VALIDATION OF THE DRUG IMPAIRED DRIVING SCENARIO (DIDS) ON THE CRCDS-MINISIM: EVALUATING SENSITIVITY TO THE EFFECTS OF CANNABIS AND ALPRAZOLAM

PROTOCOL

NCT04970342

Study Drug	Cannabis
Sponsor	National Highway Transportation Safety Administration (NHTSA)
Date of Original Protocol	Version 2.0, 1June2021
Date of Amendment	12July2021

2. SYNOPSIS

Name of Sponsor:
National Highway Transportation Safety Administration (hereafter referred to as NHTSA)

Name of Study Drug:
Cannabis

Name of Active Ingredient: Bulk cannabis (6.18% THC/ <0.025% CBD) in a 500mg dose providing 30.9 mg THC

Title of Study:
Validation of the Drug Impaired Driving Scenario (DIDS) On the CRCDS-Mini-Sim: Evaluating Sensitivity To The Effects of Cannabis and Alprazolam Protocol

Number of Sites and Study Location: This study will take place at 1 site in the US. NADS, University of Iowa, Iowa City, IA.

Phase of Development: 1

Planned Duration of Participation: Approximately 42 days, including up to 14 days for Screening, 2 days in each of 3 treatment periods, each separated by at least a 7-day washout period, and a follow-up phone call approximately 7 days after discharge from the final dosing period

Objectives:

Primary:

The primary objective of this study is to validate the Drug Impaired Driving Scenario (DIDS) using the CRCDS-2 driving simulator, by assessing the acute effects of cannabis relative to placebo on simulated driving performance. Assay sensitivity will be demonstrated by the significant effect of alprazolam 0.75 mg on driving and cognitive endpoints. Other:

- A secondary objective to assess the effects of cannabis on cognitive and psychomotor functioning relative to placebo
- Another objective is to evaluate the potential relationship between cannabis blood concentration and driving performance endpoints

Endpoints:

Key Endpoint:

- Standard Deviation of Lateral Position (SDLP)

Other Key Endpoints:

- Driving Performance Endpoints
    - Lane exceedance; including number, maximum duration, and area of exceedance
    - Excessive speed count
    - Average speed and speed deviation
    - Excessive A_y (cornering speed threshold exceeded) and Total Crashes
    - Divided Attention: Correct Responses, Omission Errors, Commission Errors, Reaction Time, Standard Deviation of Reaction Time
    - Traffic light violations

    - Gap decision making performance
    - Response to Crash Likely Events
    - Attention to mirrors task
    - Working memory task
    - Coherence
- CogScreen Symbol Digit Coding Test
    - Number of correct responses
    - Response Accuracy
    - Standard deviation of reaction time
- CogScreen Symbol Digit Coding – Immediate Recall
    - Immediate recall accuracy
- CogScreen Symbol Digit Coding – Delayed Recall
    - Delayed recall accuracy
- CogScreen Visual Sequence Comparison Test
    - Response speed
    - Response Accuracy
    - Standard deviation of reaction time
- CogScreen Divided Attention Test
    - Response speed
    - Number of premature responses
    - Response accuracy
    - Lapses
    - Multitasking scores
- CogScreen Matching To Sample Test
    - Response speed
    - Response accuracy
    - Standard deviation of reaction time
- CogScreen Pathfinder Number
    - Response speed
    - Response accuracy
    - Response coordination
- CogScreen Shifting Attention Test
    - Response speed
    - Response accuracy
    - Standard deviation of reaction time
- CogScreen Dual Task Test
    - Tracking errors
    - Number of boundary hits
    - Previous number response speed
    - Previous number response accuracy

    - Previous number standard deviation of reaction time
    - Multitasking scores
- Test of Variables of Attention (TOVA)
    - Response time variability (by quarter and overall)
    - Response speed (by quarter and overall)
    - Commission errors (by quarter and overall)
    - Omission errors (by quarter and overall)
- Self-reported readiness to drive ("Right now do you feel safe to drive?" [Yes/No])
- VAS to assess subject's motivation and self-appraisal of their driving performance
- Other self-report measures

Other:

- Changes from baseline in vital signs, clinical laboratory data, ECG parameters, and suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS)
- Relationship between blood concentration of THC and SDLP or other driving or cognition endpoints

Study Description:

This randomized, double-blind, active- and placebo-controlled, 3-arm, 3-period crossover study is designed to validate the DIDS scenarios using the CRCDS-2 driving simulator by assessing the acute effects of cannabis relative to placebo on simulated driving performance. Assay sensitivity will be demonstrated by the significant effect of alprazolam 0.75 mg on driving and cognitive endpoints.

Following a screening/training period of up to 14 days, eligible subjects will be admitted to NADS on Day 1 of Period 1. Baseline performance for cognitive testing will be obtained and subjects will practice the CRCDS2-MiniSim driving simulator, then they will be taken to a supervised off-site residential facility from the end of Day 1 procedures until the start of procedures on Day 2. Subjects will be randomized 1:1:1 into one of 6 treatment sequences as shown in the table below on Day 1. Study drug will be administered by inhalation on Day 2 (first subject dosed at approximately 08:40); precise timing is relative, as subject dosing will be staggered/offset to accommodate staffing and subject flow. Blood samples for pharmacokinetic analysis will be drawn pre-dose and again 40 minutes post-dose and 3.25 hours post-dose. Symbol Digit Coding (SDC), Pathfinder Number (PFN), Readiness to Drive Question, and the Karolinska Sleepiness Scale (KSS) will be administered approximately 30 minutes post-dose. Driving assessments will begin approximately 45 minutes following dosing (i.e., at approximately 09:25). Driving performance will be assessed via the approximate 1-hour Drug Impaired Driving Scenario (DIDS), on the CRCDS2-MiniSim driving simulator, comprised of suburban, urban and highway driving tasks. The scenario includes challenges designed to assess lane position control, speed control, safety awareness and responsivity, driving-related decision making, multitasking, and vigilance. Immediately after completing the driving simulation, subjects will be administered the visual analog scales, or VAS, followed by the cognitive test battery (SDC, Visual Sequence Comparison [VSC], Divided Attention Test – Dual [DAT-Dual], PFN, SDC Delayed Recall [SDCDR], Shifting Attention Test – Instruction, Matching to Sample [MTS], Dual Task Test – Combined [DT Combined], and Test of Variables of Attention [TOVA]). At approximately 3.5 hours post-dose the cognitive test battery (i.e., SDC, VSC, DAT-Dual, PFN, SDCDR, SAT Instruction, MTS, DT Combined, TOVA) and self-report measures will be repeated.

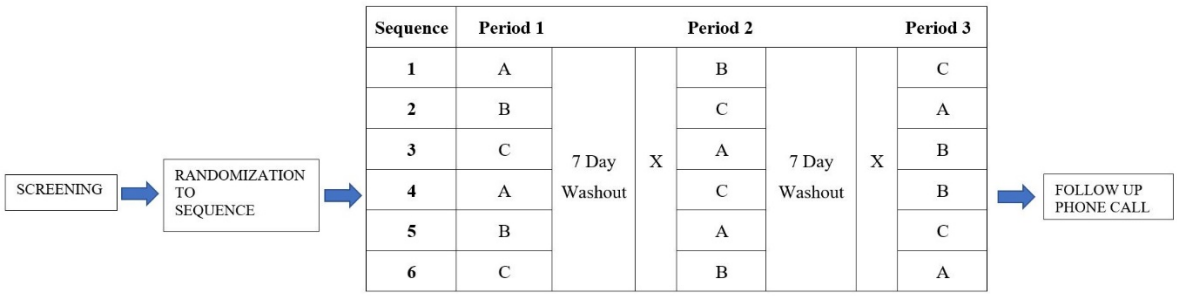
Subjects will undergo initial driving simulator training and practice during the Screening period and will complete a practice drive on Day 1 of each treatment period.

Subjects will be discharged from NADS on the afternoon of Day 2 of each period approximately 5.33 hours post-dose, provided they are medically stable for discharge in the opinion of the Investigator based on the criteria established by the medical monitor. The subject will not be able to drive themselves home and will have transportation arranged.

After a washout of at least 7 days and no more than 10 days between administration of the last dose in one period and administration of the first dose in the next period, subjects will be readmitted to NADS on Day 1 of Period 2 and receive study drug according to the assigned treatment schedule. All study assessments will remain the same as in Period 1. The same process will be repeated for Period 3.

Seven days (±2 days) after discharge from Period 3, subjects will receive a follow-up/end-of-study phone call from the site to evaluate the presence of any AEs and collect any new concomitant medication/procedure information.

Figure 1. Study Design



Screening: Up to 14 days
Randomization: 1:1:1 upon admission to NADS on Day 1; subjects will remain in residence for one night per Treatment Period
Treatment A: PPP-001 26.6mg THC/6.72mg CBD (inhaled) administered on Day 2 of Treatment Period
Treatment B: Alprazolam 0.75mg administered on Day 2 of Treatment Period
Treatment C: Placebo administered on Day 2 of Treatment Period

The schedule of assessments is provided in Table 1.

The following regimens will be assessed:

- Treatment A: cannabis (inhaled)
- Treatment B: alprazolam 0.75 mg PO
- Treatment C: placebo PO
- Subjects receive 1 tablet of alprazolam and/or matched placebo 40 minutes prior to administration of inhaled cannabis/or matching placebo on Day 2 of each treatment period.

Treatment Sequences

Sequence	1	2	3
1	A	B	C
2	B	C	A
3	C	A	B
4	A	C	B
5	B	A	C
6	C	B	A

Number of Subjects (planned): Approximately 12 subjects will be randomized and dosed to target 6 - 8 subjects completing the 3 treatments. Efforts will be made to randomize an approximately equal number of subjects by gender. Efforts will be made to randomize an approximately equal number of "low frequency" users (1-10 uses per month) and "high frequency" users (>20 uses per month).

Eligibility Criteria:

Inclusion

1. Subject understands and provides written informed consent prior to the initiation of any protocol-specific procedures.
2. Subject is able to comprehend and willing to comply with the requirements of the protocol.
3. Subject is a healthy male or female, 19 to 45 years of age, inclusive, at Screening.
4. Subject has a regular sleep pattern (usual bedtime between 21:00 and 00:00).
5. Subject has Score <10 on Epworth Sleepiness Scale at Screening.
6. Subject is able to reliably perform study assessments at Screening (On practice drive, SDLP no higher than 1 standard deviation greater than the mean for normal healthy adults completing the practice scenario; subject exhibits ≥ 11 instances of lane exceedance; or subject has fewer than 7 correct hits on the Divided Attention task; CogScreen SDC Correct no less than 1 standard deviation below the mean for healthy adults); demonstrates the ability to understand task instructions at Screening; and is physically (e.g., adequate manual dexterity, vision, and hearing) and cognitively capable of performing study tasks at Screening.
7. Subject possesses (and is willing to provide) a valid driver's license and is an active driver (minimum of approximately 3,000 miles per year for the previous 3 years).
8. Subject is determined to be (by self-report) either an infrequent user of cannabis (i.e., 1-10 uses per month) or a frequent user of cannabis (i.e., >20 uses per month) over the preceding 90 days.

9. Subject is willing to abstain from cannabis use (other than study drug) beginning 7 days prior to admission for the first treatment period (Day 1) until discharge from the facility on Day 2 of period 3.
10. Female subjects must meet one of the following criteria: 1) If of childbearing potential, female subjects agree to use two contraceptive regimens or remain abstinent during the study; or 2) if of non-childbearing potential, female subjects should be surgically sterile or in a menopausal state.

Exclusion

11. Subject has a significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, neurological, psychiatric, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease, or any other medical issue that would, in the opinion of the Investigator, present undue risk for the subject in the study.
12. Subject has a history of suicidal behavior within 24 months of Screening, has answered YES to questions 3, 4, or 5 on the C-SSRS at Screening or at any clinic admission, or is currently at risk of suicide in the opinion of an Investigator.
13. Subject has a recent history (within 6 months prior to Screening) of substance use disorder (including alcohol) (as judged by the Investigator) or regularly consumes >2 alcoholic drinks/day during the last 3 months prior to Screening (1 alcoholic drink is approximately equivalent to: beer [284 mL], wine [125 mL/4 ounces], or distilled spirits [25 mL/1 ounce]). Subjects who consume up to 3 drinks per day but less than 14 drinks per week may be enrolled at the discretion of the Investigator.
14. Subject demonstrates simulator sickness questionnaire scores which are indicative of simulator sickness as defined in the driving simulation operations manual.
15. Subject regularly consumes excessive amounts of caffeine, 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.
16. Subject smokes more than 10 cigarettes or e-cigarettes, or 3 cigars or pipes per day, or is unable to refrain from smoking during study visits.
17. Subject has been exposed to an investigational drug or device within the 30 days, or 5 half-lives (if known), whichever is longer, prior to Screening.
18. Subject has used a prescription or over-the-counter medication known to cause sedation within 7 days prior to Admission for Period 1 and is unwilling or unable to refrain from sedating medication use during study participation.
19. Subject has used any benzodiazepine, barbiturate, or $GABA_A$ modulator (e.g., eszopiclone, zopiclone, zaleplon, and zolpidem) within 28 days prior to Admission for Period 1 or is unwilling or unable to refrain from medication use during study participation.
20. Subject has a history of hepatitis B surface antigen, hepatitis C antibodies, or human immunodeficiency virus (HIV) antibodies 1 or 2.
21. Subject is pregnant or breastfeeding at Screening or any clinic admission or will attempt to become pregnant at any time during study participation.
22. Subject has a clinically significant abnormal finding on 6-lead electrocardiogram (ECG) at Screening or at any clinic admission. The ECG may be repeated once for confirmatory purposes if initial values obtained exceed the limits specified.
23. Subject has a positive urine test for drugs of abuse (other than tetrahydrocannabinol [THC]) or has a BrAC >0.0 at Screening or any admission.
24. Subject has any clinically significant abnormal physical examination finding at Screening or any clinic admission.

25. Subject participates in night shift work.
26. Subject has traveled across ≥1 time zone in the 2 weeks prior to Admission for Period 1 or is expected to travel across ≥1 time zone during the study.
27. Subject is investigative site personnel or their immediate families (spouse, parent, child, or sibling whether biological or legally adopted).

Study Drug Dosage and Mode of Administration: Cannabis will be administered by inhalation.

Reference Therapy, Dosage and Mode of Administration:

Alprazolam (active comparator) at a dose of 0.75 mg will be administered orally.

Cannabis matching placebo will be administered by inhalation.

Alprazolam matched placebo will be administered orally.

Duration of Treatment:

Subjects will receive 1 500 mg dose of cannabis active on Day 2 of one of the three periods.

Subjects will receive 1 dose of alprazolam 0.75 mg active on Day 2 of one of the three periods.

Subjects will receive placebo in all treatments.

Subjects will not receive active cannabis and alprazolam during the same period.

Statistical Methods:

A statistical analysis plan (SAP) will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the clinical study report.

Analysis Sets

Randomized Set: All subjects who are randomized

Full Analysis Set (FAS): all randomized and treated subjects that have at least one primary efficacy measure (SDLP) in any treatment period.

Safety Set (SS) will include all subjects administered at least one dose of any study drug.

PK Set will include subjects in the Safety Set who have at least one collected blood sample from which a valid blood concentration can be measured.

Primary analysis

The FAS will be used for the primary analysis.

The comparison of primary interest is cannabis versus placebo (Day 2) as a function of frequency of self-reported cannabis use. The statistical significance of alprazolam versus placebo ($p<0.05$) comparison for SDLP is considered only to validate the experiment as having the ability to detect effects (i.e., assay sensitivity).

Formal statistical tests (when performed) will be 2-sided and tested at the alpha=0.05 level of significance.

Secondary Analyses

The FAS will be used for secondary analyses.

Safety Analyses

Safety and tolerability of cannabis will be assessed by the incidence of TEAEs, and by changes from baseline in vital signs, ECG parameters, and suicidal ideation and behavior using the C-SSRS.

Safety data will be listed by subject and summarized by treatment. All safety summaries will be performed on the SS.

PK Analyses

The potential relationship between THC blood concentration and SDLP or other driving or cognition endpoints will be examined using regression techniques.

Table 1: Schedule of Assessments

	Screening	Double-Blind Treatment Periods 1 through 3[a]		
Event	**Day -14 to -1**	**Day 1 (Admission)**	**Day 2**	**Follow-up /or ET (phone)[b]**
Informed consent	X			
Inclusion/exclusion	X	X		
Demographics	X			
Medical history	X			
Epworth Sleepiness Scale	X			
Body weight/height/BMI[c]	X			
Physical examination[d] (full)	X			
Physical examination[d] (brief)		X		
HIV and hepatitis screen	X			
Urine drug & breathalyzer alcohol screen	X	X		
Vital signs[e]	X	X		
C-SSRS[f]	X			
6-lead ECG	X			
Randomization		X[g]		
Screen and Familiarize DIDS on CRCDS2-MiniSim	X (Day -14 to -3)			
Simulator Sickness Questionnaire	X (Day -14 to -3)			
Screen on CogScreen Battery and TOVA[h]	X (Day -14 to -3)			
Practice CogScreen, TOVA, and DIDS on CRCDS2-MiniSim[i]		X		

Administer study drug[j]			X	
Blood PK collection[k]			X	
CogScreen Subtests[Error! Reference source not found.], [l]			X	
TOVA [l]			X	
TBD Self-Report Scales			X	
Self-perceived safety to drive question[Error! Reference source not found.]			X	
Drug Impaired Driving Scenario[Error! Reference source not found.]			X	
VAS[m]			X	
Discharge[n]			X	
Phone call				X
Adverse events/SAEs	Ongoing from the time of consent throughout the duration of study participation			
Prior/concomitant medications[o]	X			
CRCDS2 = Cognitive Research Corporation Driving Simulator-2nd Edition; C-SSRS = Columbia Suicide Severity Rating Scale; DIDS = Drug Impaired Driving Scenario; ECG = electrocardiogram; ET = early termination; HIV = Human immunodeficiency virus; PK = pharmacokinetic, SAE = Serious adverse event; VAS = Visual Analog Scale				

[3a] Subjects will be admitted to NADS on Day 1 of each treatment period and then housed at the supervised off site residential facility under NADS staff supervision between the end of procedures on Day 1 and start of procedures on Day 2. Each treatment period will be separated by a washout of at least 7 days and no more than 10 days between administration of the last dose in one period and administration of the first dose in the next period.

Error! No bookmark name given. In the event of Early Termination, efforts should be made to obtain the safety assessments indicated for the day of discharge (Day 2).

[c] Height and weight will be measured at Screening only.

[d] A symptom-directed physical examination may be conducted at any time as needed.

[e] Vital signs will include blood pressure, heart rate, respiratory rate, pulse oximetry, and temporal temperature (°F). Heart rate and blood pressure to be collected in supine position after the subject has been resting for approximately 3 minutes.

[f] The "Baseline/Screening" C-SSRS form will be completed at Screening

[g] Subjects will be randomized to a treatment sequence on Day 1 of Period 1.

[i] Subjects will complete a training and practice CogScreen session at Screening and will complete a practice CogScreen Session in the afternoon on Day 1. Subjects will complete a practice drive on the CRCDS2 at Screening and will also complete the practice drive on the afternoon of Day 1.

Error! Reference source not found. Oral (PO) study drug (alprazolam or placebo) will be administered approximately 40 minutes prior to Inhaled study drug (cannabis or placebo) according to the treatment sequence assigned at Period 1.

[k] Three separate blood samples for PK analysis will be collected; the samples will be collected pre-dose on Day 2, at.40 minutes (±5 minutes) post-dose (PPP-001) on Days 2 and at 3.25 hours (±5 minutes) post-dose on Day 2.

Error! Reference source not found. Symbol Digit Coding, Pathfinder Number, KSS, and self-perception question will be completed prior to driving assessments. The KSS will also be administered pre-dose (cannabis).

Error! Reference source not found. CRCDS2-MiniSim drive to be completed in the morning of Day 2 starting approximately 45 minutes following dosing of cannabis. Upon completion of the drive subjects will complete the cognitive test battery and self-report questionnaires.

[m] Visual analog scales to assess subject's motivation and self-appraisal of their driving performance immediately upon completion of the driving assessment. The cognitive test battery and self-report questionnaires will be repeated at approximately 3.5 hours post-dose (cannabis).

[n] Subjects will be discharged upon completion of Day 2 assessments if deemed medically stable for discharge by the Investigator.

[o] Medications taken within 30 days of Screening and for the duration of the study will be recorded.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

1. TITLE PAGE 1
2. SYNOPSIS 2
3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES 13
LIST OF TABLES 16
LIST OF FIGURES 16
4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 17
5. INTRODUCTION 19
5.1. Study Rationale 20
5.2. Dose Rationale 22
6. STUDY OBJECTIVES AND ENDPOINTS 23
6.1. Study Objective 23
6.2. Endpoints 23
6.2.1. Key Endpoints 23
6.2.2. Other Key Endpoints 23
6.2.3. Additional Endpoint(s) 25
7. INVESTIGATIONAL PLAN 26
7.1. Overall Study Design 26
7.2. Number of Subjects 27
7.3. Treatment Assignment 27
7.4. Criteria for Study Termination 28
8. SELECTION AND WITHDRAWAL OF SUBJECTS 29
8.1. Subject Inclusion Criteria 29
8.2. Subject Exclusion Criteria 29
8.3. Subject Withdrawal Criteria 31
9. TREATMENT OF SUBJECTS 32
9.1. Study Drugs 32
9.2. Meal Timing in Relation to Study Drug Administration and Driving Simulations 32
9.3. Prior Medications, Concomitant Medications, and Restrictions 32
9.3.1. Prior and Concomitant Medications and/or Supplements 32

9.3.2. Prohibited Medications 33
9.3.3. Other Restrictions 33
9.4. Treatment Adherence 33
9.5. Randomization and Blinding 33
9.5.1. Emergency Identification of Study Drug 34
9.6. Subject Compensation 34
10. STUDY DRUG MATERIALS AND MANAGEMENT 35
10.1. Description of Study Drugs 35
10.2. Study Drug Packaging and Labeling 35
10.3. Study Drug Storage 35
10.4. Study Drug Preparation 35
10.5. Study Drug Administration 35
10.6. Study Drug Accountability, Handling, and Disposal 36
11. PHARMACODYNAMIC AND PHARMACOKINETIC ASSESSMENTS 37
11.1. Pharmacodynamic Assessments 37
11.1.1. DIDS Driving Scenario on the CRCDS2-MiniSim 37
11.1.2. CogScreen Cognitive Test Battery 37
11.1.2.1. Digit Symbol Substitution Test (CogScreen Symbol Digit Coding) 37
11.1.2.2. CogScreen Visual Sequence Comparison Test 37
11.1.2.3. CogScreen Divided Attention Test 37
11.1.2.4. CogScreen Matching to Sample Test 37
11.1.2.5. CogScreen Pathfinder Number Test 38
11.1.2.6. CogScreen Shifting Attention Test 38
11.1.3. CogScreen Dual Task Test 38
11.1.4. Test of Variables of Attention 38
11.1.5. Karolinska Sleepiness Scale 38
11.1.6. Self-perceived Safety to Drive Question 38
11.1.7. Visual Analog Scales to Assess Subjects' Self-appraisal and Motivation 39
11.2. Pharmacokinetic Assessments 39
11.2.1. Blood Sample Collection 39
11.2.2. Sample Analysis 39
12. ASSESSMENT OF SAFETY 40
12.1.1. Demography and Medical History 40

12.1.2. Weight and Height 40
12.1.3. Physical Examination 40
12.1.4. Vital Signs 40
12.1.5. Electrocardiogram (ECG) 40
12.1.5.1. Drugs of Abuse and Alcohol 40
12.1.5.2. Pregnancy Screen 41
12.1.6. Columbia-Suicide Severity Rating Scale (C-SSRS) 41
12.2. Adverse Events and Serious Adverse Events 41
12.2.1. Adverse Event Definitions 41
12.2.1.1. Adverse Event (AE) 41
12.2.1.2. Serious Adverse Event (SAE) 42
12.2.2. Relationship to Study Drug 42
12.2.3. Recording Adverse Events 43
12.2.4. Reporting Serious Adverse Events 43
12.3. Pregnancy 44
12.4. Overdose 44
13. STATISTICS 45
13.1. Data Analysis Sets 45
13.2. Handling of Missing Data 45
13.3. General Considerations 45
13.4. Demographics and Baseline Characteristics 45
13.5. Pharmacodynamic Analyses 45
13.6. Safety Analyses 48
13.6.1. Adverse Events 48
13.6.2. Physical Examinations 48
13.6.3. Vital Signs 49
13.6.4. 6-Lead Electrocardiogram 49
13.6.5. Prior and Concomitant Medications 49
13.6.6. Columbia Suicide Severity Rating Scale 49
13.7. Pharmacokinetic Analyses 49
14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS 50
14.1. Audits and Inspections 50
14.2. Ethics Committee 50

15. QUALITY CONTROL AND QUALITY ASSURANCE 51
16. ETHICS 52
16.1. Ethics Review 52
16.2. Ethical Conduct of the Study 52
16.3. Written Informed Consent 52
17. DATA HANDLING AND RECORDKEEPING 53
17.1. Inspection of Records 53
17.2. Retention of Records 53
18. PUBLICATION POLICY 54
19. LIST OF REFERENCES 55
APPENDIX A. AMOUNT OF BLOOD DRAWN PER STUDY VISIT 59
APPENDIX B. DAILY SCHEDULE OF ACTIVITIES PER PERIOD 60

LIST OF TABLES

Table 1: Schedule of Assessments 10
Table 2: Abbreviations and Definitions of Terms 17
Table 3: Treatment Sequences 28
Table 4: Treatments Administered 32

LIST OF FIGURES

Figure 1. Study Design 5

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 2: Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	adverse event
A_y	cornering speed threshold exceeded
BAC	blood alcohol concentration
BMI	body mass index
CBD	Cannabidiol
CNS	central nervous system
CPT	continuous performance test
CRCDS2	Cognitive Research Corporation Driving Simulator
C-SSRS	Columbia Suicide Severity Rating Scale
DIDS	Drug Impaired Driving Scenario
DAT	Divided Attention Test
DTT	Dual Task Test
EC	ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form
ET	early termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
$GABA_A$	γ aminobutyric acid-gated chloride channel
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
KSS	Karolinska Sleepiness Scale

Abbreviation	Definition
MTS	Matching To Sample
MMRM	mixed model for repeated measures
NADS	National Advanced Driving Simulator
NHTSA	National Highway Transportation Safety Administration
PFN	Pathfinder Number
PD	Pharmacodynamics
PK	Pharmacokinetic
PO	by mouth
QA	quality assurance
QC	quality control
QTcF	QT corrected according to Fridericia's formula
qAM	each morning
SAE	serious adverse event
SDC	Symbol Digit Coding
SAT	Shifting Attention Test
SDLP	Standard Deviation of Lateral Position
SOC	system organ class
SOP	Standard Operating Procedure
SS	Safety Set
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TOVA	Test of Variables of Attention
THC	Tetrahydrocannabinol
WHO	World Health Organization
VAS	visual analog scale
VSC	Visual Sequence Comparison

5. INTRODUCTION

Following recommendations from the National Transportation Safety Board (NTSB) that the U.S. Department of Transportation (DOT) establish a list of approved medications and classes of medications that may be used safely when operating a vehicle (NTSB, 2000 as cited in Kay and Loga, 2011) the National Highway Traffic Safety Administration (NHTSA) released its *Drugs and Human Performance Fact Sheets* (Cooper & Logan, 2004, as cited in Kay and Logan 2011) representing the current scientific knowledge in the area of drugs and human performance for 16 substances. However, studies determining effects on performance and on driving reflect myriad study methodologies. Similar efforts by the National Institute on Drug Abuse (NIDA, 2007 as cited in Kay and Logan, 2011) and by the European Union to produce lists characterizing the impairing effects of drugs yielded similarly fraught issues regarding the inability to generalize results secondary to methodological differences across studies. Subsequently, NHTSA convened an expert panel in 2008 and 2009 (Kay and Logan, 2011) with the goal of determining whether a list of drugs could be developed indicating which drugs or classes of drugs may pose a risk to driving.

Kay and Logan (2011) reported that the panel agreed that a limited number of drugs generally pose a low risk to driving when taken according to approved prescribing information under appropriate medical oversight. However, the panel also recognized that even among drugs generally considered safe for driving, adverse reactions and interactions may occur that could impair driving performance. The panel was of the opinion that some specific drugs and drug classes are clearly impairing, including sedatives, hypnotics, sedating antihistamines, narcotic analgesics, hallucinogens, antipsychotics, and muscle relaxants, even at therapeutic or sub-therapeutic doses. Furthermore, the panel noted that a potent barrier to categorizing drugs with respect to driving impairment risk is "lack of a common, standardized protocol for assessing the impairing potential of drugs," (Kay and Logan, 2011, p. 7). That is, there is recognition of the need for a structured, standardized protocol to assess the driving impairment risk of drugs, as current systematic reviews reveal inconsistencies in methodology, failures to address inconsistencies relative to dosing, time since dosing, subject characteristics and pattern of use, and the use of non-standardized testing methodologies.

As a result, a tiered assessment protocol was proposed, including the following tiers: I) pharmacology/toxicology review to identify drugs likely to impair driving; II) epidemiological review to identify the relative risk of impairment for drugs/drug classes based on comparison to control populations or by culpability assessment; and III) standard behavioral assessment (Kay and Logan, 2011). Tiers I and II identify the drugs most likely to impair driving, leading to the activation of Tier III. The current study is designed as a structured, standardized approach based on the Essential Driving Ability Domains (EDAD) Model described in Kay and Logan (2011) in order to validate a standardized protocol to evaluate drug impaired driving.

Bulk cannabis was chosen as the study drug given its known chemical properties and range of cannabis THC concentrations. This source of cannabis has been used for a series of NHTSA and NIDA sponsored driving studies conducted at NADS (Brown et al., 2019; Brown et al., 2020; Hartman, Anizan, Jang, Brown, Yun…Huestis, 2015; Hartman et al., 2015a; Hartman et al., 2015b; Hartman et al., 2016; Hartman, Brown, Milavetz, Spurgin, Pierce…Huestis, 2015;

Hartman, Jang, Spurgin, Yun, Gorelick…Huestis, February 2015; Miller et al., 2020; Smith et al., November 2018).

5.1. Study Rationale

SELECTION OF CANNABIS FOR VALIDATION OF ASSESSMENT METHODOLOGY: As the legal atmosphere surrounding cannabis use continues to evolve, the potential for increased usage among drivers raises questions regarding its effects on driving ability. Epidemiological studies have examined the relationship between cannabis use and motor vehicle crash risk, injury risk, and fatal crash risk. Cannabis tends to be the most common illicit substance present in injured drivers (Legrand et al., 2013; Brubacher et al., 2016) and the second only to alcohol as the most common recreational substance among injured drivers (ibid). While the presence of cannabis in injured drivers in Italy occurred to a lesser extent than did the presence of cocaine and benzodiazepines (Siliquini et al., 2007), another study found individuals aged 35 – 54 years who reported using cannabis within the past year had significantly greater odds of reporting having been in a motor vehicle collision (Mann et al., 2010). Cannabis use has been shown to be associated with self-reported instances of road rage, driving mistakes, and accident risk in Pakistani truck drivers (Mir et al., 2012).

Methodological and design differences and limitations notwithstanding, the majority of case-controlled studies show an increase in motor vehicle crashes (MVC) for drivers under the influence of cannabis (DeBalzoa et al., 2018; Kuypers et al., 2012; Jamt et al., 2018; Li et al., 2013; Baldock & Lindsay, 2015; Chihuri & Chen, 2017). Of two case-controlled studies that did not find an increase in crash risk, one found an association between cannabis use and unsafe driving (Dubois et al., 2015) while the other study reported inconclusive results for the effect of cannabis when used in isolation (Steinemann et al., 2018). DeBalzoa et al. (2018) found a high degree of association between cannabis use and collisions resulting in driver injuries yet concluded that risk of serious injury and fatal injury for individuals testing positive for cannabis alone was relatively low. Contradictory findings have been reported for the role of cannabis (alone) in fatal crashes (Gjerde et al., 2011; Chihuri & Chen, 2017; Martin et al., 2017).

Experimental research investigating the effects of cannabis on driving have been conducted with over-the-road and simulated driving tests. There has been little consistency in the methodology applied across researchers and generally a lack of replication. Investigators have studied drivers with markedly different characteristics which likely interact with the effect of the drug (e.g., patterns of substance use, prior driving experience, and age). Published studies also show a wide range of doses and delivery systems and generally fail to show an association between exposure and serum THC. Furthermore, driving simulator studies have not been conducted using anything approaching a standard set of driving challenges or tasks.

In spite of these methodological issues, there is general agreement that cannabis increases weaving. However, the relationship between cannabis exposure and magnitude of weaving remains to be determined. The impact of cannabis on lane crossings has been inconsistent. Cannabis (without concomitant alcohol consumption) generally results in slower driving speeds and greater headway distances in nighttime conditions. With respect to neurocognitive testing, cannabis has consistently been shown to impact performance under multitasking conditions.

SELECTION OF ALPRAZOLAM FOR USE AS ACTIVE COMPARATOR: Alprazolam is the most frequently prescribed benzodiazepine for treating panic disorder and anxiety disorders (RxList, 2005 as cited in Leufkens et al., 2007). The cognitive and psychomotor effects of alprazolam have been well-documented in older studies (Verster and Volker, 2004b as cited in Leufkens et al., 2007; Bertz et al., 1997 as cited in Leufkens et al., 2007; Ellinwood et al., 1985 as cited in Leukens et al., 2007; Greenblatt et al., 1988 as cited in Leufkens et al., 2007; Kroboth et al., 1998 as cited in Leufkens et al., 2007; Rickels, 2004 as cited in Leufkens et al., 2007; Scavone et al., 1992 as cited in Leufkens et al., 2007; Smith et al., 1984 as cited in Leufkens et al., 2007; Subhan et al., 1986 as cited in Leufkens et al., 2007; Vermeeren et al., 1995 as cited in Leufkens et al., 2007; Verster et al., 2002 as cited in Leufkens et al., 2007). While limited in number, results from the more recent studies available reveal that alprazolam has an adverse impact on driving performance. The most consistent findings are increased weaving (Leufkens et al., 2007; Stone et al., 2015; Brown et al., 2018; CRC data on file 2019 and 2020; Verster et al., 2002), increased lane departures (Sone et al., 2015; Brown et al., 2018; CRC data on file 2019 and 2020; Pearlman et al., 2020; Verster et al., 2002), and poor speed maintenance (Brown et al., 2018; Pearlman et al., 2020; CRC data on file 2017, 2019, and 2020; Verster et al., 2002). Additional safety endpoints show increased collision risk and failure to adjust speed in corners (CRC data on file 2017, 2019, 2020; Verster et al., 2002).

With regards to neurocognitive functioning, alprazolam has been shown to impair immediate and delayed recall of word lists (Leufkens et al., 2007; Reissig et al., 2014; Hindmarch et al., 2005; Snyder et al., 2005), impair tracking ability (Hindmarch et al., 2005; Leufkens et al., 2007; Verster et al., 2002), slow reaction times (Leufkens et al., 2007; Stone et al., 2015; Reissig et al., 2014; Hindmarch et al., 2005; CRC data on file 2017, 2019, 2020), and adversely affect information processing speed (Reissig et al., 2014; Hindmarch et al., 2005; CRC data on file 2017 and 2019; Pearlman et al., 2020).

PURPOSE OF PRESENT STUDY: The primary purpose of the current study is to establish a standardized protocol for assessing drug impaired driving. Validation of this methodology is to be accomplished with a study using cannabis, alprazolam, and matching placebo. As part of this research effort, investigators have worked to identify the driving tasks and cognitive abilities found to be most vulnerable to the impairing effects of cannabis. In addition, an effort was made to identify the subject characteristics associated with increased vulnerability to the impairing effects of cannabis. Worked was conducted to develop a methodology for determining when drivers are safe to resume driving after drug exposure. The current study is designed to test these hypotheses.

Simulated driving will be performed using an updated version of Cognitive Research Corporation's Driving Simulator (CRCDS2 MiniSim). The prior version of this simulator has been used in dozens of driving studies submitted for regulatory review. Driving performance will be assessed using an approximate 1-hour Drug Impaired Driving Scenario (DIDS), comprised of suburban, urban and highway driving tasks. The scenarios include challenges designed to assess lane position control, speed control, safety awareness and responsivity, driving-related decision making, multitasking, and vigilance. These domains correspond to the Essential Driving Ability

Domains described by Kay and Logan (2011). In addition, cognitive functions associated with driving performance and self-report measures will also be administered.

Consistent with the principles outlined in the FDA Guidance for Industry (2017), this study includes both a positive (active) and placebo control condition. The study is designed to assess the duration of drug effects. Readiness to resume driving will be assessed using both self-report and objective testing. Subjects will include regular (daily) users and weekly users of cannabis. The intent is to assess the impact of pattern of drug use on driving performance. A cross-over study design will be utilized to maximize statistical power.

Cannabis will be administered once in the morning on Day 2. Effects on driving and cognition will be assessed from 30 to 45 minutes after dosing. Cognitive and self-report measures will be repeated approximately 3.5 hours post-dose to assess residual effect. There will be a one-week washout between treatment periods. Subjects will be instructed to refrain from drug use for 7 days prior to treatment period 1 and to continue to abstain from (non-study) drug use for the duration of the trial.

Alprazolam was selected as the active comparator and to further validate the CRCDS-2 and the DIDS scenario. The negative effect of Alprazolam on driving performance has been demonstrated in both on-the-road and simulated driving studies (Pearlman et al., 2019; CRC, data on file; Leufkens 2009; Leufkens & Vermeeren 2014; Mets 2011; Simen 2015; Verster 2011). Additionally, as alprazolam is the most commonly prescribed psychotropic in the U.S., use of the drug remains a concern for traffic safety.

5.2. Dose Rationale

One dose of cannabis will be evaluated in this study:

- Bulk cannabis (6.18% THC/ <0.025% CBD) in a 500mg dose providing 30.9 mg THC administered by inhalation via vaporization on Day 2 in each of 3 treatment periods

This dose was selected based on comparability of THC concentrations with a currently in development medicinal cannabis medication, PPP001 (*Tetra Bio-Pharma Inc*), that provides 26.6 mg THC. Prior research conducted by the research team also demonstrates tolerability of THC concentrations of this level (6-7% THC in a 500mg vaporized dose).

The active comparator, alprazolam, will be administered at a dose of 0.75 on Day 2, based on previous demonstration of impaired performance on the driving simulator test following administration of a single oral dose at this level (CRC, data on file).

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Study Objective

The primary objective of this study is to validate the DIDS scenarios using the CRCDS-2 driving simulator, by assessing the acute effects of cannabis relative to placebo on simulated driving performance. Assay sensitivity will be demonstrated by the significant effect of alprazolam 0.75 mg on driving and cognitive endpoints. A secondary objective of the study is to assess the effects of cannabis on cognitive and psychomotor functioning relative to placebo. Another objective of this study is to evaluate the potential relationship between THC blood concentration and driving performance endpoints.

6.2. Endpoints

6.2.1. Key Endpoints

A key driving performance endpoint is Standard Deviation of Lateral Position (SDLP) after a single dose of cannabis.

6.2.2. Other Key Endpoints

- Driving Performance Endpoints
    - Lane exceedance; including number, maximum duration, and area of exceedance
    - Excessive speed count
    - Average speed and speed deviation
    - Excessive A_y (cornering speed threshold exceeded) and Total Crashes
    - Divided Attention: Correct Responses, Omission Errors, Commission Errors, Reaction Time, Standard Deviation of Reaction Time
    - Traffic light violations
    - Gap decision making performance
    - Response to Crash Likely Events
    - Attention to mirrors task
    - Working memory task
    - Coherence
- CogScreen Symbol Digit Coding Test
    - Number of correct responses
    - Response Accuracy
    - Standard deviation of reaction time
- CogScreen Symbol Digit Coding – Immediate Recall
    - Immediate recall accuracy
- CogScreen Symbol Digit Coding – Delayed Recall
    - Delayed recall accuracy
- CogScreen Visual Sequence Comparison Test

    - Response speed
    - Response accuracy
    - Standard deviation of reaction time
- CogScreen Divided Attention Test
    - Response speed
    - Number of premature responses
    - Response accuracy
    - Lapses
    - Multitasking scores
- CogScreen Matching To Sample Test
    - Response speed
    - Response accuracy
    - Standard deviation of reaction time
- CogScreen Pathfinder Number
    - Response speed
    - Response accuracy
    - Response coordination
- CogScreen Shifting Attention Test
    - Response speed
    - Response accuracy
    - Standard deviation of reaction time
- CogScreen Dual Task Test
    - Tracking error
    - Number of boundary hits
    - Previous Number response speed
    - Previous Number response accuracy
    - Previous Number standard deviation of reaction time
    - Multitasking scores
- Test of Variables of Attention (TOVA)
    - Response time variability (by quarter & overall)
    - Response speed (by quarter & overall)
    - Commission errors (by quarter & overall)
    - Omission errors (by quarter & overall)
- Self-reported readiness to drive ("Right now do you feel safe to drive?" [Yes/No])
- VAS to assess participant's motivation and self-appraisal of their driving performance
- Other self-report measures

6.2.3. Additional Endpoint(s)

Other endpoints of this study are:

- Changes from baseline in vital signs, clinical laboratory data, ECG parameters, and suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS)
- Relationship between blood concentration of THC and SDLP or other driving or cognition endpoints

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a randomized, double-blind, active- and placebo-controlled, 3-arm, 3-period crossover study to assess the effects of cannabis on simulated driving performance and related cognitive functions in healthy male and female adult cannabis users. The study design is provided in Figure 1. The schedule of assessments is provided in Table 1.

Following a screening/training period of up to 14 days, eligible participants will be admitted to NADS on Day 1 of Period 1. Baseline performance for cognitive testing will be obtained and subjects will practice the CRCDS2-MiniSim driving simulator. Participants will be randomized 1:1:1 into one of 6 treatment sequences as shown in Table 4. Study drug will be administered by inhalation on Day 2 with the alprazolam dosing approximately 40 minutes prior to the cannabis dosing (the first cannabis dose will occur at approximately 8:40); precise timing is relative, as subject dosing will be staggered/offset to accommodate staffing and subject flow. Blood samples for pharmacokinetic analysis will be drawn pre-dose and again 40 minutes post-dose and 3.25 hours post-dose. Symbol Digit Coding (SDC), Pathfinder Number (PFN), Readiness to Drive Question, and the Karolinska Sleepiness Scale (KSS) will be administered approximately 30 minutes post-dose. A baseline KSS will also be administered prior to dosing. Driving assessments will begin approximately 45 minutes following dosing. Driving performance will be assessed via the approximate 1-hour Drug Impaired Driving Scenario (DIDS), on the CRCDS2-MiniSim driving simulator, comprised of suburban, urban and highway driving tasks. The scenario includes challenges designed to assess lane position control, speed control, safety awareness and responsivity, driving-related decision making, multitasking, and vigilance. Immediately after completing the driving simulation, subjects will be administered the visual analog scales, or VAS, followed by the cognitive test battery (SDC, Visual Sequence Comparison [VSC], Divided Attention Test – Dual [DAT-Dual], PFN, SDC Delayed Recall [SDCDR], Shifting Attention Test – Instruction [SAT-Instruction], MTS, Dual Task Test – Combined [DAT – Combined], and TOVA). At approximately 3.5 hours post-dose the cognitive test battery (i.e., SDC, VSC, DAT-Dual, PFN, SDCDR, SAT – Instruction, MTS, DTT – Combined, TOVA) and self-report measures will be repeated.

Subjects will undergo initial driving simulator training and practice during the Screening period and will complete a practice drive on Day 1 of each treatment period.

Subjects will be discharged from NADS on the afternoon of Day 2 of each treatment period approximately 5.33 hours post-dose, provided they are medically stable for discharge in the opinion of the Investigator. The subject will not be able to drive themselves home and will have transportation arranged.

After a washout of at least 7 days, but no more than 10 days, between administration of the last dose in one period and administration of the first dose in the next period, subjects will be readmitted to NADS on Day 1 of Period 2 and receive study drug according to the assigned

treatment schedule. All study assessments will remain the same as in Period 1. The same process will be repeated for Period 3.

Seven days (±2 days) after discharge from Period 3, subjects will receive a follow-up/end-of-study phone call from the site to evaluate the presence of any AEs and collect any new concomitant medication/procedure information.

The schedule of assessments is provided in Table 1. The following regimens will be assessed:

- Cannabis (inhaled) on Day 2
- Alprazolam 0.75mg on Day 2
- Placebo on Day 2

Subjects will receive 0.75mg of alprazolam (over-encapsulated) or matching placebo capsule 40 minutes prior to administration of inhaled cannabis or matching placebo inhalation/vaporizer on Day 2 of each Treatment Period. Matched placebo tablets and/or vaporizers will be administered as necessary to maintain the blind across the 3 treatment regimens.

7.2. Number of Subjects

Approximately 12 subjects will be randomized and dosed. Efforts will be made to randomize an approximately equal number of male and female subjects. Efforts will be made to randomize an approximately equal number of "low frequency users" (i.e., 1 – 10 uses of cannabis per month) and "high frequency users" (i.e., > 20 uses of cannabis per month).

7.3. Treatment Assignment

Subjects will be randomized into one of 6 treatment sequences (Table 3).

Table 3: Treatment Sequences

Sequence	Treatment Period		
	1	**2**	**3**
1	A	B	C
2	B	C	A
3	C	A	B
4	A	C	B
5	B	A	C
6	C	B	A

Treatment A: Cannabis on Day 2
Treatment B: Alprazolam 0.75mg on Day 2
Treatment C: Placebo on Day 2
Note: Matched placebo capsule or vaporizers will be administered as necessary to maintain the blind across the 3 treatments.

7.4. Criteria for Study Termination

NHTSA may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to subjects, or for administrative reasons. In the event of study termination, NHTSA will provide written notification to the Investigator. The investigational site must promptly notify its ethics committee and initiate withdrawal procedures for subjects.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

Qualified subjects will meet all of the following criteria:

1. Subject understands and provides written informed consent prior to the initiation of any protocol-specific procedures.
2. Subject is able to comprehend and willing to comply with the requirements of the protocol.
3. Subject is a healthy male or female adult, 19 to 45 years of age, inclusive, at Screening.
4. Subject has a regular sleep pattern (usual bedtime between 21:00 and 00:00).
5. Subject has Score <10 on Epworth Sleepiness Scale at Screening.
6. Subject is able to reliably perform study assessments at Screening (On practice drive, SDLP no higher than 1 standard deviation greater than the mean for normal healthy adults completing the practice scenario; subject exhibits ≥ 11 instances of lane exceedance; or subject has fewer than 7 correct hits on the Divided Attention task; CogScreen SDC Correct no less than 1 standard deviation below the mean for healthy adults); demonstrates the ability to understand task instructions at Screening; and is physically (e.g., adequate manual dexterity, vision, and hearing) and cognitively capable of performing study tasks at Screening.
7. Subject possesses (and is willing to provide) a valid driver's license and is an active driver (minimum of approximately 3,000 miles per year for the previous 3 years).
8. Subject is determined to be (by self-report) either an infrequent user of cannabis (i.e., 1-10 uses per month) or a frequent user of cannabis (i.e., >20 uses per month) over the preceding 90 days.
9. Subject is willing to abstain from cannabis use (other than study drug) beginning 7 days prior to admission for the first treatment period (Day 1) until discharge from the facility on Day 2 of period 3.
10. Female subjects must meet one of the following criteria: 1) If of childbearing potential, female subjects agree to use two contraceptive regimens or remain abstinent during the study; or 2) if of non-childbearing potential, female subjects should be surgically sterile or in a menopausal state.

8.2. Subject Exclusion Criteria

Subjects who meet any of the following criteria are disqualified from participation in this study:

1. Subject has a significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, neurological, psychiatric, gastrointestinal, hematological, immunologic,

ophthalmologic, metabolic, or oncological disease, or any other medical issue that would, in the opinion of the Investigator, present undue risk for the subject in the study.

2. Subject has a history of suicidal behavior within 24 months of Screening, has answered YES to questions 3, 4, or 5 on the C-SSRS at Screening or at any clinic admission, or is currently at risk of suicide in the opinion of an Investigator.
3. Subject has a recent history (within 6 months prior to Screening) of substance use disorder (including alcohol) (as judged by the Investigator) or regularly consumes >2 alcoholic drinks/day during the last 3 months prior to Screening (1 alcoholic drink is approximately equivalent to: beer [284 mL], wine [125 mL/4 ounces], or distilled spirits [25 mL/1 ounce]). Subjects who consume 3 drinks per day but less than 14 drinks per week may be enrolled at the discretion of the Investigator.
4. Subject demonstrates simulator sickness questionnaire scores which are indicative of simulator sickness as defined in the driving simulation operations manual.
5. Subject regularly consumes excessive amounts of caffeine, defined as greater than 6 servings of coffee, tea, cola, or other caffeinated beverages per day.
6. Subject smokes more than 10 cigarettes or e-cigarettes, or 3 cigars or pipes per day, or is unable to refrain from smoking during study visits.
7. Subject has been exposed to an investigational drug or device within the 30 days, or 5 half-lives (if known), whichever is longer, prior to Screening.
8. Subject has used a prescription or over-the-counter medication known to cause sedation within 7 days prior to Admission for Period 1 and is unwilling or unable to refrain from sedating medication use during study participation.
9. Subject has used any benzodiazepine, barbiturate, or $GABA_A$ modulator (e.g., eszopiclone, zopiclone, zaleplon, and zolpidem) within 28 days prior to Admission for Period 1 or is unwilling or unable to refrain from medication use during study participation.
10. Subject has a history of hepatitis B surface antigen, hepatitis C antibodies, or human immunodeficiency virus (HIV) antibodies 1 or 2.
11. Subject is pregnant or breastfeeding at Screening or any clinic admission or will attempt to become pregnant at any time during study participation.
12. Subject has a clinically significant abnormal finding on 6-lead electrocardiogram (ECG) at Screening or at any clinic admission. The ECG may be repeated once for confirmatory purposes if initial values obtained exceed the limits specified.
13. Subject has a positive urine test for drugs of abuse (other than tetrahydrocannabinol [THC]) or BrAC > 0.0 at Screening or any admission.
14. Subject has any clinically significant abnormal physical examination finding at Screening or any clinic admission.
15. Subject participates in night shift work.
16. Subject has traveled across ≥1 time zone in the 2 weeks prior to Admission for Period 1 or is expected to travel across ≥1 time zone during the study.
17. Subject is investigative site personnel or their immediate families (spouse, parent, child, or sibling whether biological or legally adopted).

8.3. Subject Withdrawal Criteria

Subjects may withdraw from the study at any time for any reason. The Investigator may withdraw a subject from the study for any of the following reasons:

- The subject is unwilling or unable to adhere to the protocol
- The subject experiences an intolerable AE
- Other medical or safety reason, at the discretion of the Investigator and/or the Medical Monitor

If a subject is persistently noncompliant, the Investigator should discuss with the Sponsor the potential withdrawal of the subject. Any reasons for unwillingness or inability to adhere to the protocol must be recorded in the subject's eCRF, including:

- missed visits;
- interruptions in the schedule of study drug administration and/or assessments;
- non-permitted medications (Section 9.3.2);
- violation of other restrictions (Section 9.3.3).

Subjects who withdraw from the study due to an AE, regardless of Investigator-determined causality, should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant.

Subjects who withdraw from the study for any reason should have an early termination (ET) visit/phone call and the follow up phone call should take place as scheduled. The Investigator must notify the Sponsor when a subject withdraws from the study for any reason. The reason must be recorded in the subject's case report form. A subject will be deemed lost to follow-up after attempts at contacting the subject have been unsuccessful.

9. TREATMENT OF SUBJECTS

9.1. Study Drugs

Cannabis will be administered via vaporizer for an inhaled dose of 30.9mg THC on Day 2 during Treatment Period A. Alprazolam tablets at a dose of 0.75mg will be administered orally in Treatment Period B approximately 40 minutes earlier on Day 2. Matching placebo (i.e., inhaled via vaporizer or tablets, dependent on Treatment Period) will be administered during Treatment Period C. Subjects will receive active or matched placebo each morning during each Treatment Period. Placebo will be administered as necessary to maintain the blind across the 3 periods. Dosing for each treatment is outlined in Table 4.

Table 4: Treatments Administered

Treatment	Study Drug	Day 2
A	Cannabis	30.9mg THC
B	Alprazolam	0.75mg
C	Placebo	Placebo

9.2. Meal Timing in Relation to Study Drug Administration and Driving Simulations

From the time of admission on Day 1 until discharge on Day 2 of each treatment period, subjects will consume only food and beverages that are provided to them by the staff at the clinical site. Meals (e.g., breakfast, lunch, dinner, and evening snack) will be provided to the subjects while in the supervised off-site residential facility.

On the morning of testing, subjects will eat a low-fat breakfast. The breakfast menu will include non-caffeinated breakfast foods and beverages. A single serving of caffeinated beverage may be consumed prior to 6 am. Breakfast will be provided prior to the cognitive testing and driving simulation.

All other meals and snacks during inpatient periods will be provided according to standard procedures while at the supervised off-site residential facility.

9.3. Prior Medications, Concomitant Medications, and Restrictions

9.3.1. Prior and Concomitant Medications and/or Supplements

All medications (prescription and non-prescription, and herbal medications/natural health products) taken by subjects during the 30 days prior to Screening until the completion of the follow-up phone call will be recorded. The reported medications will be reviewed and evaluated by the Investigator to determine if they affect a subject's eligibility or continued participation in the study.

Subjects are permitted to take hormonal contraceptives, hormone replacement therapy, and acetaminophen (up to 2 grams per day) during the study. On a case-by-case basis, the Investigator is permitted to allow the use of concomitant medications to treat an AE. Wherever possible, the Investigator should obtain approval from the Sponsor's Medical Monitor prior to administering the medication.

9.3.2. Prohibited Medications

Prohibited medications include the following:

- any prescription or over-the-counter medication known to cause sedation within 7 days prior to admission for Period 1 and throughout study participation;
- any benzodiazepine, barbiturate, or $GABA_A$ modulator (e.g., eszopiclone, zopiclone, zaleplon, and zolpidem) within 28 days prior to Admission for Period 1 and throughout study participation;
- exposure to investigational drugs or devices within the 30 days, or 5 half-lives (if known), whichever is longer, prior to Screening and throughout study participation.

9.3.3. Other Restrictions

Subjects are restricted from the following:

- smoking during the study visits;
- Caffeinated beverages will be restricted to no more than 3 servings per day, one caffeinated beverage is allowed no later than 6am on study visit day;
- consumption of > 2 alcoholic beverages per day;
- use of drugs of abuse, other than marijuana/THC-containing products, that would result in a positive urine test at any clinic admission;
- use of cannabis products (other than study drug) beginning 7 days prior to admission for Period 1 through study completion;
- traveling across ≥1 time zone from 2 weeks prior to Admission for Period 1 and through study completion;
- female subjects are restricted from breastfeeding from Screening and through study completion.

9.4. Treatment Adherence

All study drug doses will be administered by staff at NADS. The date and time of study drug administration will be recorded. Any reasons for non-adherence will also be documented.

9.5. Randomization and Blinding

This is a randomized, double-blind, active- and placebo-controlled study. On Day 1 of Period 1, subjects will be randomized 1:1:1 into one of 6 treatment sequences (

Table 3). The active and placebo treatments are identical in appearance within each group and matched placebo will be administered as necessary to maintain the blind (Table 4).

The allocation to treatment sequence will be based on a randomization schedule generated by blinded study personnel. The randomization schedule will be kept strictly confidential, accessible only to authorized personnel until the time of unblinding. A copy of each randomization schedule will be held by the Study Pharmacist.

9.5.1. Emergency Identification of Study Drug

During the study, the blind is to be broken by the Investigator only when the safety of a subject is at risk and the treatment plan is dependent on the study drug received. All circumstances surrounding an early unblinding must be clearly documented in the source records.

In all cases where the study drug allocation for a subject is unblinded, pertinent information (including the reason for unblinding) must be documented in the subject's records and in the CRF. If the subject's or study center personnel's data have been unblinded, the subject will be permanently discontinued from the study.

9.6. Subject Compensation

Subjects will be compensated for their time and effort. Subjects who complete all study procedures successfully will receive up to $1100. For subjects that do not complete, prorated compensation will be provided as show below. For each study visit, there will be an incentive for completing one of the drives safely in the time allowed. This incentive compensation is $25 per visit.

	Base	Incentive	Max Total
Screening	$50		$50
Visit 1	$275	$25	$300
Visit 2	$300	$25	$325
Visit 3	$400	$25	$425
Total Base Pay			$1025
Max Total Compensation			$1100

Additionally, subjects will not be permitted to drive themselves after the study visits and must procure their own transportation. Based on historical costs, subjects will be reimbursed $35 per trip to cover the expenses of a taxi or rideshare.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Description of Study Drugs

Dried bulk cannabis plant material obtained from the NIDA Drug Supply Program will be used for this protocol. The active cannabis contains 6.18% THC and the placebo cannabis contains no detectable THC or CBD. Cannabis will be inhaled using a Volcano® Digit Vaporizer device. Each subject will be administered a dose of cannabis as described in Section 9.1.

Alprazolam tablets will be sourced by the pharmacy at the clinical site through commercial suppliers. Each subject will be administered a dose of 0.75mg as described in Section 9.1. Alprazolam tablets will be over-encapsulated.

Placebo capsules contain only the excipients listed for the active alprazolam capsule.

10.2. Study Drug Packaging and Labeling

Bulk cannabis received from the Research Triangle Institute via the NIDA Drug Supply Program will be maintained with appropriate labeling.

Alprazolam tablets will have commercial packaging and labeling.

Each container of study drug will be clearly labeled with study-specific information meeting all applicable regulatory requirements.

10.3. Study Drug Storage

Upon receipt of the medication, an investigator, or the responsible pharmacist or designee, will inspect the medication and acknowledge receipt in accordance with the study-specific process.

Cannabis should be stored frozen (-15 to -25°C) by the site and humidified at room temperature for 18-48 hours prior to administration. Alprazolam should be stored per the package insert requirements. The study medication may not be used for any purpose other than the present study.

The Investigator or a designee will be responsible for ensuring appropriate storage, compounding, dispensing, inventory, and accountability of all clinical supplies. An accurate, timely record of the disposition of all clinical supplies must be maintained.

10.4. Study Drug Preparation

The study drug will be dispensed or administered according to applicable standard operating procedures. Once dispensed, study drug may not be relabeled or reassigned for use by other subjects.

10.5. Study Drug Administration

A cued-puff procedure will be used to standardize the administration of cannabis. Dried bulk cannabis plant material obtained from the NIDA Drug Supply Program is ground (via herb mill/grinder provided by Volcano® manufacturer) and 500 mg is heated to a temperature of 210°C by the hot air generator to vaporize THC (Hazekamp, 2010; Pomahacova et al., 2009). The vapor is collected in a plastic balloon with a one-way valve. This valve shuts when removed

from the Volcano® device, preventing the escape of vapor. A mouthpiece is attached to the valve and allows for subject-controlled inhalation of the cannabis vapor. Each session utilizes a new balloon to ensure hygienic administration. The Volcano® Digit Vaporizer is operated according to the manufacturer's specifications.

Subjects will be trained to the Foltin Puff Procedure (Foltin, Brady & Fischman, 1986; Wilsey et al., 2013), which includes the following steps: "get ready" (5 seconds), "inhale" (5 seconds), "hold vapor in lungs" (10 seconds), and "exhale and wait" (40 seconds). The subject repeatedly inhales the vapor over 10 minutes. Subjects will be instructed to inhale at their capacity; that means without any dizziness, nausea, vomiting, panic, or difficulty breathing.

All study treatments will be administered following consumption of breakfast as outlined in Section 9.2.

10.6. Study Drug Accountability, Handling, and Disposal

The study drug provided is for use only as directed in this protocol. The Investigator or a designee must keep a record of all study drug received, used, and returned/discarded. It must be clear from the records what study drug each subject received on each dosing day.

NHTSA or designee will be permitted access to the study supplies at any time with appropriate notice during or after completion of the study to perform drug accountability reconciliation.

The Investigator, pharmacist, or qualified designee is responsible for drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

After the study is completed, all unused study medication must be returned as directed or destroyed on site per the site's SOPs.

11. PHARMACODYNAMIC AND PHARMACOKINETIC ASSESSMENTS

All PD and PK assessments will be performed at the visits and time points outlined in the Schedule of Assessments (Table 1). The time of study drug administration will be considered as time zero.

11.1. Pharmacodynamic Assessments

11.1.1. DIDS Driving Scenario on the CRCDS2-MiniSim

This study employs the Drug Impaired Driving Scenario (DIDS) comprised of suburban, urban, and highway driving tasks. The scenario includes challenges designed to assess lane position control, speed control, safety awareness and responsivity, driving-related decision making, multitasking, and vigilance. Data will be captured in electronic format. Details are provided in the Cognitive Research Corporation Driving Simulation Testing Operations Manual.

11.1.2. CogScreen Cognitive Test Battery

The CogScreen computer-based cognitive test battery will be administered by trained and certified study center personnel. Subjects enter responses by tapping a stylus on an LCD touchscreen monitor. Details are provided in the CogScreen® Examiner Manual, CogScreen LLC.

11.1.2.1. Digit Symbol Substitution Test (CogScreen Symbol Digit Coding)

Symbol Digit Coding (SDC) is a computer analogue of the conventional digit symbol-substitution task found in the revised Wechsler Adult Intelligence Scale (WAIS-R, 1981) Digit Symbol subtest. SDC will be used in this study to measure attention, visual scanning, working memory, and speed of information processing. Immediate and delayed recall for the digit-symbol pairs will also be assessed.

11.1.2.2. CogScreen Visual Sequence Comparison Test

The CogScreen Visual Sequence Comparison Test (VSC) will be used in this study to measure visual attention, working memory, visual-sequential processing, and visual-perceptual speed.

11.1.2.3. CogScreen Divided Attention Test

The CogScreen Divided Attention Test (DAT) will be used in this study to measure visual monitoring, choice visual reaction time, impulsivity, divided attention, working memory, verbal-sequential processing, visual-perceptual speed, and capacity for multitasking.

11.1.2.4. CogScreen Matching to Sample Test

The CogScreen Matching to Sample Test (MTS) will be used in the study to measure visual perceptual speed, spatial processing, and visual working memory.

11.1.2.5. CogScreen Pathfinder Number Test

The CogScreen Pathfinder Number Test (PFN) will be used to measure number sequencing skills, immediate memory, motor coordination, visual scanning.

11.1.2.6. CogScreen Shifting Attention Test

The CogScreen Shifting Attention Test (SAT) will be used to measure sustained attention, vulnerability to response interference, working memory, application of novel rules, visual scanning, and choice visual reaction time.

11.1.3. CogScreen Dual Task Test

The CogScreen Dual Task Test (DTT) will be used to measure visual-motor tracking, divided attention, and working memory.

11.1.4. Test of Variables of Attention

The Test of Variables of Attention (TOVA) will be used in this study to measure visual vigilance. The TOVA provides measures of response consistency, speed of response, impulsivity, and focus.

The TOVA will be administered by trained study center personnel. Subjects will perform the test by interacting with an electronic monitor screen. Details are provided in the TOVA Manual.

11.1.5. Karolinska Sleepiness Scale

The KSS (Akerstedt and Gillberg 1990; Akerstedt 2014) will be used to assess subjective level of sleepiness. This is a subject self-reported measure of situational sleepiness and provides an assessment of alertness/sleepiness at a particular point of time. Subjects will rate their sleepiness level using a 9-point categorical Likert-type scale with the following anchors:

(1) “extremely alert”

(2) “very alert”

(3) “alert

(4) “rather alert”

(5) “neither alert nor sleepy”

(6) “some signs of sleepiness”

(7) “sleepy, but no effort to keep awake”

(8) “sleepy, some effort to keep awake”

(9) “very sleepy, great effort to keep awake, fighting sleep”

11.1.6. Self-perceived Safety to Drive Question

Prior to driving, the subject will be asked a simple question as to whether they feel safe to drive (“Right now do you feel safe to drive?”). Subject will answer “yes” or “no”.

11.1.7. Visual Analog Scales to Assess Subjects' Self-appraisal and Motivation

Visual analog scales will be performed to assess a subject's self-appraisal of driving performance and motivation to drive one's best. Immediately after completing the driving simulation (DIDS), subjects will assess their own performance and their level of motivation to perform at their best during the DIDS.

Subjects will respond to 2 questions:

1. How well do you think you drove for the last 60 minutes?
2. How motivated did you feel to drive at your best during the last 60 minutes of driving?

Subjects will record their response to each question by drawing a vertical line on a 100-mm horizontal, linear VAS printed on paper or administered electronically. For the self-assessment of driving performance, 1 end of the line is marked "Not Satisfactory" and the other end of the line is marked "Satisfactory". For the motivation item, 1 end of the line is marked "Not Motivated" and the other end is marked "Motivated". Scores on the 100-mm linear scale will be measured to the nearest millimeter from the left with a ruler or recorded by the electronic system.

11.2. Pharmacokinetic Assessments

11.2.1. Blood Sample Collection

Separate PK blood samples will be collected and processed for analysis of THC and alprazolam blood concentrations. Three separate samples will be collected: pre-dose, at 40 minutes (± 5 minutes) post-dose on Day 2, and at 3.25 hours (± 5 minutes) post-dose on Day 2. Additional details regarding the collection and processing of PK samples will be provided in a separate PK manual.

Blood will be collected and stored into labeled sample containers until analysis. These samples (whole blood) will be refrigerated at NADS until transported to the Iowa DCI Crime Lab for analysis. The Iowa DCI Crime Lab will discard extra blood, using at least one aliquot for analysis and one aliquot for backup. The backup sample will be maintained at -70°C until study close and then discarded.

Blood volumes required for PK sampling are available in Appendix A.

11.2.2. Sample Analysis

Bioanalysis of blood samples for the determination of THC concentrations will be conducted utilizing a validated LC-MS/MS method.

12. ASSESSMENT OF SAFETY

12.1.1. Demography and Medical History

Demographic characteristics (age, race, sex, and ethnicity) and a full medical history will be documented. The Epworth Sleepiness Scale will be conducted at Screening to ensure subjects have no recent history of sleep disorder.

12.1.2. Weight and Height

Height, weight, and BMI will be measured and documented as outlined in Table 1.

12.1.3. Physical Examination

Physical examinations will be conducted to assess the subject's overall health and physical condition. A full or brief physical examination will be completed at the times outlined in Table 1. A full physical examination will include assessment of general appearance, head, eyes, ears, nose and throat (HEENT), neck/thyroid/lymphatic, cardiovascular, respiratory, gastrointestinal, and neurological systems, musculoskeletal/extremities, and skin. A brief physical examination will include assessment of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems. Unscheduled symptom-directed physical examinations may also be conducted per Investigator's discretion. Whenever possible, the same individual should perform all physical examinations for a given subject.

Any abnormality in physical examinations will be interpreted by an Investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS) in source documents.

12.1.4. Vital Signs

Vital signs will include blood pressure, heart rate, respiratory rate, pulse oximetry, and temporal temperature (°F). Heart rate and blood pressure will be collected in the supine position after the subject has been resting for approximately 3 minutes.

All abnormal vital signs will be interpreted by the Investigator or designee as abnormal NCS, or abnormal CS in source documents.

12.1.5. Electrocardiogram (ECG)

Six-lead ECGs will be performed after the subject has been resting in a supine position for at least 5 minutes. The ECG variables will include ventricular heart rate and the PR, QRS, QT, and QTcF intervals.

All abnormal ECGs will be interpreted by the Investigator as abnormal NCS, or abnormal CS in source documents. The standard intervals, any rhythm abnormalities, and the Investigator interpretation will be noted on the eCRF.

12.1.5.1. Drugs of Abuse and Alcohol

A urine drug screen will be conducted for the assessment of selected drugs of abuse (amphetamines, barbiturates, benzodiazepines, THC, cocaine, methadone, phencyclidine, opiates, 3,4-methylenedioxy-methamphetamine (MDMA), and oxycodone). A breathalyzer alcohol screen will be conducted.

12.1.5.2. Pregnancy Screen

A urine pregnancy test will be conducted for all women at Screening; thereafter, a urine pregnancy test will be conducted for women of child-bearing potential at all subsequent periods.

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

Suicidality will be monitored during the study using the C-SSRS (Posner, 2011). This scale consists of a baseline evaluation that assesses the lifetime experience of the subject with respect to suicidal ideation and behavior, and a post-baseline evaluation that focuses on suicidality since the last study visit. The C-SSRS includes 'yes' or 'no' responses for assessment of suicidal ideation and behavior as well as numeric ratings for severity of ideation, if present (from 1 to 5, with 5 being the most severe).

The "Baseline/Screening" C-SSRS form will be completed at Screening (lifetime history and past 24 months).

12.2. Adverse Events and Serious Adverse Events

12.2.1. Adverse Event Definitions

12.2.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the medicinal (investigational) product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

A TEAE is defined as an AE with onset after the first administration of any study drug or any worsening of a preexisting medical condition/AE with onset after the first administration of any study drug and through the follow-up phone call. The term study drug includes any study drug, a comparator, or a placebo administered in a clinical trial.

Laboratory abnormalities and changes from baseline in vital signs and ECGs are considered AEs if they result in discontinuation of study treatment, require therapeutic medical intervention or if the Investigator considers them to be clinically significant. Any abnormalities that meet the criteria for an SAE should be reported in an expedited manner.

All AEs that occur after any subject has signed the informed consent and throughout the duration of the study, whether or not they are related to the study, must be reported to the Medical Monitor.

Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. The Sponsor or its representative retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

12.2.1.2. Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death;
- Is immediately life-threatening;
- Requires in-patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Results in a congenital abnormality or birth defect.

An SAE may also be any other medically important event that, in the opinion of the Investigator may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization).

All SAEs that occur after any subject has signed the ICF and throughout the duration of the study, whether or not they are related to the study, must be recorded on the SAE report form provided by NADS and Acclaro. Any SAE that is ongoing when the subject completes their final study visit, will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

A prescheduled or elective procedure or routinely scheduled treatment will not be considered an SAE, even if the subject is hospitalized. The site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress, in the opinion of an Investigator, between the subject's consent to participate in the study and at the time of the procedure or treatment.

12.2.2. Relationship to Study Drug

The Investigator must make the determination of relationship to the study drug for each AE (not related or related). The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study drug.

Not Related	An AE will be considered "not related" to the use of the study drug if there is not a reasonable possibility that the event has been caused by the study drug. Factors pointing towards this assessment include but are not limited to the lack of temporal relationship between administration of the study drug and the event, the presence of biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE

Related	An AE will be considered "related" to the use of the study drug if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point towards this assessment include but are not limited to a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE, or a lack of alternative explanation for the AE

12.2.3. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. The AE term should be reported in standard medical terminology when possible. For each AE, an investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, outcome, and seriousness (if applicable), and whether or not it caused the subject to discontinue the study drug or withdraw early from the study.

Intensity will be assessed according to the following scale:

- Mild: symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s)
- Moderate: symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment (including but not limited to prescription drugs) for symptom(s) may be needed
- Severe: symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study drug; treatment for symptom(s) may be given and/or subject hospitalized

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria under Section 12.2.1.2. An AE of severe intensity may not necessarily be considered serious.

12.2.4. Reporting Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE(s), the study site must notify Acclaro or designee within 24 hours of the study site staff becoming aware of the SAE(s). The Investigator must complete, sign and date the SAE report form, verify the accuracy of the information recorded on the SAE report form with the corresponding source documents, and send a copy to Acclaro or designee.

Additional follow-up information, if required or available, should all be sent to Acclaro or designee within 24 hours of receipt on a follow-up SAE report form and placed with the original SAE information in the source documents.

Serious events occurring after the designated follow-up time for the study, should be reported to Acclaro or designee according to the timelines noted above only if the Investigator considers the SAE related to study drug.

Acclaro or designee is responsible for notifying the relevant regulatory authorities of certain events. It is the principal investigator's responsibility to notify the Ethics Committee (EC) of all SAEs that occur at his or her site. Investigators will also be notified of all suspected unexpected serious adverse reactions (SUSARs) that occur during the clinical study. Each site is responsible for notifying its EC of all SUSARs.

Appropriate personnel at NADS will unblind SUSARs for the purpose of regulatory reporting. The PI or designee will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law.

12.3. Pregnancy

If a female subject becomes pregnant after first administration of study drug, pregnancy information must be collected, recorded, and submitted to Acclaro or designee within 24 hours of learning of the pregnancy. The female subject's participation in the study will be terminated.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication. The status of the pregnancy is not followed once participation in the study ends.

12.4. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in protocol. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be recorded on an Overdose form and sent to the sponsor or designee within 24 hours of the site becoming aware of the overdose. An overdose must be reported to the sponsor or designee even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded.

13. STATISTICS

A separate statistical analysis plan (SAP) will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the clinical study report.

13.1. Data Analysis Sets

The Randomized Set is defined as all subjects who are randomized.

The Full Analysis Set (FAS) is defined as all randomized and treated subjects that have at least one primary efficacy measure (SDLP) in any treatment period.

The Safety Set (SS) is defined as all subjects administered at least one dose of any study drug.

The PK Set is defined as all subjects in the SS who have at least one collected blood sample from which a valid blood concentration can be measured.

13.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All subjects will be used in the analyses, as per the analysis populations, using all non-missing data available. No imputation process will be used to estimate missing data.

13.3. General Considerations

Continuous endpoints will be summarized with number (n), mean, standard deviation (SD), median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages.

All data supporting the development of the summary tables and figures will be listed.

13.4. Demographics and Baseline Characteristics

Demographics and baseline characteristics (age, sex, race, ethnicity, body weight, height, and BMI) will be summarized for the SS as well as the FAS separately. No formal statistical comparison between the groups will be performed.

Medical history will be listed by subject.

Pregnancy test results and drug/alcohol screens will be listed but not summarized.

13.5. Pharmacodynamic Analyses

All PD analyses will use the FAS Set.

The FAS will be used for the primary analysis. Summary statistics will be provided (mean, standard deviation, median, minimum, maximum) for each treatment. Figures will be provided for the within-subject difference scores by treatment and day as both a histogram and scatter plot. Data listings for driving simulator data will be provided.

SDLP data will be analyzed using a mixed model for repeated measures (MMRM) with fixed effects for sequence, period, and treatment and random effect for subject. A log-transformation of SDLP values to obtain normal distribution of data will be considered, if necessary. An unstructured covariance structure and Kenward-Roger degrees of freedom will be used. In the event an unstructured covariance structure fails to converge, a variance components covariance structure will be assumed. In addition to treatment effect, p-values for significance testing of period and sequence effects will be provided. Pair-wise comparisons of differences in means and two-sided 95% CIs on differences will be provided for all active treatments versus the placebo treatment.

The comparison of primary interest is cannabis versus placebo on Day 2 as a function of frequency of self-reported cannabis use. The statistical significance of alprazolam versus placebo ($p < 0.05$) comparison for SDLP is considered only to validate the experiment and having the ability to detect effects (i.e., assay sensitivity).

Formal statistical tests (when performed) will be 2-sided and tested at the alpha=0.05 level of significance. Cannabis will be considered non-inferior to placebo if the two-sided upper 95% confidence limit on the difference in SDLP between that dose and placebo is less than 4.4 cm, and it can be concluded that the effect of cannabis on driving is less than that seen at 0.05% BAC, which is a level associated with increased crash risk. No adjustment to alpha levels will be made for either the comparison of alprazolam to placebo, or for secondary endpoints or analyses.

As a supportive analysis, pair-wise, within-subject differences in SDLP greater than 4.4 cm in absolute value will be compared using McNemar test. Furthermore, these pair-wise, within subject differences in SDLP will be tested for symmetry about zero (Laska et al., 2012) using the maximally selected McNemar test. If there is no significant difference between placebo and cannabis and if the distribution of paired differences is symmetrical around zero, it can be concluded that cannabis does not impair driving.

Driving performance, cognitive, and self-report endpoints will be evaluated and presented using a mixed model for repeated measures. Lane exceedance will be log-transformed (more specifically ln[x+1]) before analyses.

A data listing for the results will be provided. Summary tables will be presented in the same format as the primary output for:

- Driving Performance Endpoints
    - SDLP
    - Lane exceedance; including number, maximum and duration of exceedance
    - Speed related measures; including speed deviation, average speed, and excessive speed count
    - Driving safety measures; including excessive Ay (cornering speed threshold-exceeded), and total number of collisions
    - Divided attention measures; including correct responses, omission errors, commission errors, reaction time, and standard deviation of reaction time

- CogScreen SDC Test
    - Number of correct responses
    - Response accuracy
    - Standard deviation of reaction time
- CogScreen Symbol Digit Coding – Immediate Recall
    - Immediate recall accuracy
- CogScreen Symbol Digit Coding – Delayed Recall
    - Delayed recall accuracy
- CogScreen Visual Sequence Comparison Test
    - Response speed
    - Response accuracy
    - Standard deviation of reaction time
- CogScreen Divided Attention Test
    - Response speed
    - Number of premature responses
    - Response accuracy
    - Number of lapses
    - Multitasking scores
- CogScreen Matching To Sample Test
    - Response speed
    - Response accuracy
    - Standard deviation of reaction time
- CogScreen Pathfinder Number
    - Response speed
    - Response accuracy
    - Response coordination
- CogScreen Shifting Attention Test
    - Response speed
    - Response accuracy
    - Standard deviation of reaction time
- CogScreen Dual Task Test
    - Tracking errors
    - Number of boundary hits
    - Previous number response speed
    - Previous number response accuracy
    - Previous number standard deviation of reaction time
    - Multitasking scores

- Test of Variables of Attention (TOVA)
    - Response time variability (Total, and Scores per quarter)
    - Response speed (Total, and Scores per quarter)
    - Commission errors (Total, and Scores per quarter)
    - Omission errors (Total, and Scores per quarter)
- KSS
- Self-Reported Readiness to Drive
- VAS to assess subject's motivation and self-appraisal of their driving performance, including readiness to drive and whether the subject feels safe to drive

For total number of collisions, differences in number of collisions for each pair-wise comparison will be provided with their corresponding Wilcoxon Signed Rank p-value. A bar chart will be provided pooling total number of collisions by 0, 1, 2, or ≥3 for all treatments. In addition, pair-wise treatment comparisons for readiness to drive will be analyzed using McNemar's test. A bar graph for percentage of subjects reporting no safe to drive will be provided by treatment and day.

13.6. Safety Analyses

Safety and tolerability of cannabis will be assessed by the incidence of TEAEs, and by changes from baseline in vital signs.

Safety data will be listed by subject and summarized by treatment. All safety summaries will be performed on the SS.

13.6.1. Adverse Events

AEs will be coded using MedDRA version 22.0 or higher. The analysis of AEs will be based on the concept of TEAEs presented by treatment. TEAEs will be summarized by System Organ Class (SOC) and preferred term, and by treatment. TEAE summaries will be provided showing the number and percentage of subjects who experienced at least one TEAE. In addition, summaries will be provided by severity (mild, moderate, or severe) and by causality (related or not related) to study drug (see Section 12.3). If more than one TEAE is coded to the same preferred term for the same subject within the same treatment period, the subject will be counted only once for that preferred term using the most severe occurrence for the summarization by severity.

TEAEs leading to discontinuation of study drug and serious TEAEs including death will also be summarized.

All AEs and SAEs (including those with onset or worsening before the start of study drug) through the end of the study will be listed.

13.6.2. Physical Examinations

Physical examination will be conducted on Day 1 of each period. The occurrence of physical examinations (yes/no) and the date of the examination will be listed by subject.

13.6.3. Vital Signs

Vital signs will be taken on Day 1 of each period. Vital signs data will be summarized by treatment and listed by subjects.

13.6.4. 6-Lead Electrocardiogram

Electrocardiogram will be conducted at screening. Electrocardiogram findings will be listed by subject. ECG parameters will be summarized by treatment.

13.6.5. Prior and Concomitant Medications

Medications will be recorded at each study visit during the study.

All medications taken within 30 days prior to Screening and through the duration of the study will be recorded. Those medications taken prior to the first dose of study drug will be denoted "Prior". Those medications taken prior to the first dose of study drug and continuing beyond the first dose of study drug or those medications started at the same time or after the initiation of the study drug will be denoted "Concomitant" (i.e., those with a start date on or after the first dose of study drug, or those with a start date before the first dose of study drug that are ongoing or with a stop date on or after the first dose of study drug).

Medications will be presented according to whether they are "Prior" or "Concomitant" as defined above. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

Details of prior and concomitant medications/procedures will be listed by subject, start date, and verbatim term.

13.6.6. Columbia Suicide Severity Rating Scale

The C-SSRS will be administered at screening. Suicidality data collected on the C-SSRS will be summarized and listed for the SS. Listings will include behavior type and/or category for Suicidal Ideation and Suicidal Behavior of the C-SSRS.

13.7. Pharmacokinetic Analyses

The potential relationship between THC blood concentration and SDLP or other driving or cognition endpoints will be examined using regression techniques.

THC and alprazolam concentrations will be listed by subject and summarized by day.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Audits and Inspections

Authorized representatives, a regulatory authority, an EC or IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a NHTSA audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The Investigator should contact Acclaro immediately if contacted by a regulatory agency about an inspection.

14.2. Ethics Committee

Acclaro will obtain EC approval for the investigation for this cooperative human subject research project that provides coverage for the NADS research effort. NADS will coordinate ceding of oversight from the University of Iowa' Human Subjects Office to Advarra. Initial EC approval, and all materials approved by the EC for this study including the subject consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Acclaro may conduct a quality assurance audit. Please see Section 14.1 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or EC as appropriate.

The Principal Investigator is responsible for providing the IRB or EC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Acclaro will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or EC according to local regulations and guidelines.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH and GCP guidelines, as well as all applicable regulatory requirements.

16.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the subject.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

Acclaro will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

17.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for the period outlined in the site contract. If it becomes necessary for Acclaro or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

18. PUBLICATION POLICY

No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between NHTSA, Acclaro, and the Investigator.

19. LIST OF REFERENCES

Akerstedt T, Gillberg M. Subjective and objective sleepiness in the active individual. *Int J Neurosci.* 1990 May;52(1-2):29-37.

Akerstedt T, Anund A, Axelsson J, et al. Subjective sleepiness is a sensitive indicator of insufficient sleep and impaired waking function. *J Sleep Res.* 2014; 23:242-254.

Baldock, M. R. J., & Lindsay, V. L. Examination of the Role of the Combination of Alcohol and Cannabis in South Australian Road Crashes. *Traffic Injury Prevention.* (2015); *16*(5), pp-443-449. Retrieved from http://dx.doi.org/10.1080/15389588.2014.969804

Brown, T.L., Milavetz, G., Gaffney, G., & Spurgin, A. Evaluating drugged driving: Effects of exemplar pain and anxiety medications. *Traffic Injury Prevention.* 2018; *19*(S1), S97-S103.

Brown, T., McConnell, M., Rupp, G., Meghdadi, A., Richard, C., Schmitt, R., Gaffney, G., Milavetz, G., & Berka, C. Correlation of EEG Biomarkers of Cannabis with Measured Driving Impairment. *Traffic Injury Prevention*. 2019; https://doi.org/10.1080/15389588.2019.1662256

Brown, T., Richard, C., Meghdadi, A., Poole, J., Fink, A., Stevanović Karić, M., McConnell, M., Rupp, G., Schmitt, R., Gaffney, G., Milavetz, G., & Berka, C. EEG Biomarkers Acquired During a Short, Straight-line Simulated Drive to Predict Impairment from Cannabis Intoxication. *Traffic Injury Prevention*. 2020; https://doi.org/10.1080/15389588.2020.1814957

Brubacher, J. R., Chan, H., Martz, W., Schreiber, W., Asbridge, M., Eppler, J., … Brant, R. Prevalence of alcohol and drug use in injured British Columbia drivers. *BMJ Open*. 2016; *6*(3), 10p. Retrieved from http://dx.doi.org/10.1136/bmjopen-2015-009278

Chihuri, S., Li, G., & Chen, Q. Interaction of marijuana and alcohol on fatal motor vehicle crash risk: a case-control study. *Injury Epidemiology*. 2017; *4*(1) (no pagination). https://doi.org/10.1186/s40621-017-0105-z

CRC data on file: 2017, 2019, 2020.

Del Balzoa, G., Gottardoa, R., Mengozzi, S., Dorizzi, R. M., Bortolotti, F., Appolonovac, S., Tagliaroa, F. "Positive" urine testing for Cannabis is associated with increased risk of traffic crashes. *Journal of Pharmaceutical and Biomedical Analysis*. 2018; 151, 71–74.

Dubois, S., Mullen, N., Weaver, B., Bedard, M. The combined effects of alcohol and cannabis on driving: Impact on crash risk. *Forensic Science International.* 2015; *248*, 94-100.

Food and Drug Administration Center for Drug Evaluation and Research. Evaluating Drug Effects on the Ability to Operate a Motor Vehicle Guidance for Industry. November 2017.

Gjerde, H., Normann, P. T., Christophersen, A. S., Samuelsen, S. O., Morland, J. Alcohol, psychoactive drugs and fatal road traffic accidents in Norway: A case-control study. *Accident Analysis and Prevention.* 2011; *43*, 1197-1203

Hartman, R. L., Anizan, S., Jang, M., Brown, T. L., Yun, K., Gorelick, D. A., Milavetz, G., Spurgin, A., Gaffney, G., & Huestis, M. A. Cannabinoid Disposition in Oral Fluid after Controlled Vaporizer Administration with and without Alcohol. Forensic Toxicology. 2015; 1-19. https://doi.org/DOI 10.1007/s11419-015-0269-6

Hartman, R. L., Brown, T. L., Milavetz, G., Spurgin, A., Gorelick, D. A., Gaffney, G., & Huestis, M. A.. Controlled Cannabis Vaporizer Administration: Blood and Plasma Cannabinoids with and without Alcohol. Clinical Chemistry. 2015a; 61(6), 850-869.

Hartman, R. L., Brown, T. L., Milavetz, G., Spurgin, A., Gorelick, D. A., Gaffney, G., & Huestis, M. A. Controlled Vaporized Cannabis, with and without Alcohol: Subjective Effects and Oral Fluid-Blood Cannabinoid Relationships. Drug testing and analysis. Drug Testing and Analysis. 2015b; https://doi.org/DOI:10.1002/dta.1839

Hartman, R. L., Brown, T. L., Milavetz, G., Spurgin, A., Pierce, R., Gorelick, D. A., Gaffney, G., & Huestis, M. A. Cannabis Effects on Driving Longitudinal Control With and Without Alcohol. Journal of Applied Toxicology. 2016; https://doi.org/10.1002/jat.3295

Hartman, R. L., Brown, T. L., Milavetz, G., Spurgin, A., Pierce, R. S., Gorelick, D. A., Gaffney, G., & Huestis, M. A.. Cannabis Effects on Driving Lateral Control with and without Alcohol. Drug and alcohol dependence. 2016; 154, 25-37.

Hartman, R. L., Jang, M., Spurgin, A., Yun, K., Gorelick, D. A., Milavetz, G., Brown, T. L., Gaffney, G., & Huestis, M. A. Cannabinoid Disposition in Oral Fluid after Controlled Cannabis Vaporizer Administration. American Academy of Forensic Sciences Annual Conference. February 2015; Orlando, FL.

Hindmarch, I., Trick, L., & Ridout, F. A double-blind, placebo- and positive-internal-controlled (alprazolam) investigation of the cognitive and psychomotor profile of pregabalin in healthy volunteers. *Psychopharmacology*. 2005; *183,* 133-143.

Jamt, R. E. G., Gjerde, H., Romeo, G., Bogstrand, S. T. Association between alcohol and drug use and arrest for driving under the influence after crash involvement in a rural area of Norway: A case-control study. *BMJ Open.* 2018; *9*: e023563. doi:10.1136/bmjopen-2018-023563

Kay GG, Hochadel T, Sicard E, Natarajan KK, Kim NN. Next-day residual effects of flibanserin on simulated driving performance in premenopausal women. *Hum Psychopharmacol.* 2017 Jul;32(4).

Kay, GG and Logan, BK. Drugged driving expert panel report: A consensus protocol for assessing the potential of drugs to impair driving (DOT HS 811 438). *National Highway Traffic Safety Administration*. 2011.

Kuypers, K. P. C., Legrand, S.-A., Ramaekers, J. G., Verstraete, A. G. *A Case-Control Study Estimating Accident Risk for Alcohol, Medicines and Illegal Drugs. PLOS ONE*. 2012; 7(8), e43496.

Laska, E, Meisner, M, Wanderling, J. A maximally selected test of symmetry about zero. *Statistics in Medicine.* 2012; 31(26), 3178 – 3191.

Legrand, SA, Silverans, P, de Paepe, P, Buylaert, W, Verstraete, AG. Presence of psychoactive substances in injured Belgian drivers. *Traffic Injury Prevention*. 2013; 14(5), 461-468

Leufkens TR, Vermeeren A. Zopiclone's residual effects on actual driving performance in a standardized test: A pooled analysis of age and sex effects in 4 placebo-controlled studies. Clinical Therapeutics. 2014; 36(1), 141–150.

Leufkens TRM, Lund JS, Vermeeren A. Highway driving performance and cognitive functioning the morning after bedtime and middle-of-the-night use of gaboxadol, zopiclone and zolpidem. *Journal of Sleep Research*. 2009; 18(4), 387–396.

Leufkens, T.R.M., Vermeeren, A., Smink, B.E., van Ruitenbeek, P., Ramaekers, J.G., (2007). Cognitive, psychomotor, and actual driving performance in healthy volunteers after immediate and extended release formulations of alprazolam 1mg. *Psychopharmacology, 191,* 951-959.

Li, G., Brady, J. E., & Chen, Q. Drug use and fatal motor vehicle crashes: A case-control study. *Accident Analysis and Prevention*. *2013;* 60, 205–210. https://doi.org/10.1016/j.aap.2013.09.001

Mann, R., Stoduto, G., Butters, J., Ialomiteanu, A., Boase, P., Asbridge, M., Chipman, M., Wickens, C. M. Age group differences in collision risk. *Journal of Safety Research.* 2010; 41, 445-449.

Martin, J.-L., Gadegbeku, B., Wu, D., Viallon, V., & Laumon, B. Cannabis, alcohol and fatal road accidents. *PLoS ONE*. 2017; 12(11), 1–16. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=asn&AN=126108805&site=ehost-live&scope=site

Mets MA, de Vries JM, de Senerpont Domis LM, Volkerts ER, Olivier B, Verster JC. Next-day effects of ramelteon (8 mg), zopiclone (7.5 mg), and placebo on highway driving performance, memory functioning, psychomotor performance, and mood in healthy adult subjects. *Sleep.* 2011; 34(10), 1327–1334.

Miller, R., Brown, T., Lee, S., Tibrewal, I., Gaffney, G., Milavetz, G., Hartman, R., Gorelick, D., Compton, R., & Huestis, M. Impact of Cannabis and Low Alcohol Concentration on Divided Attention Tasks during Driving. *Traffic Injury Prevention.*2020; https://doi.org/10.1080/15389588.2020.1814956

Mir, M. U., Khan, I., Ahmed, B., Razzak, J. A. Alcohol and marijuana use while driving--an unexpected crash risk in Pakistani commercial drivers: a cross-sectional survey. *BMC Public Health.* 2012; 12(145). https://doi.org/10.1186/1471-2458-12-145

Pearlman, E.M., Wilbraham, D., Dennehy, E.B., Berg, P.H., Tsai, M., Doty, E.G., & Kay, G. G. Effects of Lasmiditan on simulated driving performance: Results of two randomized, blinded, crossover studies with placebo and active controls. *Human Psychopharmacology: Clinical and Experimental.* 2020; *35 (5)*. https://doi.org/10.1002/hup.2732

Posner, K. Brown, GK, Stanley, B, Brent DA, Yershova, KV, Oquendo, MA…Mann, JJ. The Columbia-Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. *American Journal of Psychiatry.* 2011; 168(12): 1266-1277.

Reissig, C.J., Harrison, J.A., Carter, L.P., & Griffiths, R.R. Inhaled v. oral alprazolam: subjective, behavioral and cognitive effects, and modestly increased abuse potential. *Psychopharmacology.* 2015; *232,* 871-883.

Siliquini, R., Piat, S. C., Gianino, M. M., & Renga, G. Drivers Involved in Road Traffic Accidents in Piedmont Region: Psychoactive Substances Consumption. *Journal of Preventive Medicine and Hygiene*. 2007; 48(4), pp-125-128. Retrieved from https://trid.trb.org/view/874750

Simen, AA, Gargano C, Cha JH, Drexel M, Bautmans A, Heirman I, Laethem T, Hochadel T, Gheyle L, Bleys K, Beals C, Stoch A, Kay GG, Struyk, A. A randomized, crossover, placebo-controlled clinical trial to assess the sensitivity of the CRCDS Mini-Sim to the next-day residual effects of zopiclone. *Therapeutic Advances in Drug Safety.* 2015; 6(3), 86–97.

Smith, S., Stone, B., Meghdadi, A., Spurgin, A., Brown, T., & Berka, C.. *Neurophysiological Indices of Cannabis and Impairment Society for Neuroscience*. 2018, 3-7 November; San Diego, CA.

Snyder, P.J., Werth, J., Giordani, B., Caveney, A.F., Feltner, D., & Maruff, P. A method for determining the magnitude of change across different cognitive functions in clinical trials: The effects of acute administration of two different doses of alprazolam. *Human Psychopharmacology.* 2005; *20,* 263 – 273.

Steinemann S., Galanis D., Nguyen T., & Biffl W. Motor vehicle crash fatalities and undercompensated care associated with legalization of marijuana. *Journal of Trauma and Acute Care Surgery*. 2018; 85(3), 566–571. https://doi.org/10.1097/TA.0000000000001983

Stone, B.T., Correa, K.A., Brown, T.L., Spurgin, A.L., Stikic, M., Johnson, R.R., & Berka, C.

Behavioral and neurophysiological signatures of benzodiazepine-related driving impairments. *Frontiers in Psychology.* 2015; *6,* doi: 10.3389/fpsyg.2015.01799.

Verster JC, Spence DW, Shahid A, Pandi-Perumal SR, Roth T. Zopiclone as positive control in studies examining the residual effects of hypnotic drugs on driving ability. *Current Drug Safety.* 2011; 6(4),209–218.

Verster, J.C., Volkerts, E.R., & Verbaten, M.N. Effects of alprazolam on driving ability, memory functioning and psychomotor performance: A randomized, placebo-controlled study. *Neuropsychopharmacology.* 2002; *27,* 260 – 269.

APPENDIX A. AMOUNT OF BLOOD DRAWN PER STUDY VISIT

	Pharmacokinetic Sampling	**Total**
Day 2	8 mL x 3	24 mL
Total	24 mL	24 mL

Blood volumes shown in the table are approximate. At each blood draw, two 4 mL draws will be made for a total of 8 mL. Additional blood samples may be taken if needed to follow-up on individual subject safety.

APPENDIX B. DAILY SCHEDULE OF ACTIVITIES PER PERIOD

Activity	Study Day	Location	Time	Time Post-Dose (Cannabis)
Admission and Intake	Day 1	NADS	3:00pm	-17 hours 40 minutes
Cognitive Battery Practice	Day 1	NADS	3:55pm	-16 hours 45 minutes
CRCDS2 Practice	Day 1	NADS	4:30pm	-16 hours 10 minutes
Transport to supervised off-site residential facility	Day 1	In transit	6:00pm	-14 hours 40 minutes
Dinner	Day 1	Off-site residential facility (supervised)	6:00pm to 8:00pm	-14 hours 40 minutes to -12 hours 40 minutes
Bedtime	Day 1	Off-site residential facility (supervised)	10:00pm	-10 hours 40 minutes
Awakened	Day 2	Off-site residential facility (supervised)	5:45am to 6:00am	-2 hours 55 minutes to -2 hours 40 minutes
Breakfast	Day 2	Off-site residential facility (supervised)	6:30am	-2 hours 10 minutes
Transport to NADS	Day 2	In transit	7:15am	-1 hour 25 minutes
Arrival at NADS	Day 2	NADS	7:30am	-1 hour 10 minutes
Blood Draw & KSS	Day 2	NADS	7:45am	-55 minutes
Alprazolam dosing	Day 2	NADS	8:00am	-40 minutes
Cannabis dosing	Day 2	NADS	8:40am	0

SDC, PFN, KSS, Readiness to Drive Question	Day 2	NADS	9:10am	30 minutes
Blood Draw	Day 2	NADS	9:20am	40 minutes
CRCDS2	Day 2	NADS	9:25/9:30am	45 minutes
VAS, SDC, VSC, DAT, PFN, SDCDR, SAT, MTS, DT, TOVA	Day 2	NADS	10:30am	1 hour 45 minutes
Lunch	Day 2	NADS	11:20	2 hours 40 minutes
Blood Draw	Day 2	NADS	11:55am	3 hours 15 minutes
SDC, VSC, DAT, PFN, SDCDR, SAT, MTS, DT, TOVA, Self-Report Measures	Day 2	NADS	12:10pm	3 hours 30 minutes
Discharge	Day 2	NADS	2:00pm	5 hours 20 minutes