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To: ClinicalTrials.gov

This is a cover page to the redacted SAP for APN-006 titled Phase 2, Randomized, 3-Period, Placebo-Controlled Crossover Study to Evaluate the Efficacy and Safety in Obstructive Sleep Apnea of AD036 versus Placebo or Atomoxetine.

The APN-006 SAP is associated with NCT 04445688.

The following proprietary information was redacted from the SAP for APN-006:

- IND number
- Reference to the CRO (Contract Research Organization).

Sincerely,

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Phase 2, Randomized, 3-Period, Placebo-Controlled Crossover Study to Evaluate the Efficacy and Safety in Obstructive Sleep Apnea of AD036 versus Placebo or Atomoxetine

Protocol Number:	APN-006
Protocol Version:	3.0
Protocol Date:	15 September 2020

STATISTICAL ANALYSIS PLAN

Version 1.1

18 September 2020

Phase 2, Randomized, 3-Period, Placebo-Controlled Crossover Study to Evaluate the Efficacy and Safety in Obstructive Sleep Apnea of AD036 versus Placebo or Atomoxetine

STATISTICAL ANALYSIS PLAN

Version 1.1

18 September 2020

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SAP Revisions

Version 1.0 of the SAP was finalized at the time of Protocol version 2.0 (13APR2020). The following table details the changes made to the SAP due to subsequent protocol amendments.

Protocol Version # Date	SAP Section	Modification	Description and Rationale
3.0 15SEP2020	2.1.3	Removed endpoint 'Fraction of apneas'.	NA

Table of Contents

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AHI	apnea-hypopnea index
AE	adverse event
ATC	anatomical, therapeutic, and chemical
CSR	clinical study report
CYP2D6	cytochrome P450 2D6
ECG	electrocardiogram
eCRF	electronic case report form(s)
EDC	electronic data capture
HSAT	Home sleep apnea test
ICF	informed consent form
MedDRA	medical dictionary for regulatory activities
mITT	modified intent to treat
NAW	number of awakenings
NREM	non-rapid eye movement
ODI	oxygen desaturation index
OSA	obstructive sleep apnea
PT	preferred term
REM	rapid eye movement
SAE	serious adverse event
SaO2	oxygen saturation

Abbreviation	**Definition**
SAP	statistical analysis plan
SE	sleep efficiency
SOC	system organ class
SOL	sleep onset latency
TST	total sleep time
WASO	wake after sleep onset
WHO	world health organization

1. INTRODUCTION

This statistical analysis plan (SAP) is based on the Protocol # APN-006 Version 2.0, dated 13 April, 2020, titled "Phase 2, Randomized, 3-Period, Placebo-Controlled Crossover Study to Evaluate the Efficacy and Safety in Obstructive Sleep Apnea of AD036 versus Placebo or Atomoxetine." AD036 is a new fixed-dose combination of atomoxetine and oxybutynin being developed for the treatment of obstructive sleep apnea (OSA). Study APN-006 is designed to confirm and extend safety and efficacy findings from Study APN-002, a Phase 2 study of AD036 in OSA. See the study protocol for full details.

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. Primary Objective

The primary objective is to evaluate the efficacy of AD036 compared to placebo as measured by the 4% definition of apnea-hypopnea index (AHI).

2.1.2. Secondary Objectives

The secondary objectives include:

- To evaluate the efficacy of AD036 compared to placebo as measured by hypoxic burden and the 4% definition of oxygen desaturation index (ODI).
- To evaluate the efficacy of AD036 compared to atomoxetine on measures of hypoxic burden, AHI(4%), and ODI(4%).

2.1.3. Tertiary Objective

The tertiary objectives are to evaluate the effects of AD036 compared to both placebo and atomoxetine on:

- Total time with SaO2 <90%
- Snoring index
- Sleep stages distribution and % of time in the various sleep stages
- Arousal index
- Proportion of participants with ≥50% reduction in AHI and ODI endpoints
- Fraction of hypopneas
- Alternative measures of AHI and ODI

2.2. Endpoints

2.2.1. Primary Endpoint

The primary efficacy endpoint is as follows:

- AHI(4%), AD036 vs. placebo

2.2.2. Secondary Endpoints

The secondary efficacy endpoints are as follows:

- Hypoxic burden(4%) and ODI(4%), AD036 vs. placebo
- Hypoxic burden(4%), AHI(4%) and ODI(4%), AD036 vs. atomoxetine

2.2.3. Tertiary Endpoints

The tertiary efficacy endpoints are as follows:

- Total time with SaO2 <90%
- Snoring index
- Sleep stages distribution and % of time in the various sleep stages
    - Total Sleep Time (TST)
    - Sleep Efficiency (SE)
    - Wake After Sleep Onset (WASO)
    - Number of Awakenings (NAW)
    - Sleep Onset Latency (SOL)
    - Percentage of TST spent in sleep stage N1 (Stage N1%)
    - Percentage of TST spent in sleep stage N2 (Stage N2%)
    - Percentage of TST spent in sleep stage N3 (Stage N3%)
    - Percentage of TST spent in sleep stage R (Stage R%)
- Arousal index
- Proportion of participants with ≥50% reduction, AHI and ODI endpoints
- Fraction of hypopneas
- Alternate measures of AHI, ODI and HB
    - AHI(4%) in non-rapid eye movement (NREM) sleep
    - AHI(4%) in rapid eye movement (REM) sleep
    - AHI(4%) adjusted for position
    - AHI(4%) in supine position
    - AHI(3% or arousal)

- HB(3%)
- HB(total)
- ODI(3%)

3. INVESTIGATIONAL PLAN

3.1. Study Design

Patients who participated in Study APN-002 are eligible for enrollment, as are new patients who meet enrollment criteria. A total of 54 Patients with baseline characteristics that, based on Study APN-002 findings, predict increased responsiveness to AD036, will be planned for enrollment.

Objective OSA inclusion criteria for patients who participated in Study APN-002 will be determined based on the Study APN-002 baseline PSG exam (applies also to patients who were screened but did not meet the study PSG criteria). Objective OSA inclusion criteria for new patients can be based on a previous full night PSG or home sleep apnea test (HSAT) conducted at the site within 4 months prior to enrollment. If such results are not available, a screening HSAT may be conducted during the screening period, but such testing generally should be limited to patients with documented previous sleep apnea test results (e.g. previous sleep study outside 4-month window) indicating the patient is still likely to meet objective OSA study enrollment criteria.

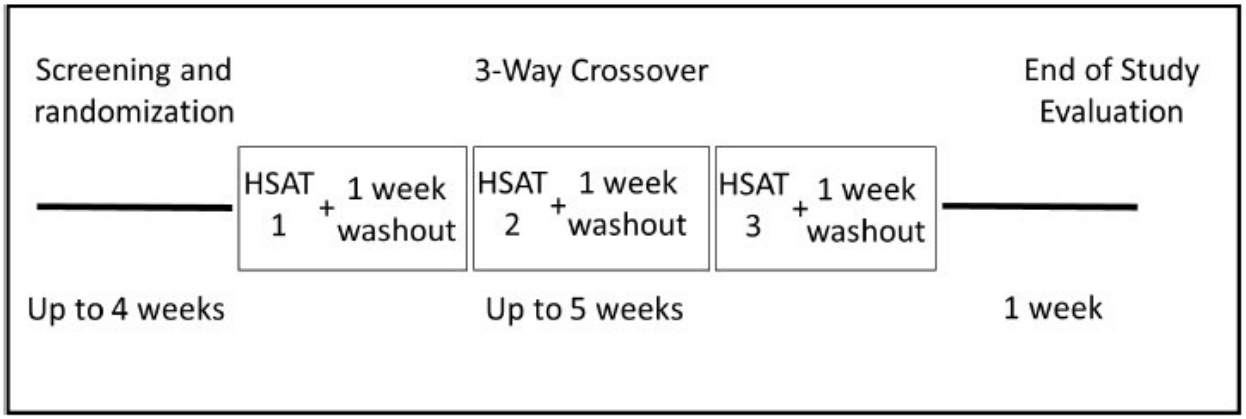
There are 3 randomized crossover HSAT nights. Each HSAT night is followed by a 1-week washout period. Dosing of the study treatment will occur immediately prior to bedtime. Patients will be randomized to treatment sequence with one of the following experimental treatments on each HSAT night:

- A: Atomoxetine 80 mg + oxybutynin 5 mg
- B: Atomoxetine 80 mg + placebo
- C: Placebo + placebo

Overall study duration will be up to 10 weeks, as follows:

- Screening, up to 4 weeks;
- 3-period crossover, approximately 5 weeks;
- End of study evaluation, 1 week after end of crossover period

Figure 1: Overview of Study Design



HSAT = home sleep apnea test.

3.2. Treatment

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Study treatments include atomoxetine 80 mg + oxybutynin 5 mg, atomoxetine 80 mg + placebo, and placebo + placebo, taken immediately before the participant's planned bedtime on HSAT nights, in randomized order.

3.2.1. Randomization Scheme and Treatment Arm Assignment

The randomization scheme will allocate subjects to one of the following 6 treatment sequences: A – B – C, B – C – A, C – B – A, A – C – B, B – A – C, or C – A – B (using treatments A, B, and C as defined in Section 3.1).

3.2.2. Blinding

Not applicable.

3.2.3. Dosing Schedule

There are 3 randomized crossover HSAT nights. Each HSAT night is followed by a 1-week washout period. Dosing of the study treatment will occur immediately prior to bedtime. Patients will be randomized to treatment sequence with one of the experimental treatments taken on each HSAT night.

3.2.4. Study Treatment Compliance

Site personnel will contact participants remotely each HSAT night to assist with HSAT equipment use and to confirm study drug dosing.

Participants will be required to return any unused study drug. Unused study drug will be counted and recorded by study personnel to assess study treatment compliance.

4. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

In general, continuous variables will be summarized by presenting the population sample size (N), number of patients with available data (n), mean, standard deviation (SD), median, minimum, and maximum. In summaries of change from baseline safety variables, only patients with both baseline and post baseline data will be included. Categorical variables will be summarized by presenting the number and percentage of patients within each category. Calculation of percentages will exclude missing data as a category. Where appropriate, descriptive statistics may be presented with 95% confidence intervals (CIs).

All tabulations will be based on pooled data across centers.

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.

CTI Clinical Trial and Consulting Services (Covington, KY) will perform all efficacy and safety analyses. 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 Assurance

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

Data may be made available to CTI Biostatistics for programming purposes prior to database lock at a time when source verification and query 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

4.2.1. Enrolled Population

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

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

The mITT Population comprises all participants who take at least 1 dose of any of the study treatments and have at least 1 measurement on the primary endpoint. Participants will be analyzed for efficacy according to the treatment sequence into which they are randomized

4.2.3. Safety Population

The Safety Population consists of all participants who are randomized and receive at least 1 dose of any of the study treatments. Participants will be analyzed for safety based on the treatment received. Treatment received is defined as the actual treatment taken during each period.

4.2.4. Per Protocol (PP) Population

The PP Population consists of all participants without any major protocol violations that could influence efficacy assessment, and who are compliant with the study medication.
Participants in this population will be analyzed based on the treatment received. Treatment received is defined as the actual treatment taken during each period.

4.3. Assessment Windows

Data will be summarized by nominal study visit recorded in the database. There will be no windowing of any endpoint.

4.4. Handling of Dropouts or Missing Data

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

4.5. Multiple Comparisons

All hypothesis tests will be reported using the nominal 0.05 alpha level. There will be no adjustments for multiple comparisons of any endpoint.

4.6. Data Derivations and Transformations

Study Day will be calculated as:

- Date of assessment – date of randomization + 1 for assessments done on or after date of randomization
- Date of assessment – date of randomization for assessments done before date of randomization

For each efficacy and safety endpoint, the baseline value will be calculated as the last non-missing value prior to randomization (except where unscheduled assessments are performed the baseline value should be the value recorded at Screening). Where applicable, change from baseline values will be calculated as the assessment value minus the baseline value; percent change from baseline values will be calculated as the change from baseline value divided by the baseline value.

5. STUDY PATIENTS

5.1. Disposition of Patients

A table of frequency counts and percentages of all patients who are enrolled, randomized, and included in each analysis population will be provided. Patient disposition including study completion status and reasons for early termination will be tabulated by treatment sequence and overall. A by-patient listing will be provided.

5.2. Protocol Deviations

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

5.3. Demographic

Descriptive statistics will be used to summarize the demographic characteristics (age, gender, race,

ethnicity, height, weight, and BMI) by treatment sequence and overall using the Safety Population. A by-patient listing will also be provided.

5.4. Baseline Safety Characteristics

The results of the following assessments completed during the Screening visit will be summarized overall using the Safety Population:

- Clinical laboratory assessments (hematology, serum chemistry, urinalysis, CYP 2D6, HbA1C, pregnancy test, and alcohol breath test and urine drugs of abuse). CYP 2D6 and pregnancy test will be in listings only.
- Vital signs (respiratory rate, temperature, heart rate, and systolic and diastolic blood pressure)
- ECG (heart rate, pulse rate, QRS, QT, and QTcF)

A by-patient listing will also be provided for each baseline assessment above.

5.5. Medical History

All medical conditions and surgical procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. The number and percent of patients with each medical condition and surgical procedure will be presented by MedDRA system organ class (SOC), preferred term (PT) overall for the Safety Population. Each patient will be counted only once per SOC and PT. A by-patient listing will also be provided.

5.6. Prior and Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary version MAR2020. The number and percent of patients using each medication will be tabulated by Anatomical Therapeutic Chemical (ATC) level 3, preferred name overall. Each prior or concomitant medication reported more than one time will only be counted once per patient for each ATC level and preferred name. A by-patient listing will also be provided.

6. EFFICACY ANALYSIS

6.1. Primary Efficacy Analysis – AHI(4%)

The primary efficacy endpoint is the AHI(4%) value. The primary endpoint will be analyzed using a within-subject ANOVA model including treatment sequence, treatment, and visit as fixed effects. Robust variance estimates for the fixed effects will be used for testing treatment differences. Within subject variability (nested within treatment sequence) will be modeled using an unstructured (i.e., TYPE = UN) covariance pattern. The primary comparison of interest will be the difference between the AD036 and placebo treatment conditions. Model based point estimates (i.e., least square [LS] means for each treatment condition and the difference between conditions), 95% confidence interval for the difference, and p-value will be reported.

If the model shows there is a visit (i.e. period) effect, then ad hoc analyses will be performed.

A sensitivity analysis will be performed using the PP Population on the primary efficacy endpoint using the same methods described above.

6.2. Secondary Efficacy Analysis

6.2.1. AHI(4%)

The secondary comparison of interest between AD036 and atomoxetine will be the tested using the within-subject ANOVA model described in Section 6.1. Model based point estimates of the difference between AD036 and atomoxetine, 95% confidence interval for the difference, and p-value will be reported with the primary efficacy analysis.

Descriptive statistics for the reported AHI(4%) value and change from baseline in AHI(4%) will be presented by treatment condition.

6.2.2. Hypoxic burden(4%)

Similar within-subject ANOVA methods as described for the primary analysis will be used for the analysis of hypoxic burden. The comparisons of interest will be the differences between the AD036 and placebo treatment conditions and between the AD036 and atomoxetine treatment conditions. Model based point estimates (i.e., LS means for each treatment condition and the differences between conditions), 95% confidence interval for the differences, and p-values will be reported.

Descriptive statistics for the reported hypoxic burden(4%) value and change from baseline in hypoxic burden(4%) will be presented by treatment condition.

6.2.3. ODI(4%)

Similar within-subject ANOVA methods as described for the primary analysis will be used for the analysis of ODI(4%). The comparisons of interest will be the differences between the AD036 and placebo treatment conditions and between the AD036 and atomoxetine treatment conditions. Model based point estimates (i.e., LS means for each treatment condition and the differences between conditions), 95% confidence interval for the differences, and p-values will be reported.

Descriptive statistics for the reported ODI(4%) value and change from baseline in ODI(4%) will be presented by treatment condition.

6.5. Tertiary Efficacy Analyses

Tertiary efficacy endpoints will be analyzed using similar methods as described for the primary analysis or by descriptive statistics by treatment condition (See Section 2.2.3), as appropriate for the endpoint.

Additional clarifying details for the analysis of some of these endpoints is as follows:

- ≥50% AHI reduction
    - Displays will be created for the AD036 and atomoxetine treatment conditions compared to the placebo condition (i.e., the % reduction will be defined as the difference in the AD036 and placebo values divided by the placebo value).

- ≥50% ODI reduction
    - Displays will be created as above for ≥50% AHI reduction.
- Fraction of hypopneas
    - Fraction of hypopneas will be calculated by using the number of hypopneas divided by the total number of apneas plus hypopneas.
- AHI adjusted for position
    - Similar within-subject ANOVA methods as described before for the primary analysis will be used for a tertiary analysis of AHI(4%) including % time supine (%TS) as a covariate. The comparison of interest will be the difference between the AD036 and placebo treatment conditions. Model based point estimates (i.e., LS means for each treatment condition and the difference between conditions), 95% confidence interval for the difference, and p-value will be reported. The comparison of AD036 and atomoxetine treatment conditions will also be presented.

7. SAFETY ANALYSIS

Safety assessments will include measurement of adverse events (AEs) and serious AEs (SAEs).

The analyses will be descriptive and will be based on the Safety Population. The safety assessments will be summarized by the treatment the subject actually received within each period.

7.1. Extent of Exposure

The number and percentage of patients receiving study treatment will be summarized by treatment condition and overall.

7.2. Adverse Events

An AE is any untoward medical occurrence in a participant or clinical study participant, 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. Each TEAE will be assigned to a treatment condition based on the treatment period it started in. There are a total of three (3) treatment periods. For example, a TEAE will be assigned to Treatment Period 1 if the AE start date/time is after the date/time of dosing in Treatment Period 1 and prior to the date/time of dosing in Treatment Period 2.

7.2.2. Adverse Event Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday 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 one of the predefined outcomes as described in the definition 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 and investigated.
- 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 minimal 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 the criteria used when determining regulatory reporting requirements.

7.2.4. Serious Adverse Events

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

- Results in death;
- Is life-threatening;

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

7.2.5. Adverse Event Summaries

Adverse event data will be displayed in listings by patient. The number and percentage of patients with AEs will be tabulated by SOC and PT. A patient with multiple 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 the informed consent process and before the end of study, regardless of relationship to study drug, will be included and presented by MedDRA SOC and PT.

For TEAEs, the following will be summarized by treatment condition and presented for the Safety Population.

i. An overall summary of TEAEs, which includes:
   a. the number and percentage of patients experiencing any TEAE
   b. the number and percentage of patients experiencing any TEAE by strongest relationship to study medication
   c. the number and percentage of patients experiencing any TEAE by greatest intensity
   d. the number and percentage of patients experiencing any TESAE

ii. the number and percentage of patients experiencing any TEAE by SOC, PT

iii. the number and percentage of patients experiencing any TEAE by SOC, PT and the greatest intensity

iv. the number and percentage of patients experiencing any TEAE by SOC, PT and the strongest relationship to study medication

v. the number and percentage of patients experiencing any TEAE leading to study discontinuation by SOC and PT.

In the overall summary of AEs table , besides tabulating the number and percentage of patients, the total number of AE episodes will also be provided. If a patient has repeated episodes of a particular AE within a treatment period, all episodes will be counted in the summary table and displayed by treatment condition.

For displays by SOC and PT, each subject will be counted only once per SOC and PT within each treatment condition.

All occurrences of all AEs will be listed for each patient, grouped by treatment condition. The listing will contain the following information: treatment sequence, treatment condition, verbatim term, SOC, PT, intensity, relationship to study medication, date and day of onset, date and day of resolution, treatment given to treat the adverse event, the outcome, whether the event was an SAE, whether it led to withdrawal. Listings will be sorted by patient identification number, onset date, SOC, and PT. If onset year is non-missing but month and/or date is missing, then the day of the

most recent study drug dose will be imputed as onset date.

8. INTERIM ANALYSIS

No formal interim analysis is planned.

9. SAMPLE SIZE AND POWER CALCULATIONS

A total of 54 patients (9 per sequence) will enter the 3-treatment crossover study. The study will have 90% power to detect a treatment difference at a two-sided 0.05 significance level, if the true difference between treatments on AHI is -11.0 units. This assumes that the within-patient standard deviation is 12, estimated from Study APN-002 using a subset of 92 patients with baseline Fhypopnea ≥65%.

10. APPENDICES

10.1. Appendix A: Schedule of Activities

Procedures	Screen-ing	3-Period Crossover at Home						End of Study Evaluation[1]	Notes
		HSAT 1	Wash-out[2]	HSAT 2	Wash-out	HSAT 3	Wash-out		
Trial Day/Duration	**Up to 4 weeks**	**Up to 5 weeks**						**1 week post crossover period**	
Informed consent	X								
Enrollment criteria	X								
History and Physical	X								Includes vital signs and weight
12-lead ECG	X								
Clinical laboratory and serum pregnancy test (WOCBP only)	X								CYP2D6 test only at Screening and only for patients not previously screened in Study APN-002
Drugs of abuse and ethanol testing	X								
Instruct and remotely oversee HSAT use	X[3]	X		X		X			
Randomization		X							Occurs after enrollment criteria met, prior to HSAT 1
Dispense study drug		X		X		X			
HSAT	X[3]	X[4]		X		X			HSAT device provided prior to each HSAT night
Study drug dosing		X		X		X			Dose at lights out; site verifies dosing remotely
AE/SAE monitoring	X	X	X	X	X	X	X	X	
Prior/concomitant medication monitoring	X	X	X	X	X	X	X	X	

Abbreviations: AE = adverse event; HSAT = home sleep apnea test; QHS = taken at bedtime; SAE = serious adverse event; WOCBP = women of childbearing potential.

[1] Can be conducted remotely
[2] Each washout period is at least 7 days
[3] Screening HSAT only for patients without prior qualifying sleep study, and only after other study enrollment criteria confirmed as met. Screening HSAT is conducted and read by site (not by central reading center).
[4] Remote instruction on use of HSAT and drug dosing confirmation provided by study site for each HSAT night

10.2. Appendix B: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Hematocrit Hemoglobin Platelet Count RBC Count	RBC Indices	WBC count with Differential
Serum Chemistry	Albumin BUN Creatinine Potassium Sodium Bilirubin Total Protein	ALT AST Alkaline phosphatase Calcium Glucose Chloride Bicarbonate	
Routine Urinalysis	Specific gravity pH, protein (albumin), glucose, ketones, blood (RBC), WBC by dipstick Microscopic examination (if blood or protein is abnormal)		
Other Tests	• CYP 2D6 (only at Screening Visit, only for new patients not previously tested in Study 002) • HbA1c (Screening Visit only) • Serum hCG pregnancy test at screening. Additional testing may be performed if needed in WOCBP. • Alcohol breath test and urine drugs of abuse (marijuana, cocaine, amphetamine, methamphetamine, opiates, phencyclidine)		

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CYP2D6 = cytochrome P450 2D6; γ-GTP = gamma guanosine-5'-triphosphate; HbA1c = hemoglobin A1c (glycated hemoglobin); hCG = human chorionic gonadotropin; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; RBC = red blood cell count; WBC= white blood cell; WOCBP = women of childbearing potential.

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Rachael Gilbert Runyan rrunyan@ctifacts.com Manager, Biostatistics CTI Clinical Trial and Consulting Services Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 5953F54F-F52D-42E0-9BA1-7E8D870EEDAB Using IP Address: 208.102.126.206 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 9/18/2020 11:49:01 AM Viewed: 9/18/2020 12:19:30 PM Signed: 9/18/2020 12:22:20 PM
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Signer Events	Signature	Timestamp
Ronald Farkas rfarkas@apnimed.com Chief Medical Officer Ron Farkas Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 2A5F46E3-93FC-40C7-8A20-AB4EF320DAB7 Using IP Address: 71.179.160.191 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 9/18/2020 12:22:23 PM Resent: 9/22/2020 1:23:30 PM Viewed: 9/22/2020 1:46:38 PM Signed: 9/22/2020 1:47:45 PM
Electronic Record and Signature Disclosure: Accepted: 7/17/2020 9:40:08 AM ID: 7410fab0-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

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	9/22/2020 1:23:30 PM
Certified Delivered	Security Checked	9/22/2020 1:46:38 PM
Signing Complete	Security Checked	9/22/2020 1:47:45 PM
Completed	Security Checked	9/22/2020 1:47:45 PM

Payment Events	Status	Timestamps

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