-time curve from the time 0 to T_{last}
AUC_{0-inf} (h*ng/mL),	Area under the concentration-time curve from the time 0 extrapolated to infinity
$T_{1/2}$ (h)	Terminal elimination half-life
T_{last} (h)	Time of last measurable (positive) observed concentration
λ_Z (1/h)	Individual estimate of the terminal elimination rate constant, calculated using log-linear regression of the terminal portions of the plasma concentration-versus-time curves

8.1.6 Summary Statistics

Summary statistics of the individual concentration data and derived parameters will be calculated with Phoenix® WinNonlin® for the PK population. Summary statistics will be calculated for concentrations at each individual time point and for all PK parameters.

Concentration data will be summarized by group using the following statistics: number of observations (N), mean, SD, minimum (min), median, maximum (max), and coefficient of variation percentage (CV%). Pharmacokinetic parameters will be summarized using these same statistics, as well as geometric mean and geometric mean CV%.

Summary statistics will be displayed with the same precision as the individual values (Section 10.2) with the exception of N and CV% which will be presented with 0 and 1 decimal place, respectively; SD and CV% will not be calculated when N<3, and only min and max will be reported if N=1.

9. SAFETY

For the treatment phase, the following safety endpoints will be evaluated: incidence, maximum severity and maximum relationship of AEs, AEs leading to discontinuation and SAEs, clinical laboratory assessments (hematology, biochemistry, urinalysis), vital signs [e.g. systolic and diastolic blood pressure, pulse rate, respiratory rate, oral temperature, SpO_2], continuous SpO_2 monitoring, continuous $EtCO_2$ monitoring, ECGs, physical examination findings, and Columbia-Suicide Severity Rating Scale (C-SSRS). All safety analyses will be conducted on the Safety population. By-subject listings of adverse events will be based on the Qualification Safety population if occurring in the qualification phase and the Safety population if occurring in the treatment phase. All other listings for safety endpoints will be based on the Qualification Randomized population.

9.1 Adverse Events

9.1.1 Qualification Phase

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

9.1.2 Treatment Phase

An AE is defined as any untoward medical occurrence in a clinical investigation 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 laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Treatment emergent adverse events (TEAEs) are AEs not present prior to the exposure to study treatment or AEs already present that worsen in intensity or frequency following exposure to study treatment.

All TEAEs will be assigned to a treatment using the following rules:

- A TEAE will be assigned to the last treatment taken by the subject where the date and time of the last treatment dosing is on or before of the start date and time of the event. Such assignment will be performed irrespective of any washout period between the start and stop dates of the TEAE.
- Any TEAE started during the follow-up period will be assigned to the last treatment that the subject has taken.

9.1.2.1 Severity Categorization

The severity of AEs must be recorded during the course of the event, including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of the study drug, must be recorded as new AEs on the appropriate electronic case report form (eCRF) page.

The medical assessment of severity is determined by using the following definitions:

Term	Severity Definition
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.

9.1.2.2 Relationship Categorization

The causality assessment must be documented in the source document and the AE will should be considered as “reasonable possibility” and “not reasonable possibility”.

The following additional guidance may be helpful:

Term	Relationship Definition
Reasonable Possibility	A temporal relationship exists between the AE onset and administration of the investigational product that cannot be readily explained by the subject’s clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related,

Term	Relationship Definition
	based on the known therapeutic and pharmacologic actions or AE profile of the investigational product. In case of cessation or reduction of the dose the AE may abate or resolve and it may reappear upon rechallenge.
No Reasonable Possibility	Evidence exists that the AE has an etiology other than the investigational product. For SAEs, an alternative causality must be provided (e.g., preexisting condition, underlying disease, intercurrent illness, or concomitant medication).

9.1.2.3 General Summary of Treatment-Emergent Adverse Events

An overall summary table of all TEAEs by treatment at onset and overall for the treatment phase will be produced to present data below:

- Number and percentages of subjects (number of events) with any TEAE
- Number and percentages of subjects (number of events) with study drug discontinued due to TEAE
- Number and percentages of subjects (number of events) with severe TEAE
- Number and percentages of subjects (number of events) with any related TEAE
- Number and percentages of subjects (number of events) with any serious TEAE
- Number and percentages of subjects (number of events) with any serious TEAE leading to death

The denominator for percentages will be the total number of subjects in the Safety population by treatment and overall.

9.1.2.4 Summaries of Treatment-Emergent Adverse Events

- Summary of TEAEs by System Organ Class (SOC), Preferred Term (PT), and Treatment
    - A summary of the number and percentages of subjects who experienced at least one TEAE, and the number and percentages of subjects who experienced each SOC and each PT within each SOC will be presented by treatment and overall. In addition, the number of events will be summarized for each of these categories.

- Summary of TEAEs by SOC, PT, Treatment and Maximum Severity
    - A summary of the number and percentages of subjects who experienced at least one TEAE by maximum severity as well as the number and percentages of subjects who experienced each SOC and each PT within each SOC by maximum severity will be presented by treatment. For this analysis, if a subject has more than one occurrence of the same PT, then the PT will be counted only once for that subject under the maximum severity at which it was experienced (mild, moderate or severe).

- Summary of TEAEs by SOC, PT, Treatment and Maximum Relationship
    - A summary of the number and percentages of subjects who experienced at least one TEAE by maximum relationship as well as the number and percentages of subjects who experienced each SOC and each PT within each SOC by maximum relationship will be presented by treatment. For this analysis, if a subject has more than one occurrence of the same PT, then the PT will be counted only once for that subject under the maximum relationship at which it was experienced (reasonable possibility or no reasonable possibility).

9.2 Clinical Laboratory Evaluations

General biochemistry, hematology, and urinalysis assessments, and other laboratory tests are listed in Table 6.

Table 6: Clinical Laboratory Assessments

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

*Serology will be done at screening only.

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 laboratory test and visit.

All laboratory data will be listed by laboratory panel and test. Laboratory abnormalities and clinically significant abnormalities during the treatment phase will also be listed.

9.2.1 Viral Screen

A screening viral screen will be done for HIV 1/2 Antibody, Hepatitis B Virus Surface Antigen, and Hepatitis C Virus Antibody. The results of the viral screen will be listed.

9.2.2 Urine Drug Screen and Urine Alcohol Testing

UDS will test for the following drugs of abuse: amphetamines, barbiturates, cannabinoids, cocaine, opiates, benzodiazepines, and phencyclidine.

Urine alcohol testing may be requested any time during the study. The results of UDS and urine alcohol testing will be listed.

9.2.3 Pregnancy and Follicle Stimulating Hormone (FSH) Tests

A listing will be done for pregnancy and FSH tests. Serum pregnancy test will be done at screening. Urine pregnancy test will be done at each admission to the qualification phase and, if applicable, treatment phase, and at Day 14/early termination. For postmenopausal women, an FSH test will be done at screening.

9.3 Vital Signs

Scheduled time points in the treatment phase for blood pressure, pulse rate, oxygen saturation (SpO_2), and respiratory rate will include predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, and 24 hours (±15 minutes) postdose. For $EtCO_2$, scheduled time points in the treatment phase will be recorded pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose.

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 time points. Vital signs will be summarized using descriptive statistics (n, mean, SD, minimum, median, and maximum). All vital signs, including oral temperature, will be listed. Abnormal and clinically significant abnormal findings will be listed.

9.4 12-Lead Electrocardiograms

The ECG variables will include ventricular heart rate and the PR, QRS, QT, and QTcF intervals.

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 and clinically significant findings in ECG data will be listed.

9.5 Physical Examination Findings

Physical examination includes a review of the following: head, eyes, ears, nose, throat (HEENT), neck, chest, back, abdomen, extremities and neurological function.

Physical examination findings will be presented in a listing by subject and visit.

9.6 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS will be used to assess 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.

Two versions of the C-SSRS will be used in this study: the Baseline/Screening version (lifetime history and past 12 months) and the Since Last Visit version. The Screening version of the C-SSRS will be administered at Visit 1 (Screening). The Since Last Visit version of the C-SSRS will be administered at all subsequent assessment times.

The C-SSRS will be listed by subject and visit.

10. DATA HANDLING AND PRESENTATION

All safety and statistical outputs will be generated using SAS software, version 9.4. Pharmacokinetic outputs will be generated using WinNonlin version 8.0 or higher.

All programs used to generate statistical analyses will be validated according to Altasciences's SOPs.

The analyses described in this plan are considered a priori, in that they have been defined prior to database lock and prior to breaking the blind. Any analyses performed subsequent to database lock and breaking the blind that are not described within the present plan will be considered post hoc and secondary. Post hoc analyses will be labeled as such in the corresponding statistical output and identified in the clinical study report (CSR).

10.1 Safety Analysis Presentation

Adverse events and medical history will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) terminology as defined in the study data management plan (DMP).

Prior and concomitant medications will be coded with the World Health Organization Drug Dictionary- Enhanced (WHO-DDE) as defined in the study DMP.

In general, all safety summary tables will be presented for the Safety population. Summaries for AEs will be presented by treatment. Summaries for other safety endpoints will be presented by treatment if the endpoints are measured at the end of each period or by treatment sequence if the endpoints are measured not at the end of each period but at the end of study only.

In general, the data listings will include all randomized subjects up to the point of study completion or discontinuation; exceptions will be listings pertaining to a subset of subjects only (e.g., subjects with protocol deviations) or a subset of records/events (e.g., abnormal laboratory values).

Categorical variables will be summarized using the PROC FREQ procedure. Continuous variables will be summarized using the PROC UNIVARIATE procedure. For natural log (ln)-transformed endpoints, geometric mean, geometric SD, and CV% will also be presented.

The following general comments also apply to all statistical analyses and data presentations:

- Duration variables will be calculated using the general formula: (end date - start date) +1.
- If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table (e.g., a character string is reported for a parameter of the numerical type), a coded value must be appropriately determined and used in the statistical analyses. In general, a value or lower and upper limit of normal range such as '<10' or '≤5' will be treated as '10' or '5' respectively, and a value such as '>100' will be treated as '100'. However, the actual values as reported in the database will be presented in data listings.
- When assessments are repeated for a given time point or performed at unscheduled times, only the result which is the closest to the dosing time will be included in summary tables.

In general, summary statistics for raw variables (i.e., variables measured at the study site or central laboratory) will be displayed as follows:

- Minima and maxima will be displayed to the same number of decimal places as the raw data.
- Means, medians, and quartiles will be displayed to 1additional decimal place.
- Standard deviations will be displayed to 2 additional decimal places.
- Percentages will be displayed to 1 decimal place. Percentages between 0 and 0.1 (exclusive) will be displayed as '<0.1'.
- P-values will be displayed to 3 decimal places. P-values that are less than 0.001 will be displayed as '<0.001'.

The numbers of decimal places for summary statistics of derived variables (i.e., variables that are not measured by the study site but are calculated for analysis based on other measured variables) will be determined on a case by case basis. In general:

- Minima and maxima will be displayed to the commonly used unit of precision for the parameter.
- Means, medians, quartiles, and confidence limits will be displayed to 1 additional decimal place.
- Standard deviations will be displayed to 2 additional decimal places.

10.2 Pharmacokinetic Analysis

In general, all PK summary tables will be presented for the PK population.

Individual raw PK concentrations will be displayed with the same precision as received from the bioanalytical laboratory.

Precision for individual PK parameters will be displayed as follows:

- C_{max} and AUC_{0-T} will be displayed with the same precision as the raw PK concentration data
- Parameters associated with time (i.e. T_{max} and T_{last}) will be displayed with 2 decimal places

Summary statistics for concentration and PK parameters will be displayed with the same precision as the individual values, with the exception of N and CV% which will be presented with 0 and 1 decimal place, respectively.

10.3 Analysis Time Points

Unless otherwise specified, the baseline value will be defined as the last non-missing evaluation prior to the first dose of study medication in each treatment period.

10.4 Methods for Handling Missing Data

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

The occurrence of missing PD data will be minimized by only including subjects who are rousable, and complete PD assessments in the qualification phase. In addition, all reasonable attempts will be made to rouse subjects for completion of the PD assessments in both the

qualification and treatment phases. Missing PD assessments, including reasons for the missing data, will be listed by subject, and examined on a case-by-case basis to determine if these affect subject allocation (i.e., inclusion in the Modified Completer population). If for a given PD measure, the predose value is missing, calculation of CFB_{min} and TA_AOE will not be possible, and the subject will not be included in the Modified Completer population for that PD endpoint. If the actual date and/or time of a postdose PD assessment is unknown, but there is a result at that time point, the value will be used in descriptive statistics of treatment by time point 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.

11. INTERIM ANALYSES AND DATA SAFETY MONITORING

No interim analyses are planned for this study.

12. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

Protocol Section	Original Text	SAP Section	Change
Study Synopsis: Pharmacokinetic Endpoints; Table 8. Pharmacokinetic Parameters	Pharmacokinetic Parameters: C_{max}, T_{max}, AUC_{0-T}, Tlast	Table 1: Objectives and Related Endpoints and Table 5: Pharmacokinetic Parameters in Plasma	Additional PK Parameters: AUC_{0-1} AUC_{0-2}, AUC_{0-12}, AUC_{0-24}, AUC_{0-inf} , $T_{1/2}$, λ_Z
Study Synopsis: Active Control, Dose, and Mode of Administration, Placebo, Dose, and Mode of Administration; Section 3.2 Study Treatments	one Swedish Orange Opaque AAEL-DB capsule	Section 3.3 Treatments	Replace original text for GE-IR and placebo-to-match with one size 0 opaque white capsules with no markings
8.4.1 Qualification Phase	Demographics and baseline characteristics will be summarized for the Qualification Safety populations. Qualification passes and failures will be listed separately.	6.1.1 Qualification Phase	Demographics and baseline characteristics will be summarized for the Qualification Randomized and Safety populations rather than just the Qualification Safety population. Subjects who did not complete the qualification phase or were not randomized into the treatment phase will also be summarized.
8.4.2 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	6.1.2 Treatment Phase	Demographics and baseline characteristics will be summarized for treatment phase populations Safety population. Recreational drug use history, alcohol use history, and smoking history will be summarized for the Randomized population rather than

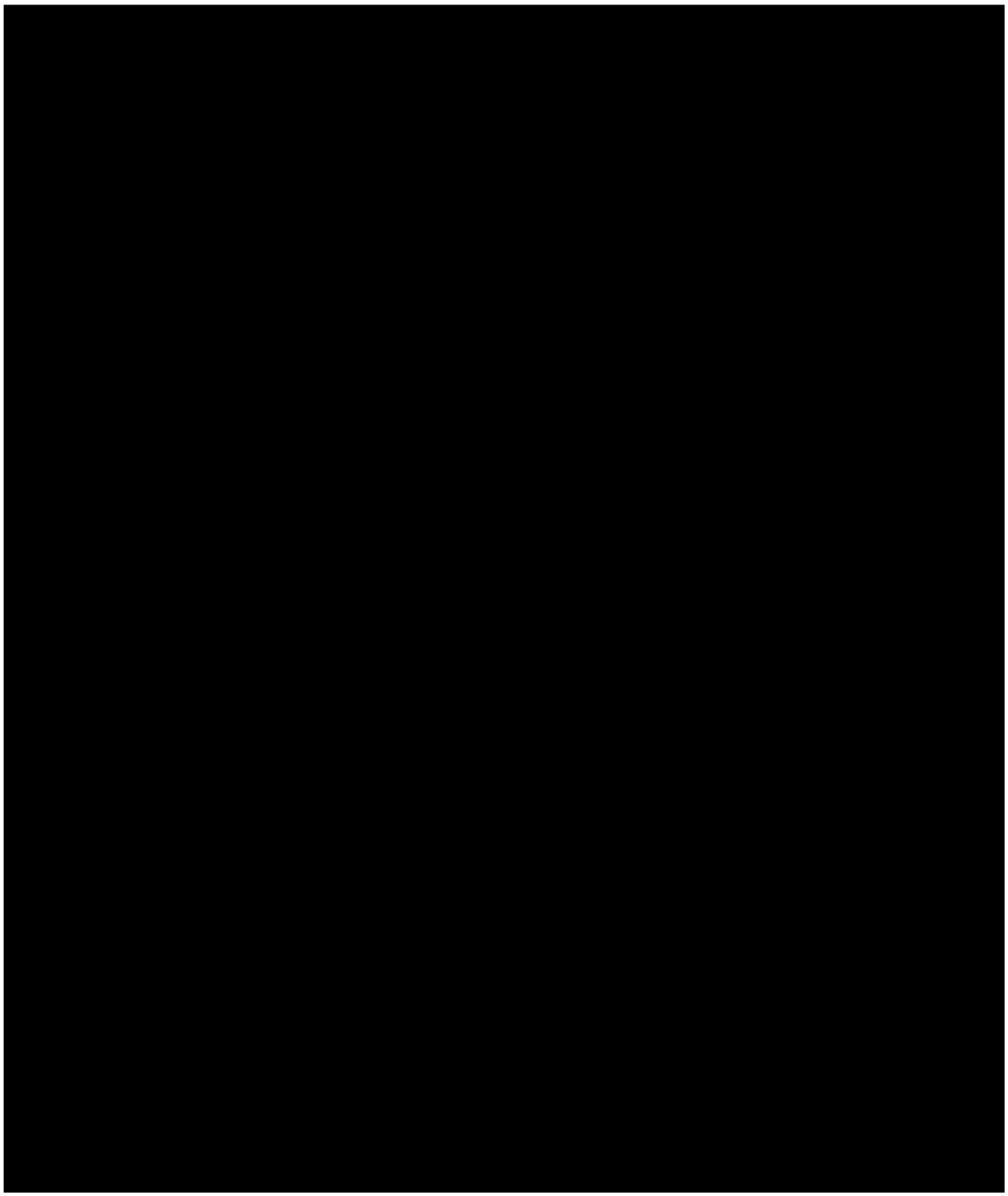
Protocol Section	Original Text	SAP Section	Change
	maximum for continuous variables, and the proportion of subjects for categorical variables) for the Safety population.		the Safety population.
8.5.2 Pharmacodynamic Statistical Methodology	Drug Liking and Take Drug Again VAS E_{max} from the Qualification phase will be summarized by treatment and paired difference for the Modified Completer population.	7.4 Analysis of Pharmacodynamics Measures	E_{max} of Overall Drug Liking and High VAS have been added.
8.7.3.1 Qualification Phase	The Qualification Randomized population will be used to list all AEs occurring in the Qualification phase.	9.1.1 Qualification Phase	The Qualification Safety population rather than the Qualification Randomized population will be used to list all AEs occurring in the Qualification phase.

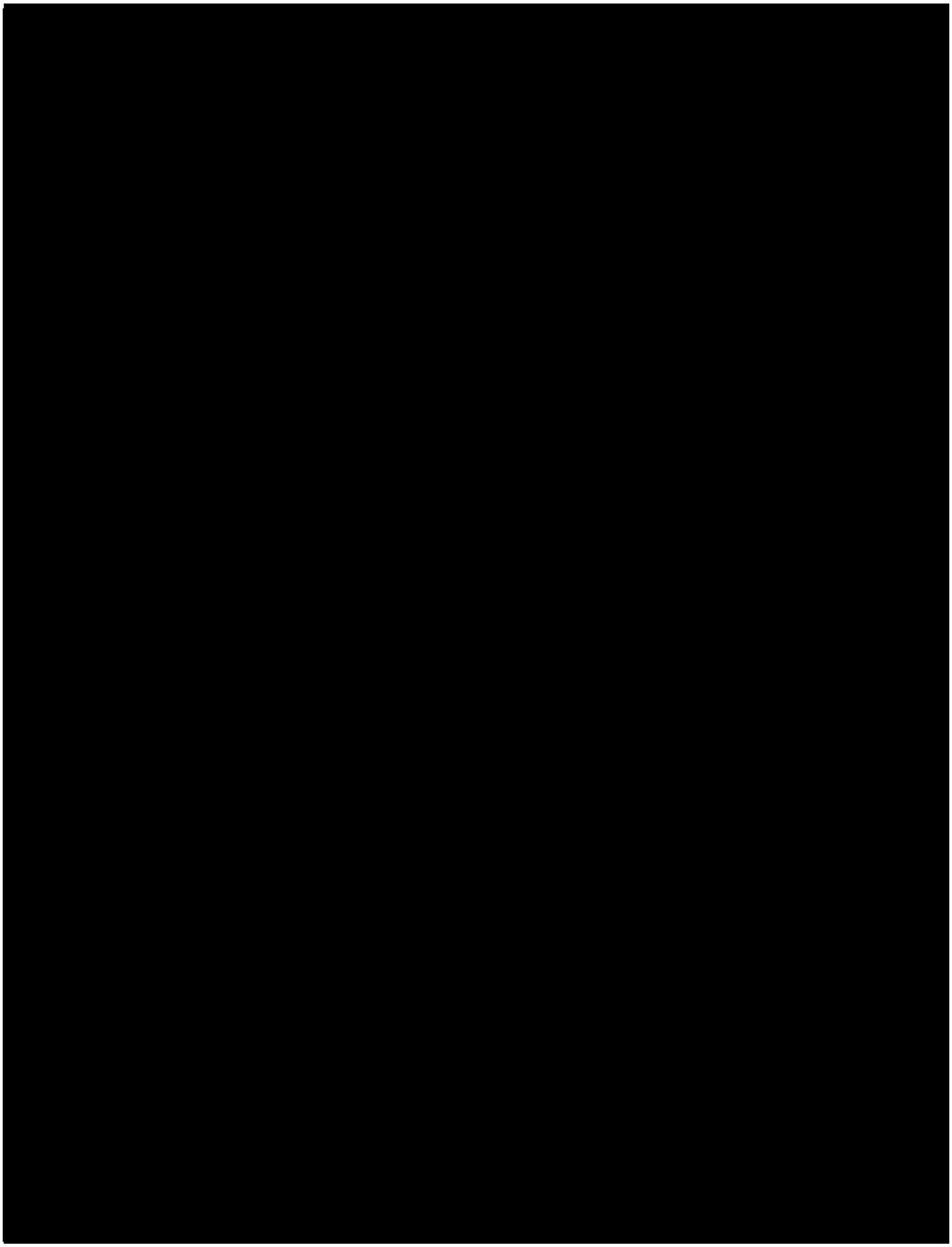
13. GENERAL INFORMATION RELATED TO DATA PRESENTATIONS

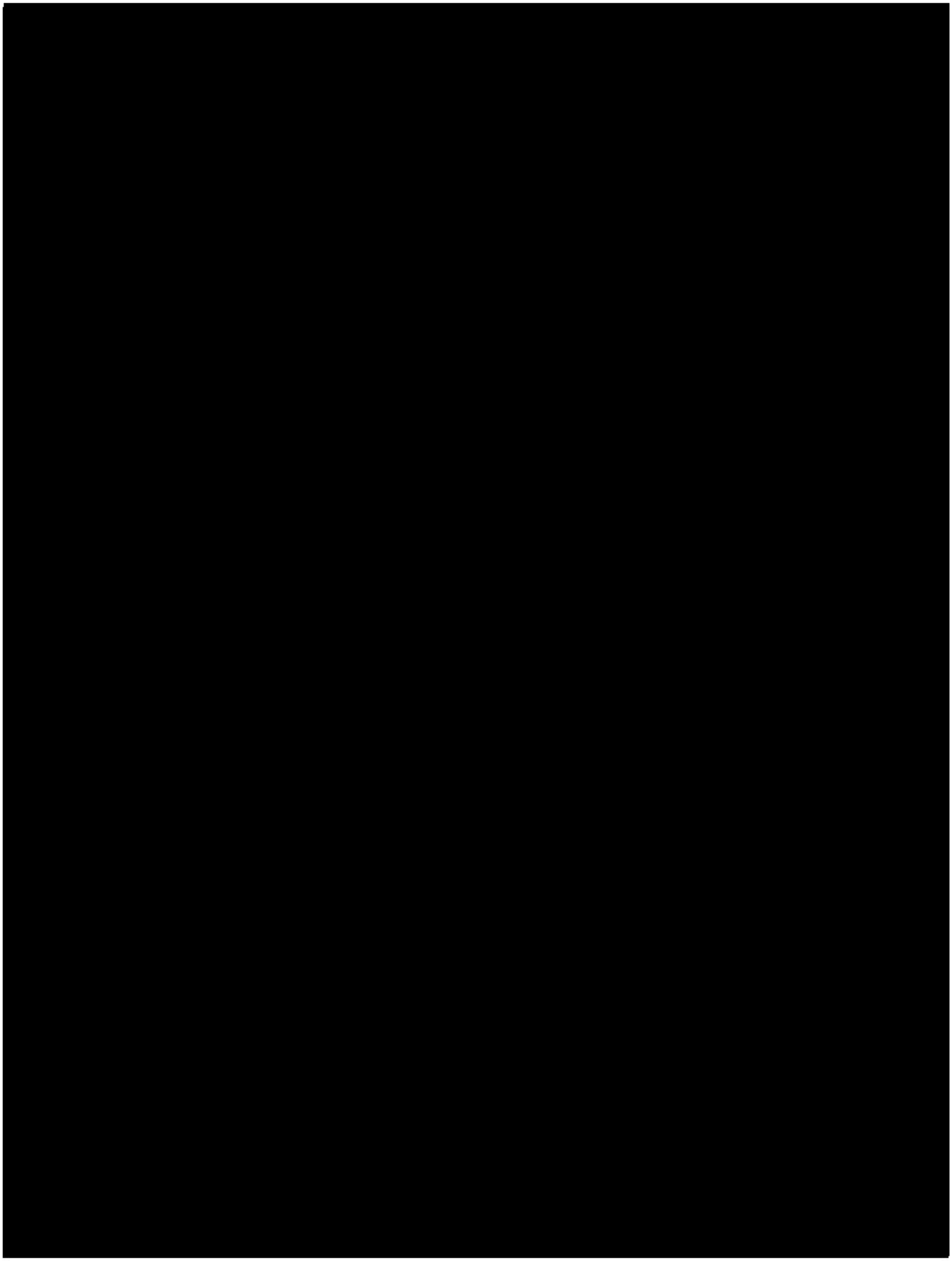
The formats and layouts of tables, figures and listings (TFLs) will be provided in a separate document and are common displays. Their numbering and general content follow the International Conference on Harmonisation (ICH) E3 guidelines. Each TFL will have a template number which links it to the Indices of TFLs presented below. Actual formats and layouts may be altered slightly from those presented as necessary to accommodate actual data or statistics. Minor format changes will not require updates to the SAP, rather they may be documented in a Note to SAP.

13.1 INDEX OF TABLES

The following tables will be produced (table numbers and titles may be different in the final versions):







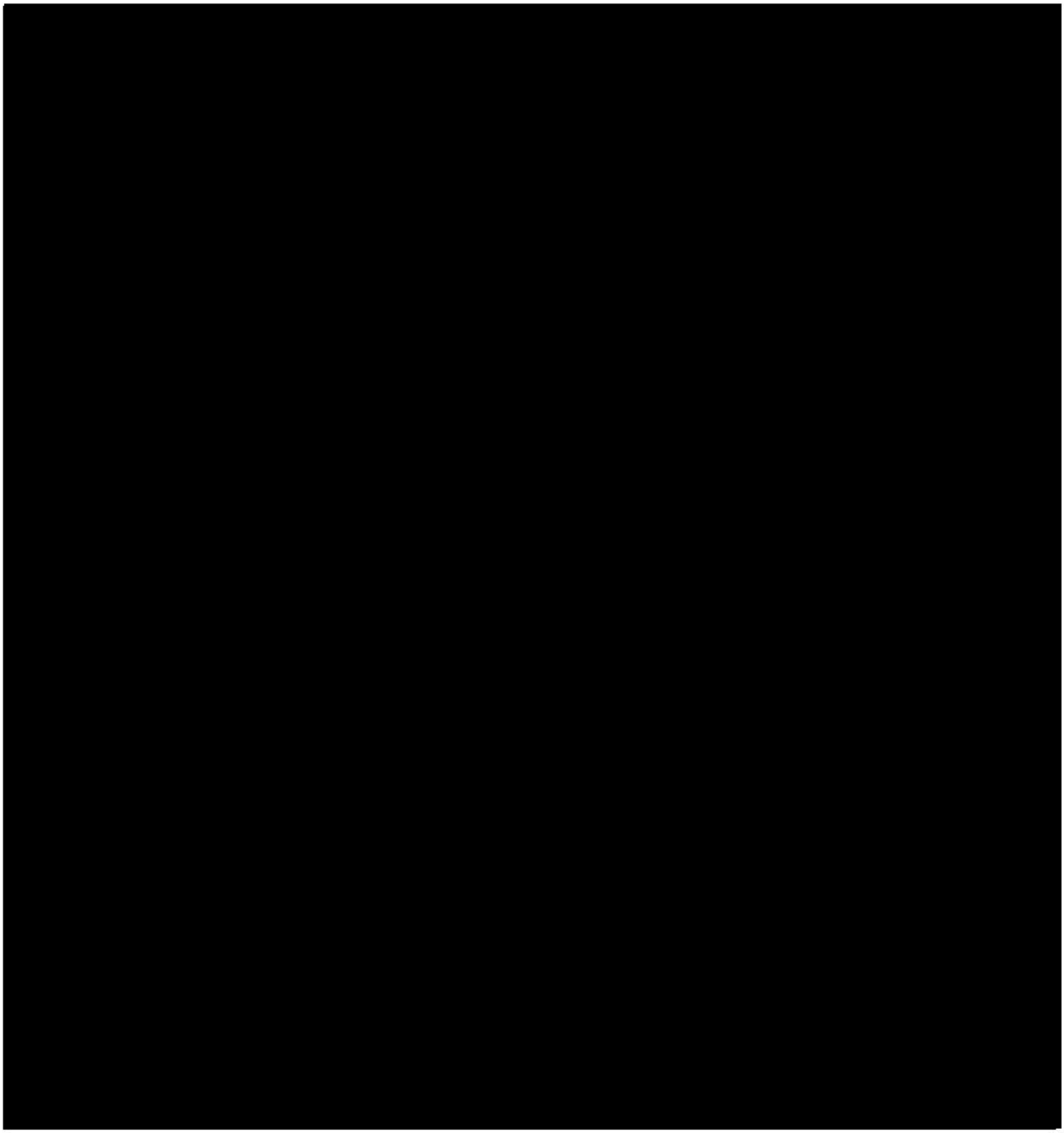
13.2 INDEX OF FIGURES

The following figures will be produced (figure numbers and titles may be different in the final versions):

13.3 INDEX OF LISTINGS

The following listings will be produced (listing numbers and titles may be different in the final versions):

Note that if the Qualification Randomized population is the same as the Qualification Safety population, the Qualification Randomized population will be changed to the Qualification Safety population. Likewise, if the Randomized population is the same as the Safety population, the Randomized population will be changed to the Safety population.



[redacted]

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APPENDIX A: STUDY SCHEDULE

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

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

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

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

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

[n] Conducted during the qualification and treatment phases within 1 hour prior to dosing and approximately (±15 minutes) at 0.5, 1, 1.5, 2 hours postdose and approximately (±30 minutes) at 3, 4, and 6 hours postdose.
[o] Blood samples will be collected as indicated in Table 4 of the protocol. When clinical activities are scheduled to occur at the same time, pharmacodynamic data collection (vital signs then subjective measures) is to be prioritized, followed by PK blood sampling.

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

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

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

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

[t] Covid-19 testing will be performed prior to admission for the qualification phase and, if applicable, upon re-admission for the treatment phase.