CTI CLINICAL TRIAL & CONSULTING

Phase 2 Randomized Double-Blind Placebo-Controlled Parallel-Arm Dose Finding Study to Compare Fixed Dose Combinations of Atomoxetine/Aroxybutynin (AD109) and Atomoxetine/Trazodone (AD504) to Atomoxetine alone or Placebo in Obstructive Sleep Apnea

Protocol Number:	*MARIPOSA!* APC-005
Protocol Version:	2.0
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STATISTICAL ANALYSIS PLAN

Version 1.0

Phase 2 Randomized Double-Blind Placebo-Controlled Parallel-Arm Dose Finding Study **to Compare Fixed Dose Combinations of Atomoxetine/Aroxybutynin (AD109) and Atomoxetine/Trazodone (ADS04) to Atomoxetine alone or Placebo in Obstructive Sleep Apnea**

STATISTICAL ANALYSIS PLAN
Version 1.0

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
	Treatment Arm Abbreviations[1]
At75/Ar5	Atomoxetine 75 mg/aroxybutynin 5 mg tablet *(Ann* 1)
At75/Ar2.5	Atomoxetine 75 mg/aroxybutynin 2.5 mg tablet*(Ann* 2)
At75	Atomoxetine 75 mg tablet *(Ann* 3)
p	Placebo tablet *(Ann 4)*
At75+P	Atomoxetine 75 mg tablet+ placebo capsule *(Ann* 5)
P+P	Placebo tablet + placebo capsule *(Ann 6)*
At75+Trl00	Atomoxetine 75 mg tablet+ trazodone 100 mg capsule *(Ann* 7)
At75+Tr50	Atomoxetine 75 mg tablet+ trazodone 50 mg capsule *(Ann* 8)
AD109	Combined atomoxetine and aroxybutynin drug (including the At75/Ar5 and At75/Ar2.5 treatment arms)
AD504	Combined atomoxetine and trazadone drug (including the At75+Trl00 and At75+Tr50 treatment arms)
	PSG Parameter Abbreviations
AHI4	Apnea-Hypopnea-Index (4% desat for hypopneas)
AHI3PA	Apnea-Hypopnea-Index (3% desat or arousal for hypopneas)
AHINREM	Apnea-Hypopnea-Index NREM
AHIREM	Apnea-Hypopnea-Index REM
ARIS	Apnea-Hypopnea-Index (4% desat for hypopneas) Supine
ARI	Arousal Index, total
ARILM	Arousal index leg movements
ARIR	Arousal Index respiratory
ARISP	Arousal Index spontaneous
HB3pa	Hypoxic Burden calculated for AH! (3% desat or arousal for hypopneas)

[1] The following conventions were used inthe treatment ann abbreviations: number= number of mg, At= Atomoxetine, Ar= Aroxybutynin, P=Placebo, Tr= Trazadone. "f' =same pill, and"+"= separate pills.

Abbreviation	Definition
HB4	Hypoxic Burden calculated for AHI (4%desat for hypopneas)
HBtotal	Hypoxic Burden calculated as area under the baseline oxygen saturation ctuVe, regardless of respiratory events
MDES	Mean desaturation
Nl	Stage NI
NIP	Stage NI%
N2	StageN2
N2P	StageN2%
N3	StageN3
N3P	StageN3%
NAW	Number of Awakenings
0D!3	Oxygen Desaturation Index >3%
0D14	Oxygen Desaturation Index >4%
R	StageR
RP	StageR%
SaO2LT90	Total time with SaO2 <90%
SE	Sleep Efficiency
SOL	Sleep Onset Latency
TS	Time Supine
TSP	Time Supine Percent
TST	Total Sleep Time
WASO	Wake After Sleep Onset

Other abbreviations

AE	adverse event
AHI	apnea-hypopnea index
ATC	anatomical, therapeutic, and chemical

Abbreviation	Definition
CI	confidence interval
CRO	contract research organization
CSR	clinical study report
DBP	diastolic blood pressure
DSST	digit symbol substitution test
ECG	electrocardiogram
ESS	Epworth sleepiness scale
eCRF	electronic case report form(s)
EoS	end of study
HB	hypoxic burden
HR	heart rate
ICF	informed consent form
LS	least square
LoglO	log base 10
MedDRA	medical dictionary for regulatory activities
mIIT	modified intent to treat
NREM	non-rapid eye movement
ODI	oxygen desaturation index
OSA	obstructive sleep apnea
PGI-S	participant global impression - severity
PK	pharmacokinetic
pp	per protocol
PROMIS	patient reported outcomes measurement information system
PSG	polysomnography
PT	preferred term

Abbreviation	Definition
PVT	psychomotor vigilance test
QQW	quality andquantity of work
REM	rapid eye movement
RTSM	randomization & trial supply management
SAE	serious adverse event
SaO2	oxygen saturation
SAP	statistical analysis plan
SAQLI	short sleep apnea quality of life index
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
V#	visit# (e.g., PSG V2 = PSG Visit 2)
VOLT	visual object learning task
WHO	World Health Organization

1. l1''TRODUCTION

Thisstatistical analysis plan (SAP) is based on the Protocol# MARIPOSA/APC-005 Version 2.0, dated 15 September 2021, titled "Phase 2 Randomized Double-Blind Placebo-Controlled Parallel-Ann Dose Finding Study to Compare Fixed Dose Combinations of Atomoxetine/Aroxybutynin (AD109) and Atomoxetine/I'razodone (AD504) to Atomoxetine alone or Placebo in Obstructive Sleep Apnea." The MARIPOSA Study (APC-005) is a randomized, double blind, placebo-controlled, parallel-arm I-month study in participants with Obstructive Sleep Apnea (OSA). Previous studies conducted by the sponsor and academic investigators indicate that the combination drugcomposed of atomoxetine with either aroxybutynin (designated ADI09)or with trazodone (designated AD504) is effective for the treatment of OSA.

The present study is designed to advance dose-finding for AD109 and AD504 over a I-month period of dosing in participants with moderate to severe OSA.

This document details the statistical methods planned to perform the final analyses of this study.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Plimary Objective

The primary objective is to evaluate the efficacy of atomoxetine combined with aroxybutynin (AD109) compared to placebo in the treatment of moderate to severe OSA.

2.1.2. Secondary Objectives

The secondary objectives are to evaluate the efficacy of

- atomoxetine combined with trazadone (AD504) and
- atomoxetine alone

compared to placebo in the treatment of moderate to severe OSA.

2.1.3. Exploratory Objectives

The exploratory objectives are:

- evaluate the relative efficacy of dose level within the treatment arms in the treatment of moderate to severe OSA whencompared to atomoxetine and placebo,
- evaluate the impact of the treatment arms on participant self-assessments (e.g., quality of life), and
- explore additional PSG parameters as supplemental measures of treatment efficacy in OSA patients.

2.2. Endpoints

2.2.1. Plimary Endpoint

The primary efficacy endpoint is as follows:

1. Change in apnea-hypopnea index based on 4% hypopnea desaturation (AHI4), combined atomoxetine/aroxybutynin dose aims (At75/Ar5 and At75/Ar2.5; AD109) vs. combined placebo aims (P and P+P; Placebo).

2.2.2. Secondary Endpoints

The secondary efficacy endpoints are as follows:

2. Change in AHI4, combined atomoxetine + trazadone dose aims (At75+Tr100 and At75+Tr50; AD504) vs. Placebo.
3. Change in AHI4, combined atomoxetine dose aims (At75 and At75+P; Atomoxetine) vs. Placebo.

2.2.3. Tertiary and Exploratory Endpoints

R1>maining tested endpoints (tertiary):

4. Change in Total Sleep Time (TST), AD109 vs. Atomoxetine
5. Change in TST, AD504 vs. Atomoxetine
6. Change in Arousal Index, total (ARI), AD109 vs. Atomoxetine
7. Change in ARI, AD504 vs. Atomoxetine

The exploratory efficacy endpoints are as follows:

- Core (modeled) polysomnography (PSG) parameters; cross arm comparisons
  - Change in AHI4- remaining comparisons
  - TST - remaining comparisons
  - ARI- remaining comparisons
  - Change in hypoxic burden based on 4% hypopnea desaturation (HB4)
  - Log base 10 ofHB4 (logl0(HB4+1))
  - Change in AHI based on 3% hypopnea desaturation plus arousals (AHI3pa)
  - Change in total time withoxygen saturation (SaO2) <90% (SaO2LT90); cross-arm compansons
- Participant self-assessments (all change from baseline); cross arm comparisons
  - Participant Global Impression - Severity (PGI-S)
  - Short Sleep Apnea Quality of Life Index (SAQLI)

- Patient Reported Outcomes Measurement Information System (including sleep-related impairment, sleep disturbance, and fatigue; PROMIS)
- Epworth Sleepiness Scale (ESS)
- Quality and Quantity of Work (QQW)

- Proportion of participants with:2:50%reduction in AHl4withsensitivityof:2:40% reduction inAHI4
- PSG parameters receiving only descriptive statistics
  - PSG sleep and arousal parameters (all change from baseline); cross arm compansons
    - Sleep quality and percentage of time in the various sleep stages
      - Sleep Efficiency (SE)
      - WakeAfterSleepOnset(WASO)
      - Sleep Onset Latency (SOL)
      - Number of Awakenings (NAW)
      - Percentage of total sleep time (TST) spent in sleep stage NI (NIP)
      - Percentage of TST spent in sleep stage N2 (N2P)
      - Percentage of TST spent in sleep stage N3 (N3P)
      - Percentage of TST spent in sleep stage R (RP; same as REM)
    - Arousal indices (respiratory, spontaneous, and leg movements; ARIR, ARISP, and ARILM respectively)
    - Apnea Index (AI)
  - PSG respiratory parameters (all change from baseline); cross arm comparisons
    - AHI4 in rapid eye movement (REM) sleep (AHIREM)
    - AHI4 in non-rapid eye movement (NREM) sleep (AHINREM)
    - AHI4 in supine position (AHIS)
    - HB4 in REM sleep (HB4REM)
    - HB4 in NREM sleep (HB4NREM)
    - HB calculated as area under the baseline oxygen saturation curve, regardless of respiratory events (HBtotal)
    - Change in oxygen desaturation index based on 4% desaturation definition OD14)
    - ODI based on 3% desaturation definition (OD13)

2.2.4. Safety Endpoints

The safety endpoints are as follows:

- Physical exam, vital signs, clinical laboratory assessment
- Spontaneous adverse events (AE), including the post-dosing period
- Digit Symbol Substitution Test (DSST), Psychomotor Vigilance Test (PVT), Visual Object Leaming Task (VOLT)
- PSG parameters: heart rate (HR).
- 12-lead Electrocardiogram (ECG) parameters (including QT)

3. I1''VESTIGATIONAL PLAN

3.1. Study Design

The MARIPOSA Study(APC-00S) is a randomized double-blind, placeb◆ontrolled parallel arm study in participants with obstructive sleep apnea (OSA) designed to advance dose-fmding for AD109 and ADS04 over a I-month period of dosing (see protocol and Appendix A for additional details and schedule of events). Participants will undergo initial pre-screening to determine potential studyeligibility (seeprotocol forspecific eligibility requirements).Participants who meet all enrollment criteria will be randomized to one of 8 parallel treatment arms:

1. Atomoxetine 7S mg/aroxybutynin S mg tablet (At7S/ArS; n ═ 40)
   a. Week 1: atomoxetine 37.S mg/aroxybutynin2.Smg tablet
   b. Weeks 2-4: atomoxetine 75/aroxybutynin Smg tablet
2. Atomoxetine 7S mg/aroxybutynin 2.S mg tablet (At7S/Ar2.S; n ═ 40)
   a. Week 1: atomoxetine 37.S/aroxybutynin 2.S mg tablet
   b. Weeks 2-4: atomoxetine 75 mg/aroxybutynin2.S mg tablet
3. Atomoxetine 7S mg tablet (At7S; n ═ 30)
   a. Week 1: atomoxetine 37.S mg/placebo tablet
   b. Weeks 2-4: atomoxetine 7S mg/placebo tablet
4. Placebo tablet (P; n ═ 30).
   a. Week 1: placebo tablet
   b. Weeks 2-4: placebo tablet
S. Atomoxetine 7S mg tablet+ Placebo capsule (At7S+P; n ═ 30)
   a. Week 1: atomoxetine 37.S mg tablet+ placebo capsule
   b. Weeks 2-4: atomoxetine 7S mg tablet+ placebo capsule
6. Placebo tablet+ placebo capsule (P+P; n ═ 30)
   a. Week 1: placebo tablet+ placebo capsule
   b. Weeks 2-4: placebo tablet+ placebo capsule
7. Atomoxetine 7S mg tablet+ trazodone 100 mg capsule (At7S+Tr100; n ═40)
   a. Week 1: atomoxetine 37.S mg tablet+ trazodone SO mg capsule
   b. Weeks 2-4: atomoxetine 7S mg tablet+ trazodone 100 mg capsule

8. Atomoxetine 7S mg tablet+ trazodone SO mg capsule (At7S+TrS0; n = 40)
    a. Week 1: atomoxetine 37.S mg tablet+ trazodone SO mg capsule
    b. Weeks 2-4: atomoxetine 7Smg tablet+ trazodone SO mg capsule

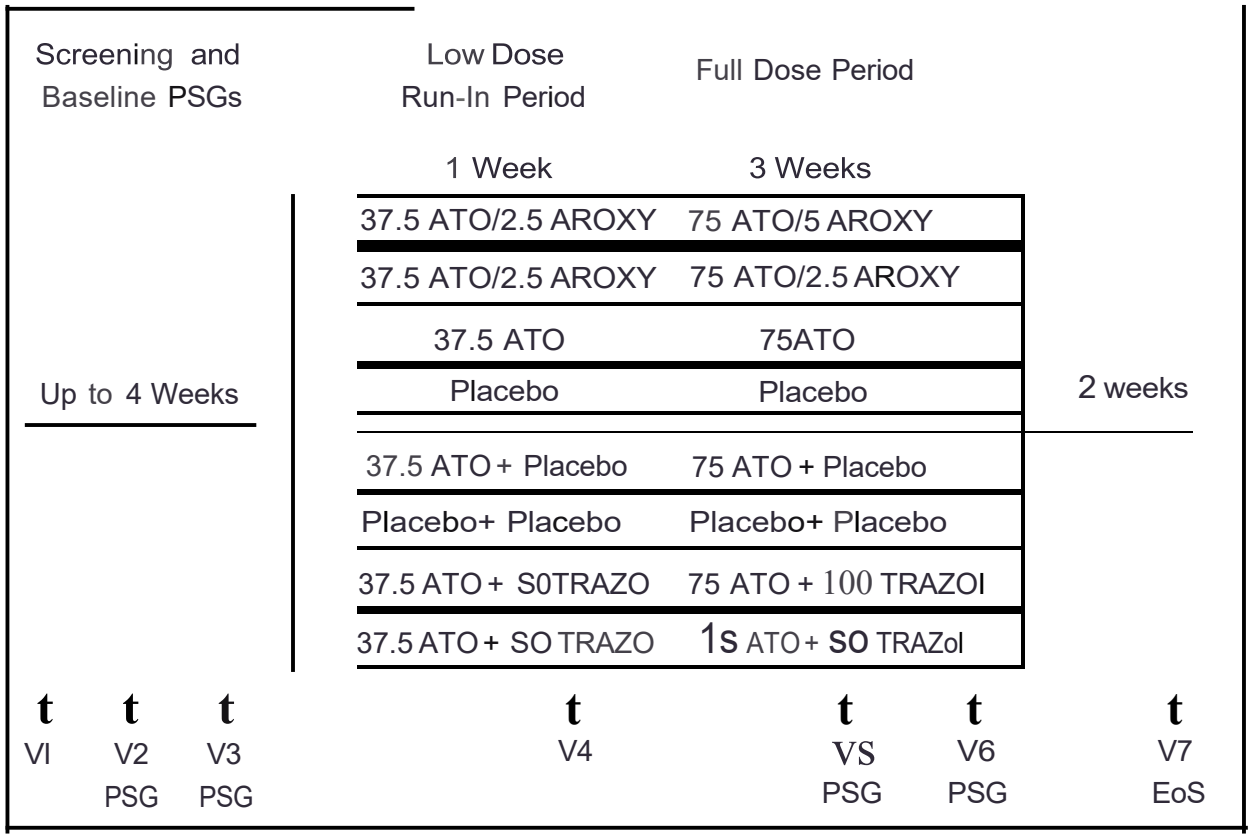
Adverse event and concomitant medication monitoring will occur at each study visit, and study sites contact participants by phone mid-week of the run-in period and mid-week of the first week of full-dose period, for adverse event andconcomitant medication monitoring, and review of study procedures and visit schedule.

Overall studyduration will be upto 10 weeks.

A total of280 participants will be enrolled in the ratio indicated above (4 / 4 / 3 / 3 / 3 / 3 / 4 / 4)

Dose reduction is not permitted; dosing is discontinued if the studydrug to which the participant is randomized is not tolerated. Participants who withdraw from the study will not be replaced.

Figure1: Overview of Study Design



AROXY = aroxybutynin; ATO = atomoxetine; EoS = End of Study; PSG = polysomnography; TRAZO = trazodone; V = Visit

3.2. Treatment

Study drug is taken immediately prior to lights out and consists of either 1 tablet (arms 1-4) or 1 tablet plus 1 capsule (arms S-8). The formulations found in the table below are used in this study (combined as described in Section 3.1):

Table 2: Study Drugs Administered

Study Treatment Name:	Atomoxetine hydrochloride/R.-oxybutynin chloride	Atomoxetine hvdrochloride	Trazodone hvdrochloride	Matching Placebo
Dosage Formulation:	Tablet	Tablet	Capsule	Tablet or capsule
Dosage Level:	37.Smg / 2.Smg 75mg/2.5mg 75Illll *I* 5Illll	37.Smg 75mg	50mg 100mg	***NIA***
Route of Administration:	Oral			
Dosing Instructions:	**1** tablet administl!l'ed with up to 240 mL water, OR 1 tablet and 1 capsule administered together with upto 240mL water			
Storage/ Packaging/ Labeling:	Store at room temperature in the labeled and provided IIDPE bottles.			

3.2.1. Randomization Scheme and Treatment Arm Assignment

The randomization scheme will allocate participants to one of the eight treatment arms: Arm 1: At7S/ArS; Arm 2: At7S/Ar2.S; Arm 3: At7S; Arm 4 P; Arm S: At7S+P; Arm 6 P+P; Arm 7: At7S+Trl00; and Arm 8: At7S+TrS0.

If fewer than eight treatment arms are available for randomization at a site, forced randomization will be applied and the participant will be randomized amongst the available arms.

Participants who withdraw from the study will not be replaced.

3.2.2. Blinding

The participant, investigator, site personnel (including those required for study drug administration), study personnel, Sponsor, Medical Monitor, CRO's Drug Safety and Pharmacovigilance staff, as well as the CRO staff dealing with blinded site study staff will be blinded to theidentity of thestudytreatment. The centralized technologists/technicians (e.g., PSG, lab, questionnaire) will be blinded to treatment assignment whenever reasonable (e.g., any PK related labs may be partially or fully unblinding due to the nature of the results).

The CTI RTSM Administrator and the unblinded statistician who reviews the production randomization list will be unblinded.

The tablets will be of identical outward appearance as will the capsules. In this manner, blinding occurs in two treatment clusters:Tablet Cluster, containing arms 1-4(Af7S/Ar5, At7S/Ar2.S, At7S, P) and Tablet+ Capsule Cluster, containing arms S-8 (Af7S+Trl00, At7S+TrSO, At7S+P, P+P). Each cluster contains a placebo (P vs P+P) and a pure Atomoxetine (At7S vs At7S+P) arm. It will be impossible to distinguish treatment intra-cluster, but the treatment's cluster will be distinguishable.

3.2.3. Dosing Schedule

Participants are to take studydrug daily, prior to lights out.

3.2.4. Study Tl'eatment Compliance

1) The Investigator or designee must maintain a log to confum appropriate temperature conditions have been maintained during transit for all study drugs received and any discrepancies are reported and resolved before use of the studydrug.

2) Only participants enrolled in the study may receive study drugs and only authorized site staff may supply or administer study drugs. All study drugs must be stored in a secure, environmentallycontrolled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

3) The Investigator, institution, or the head of the medical institution (where applicable) is responsible for studydrug accountability, reconciliation, andrecord maintenance (i.e., receipt, reconciliation, and final disposition records).

4) After receiving Sponsor approval in writing, sites are responsible for returning all unused or partially used study drug to the Sponsor or designated third party or for preparing the study drug for destruction via incineration.

4. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

In general, continuous variables will be summarized by presenting the sample size (N), number of participants with available data (n), mean, standard deviation (SD), median, roioironm, and maximum. In descriptive ◆nmmariP.s of change from baseline, onlyparticipants with both baseline and post baseline data will be included. Categorical variables will be summarized by presenting the number and percentage of participants within each category. Calculation of percentages will exclude missing data as a category. Where appropriate, descriptive statistics maybe presented with 95%confidence intervals (Cls).

All tabulations will be based on pooled data across centers.

Unless otherwise specified, listings will be ordered by treatment arm, participant identification, and relevant date (e.g., visit date, test date, onset date). *Unscheduled measures will appear in listings, but not be used in analysis* (except if baseline).

The data analyses will be performed using SAS for Windows, version 9.4 or higher (SAS, Cary, NC), except where other software may be deemed more appropriate.

Any changes to the analyses that are not included in this SAP will be documented in the clinical study report (CSR).

4.1. Data Quality A5surance

Once all the source verification is complete, all queries are resolved, and the database has been updated appropriately, thedatabase will be locked and made available to CTI Biostatistics forfinal analysis.

Data may be made available to CTI Biostatistics for programming purposes priorto database lock at a time when source verification andquery resolution is ongoing.

All SAS programs used to create analysis data sets, tables, and listings will be independently programmed by two individuals. The independent SAS outputs produced will be compared, and the SAS programs will be updated until the outputs match.

4.2. Analysis Sets

4.2.l. Em·olled Set

The Enrolled Set is defined as all participants who signed the informed consent form (ICF; including screening failures).

4.2.2. Modified Intent-To-Treat Analysis (mITT) Set

The mITT set comprises all participants who are randomized, take at least 1 dose of any of the studydrugs, and have at least 1 measurement on the primary endpoint.

Participants will be analyzed for efficacy according to the treatment group into which they are randomized.

4.2.3. Safety Set

The Safety Set consists of all participants who are randomized and receive at least 1 dose of any of the study drugs. Participants will be analyzed for safety based on the drug received.

4.2.4. Per Protocol (PP) Set

The PP Population consists of all participants (in the mITI set) without any major protocol violations that could influence efficacy assessment.

4.3. Assessment \Vindows

Data will be summarized by the eCRF (Study Visit) in which it was collected. No windows will be used for assessment.

4.4. Handling of Dropouts or Missing Data

Missing data will remain missing. No imputation of missing data will be performed.

4.4.1. PSG Parameter Exclusions

The criteria for use andexclusion of PSG data from analysis is described here.

RE!VI exclusion: If Stage R <10 minutes, then any AHI and HB parameters during REM will be excluded.

Time supine (TS) exclusion: IfTS < 10 minutes, then any AHI and ODI parameters in supine position will be excluded.

Case 1: There is greater than 4 hours of good quality recorded data.

- IfTST <120 mins, then only TST, TIB, and sleep stages (NI, N2, N3, R, NIP, N2P, N3P, RP) will be used in analysis.
- If TST ◆120 mins, then all planned parameters will be included in analysis except parameters excluded due to the REM and TS exclusions.

Case 2: There is lessthan or equal to 4 hours of good quality recorded data.

- IfTST <120 mins, then none of the parameters will be included in the analysis.
- IfTST ◆120 mins, then all planned parameters will be included in analysis except TST, sleep stages, and any parameters excluded due to the REM and TS exclusions.

4.5. Multiple Comparisons

Primary and secondary hypotheses will be tested sequentially in the order they appear in Section 2.2.1 and Section 2.2.2. **All** hypothesis tests will test that the two-sided p-value is less than 0.05. All hypothesis tests for exploratory endpoints will also be reported using the nominal 0.05 two-sided alpha level.

4.6. Data Derivations and Transformations

Study Day will be calculated as:

- Date of assessment- date of first dose of studydrug+ 1, for assessments done on or after date of first dose study drug
- Date of assessment- date of first dose of studydrug, for assessments done on or after date of first dose of studydrug

For PSG parameters, the baseline will be the mean of the non-excluded, non-missing values (see Section 4.4.1) recorded for the PSG Visit 2 and PSG Visit 3. Explicitly,

$$\text{Baseline PSG value} = \begin{cases} \dfrac{\text{PSGVal2} + \text{PSGVal2}}{2} & \text{if both are valid} \\ \text{PSGVal3} & \text{if PSGVal2 is not valid} \\ \text{PSGVal2} & \text{if PSGVal3 is not valid} \\ \text{Null} & \text{if neither PSGVal2 nor PSGVa13 is valid} \end{cases}$$

where PSGValj is the parameter measurement recorded at the PSG Visitj,j=2, 3.

For other efficacy and safety endpoints, the baseline value will be calculated as the last non-missing value prior to first drug dose taken (except where unscheduled assessments are performed the baseline value should be the value recorded during the screening or baseline PSG visits). If multiple measurements are taken for a single visit, thenonly thelast non-missing measure will be used. This includes

The exception will be systolic and diastolic blood pressure (SBP and DBP respectively), where the mean of the non-missing measures 1, 2, and 3 will be used for a visit (including for baseline).

Where applicable, change from baseline values will be calculated as:

$$\text{Change from Baseline} = \text{assesment value} - \text{baseline value},$$

while the percent change from baseline values will be calculated as:

$$\text{percent change from baseline} = \frac{\text{change from baseline}}{\text{baseline value}} \times 100\%.$$

For the endpoints that look for the proportion of participants with 2,cx% reduction, participants will be assigned a visit level indicator:

$$\text{Indicator of } \geq xx\% \text{ reduction} = \begin{cases} 1 & \text{if percent change from baseline} \leq xx\% \\ 0 & \text{otherwise} \end{cases}$$

where xx% represents a percent (e.g., 50%).

4.7. Treatment Arm Classes and Blinding Clusters

There are twonon-nested categorizationsofthetreatment arms: combined arm andblinding cluster (see table below). These are particularly relevant for the models usedin the efficacy analysis.

Table 3: Treatment Arm Classifications

Treatment Arm	Analytic **Treatment Arm**	**Dose level**	Combined Arm	**Blinding** Cluster
At75/Ar5	At75/Ar5	High	AD109	Tablet
At75/Ar2.5	At75/Ar2.5	Low		

Treatment Arm	Analytic Treatment Arm	Dose level	Combined Arm	Blinding Cluster
At7S At7S+P	Atomoxetine	Low*	Atomoxetine	Tablet Tablet + Capsule
p P+P	Placebo	Low*	Placebo	Tablet Tablet + Capsule
At7S+Tr100 At7S+TrS0	At7S+Tr100 At7S+TrS0	High Low	ADS04	Tablet + Capsule

• Lowas a reference only.

Generally speaking, combined arms will be used in efficacy analyses and treatment arms will be used for the safety analyses andlistings.

4.8. Linear Modeling

Linear Modeling will be usedto compare combined anns/treatmentarms effects onselect efficacy endpoints using PROC GLIMMIX. When modeling is employed, point estimates (e.g., mean, difference of means) and inferential statistics(e.g., confidence interval, p-values) will beestimated using least square (LS) methods. The atomoxetine andplacebo combined arms willnot beanalyzed separately, unless otherwise stated. For model-based LS means of the combined arms for AD109 or ADS04, the weighting will be 0.S and 0.S for both the high and low dose. Unless otherwise stated, the link will be identity and the distribution gaussian.

4.8.1. Repeated I\lleasure Modeling

When theendpoint has repeated measures (e.g., change from baseline for PSG parameters), unless stated otherwise, the model will include:

baseline value, combined arm, visit, combined arm * dose level, combined arm * visit, combined arm * dose level • visit.

Within participant variability will be modeled using an unstructured (e.g., TYPE= UN, CHOL) covariance pattern. The unstructured covariance parametrized through its Cholesky root is to be used for models in which convergence fails for the completelyunstructured covariance.

4.8.2. Non-repeated Measure Modeling

For non-repeated endpoints (e.g., change from baseline for questionnaires), unless stated otherwise, the model will include the combined arm, combined arm • dose level. No participant level random effects will be employed.

4.9. Standard Desc1iptive Statistic Summa1ies and Listings

The standard descriptive statistics summaries will be for the combined arms (AD109, ADS04, atomoxetine, placebo) with a breakdown of the AD109 and ADS04 into the individual treatment arms (At75/ArS, At75/Ar2.S, At7S+Trl00, At7S+TrS0) as well as two overalls (one for AD109 and one for ADS04). Each tabular summary will be presented in two separate collections:

1. an AD109 variant containing AD109, At75/Ar5, At75/Ar2.S, atomoxetine, placebo, and overall (containing participants in AD109, atomoxetine, and placebo),
2. an ADS04 variant containing ADS04, At7S+Trl00, At7S+TrS0, atomoxetine, placebo, and overall (containing participants in ADS04, atomoxetine, and placebo).

Note that the atomoxetine and placebo combined arm results will be the same in the two collections.

The listings will *not* be separated and will include both AD109 and ADS04 treatment arms in a single listing.

5. STUDY PARTICIPANTS

Unless otherwise stated, these snmmariPS will use the Safety Set.

5.1. Disposition of Pa1iicipants

A table of frequency counts and percentages of all participants who are enrolled, randomized, and included in each analysis set will be provided for the Enrollment Set (by treatment arm, when applicable). Participant disposition including study completion status and reasons for early termination will be tabulated by planned treatment arm (when applicable) and overall. **A** by-participant listing will be provided. Additionally, a randomization listing (including planned treatment arm) will be provided for all Randomized Participants.

5.2. Protocol Deviations

Two separate by-participant listings for major and minor protocol deviations will be provided.

5.3. Demographic

Descriptive statistics will be used to summarizethe demographic characteristics(age, gender, race, ethnicity, heigllt, weigllt, and BMI) by treatment arm and overall using the Safety Set. A by-participant listing will also be provided.

5.4. Baseline Characteristics

The following baseline values will be summarized overall using the Safety Set.

PSG Parameters

- AHI4

- AHI3PA
- ARI
- HB4 (take log andidentity)
- SaO2LT90
- TST
- HR(PSG)

Non-PSG parameters:

- CSSA Total Score without craving questions
- Blood pressure (SBP and DBP)

A by participant listing of baseline values will be provided for the characteristics appearing in the baseline table.

S.S. **Medical History**

All medical conditions and surgical procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, at least version 24.1). The number and percent of participants witheachmedical condition and surgical procedure willbe presented by treatment armandoverall, for MedDRA system organ class (SOC) and preferred term (PT). Each participant will be counted only once per SOC and PT. A by-participant listing will also be provided.

5.6. Prior and Concomitant Medications and Devices

Prior medications and devices are defined as those initiated and stopped prior to the date of first dose of studydrug. Any medication or deviceused at least once on or after thefirst studytreatment date during the study will be defined as a concomitant.

Prior and concomitant medications will be coded using the Global World Health Organization (WHO) Drug Dictionary (WHODrug-Global-B3, at least version 202109). The number and percent of participants using each medication will be tabulated by treatment arm: overall, by Anatomical Therapeutic Chemical (ATC) level 3, and by preferred name. Each prior or concomitant medication reported more than one time will onlybe counted once per participant for each ATC level and preferred name.

Prior and concomitant devices will be coded using MedDRA. The number and percent of participants using each device will be tabulated by treatment arm: overall, by SOC (e.g., surgical and medical procedures) and by PT (e.g., positive airway pressure therapy). Each prior or concomitant device reported more than one time will only be counted once per participant for each SOC and PT.

A by-participant listing will also be provided separately for medications anddevices.

6. EFF1CACY ANALYSIS

Unless otherwise stated, the mITT Set will be used for efficacy analyses. Thestandard descriptive statistics summaries (see Section 4.9) will be used for the AD109 collection (At75/Ar5, At75/Ar2.5, AD109, atomoxetine, placebo, AD109 overall) and the AD504 collection (At75+Tr100, At75+Tr50, AD504, atomoxetine, placebo, AD504 overall) separately.

6.1. Primary and Secondary Efficacy Analysis of AHI4

Comparisons will be performed as described in Section 4.5. A repeated measures model (see Section 4.8) will be used to model change in AHI4 from baseline for both the AD109 and AD504 collections.

AD109 l\llodel

For the AD109 models - one for combined arms and one for analytic treatment arms - only participants from the AD109, atomoxetine, and placebo combined arms will be included in the model. Model based LS mean estimates will be provided for the following:

- LS mean change from baseline by combined arm (AD109, atomoxetine, and placebo - *sensitivity)* and the treatment arms within the AD109 combined (At75/Ar5, At75/Ar2.5)
- difference in LS mean change from baseline between:
    1. AD109 and placebo *(primary,* 1st comparison),
    2. At75/Ar5 and placebo,
    3. At75/Ar2.5 and placebo,
    4. Atomoxetine and placebo *(secondary,* 3rd comparison),
    5. AD109 andatomoxetine,
    6. At75/Ar5 and atomoxetine,
    7. At75/Ar2.5 and atomoxetine, and
    8. At75/Ar5 and At75/Ar2.5.

A 95% confidence interval and two side p-value for the null hypothesis (of0 for the mean change from baseline and of equality for the difference in mean change) will be provided for both the LS mean and difference in mean change from baseline. The description in parentheses is the status of the comparison if it is not an exploratory comparison.

ADS04 l\llodel

For the AD504 models, only patients from the AD504, atomoxetine, and placebo combined arms will be included in the models. Thesame LS mean results will be provided with AD504 replacing AD109, At75+Tr100 replacing At75/Ar5, and At75+Tr50 replacing At75/Ar2.5. Two of the LS mean change from baseline comparisons will have a different status:

1. AD504 and placebo *(secondary,* 2nd comparison) and
2. Atomoxetine and placebo *(sensitivity).*

Desc1iptive Statistics

Standard descriptive statistics will be presented for the reported AHI4 value and change from baseline in AHI4 for PSG Visit 5 and PSG Visit 6.

6.1.1. Sensitivity Analysis.

A sensitivity analysis will be performed using the PP and the Safety Set with the same models and results reported.

Relationship between study arm and discontinuation

Kaplan Meier (KM) survival analysis will be performed, where survival is defined as *not* having an \lllplanned discontinuationof investigational product (IP). The survival probabilities with 95% confidence intervals will be provided for study days 7, 14, 21, 28, and 35 according to standard descriptive analysis arms for the Safety Set. Additionally, KM survival curves will be presented for both AD109 family and the control arms (Atomoxetine and placebo) and the AD504 family and the control arms.

6.2. Secondary Efficacy Analysis

The Secondary Efficacy Analysis arecontained in model results for the Primary Efficacy Analysis (Section 0) and are denoted by *secondary.*

6.3. Tertiary and Exploratory Efficacy Analyses

6.3.1. PSG Parnmeters

The analysis of PSG parameters will come in two classes: those with both model-based on change from baseline and descriptive statistics as described in Section 0 and those only receiving the descriptive statistics as described in Section 0.

The endpoints to receive both model-based and descriptive analyses are:

- AHI4 (select comparisons contained in Section 0 and denoted by *exploratory),*
- TST (AD109 and AD504 vs. Atomoxetine are the 4th and 5th comparisons)
- ARI (AD109 and AD504 vs. Atomoxetine are the [illegible] and Jlh comparisons)
- Log10(HB4+1), HB4,
- AHI3pa,
- SaO2LT90.

Additionally, the AHI4 model will be repeated using TSP as a covariate. The p-value will be reported for TSP.

The endpoints which will only have descriptive statistics analyses are:

- sleep quality and percentage ofTST insleep stages (SE; WASO; SOL; NAW; NIP, N2P, N3P, RP),
- arousal indices (ARIR; ARISP; ARILM), AI, and
- additional respiratory PSG parameters (AHINREM; AHIREM; ARIS; HB3pa; HBtotal; OD13; OD14).

Additionally, as it is used as a covariate in a model, the descriptive statistics will be provided for TSP.

6.3.2. Participant Self Assessments

Participant self-assessments are not scheduled for multiple post-baseline measures. Non-repeated measures models (seeSection 4.8) will be used to model change from baseline forthescores (PGI-S; Short SAQLI - total score, PROMIS - t-scores and raw total scores for sleep-related impairment, sleep disturbance, and fatigue; ESS - total score; QQW - total score) with the same model structure and reported outputs as described in Section O for the repeat measure models.

Standard descriptive statistics for the value and change from baseline will be presented for PSG Visit 6 for the same scores.

For the scores made up of components (Short SAQLI; PROMIS; ESS; QQW), the components will be treated as equidistant intervals. The standard descriptive statistics for value and change from baseline will be reported for PSG Visit 6.

Additionally, the same models will be run for the scores (PGI-S; Short SAQLI - total score, PROMIS - t-scores forsleepimpairment, sleep-related disturbance, and fatigue; ESS-total score; **QQW** - total score) on each of the following three daytime sleepiness classifications defined via baseline ESS score:

- below average daytime sleepiness (baseline ESS score::S6),
- above average daytime sleepiness (6< baseline ESS score ::S10), and
- excessive daytime sleepiness (10 < baseline ESS score).

6.3.3. Proportion ofpa1iicipants with ≥50% ≥40%) reduction in AHI4

Multiple repeated measures models (see Section 4.8.1) will be used to model the probability of a ≥50% reduction in AHI4 from baseline. A logit link with binomial distribution will be employed. For the AD109 model, only participants from the AD109, atomoxetine, and placebo combined arms will be included in the model. The model-based LS means estimates will be provided for the odds ratios for a≥50% reduction for

1. AD109 vs placebo,
2. At75/Ar5 vs placebo,
3. At75/Ar2.5 vs placebo,
4. Atomoxetine vs placebo,
5. AD109 vs atomoxetine,
6. At75/Ar5 vs atomoxetine,
7. At75/Ar2.5 vs atomoxetine, and
8. At75/Ar5 vs At75/Ar2.5.

The 95% confidence inteivals and respective two sided p-values (for null hypothesis) will be provided for the odds ratios. For the AD504 model, only patients from the AD504, atomoxetine, and placebo combined arms will be included in thein the models. Thesame LS means results will be provided with AD504 replacing AD109, At75+Tr100 replacing At75/Ar5, and At75+Tr50 replacing At75/Ar2.5

The proportion, with 95% CI, of participants with≥50% reduction in AHI4 will be presented by combined arm in the same table as the models.

Additionally, the same model and results will be repeated for the outcome of≥40% reduction in AHI4.

6.3.4. Efficacy Listings

Listings will be provided for the PSG parameters clustered thematically. Listings will also be providedseparately forPGI-S, PROMIS - sleep-related impairment, sleepdisturbance, and fatigue (including totals and components), Short SAQLI (total and components), ESS (total and components), and QQW (total and components). The listings will contain all participants in the safety set with an indicator of whether the participant is in the mITT.

7. SAFETY ANALYSIS

Unless otherwise stated, the Safety Set will be used forefficacy analyses. The standard descriptive statistics summaries (see Section 4.9) will be used for the AD109 collection (At75/Ar5, At75/Ar2.5, AD109, atomoxetine, placebo, AD109 overall) and the AD504 collection (At75+Tr100, At75+Tr50, AD504, atomoxetine, placebo, AD504 overall) separately.

7.1. Extent of Exposure

For both the phase in low dose and high dose (both pills when appropriate), the number and percentage of participants receiving study treatment as well as number of days dosed, number of treatments taken, and the difference between the two will be summarized. Additionally, the

number and percent of participants who received treatment for PSG Visit *5* and PSG Visit 6 will be summarized.

By-patient listings of exposure andaccountabilitywill be provided.

7.2. **Adverse Events**

An AEis anyuntoward medicaloccurrence in a participant or clinical studyparticipant, temporally associated with the use of a study treatment, whether or not considered related to the medicinal product.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

7.2.1. Treatment-emergent Adverse Events

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to exposure of study drug or an event already present that worsens in either severity or frequency following exposure.1bis will include any AE from the day of the first dose of studydrugto participant end of study.

7.2.2. Adverse Event Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the studyand assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minima) rliscomfort and not interfering witheveryday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

An event is defined as 'serious' when it meets at least oneof the predefined outcomes as described in thedefinition of an SAE, NOT when it is rated as severe.

7.2.3. Adverse Event Relationship to Study Medication

The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered andinvestigated.
- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minima) information to include in the initial report to the CRO. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the CRO.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of thecriteria used when determining regulatory reporting requirements.

7.2.4. Se1ious Advel'se Events

An SAE is defined as any untoward medical occurrence that, at anydose:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalizationor prolongation of existing hospitalization;
- Results in persistent disability/incapacity;
- Is a congenital anomaly/birth defect;
- Other situations.

7.2.S. Advel'se Events of Special Intel'est

AEs of special interest include the following:

- Cardiac effects: atomoxetine and trazodone are associated with adverse cardiac events, including anhythmia and QT interval prolongation, and similar events have been reported in post-marketing experience for oxybutynin, which contains aroxybutynin.
- Urine outflow: atomoxetine and aroxybutynin are associated with urinary retention.
- Suicidal ideation: Both atomoxetine and trazodone carry boxed warnings for suicidal thoughts and behaviors, noting that in adults, the target population for the proposed OSA study, an increased risk was not identified.
- Daytinie sleepiness: each of the three drugs can be associated with daytime somnolence.

7.2.6. AdveJ'se Event Summa1ies

Adverse event data will be displayed in listings by participant. The number and percentage of participants with AEs will be tabulated by SOC and PT. A participant withmultiple AEs within a SOC or PT will be counted once toward the total for the total for the SOC or PT.

All AEs (serious and non-serious) occurring after completion of theinformed consent process and before theend of study, regardless of relationship to studydrug, will be included and presented by MedDRA SOC and PT.

For TEAEs, the following will be standard summaries for the Safety Set.

1. An overall summary ofTEAEs, which includes:
   a. the number and percentage of participants experiencing any TEAE
   b. the number and percentage of participants experiencing any TEAE by strongest relationship to study medication
   c. the number and percentage of participants experiencing any TEAE by greatest intensity
   d. the number and percentage of participants experiencing any TESAE
   e. the number and percentage of participants experiencing any TEAE of special interest

11. the number and percentage of participants experiencing any TEAE by SOC, PT

rn. the number and percentage of participants experiencing an TEAE of special interest by SOC,PT

1v. the number andpercentage of participants experiencing anyTEAE by SOC, PTand the greatest intensity

v. the number andpercentage of participants experiencing anyTEAE by SOC, PTand the strongest relationship to study medication

vi. the number and percentage of participants experiencing any TEAE leading to study discontinuationby SOC and PT.

In the overall summary of TEAEs table, besides tabulating the number and percentage of participants, the total number ofTEAE episodes will also be provided.

For displays by SOC and PT,

- anyparticipant with multiple events in one SOC will be counted once for that SOC, and
- anyparticipant with multiple events in one PT will be counted once for that PT[2].

[2] As a single participant may be represented in multiple PTs withinan SOC, the PT countswithin an SOCmay be higher than the SOC count itself

Occurrences of all AEs (including pre-TEAE) will be listed for each participant. The listing will contain the following information: treatment arm, AE identifier as provided, verbatim teim, SOC, PT, intensity, relationship to study medication, date and day of onset, date and day of resolution, treatment given to treat the adverse event, action taken, the outcome, whether the event was an SAE, whether the event was a special interest AE, whether it led to withdrawal. Listings will be sorted by treatment arm, participant identification,AE identifier, SOC, and PT.

If applicable (i.e., if there are any SAE's), a by participant SAE listing will be provided with treatment arm, AE identifier, verbatim teim, and free text description(s).

A graphical representation for each distinct PT(within anSOC) forTEAEs which appears in more than 10 participants will be given (one figure per type of SOC/PT meeting the conditions). The horizontal axis will be the study days and the vertical axis will be individual participants. Participants will be ordered by treatment arm followed by ascending onset study day and descending longest duration. For each participant and TEAE, a bar will extend from onset study dayto studyday resolved (multiple bars if the TEAE occurs in multiple separate episodes).

7.3. Clinical Laboratory Values

Scheduled quantitative safety clinical laboratory values (from dipstick urinalysis, hematology3, and serum chemistry) will be summarized for PSG Visit 6 by presenting descriptive statistics of actual values and changes from baseline.

A by-participant listing of standard safety (routine urinalysis - dipstick and microscopic; hematology; serum chemistry) and screening and other clinical laboratory values (HblAC; FSH; EGRF; urine drug screening - first and confirmation) will also be provided. Unscheduled visits will not be used in the analyses but will be included in the listing.

7.4. Vital Signs

Vital signdata will besummarized bypresenting descriptive statistics of actualvalues and changes from baseline by treatment arm for visits: Clinic Visit 4, PSG Visit 5, PSG Visit 6, End of Study (EoS) Visit 7 or EoS Unscheduled. Vital sign parameters include respiratory rate, temperature, systolic blood pressure, diastolic blood pressure, heart rate, and weight.

A by-participantlisting will be provided for vital signs and blood pressure measures.

7.5. Electrocardiogram

ECG values will be presenting descriptive statistics of actual values and changes from baseline by treatment arm for PSG Visit 6. ECG values include HR, PR, QRS, QT, QTcF.

A by-participantlisting of ECG values will also be provided.

[3] For blood spectrum, onlytotals will be used in the computations.

7.6. CSSA

End of study individual components (treated as equidistant inteivals) and total score, excluding craving questions ("Study Drug Craving" and "Craving Frequency") values, will be summarized by presenting descriptive statistics of actual values and changes from baseline for EoSVisit 7. The cravings questions and total score with craving questions will be summarized for the EoS Visit 7 or EoS Unscheduled.

A by-participant listing will also be provided.

7.7. Psychomotor Skill Tests

Motor skill tests will be summarized by presenting descriptive statistics of actual values and changes from baseline by visit (PSG Visit 5 and PSG Visit 6) and treatment arm. Motor skill tests include DSST (correct responses only), PVT (lapses, mean RT- including reciprocal, fastest, and reciprocal slowest) and VOLT(% correct, sensitivity, specificity, duration).

A by-participant listing will be provided for each of the tests.

7.8. PSG Parameters

PSG safety data will be snmmari:i:ed by presenting descriptive statistics of actual values and changes from baseline by treatment arm for PSG Visit 5 and PSG Visit 6. The PSG safety parameter will be HR.

Change from baseline for HR (PSG) will be modeled as in Section O using the Safety Set with the same reported results.

The PSG listing was previously described and will include the safety parameters.

8. INTERilVI ANALYSIS

No formal interim analysis is planned.

9. SAI\IIPLE SIZE AND PO"'ER CALCULATIONS

Sample size was based on efficacy finding; in previous Apnimed Studies. The present study will have >90% power to detect a treatment difference on the primary endpoint at a two-sided 0.05 significance level if the true difference between the active arm and placebo arm on Alil4 is 11 units and the within-subject standard deviation is 11.

10. APPENDICES

IO.I. Appendix A: Schedule of Activities

Pt'Ortdtu&#65533;s	Srretning[1] an&#65533; B:astllne PSG·			Trratmcnt P('riod						.EOS
				OHS Run-in do,;f		OHS FuU-dost				
	VI	PSG \"1	PSG V3	At-bome dosi.n2	Cllnlr V4	Af-bOOlt dosin2	PSG V5	Ar-bome do.sin2	PSG \"6	\'7
Trial Doy/Dm·artou	U1) to 4 weeks			Dav 1-7±2	DAY7 ± 2	DAV 8-21 ± 2	Dav 21 ± 2	DAy 22-28 ± 2	Dsw 28±2	Dny 42± 2
lufomtcd consent	X									
Enrolhuem c1i1etia	X	X	X							
Clillic.al lab cesc	X								X'	
Pre.g1t.lncy test,	X									
PSG		X	X				X		X	
Dispense study dmg [6]			X		X					
Adminii.ltalion of s.mdy <1rt1g[1]									X	
12-leaclECG	X								X'	
Vital sig1ls and weighii	X				X		X		X	X
AE/SAE wouitoring[9]										
Prior/concomitant m«t.ica1ions										
ESS. Shon SAQLI. POl·S. Qt1'llltity and Quali,yof Work. PROMIS sleep iwpain11en1. PROt,.1IS sleep dim1rbance. PROMIS fatigue	xio		X						X	
C'SSA	X									X
DSST. PVT, VOLT[11]			X				X		X	

Abbre,i.atioos: AE=advene event; CSSA=cocaineselectiveseverity assessment; DSST=Digit Symbol Substitution Test; ECG= eled:rocardiogram.;EoS=endof study; ESS=Epworth Slffpine:ss Scale; PGI-S =Participant GlobalImpression -Severity; PROMIS= Patient Reported Outcomes Measurement lofonnation Systems; PSG = polysomnography; PVT= psychomotor\'igilance task; QHS= each night;SAE= serious ad;w,e eveDt; SAQU= SleepApaea Quality of LifeIndex;VOLT= Visua!ObjectLeanwigTask; WOCBP=womenofchildbearingpo1m6al.

1 Following pre-screeoing, participants 'Mlocontinue to meeteligi'bility requirements will undergo initial screening at theclinicalsite a.tVL Only participants lnlomeetall nonPSG based enrollme.nt criteria undergo PSGa.tV2.Onlyifthe AHI(4%) ofV2 PSGis 750, inclusi:ve, is the participant eligi'ble for the V3 PSG. Mean AHI(4%) ofV2 and V3 must be10-45 inclusive for enrollment.

2 V2 and V3 PSGsaveragesserve as baselinefor cakula.tion of PSGe.fticacy outcomes.

3 Fmalstudyeligibility is determinedthemommg after tb.eV3 PSG, basedoo V2 and V3PSGmd bythesite(PSGsaremd separatelylate,bytheoeob'al rudmgceote, for endpointca.kulatioo);eligible participants are ralldomized.

4 Caobe conducted either eveningor mor:uing of PSG.

5 Addition.alpregnancy testing may be doneat othertimeswhen clinically indicated, e.g. ifa menstrual cycle is missed or when pregnancy is otherwisesuspected.

6 Runio study drugdistn'buted a.t V3following raodomizatioo (cm bedistn'buted up to twodays laterif necessary forscheduling); full dose study drugdistn'buted a.tV4; wmsedstudydrugis returned to the site at V4 (JUD-io drug) aod V6 (full-dose drug).

7 Studydrugis dosed immediately prior to tigbts-ou\ iocludiog at V5 and V6PSG; dose for PSG nights is from tbesupply pro,,ded to the partjcipaot at V4.

S On PSG \'isits vitalsignsaremeasured andrecorded both evening of PSGand morning after PSG.

9 Sitescootactparticipaotsbyphooe mid-week ofJUD-io period (day 3-4)and mid-week firstweek of full-dose period(day10-11), for AE/SAE=Ditoriog andmiew ofstudyprocedlU'es; AE/SAEcollection begins withrandomization

10 At VI ooly PGI-S is me>sUJ'ed (for use asenrollment criterion). At V3and V6 all listed endpoints are measured,including PGI-S, the e;-eoiog of the PSG =

11Administer DSST, PVTand VOLT momiag after PSG

10.2. Appendix B: Protocol-Required Safety Laboratory Assessments

Lnbornlory Assessments	**Pnrnmete1·s**		
Hematology	Hematocrit Hemoglobin Platelet Cow1t RBC Cornn	RBC Indices (MCV. MCH.MCHC)	\VBC count with Differential
Serum Chemistry	Albumin BUN Creatinine Potassium Sodium Bilimbin	ALT AST Alkaline phospharase Calcium Magnesium Total Protein	Glucose Total cholesterol Chloride Bicarbonate Uric acid
Routine Uiinalysis	Specific gravity. bili.111bin. color. appearance. leukocyte esterase. nitrite. pH. protein (albumin). glucose. ketones. occult blood. urobilinogen Microscopic examination (if positive protein. leukocyte esterase. blood or niuire)		
Other Tests	• HbAlc (Screening Visit only) • Senun hCG pregnancy test at screening. Additional resring may be perfonned if needed in WOCBP. • Urine. rest of dmgs of abuse (marijuana. cocaine. amphetamine. methamphetamine. opiates. phencyclidine) • FSH may be pe1fonned to aid in detennination of menopausal status		

AbbreYiations: ALT= alanine aminotransferase: AST= aspartate aminotransferase: BUN =blood Iffea nitrogen: FSH = follicle stimulating hom1one: HbAlc = h-e:moglobin Ale (.glycated hemo,globin): hCO = human chorionic sonadotropin; RBC = red blood cell coum; WBC= white blood cell: WOCBP = women of cbildbeat"ing poten1ial.

DocuSign

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Bryce Weaver bweaver@ctifacts.com Biostatistician II CTI Clinical Trial and Cons-utmg Services- Part 11 Security Levet Email, Account Authentication (Required)	Bryce Weaver Signature Adoption: Pre-selected Style Signed by link sent to bweaver@ctifacts.com Signature ID: 7AB7AB9F-099E-4A-7C-B1FOB820EACB UsingIP Address: 216.68.75.226 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 4/4/2022 8:16:42 AM Viewed: 4/412022 8:17:34 **AM** Signed: 414/2022 8:17:57 **AM**
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Rachael Gilbert Runyan rrunyan@ctifacts.com Assistant Director, Biostatistics CTI Clinical Trial and Cons-utmg Services Security Levet Email, Account Authentication (Required)	Rachael Gilbert Runyan Signature Adoption: Pre-selected Style Signed by link sent to rrunyan@ctifacts.com Signature ID: 5953F54F-F52D-42E0-9BA1-7E8D870EEDAB UsingIP Address: 216.68.75.226 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve thisdocument	Sent: 4/4/2022 8:16:42 **AM** Viewed: 4/41202211:04:31 **AM** Signed: 414/2022 11:04:50 **AM**
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Signer Events	Signature	Timestamp
Ronald Fall<as rfarkas@apnimed.com Chief Medical Officer Ron Farkas Security Levet Email, Account Authentication (Required)	Ronald Farkas Signature Adoption: Pre-selected Style Signed by link sent to rfarkas@apnimed.com Signature ID: 2ASF46E'.>93F C7 AB4EF320DAB7 Using IP Address: 71.179.88.153 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 4/4/2022 8:16:42 **AM** Viewed: 4/412022 8:20:29 **AM** Signed: 414/2022 8:21:48 **AM**
Electronic Record and Signature Disclosure: Accepted: 7/17/2020 9:40:0S **AM** ID: 741Ofab0-c816-4828-a4ed-9fb902e0e97a		
In Person Signer Events	**Signature**	**Timestamp**
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
Amy Holman aholman@ctifacls.com Assistant Director, Clinical Project Management CTI Clinical Trial and Cons-utmg Services Security Levet Email, Account Authentication (Required) Electronic Record and Signature Disclosure: Accepted: 7/10/2020 12:52:49 **PM** ID: dedcf01e-0199-4c6e-ae5b-ea258cd55136	**COPIED**	Sent: 4/4/2022 8:16:43 AM Viewed: 4/412022 9:09:25 **AM**
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**
Envelope Sent	Hashed/Encrypted	4/4/2022 8:16:43 **AM**
CertifiedDelivered	Security Checked	4/4/2022 8:20:29 **AM**
Signing Complete	Security Checked	4/4/2022 8:21:48 **AM**
Completed	Security Checked	4/4/202211:04:SOAM
Payment Events	**Status**	**Timestamps**
Electronic Record and Signature Disclosure		

ELECTRONIC RECORD M'D SIGNATURE DISCLOSURE

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