Official Title: A Phase 2, Randomized, Double-Blind, Multi-Center, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety, Tolerability, and Efficacy of V117957 in Subjects with an Alcohol Use Disorder who are Experiencing Insomnia Associated with Alcohol Cessation

NCT #: NCT04035200

Date of Document: September 27, 2019

Protocol Number:	OAG2002
Title:	A Phase 2, Randomized, Double-Blind, Multi-Center, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety, Tolerability, and Efficacy of V117957 in Subjects with an Alcohol Use Disorder who are Experiencing Insomnia Associated with Alcohol Cessation
Sponsor:	Imbrium Therapeutics One Stamford Forum Stamford, CT 06901-3431 USA
Test Drug:	V117957
Phase:	Phase 2
Approval Date:	September 27, 2019
Amendment No:	1
GCP Statement:	This study is to be performed in compliance with ICH and applicable Good Clinical Practices (GCPs) and federal and local regulations.
Confidentiality:	This document is confidential. It contains proprietary information of Imbrium Therapeutics. Any viewing or disclosure of such information that is not authorized in writing by the sponsor (or designee) is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

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Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
[Amendment 1]	*27-September-2019*
OAG2002	*03-April-2019*

Amendment 1 (27-September-2019)

Overall Rationale for the Amendment:

- Update the inclusion criteria to allow Women of Child Bearing Potential (WOCBP) onto the study.
- Moved some secondary endpoints to exploratory endpoints.
- Made clarifications to The Schedule of Activities and the Study Flow tables.
- [redacted]
- Other typos, clarifications.

Section # and Name	**Description of Change**	**Brief Rationale**
Synopsis – Investigator Centers	Change from: ~15 Change to: 20	Confirmed number of sites
[redacted]	[redacted]	[redacted]
Synopsis – Inclusion Criteria [redacted]	Change from: A female participant is eligible to participate if she is not of childbearing potential. Females of non-child-bearing potential include: Females who are postmenopausal must have been postmenopausal ≥ 1 year and have an elevated serum FSH value greater than 40mIU/mL. Documentation of sterilization will be required. Nonsurgically sterilized males with a sexual partner of childbearing potential must be willing to use adequate and reliable contraception throughout the study (eg, heterosexual abstinence or barrier with additional spermicidal foam or jelly, or the use of intrauterine device or hormonal contraception by female subjects and partners of male subjects).	Study to include women of child bearing potential

	Change to: A female participant is eligible to participate if she is not pregnant and not breastfeeding. Both females of childbearing potential (ie, not medically or surgically sterilized or not postmenopausal more than 1 year with confirmatory FSH) and nonsurgically sterilized males with a sexual partner of childbearing potential must be willing to use adequate and reliable contraception throughout the study (eg, heterosexual abstinence or barrier with additional spermicidal foam or jelly, or the use of intrauterine device or hormonal contraception by female subjects and partners of male subjects)	
Synopsis – Exclusion Criteria [redacted]	Change from: Use of any medication that affects sleep and/or wake function during the week before starting the screening period. Change to: Use of any medication that affects sleep and/or wake function during the week before starting the Consensus Sleep Diary-Morning (CSD-M).	
Synopsis – Secondary Efficacy Variables, Exploratory Variables [redacted]	Change from: The secondary efficacy variables will be derived from PSG recordings as well as CSD-M (sleep diary) data: • SE: Sleep efficiency • LPS: Latency to persistent sleep • TST: Total sleep time • NAW: Number of awakenings • WASO by hour, TST by hour, NAW by hour • WASO in first half of night (WASO1H), WASO in second half of night (WASO2H) • Total minutes of stages N1, N2, N3 and rapid eye movement (REM) • Percentage of stages N1, N2, N3 and REM with TST denominator and with Time in Bed (TIB) denominator • REM latency • Number of transient arousal/ shifts to wake or N1 Change to: The secondary efficacy variables will be derived from PSG recordings as well as CSD-M (sleep diary) data: • SE: Sleep efficiency	Moved some secondary endpoints to exploratory

	• LPS: Latency to persistent sleep • TST: Total sleep time • NAW: Number of awakenings	
Synopsis - Secondary Efficacy Variables [redacted]	Deleted sTIB: subject estimated Time in Bed, time from lights out to time out of bed	Deleted this specific variable as included in another variable
[redacted]	[redacted]	[redacted]
Synopsis – Secondary Efficacy Analyses	Change from: The baseline, post baseline, and change from baseline of all sleep variables as measured by PSG (including TST, SE, LPS, total minutes of stages N1, N2, N3, REM, and REM latency, etc), and all sleep variables as measured by CSD-M (including sleep quality, sTST, sWASO, sSOL, sTIB, sSE, etc) will be summarized by treatment group with descriptive statistics and presented graphically. Change to: The baseline, post baseline, and change from baseline of all sleep variables as measured by PSG (including TST, SE, LPS, NAW), and all sleep variables as measured by CSD-M (including sleep quality, sTST, sWASO, sSOL, sSE, etc) will be summarized by treatment group with descriptive statistics and presented graphically.	Removed wording that applied to endpoints moved to exploratory
[redacted]	[redacted]	[redacted]

1. Synopsis

Name of Company: Imbrium Therapeutics		**Protocol Number:** OAG2002
Name of Finished Product: N/A	**Name of Active Ingredient:** V117957	
US IND/EUDRACT No.: [redacted]		
Full Title of the Study: A Phase 2, Randomized, Double-Blind, Multi-Center, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety, Tolerability, and Efficacy of V117957 in Subjects with an Alcohol Use Disorder who are Experiencing Insomnia Associated with Alcohol Cessation		
Investigator(s)/Center(s):20 sites		
Planned First Subject First Visit: 3Q2019	**Phase of Development:** Phase 2	
Objectives: **Primary:** To evaluate the safety, tolerability, and efficacy of V117957 in subjects with an alcohol use disorder, who experience insomnia associated with alcohol cessation, compared to placebo. **Secondary:** Assess sleep components as measured by polysomnography, assess self-reported sleep outcomes measured by patient diary, and assess next day residual effects of study drug. [redacted] [redacted]		
Study Design (Methodology): This is a phase 2, randomized, double-blind, multi-center, placebo-controlled, parallel-group study in subjects with an alcohol use disorder (AUD), who are experiencing insomnia associated with alcohol cessation (IAAC). The total duration of the study for a given subject is up to 59 days inclusive of a 21-day screening period, 21-day treatment period, 3-day washout period, and follow-up period of up to 14 days. During the screening period subjects will be assessed to determine eligibility for enrollment in the study. Subjects complete the Consensus Sleep Diary-Morning (CSD-M) at home and if at least 3 nights of any 7-night period indicate insomnia, they will enter a sleep lab for 2 consecutive nights of polysomnography (PSG) evaluation. During the treatment period, eligible subjects will be randomly assigned to V117957 1 mg QHS, V117957 2 mg QHS or placebo QHS (approximately 50 per arm, in a 1:1:1 ratio). Eligible subjects will be required		

to attend clinic visits (days 1, 3, 8, 15 and 20) and overnight sleep lab visits (days 1, 2, 20 and 21). On every day of the treatment period, the subject will complete the CSD-M. At sleep lab visits, the subject will undergo PSG and complete the Digit Symbol Substitution Test (DSST), Karolinska Sleepiness Scale (KSS), and Profile of Mood States-Brief Form (POMS™-Brief). At clinic visits, subjects will complete: the Columbia-Suicide Severity Rating Scale (C-SSRS), Hospital Anxiety and Depression Scale (HADS); will undergo clinical laboratory testing, drug/alcohol screening, vital sign measurements, 12-lead electrocardiogram and a neurological exam. Adverse events and concomitant medications will be assessed. Blood samples for sparse pharmacokinetic (PK) analysis will also be collected during clinic visits.

During the washout period, (days 22 and 23) subjects will receive placebo treatment in a single-blind manner and undergo PSG testing. An end of treatment (EOT) clinic visit will be conducted on day 24.

The subject will return home and continue to complete the CSD-M [redacted] and will return for a clinic visit approximately 1 week after the last double-blind treatment dose to perform end of study (EOS) evaluations. A follow-up phone contact to assess safety will be done approximately 1 week after EOS visit.

Planned Number of Subjects (including sample size rationale):

Planned total number of randomized subjects is approximately 150 (~50 per treatment group) to ensure at least 30 subjects per group complete treatment.

A sample size of 30 subjects per treatment group has >80% power for detecting a statistically significant difference vs. placebo of 30 minutes (SD=45 minutes) for WASO, based on a 1-sided 2-sample t-test at 5% significance level.

Criteria for Inclusion/Exclusion:

Inclusion Criteria:

Participants are eligible if they meet all the following criteria:

1. Male or female, 18-64 years of age with a body weight of 50-100 kg (110-220 lbs) and a body mass index (BMI) of 18-32 kg/m^2.
2. Otherwise healthy as determined by medical evaluation that includes: medical history, physical examination, neurological exam, laboratory tests, vital signs, and cardiac monitoring.
3. History of moderate or severe alcohol use disorder (AUD) categorized based on DSM-5 criteria, as follows:
   - Moderate as defined by presence of 4-5 of the 11 criteria
   - Severe as defined by the presence of ≥ 6 of the 11 criteria.
4. At least 3 weeks and not more than 6 months since last alcoholic beverage intake at the time of study screening. Any subject who completed an alcohol detoxification program must be at least 7 days from completion of the program at the time of screening.
5. Persistent insomnia that emerged or worsened during AUD period, or during or after alcohol cessation characterized by:

   Screening period patient diary data indicating that in at least 3 nights of any 7-day period:
   a. subjective total sleep time (sTST) is ≤6.5 hours; and,
   b. subjective sleep onset latency (sSOL) is ≥30 minutes; and,
   c. subjective wakefulness after sleep onset (sWASO) is ≥1 hour; and,

d. subjective time in bed (sTIB) sleeping or trying to sleep is between 7 and 9 hours in duration and the [regular] sleep time is between 21:00 and 24:00 and the [regular] wake time is between 05:00 and 09:00.

Screening period sleep lab polysomnography (PSG) data indicating:

e. latency to persistent sleep (LPS) is ≥20 min as averaged on 2 consecutive night PSGs with neither night <15 min; and,
f. wakefulness after sleep onset (WASO) is ≥30 min as averaged on 2 consecutive night PSGs with neither night <20 min; and,
g. sleep efficiency (SE) is ≤ 85% as averaged on 2 consecutive night PSGs with neither night >87.5%.

6. A female participant is eligible to participate if she is not pregnant and not breastfeeding. Both females of childbearing potential (ie, not medically or surgically sterilized or not postmenopausal more than 1 year with confirmatory FSH) and nonsurgically sterilized males with a sexual partner of childbearing potential must be willing to use adequate and reliable contraception throughout the study (eg, heterosexual abstinence or barrier with additional spermicidal foam or jelly, or the use of intrauterine device or hormonal contraception by female subjects and partners of male subjects)
7. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
8. Willing to refrain from a behavioral or other treatment program for insomnia during participation in the study.

Exclusion Criteria:

Participants are excluded from the study if they meet any of the following criteria:

Medical Conditions

1. Current diagnosis of a sleep-related breathing disorder including obstructive sleep apnea (with or without continuous positive airway pressure (CPAP) treatment), periodic limb movement disorder, restless legs syndrome, circadian rhythm sleep disorder, narcolepsy, or an exclusionary score on any of the following:
   a. STOPBang: score ≥ 5
   b. International Restless Legs Scale: score ≥ 16
   c. Epworth Sleepiness Scale: Score > 10.
2. An apnea-hypopnea index (AHI) score of >10 or a periodic limb movement arousal index (PLMAI) score of > 15 recorded during the screening period PSG.
3. Documented history of insomnia prior to onset of the alcohol use disorder (AUD), which did not worsen during the AUD period or during or after alcohol cessation.
4. Comorbid nocturia or other conditions (eg. benign prostatic hyperplasia) resulting in frequent need to get out of bed to use the bathroom during the night (≥3 times per night average).
5. Any lifetime history of suicidal ideation with intent, with or without a plan at the time of or within 6 months before screening (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the C-SSRS).
6. Any lifetime suicidal behavior (per the Suicidal Behavior section of the C-SSRS).
7. Diagnosis of premenstrual dysphoric disorder (females).

8. History of or any current conditions that might interfere with drug absorption, distribution, metabolism, or excretion (including any surgical interventions for weight loss).
9. Any history of seizures (except related to alcohol withdrawal) or head trauma with sequelae.
10. Known human immunodeficiency virus (HIV) positive.
11. HBsAg or anti-HCV positive (tested at screening).
12. History of diagnosed, active liver disease or elevated liver enzymes/billirubin:
    a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2.5 times upper limit of normal (ULN)
    b. Total bilirubin ≥ 1.5 times ULN (except due to confirmed Gilbert's Syndrome).
13. History of kidney stones or renal insufficiency or abnormal kidney function at screening as evidenced by abnormal blood urea nitrogen (BUN) and creatinine values and an estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73 m^2.
14. Abnormal cardiac conditions including uncontrolled hypertension. (> 140 mm Hg systolic / 90 mm Hg diastolic). Subjects with QTcF > 450 msec (male) and QTcF > 470 msec (female) confirmed on repeat ECG.
15. Any history and/or current evidence of other medical (e.g., cardiac, respiratory, gastrointestinal, renal, malignancy other than basal cell carcinoma), neurological, or psychiatric conditions that, in the opinion of the investigator, could affect the subject's safety or interfere with the study assessments.

Prior/Concomitant Therapy

16. Use of any medication that affects sleep and/or wake function during the week before starting the Consensus Sleep Diary-Morning (CSD-M).
17. Subjects currently undergoing treatment of other addictions in addition to alcohol (eg. nicotine, cocaine, opioids, methamphetamine, etc. or other substances)
18. Excessive caffeine consumption ≥300 mg/day (e.g., approximately three 6-oz cups of caffeinated coffee, **or** three 12-oz caffeinated sodas, or three 8-oz caffeinated tea beverages).

Prior/Concurrent Clinical Study Experience

19. Dosing in a clinical drug study during the 30 days (or 5 half-lives of investigational drug treatment, whichever is longer) preceding the initial dose of study drug dispensed in this study.
20. Subjects previously exposed to V117957.
21. Subjects with hypersensitivity to V117957 or any of its ingredients.

Diagnostic assessments

22. Positive urine drug screen or alcohol screen at any time during the study, except for cannabis on a case-by-case basis.
23. History of drug use disorder over the past year, other than alcohol/nicotine/caffeine/cannabis.

Other Exclusions

24. Unwillingness to avoid napping during each confinement when not undergoing PSG
25. Scheduled for surgery during the study.

26. Plans to travel across more than 3 time zones in the 2 weeks before screening, or during study participation.
27. Night or rotating shift worker.
28. The investigator believes the subject to be unsuitable for reason(s) not specifically stated in the exclusion criteria (ie, subjects whose history may indicate a likelihood of relapse).

Test Treatment, Dose, and Mode of Administration:

All doses will be administered with water in the evening at bedtime, at least 1 hour after the last meal of the day, for up to 21 consecutive nights during the double-blind treatment period.

- V117957 1 mg, tablet, oral administration
  Subjects assigned to 1 mg V117957 will take 2 tablets, each containing 0.5 mg V117957
- V117957 2 mg, tablet, oral administration
  Subjects assigned to 2 mg V117957 will take 2 tablets, each containing 1 mg V117957

Reference Treatment, Dose, and Mode of Administration:

All doses will be administered with water in the evening at bedtime, at least 1 hour after the last meal of the day, for up to 23 consecutive nights (21 nights during the double-blind treatment period to subjects assigned to placebo and for 2 nights during the washout period to all subjects).

- Placebo tablet, oral administration
  Subjects assigned to placebo will take 2 placebo tablets

Concomitant Medication:

Medications for chronic conditions, such as antihypertensives, lipid lowering agents, acetaminophen, NSAIDs and vitamins, are allowed as long as the subject is on a stable regimen throughout their study participation.

Duration of Treatment and Study Duration:

Total study duration is approximately 59 days.

Screening period is up to 21 days; double-blind treatment period is 21 days; washout period is 3 days; and the follow-up (safety) period is approximately 14 days.

Study Procedures:

Screening period (up to 21 days):

The screening period is 21 days prior to randomization. Screening activities consist of demography, medical and medication history, physical and neurological exam, 12-lead electrocardiogram (ECG), and vital sign measurements (systolic/diastolic blood pressure, pulse rate, respiratory rate, and oral temperature), pulse oximetry (SpO2), drug and alcohol screen, hepatitis B and C screen, serum pregnancy test (females only), FSH test for post menopausal women, clinical laboratory assessments, inclusion/exclusion criteria evaluation (including completion of the C-SSRS), the CSD-M including assessment of insomnia [redacted] If the CSD-M shows insomnia the subject should be scheduled for PSG testing to confirm insomnia.

Double-blind treatment period:

Treatment activities consist of a urine pregnancy test (females only), C-SSRS, HADS, drug and alcohol screen, neurological exam, ECG, vital sign measurements, AEs and concomitant medications, CSD-M, [redacted] PSG tests – 2 at the beginning and 2 at the end of the period, DSST, KSS, POMS-Brief, clinical laboratory assessments, sparse PK sampling and receive study drug treatment. During the double-blind treatment period subjects will be dosed in the sleep lab and will take medication home with them for daily nighttime dosing. Subjects will return to the clinic on days 8, 15 and 20 for study procedures.

Washout period:

The washout period includes an assessment of vital sign measurements, AEs and concomitant medications. The CSD-M, DSST, KSS, POMS-Brief and C-SSRS will be completed. Study drug treatment and PSG assessments will be performed.

The end of treatment (EOT) visit consists of weight, physical and neurological exams, serum pregnancy test, C-SSRS, HADS, drug and alcohol screen, ECG, vital sign measurements, AEs and concomitant medications, CSD-M, [redacted] PSG, DSST, KSS, POMS-Brief, and clinical laboratory assessments.

Follow up:

The end of study visit will occur approximately 7 days after the last double-blind treatment dose and consists of vital signs, assessment of AEs and conmeds, CSD-M[redacted].

A follow up phone call approximately 7 days after the EOS visit will consist of an assessment of AEs and concomitant medications.

Criteria and Methods for Evaluation:

Primary Efficacy Variable:

The primary efficacy variable will be derived using 2 consecutive nights of data from polysomnography (PSG):

- Change from baseline of wakefulness after sleep onset (WASO) measured by PSG

Secondary Efficacy Variables:

The secondary efficacy variables will be derived from PSG recordings as well as CSD-M (sleep diary) data:

- SE: Sleep efficiency
- LPS: Latency to persistent sleep
- TST: Total sleep time
- NAW: Number of awakenings

The secondary efficacy variables derived from the CSD-M (sleep diary) include the following:

- sSleep: subject estimated sleep quality
- sTST: subject estimated amount of time spent asleep
- sWASO: subject estimated minutes of wakefulness during the night after initial sleep onset
- sSOL: subject estimated minutes from lights off to sleep onset
- sSE: subject estimated proportion of time spent asleep per time spent in bed derived from sTST divided by sTIB

- sNAW: subject estimated number of awakenings
- subject estimated morning sleepiness on awakening

Additional secondary efficacy variables:

- Proportion of responders derived from PSG [redacted]
- Rebound insomnia endpoints [redacted] during the washout/follow-up period

Pharmacodynamic Variables:

The pharmacodynamic variables assessing next-day residual effects:

- DSST: Digit Symbol Substitution Test
- KSS: Karolinska Sleepiness Scale
- POMS-Brief: Profile of Mood States- Brief

Safety Variables:

The safety variables assessing safety and tolerability of V117957:

- Adverse events [redacted]

[redacted]

Efficacy Analysis:

Analysis Populations

Enrolled population: The group of subjects who sign informed consent.

Randomized safety population: The group of subjects who are randomized and receive at least 1 dose of the study drug and have at least 1 safety assessment.

Full analysis population: The group of subjects who are randomized, receive study drug, and have at least 1 valid efficacy measurement.

Per protocol population: The group of subjects who are included in the full analysis population but excluding those with major protocol deviations and those who do not receive the actual treatment they were randomized to receive.

[redacted]

Efficacy Analysis

Listings, tables, and figures of efficacy variables will be based on the full analysis population.

Primary Efficacy Analyses

Polysomnography recordings will be collected and scored by a central reader. Sleep stages will be scored following American Academy of Sleep Medicine (AASM) standard criteria based on 30-second epochs. The 2 PSG nights at baseline and post baseline PSGs performed during each sleep lab visit will be averaged before comparison.

The baseline, post baseline, and change from baseline of WASO will be summarized by treatment group using descriptive statistics and presented graphically. The statistical analysis to compare change from baseline of V117957 versus placebo will be performed by using a mixed model with factors of age group, treatment as fixed effects, baseline measurement of WASO as a covariate, and subject as a random effect. 90% confidence intervals (CIs) and P-values comparing placebo and each V117957 dose will be summarized. Plots of the least squares (LS) mean change from baseline and 90% CIs, will be produced by treatment group and visit. The impact of significant amount of missing data may be explored by using different imputation methods as sensitivity analyses.

Secondary Efficacy Analyses

The baseline, post baseline, and change from baseline of all sleep variables as measured by PSG (including TST, SE, LPS, NAW), and all sleep variables as measured by CSD-M (including sleep quality, sTST, sWASO, sSOL, sSE, etc) will be summarized by treatment group with descriptive statistics and presented graphically.

PSG data will be analyzed similarly as outlined above for the primary endpoint if they are continuous variables and follow normal distribution. Categorical endpoints will be analyzed by logistic regression or Cochran-Mantel-Haenszel test if stratified by a factor and presented graphically if appropriate.

For CSD-M sleep diary data which will be processed into weekly data, the statistical analysis to compare change from baseline of V117957 versus placebo will be performed by using a mixed model with repeated measures (MMRM) with factors of age group, treatment, visit (first 2 nights, week 1, week 2, and week 3), and treatment-by-visit interaction as fixed effects, and baseline measurement as a covariate. 90% confidence intervals (CIs) and P-values comparing placebo and each V117957 dose will be summarized. Plots of the least squares (LS) mean change from baseline and 90% CIs, will be produced by treatment group and visit.

[redacted]

Pharmacodynamic Analyses

Listings, tables, and figures of next day residual effects measured by DSST, KSS, and POMS-Brief will be based on the full analysis population. Descriptive statistics will be tabulated by treatment and presented graphically. The analysis will be performed similarly as outlined above for the primary endpoint.

[redacted]

Safety Analyses

All safety data [redacted] will be listed for subjects in the enrolled and randomized safety populations.

AEs will be categorized into preferred terms and associated system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs (TEAEs) will be defined as AEs that start after or increase in intensity after the first dose of study drug. TEAEs will be summarized by presenting the incidence of AEs for each treatment group by the MedDRA preferred term, nested within System Organ Class for the safety population. Medical history will be coded to MedDRA terms. Coded medical history terms will be summarized for all subjects in the randomized safety population.

[redacted] Concomitant and prior medications will be coded using the latest version of the WHO-DD and presented in tables and listings.

Interim Analysis

After approximately half of the planned subjects have completed the end-of-study visit, an interim analysis may be performed [redacted] The results of the analysis will not be conveyed to the study team or to the clinical sites.