Statistical Analysis Plan

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Revision History

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I confirm that I have reviewed this document and agree with the content.

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1. Glossary of Abbreviations

Abbreviation	Description
ABPM	Ambulatory blood pressure monitoring
AE	Adverse Event
AHI	apnea-hypopnea index
AHI3a	apnea-hypopnea index based on 3% hypopnea desaturation plus arousals
AHI4	apnea-hypopnea index based on 4% hypopnea desaturation
ARI	Arousal Index - total
ARIR	Arousal Index - Respiratory
ATC	Anatomical Therapeutic Chemical
ALT	alanine aminotransferase
AROX	aroxybutynin
AST	aspartate aminotransferase
ATO	atomoxetine
BDRM	Blinded Data Review Meeting
BMI	Body Mass index
BUN	Blood urea nitrogen
CI	Confidence Interval
CMH	Cochran-Mantel Haenszel
CRF	Case Report Form
CSR	Clinical study report
DMC	Data Monitoring Committee
DSST	Digit Symbol Substitution Test
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of Study evaluation
ESS	Epworth sleepiness Scale
FAS	Full Analysis Set
FMQs	FDA Medical Queries
FSH	Follicle stimulating hormone
HB4	Hypoxic burden based on 4% hypopnea desaturation
HbA1c	Hemoglobin A1c (glycated hemoglobin)
hCG	Human chorionic gonadotropin
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational medicinal product
IRT	Interactive Response Technology
LOCF	Last Observation Carried Forward

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Abbreviation	Description
MAR	Missing at Random
MADRS-S	Self-reported Montgomery-Asberg depression rating scale
M-CSSA	Modified cocaine selective severity assessment
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
MNAR	Missing not at Random
MWPC	Meaningful Within Patient Change
NREM	Non-rapid eye movement
ODI3	Oxygen desaturation index based on 3% hypopnea desaturation
OSA	Obstructive Sleep Apnea
PAP	Positive Airway Pressure
PGI-C	Patient global impression -Change
PGI-S	Patient global impression Severity
PPS-A	Per-Protocol Set for AHI4
PPS-P	Per-Protocol Set for PROMIS-Fatigue
PRO	Patient Reported Outcome
PROMIS	Patient Reported Outcomes Measurement Information System;
PSG	Polysomnogram
PT	Preferred Term
PVT	Psychomotor Vigilance Test
RBC	red blood cell count
REM	Rapid eye movement
QTc	Corrected QT Interval
QTcF	Corrected QT Interval Fridericia
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Sleep efficiency
SI	Standard International System of Units
SoA	Schedule of Activities
SOC	System Organ Class
SOL	Sleep onset latency
SOP	Standard Operating Procedure
Spielberger	Short version of Spielberger state-trait anxiety inventory
SS	Safety Set
STAI	Spielberger Anxiety Inventory – Short Form
TEAE	Treatment-Emergent Adverse Event

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Abbreviation	Description
TFL	Table, Figure and Listing
TIA	Stroke and Transient Ischemic Attack
TST	Total sleep time
VLT	Verbal learning task
WASO	Wake after sleep onset
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of childbearing potential

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2. Purpose

This statistical analysis plan (SAP) outlines the statistical methods for the display, summary and analysis of data collected within the scope of Protocol APC-APN-304. The purpose of this plan is to provide general guidelines from which the analysis will proceed. Deviations from these guidelines will be substantiated by sound statistical rationale and will be documented in the clinical study report (CSR). If there are differences between the protocol and the SAP, this SAP will take precedence.

The SAP should be read in conjunction with the study protocol and the case report forms (CRFs). This version of the SAP has been developed using the version of the protocol mentioned above.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all tables, figures, and listings.

2.2. Timings of Analyses

Final Analysis: The primary analysis of safety and efficacy is planned after all participants complete the final study visit or terminate early from the study.

Data Monitoring Committee ***(DMC) Analysis:*** For this study, DMC analyses will be performed for the independent DMC to review the accumulated safety data, participant disposition and limited efficacy data after approximately 50 participants have completed at least 3 months of study drug therapy and every 3 months thereafter through the end of the study. Further description of the DMC analyses can be found in the most recent version of the DMC charter. An unblinded team from Syneos Health Biostatistics will perform the analyses as described in Section **Error! Reference source not found.**3 of this SAP to maintain the blinding of the study.

Interim Analysis: No interim analysis is planned for this study.

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3. Study Objectives, Endpoints and Estimands

Objectives	Endpoints/Assessments
Primary Objective Compare efficacy on airway obstruction of AD109 vs placebo in participants with mild to severe OSA at 26 weeks	**Primary Endpoint** • Change from baseline in apnea-hypopnea index based on 4% hypopnea desaturation (AHI4) at week 26
Secondary Objective Compare efficacy on OSA symptoms and oxygenation of AD109 vs placebo in participants with mild to severe OSA at 26 weeks	**Key Secondary Endpoints** • Change from baseline in ODI3 at week 26 • Change from baseline in HB4 (on the natural log scale) at week 26 • Proportion of participants with ≥50% reduction in AHI4 at 26 weeks • Change from baseline in PROMIS-Fatigue T-score at week 26 **Secondary Endpoints** • Change from baseline in PGI-S for fatigue at week 26 • PGI-C for fatigue at week 26 • Change from baseline in ESS at week 26 • Change from baseline in PROMIS-Sleep Impairment T-score at week 26
Tertiary Objective Compare efficacy on airway obstruction and OSA symptoms of AD109 vs placebo in participants with mild to severe OSA at 51 weeks	**Tertiary Endpoints** The following are assessed as change from baseline at week 51 or as specified • AHI4 • ODI3 • HB4 • Proportion of participants with ≥50% reduction in AHI4 at week 51 • PROMIS-Fatigue T-score • PGI-S for Fatigue • PGI-C for fatigue at week 51 • ESS • PROMIS-Sleep Impairment T-score

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Exploratory Objective Examine effects of AD109 on PSG sleep parameters, additional measures of airway obstruction, and at additional time points,	**Exploratory Endpoints** • Sleep architecture and sleep stage distribution at week 13, 26 and 51 • Above listed measures (Primary, Secondary, Tertiary) at week 13 • Percent of participants with AHI4<15, <10 and <5 at week 13, 26 and 51 • Proportion of participants with AHI4 reduction of ≥ 30% to ≥ 90% by 10% increments at week 13, 26 and 51 • Change from baseline in AHI3a, HB3a, and ODI4 at week 13, 26 and 51, as applicable • Change from baseline in Non-Rapid Eye Movement Apnea-Hypopnea Index [NREM AHI] at week 13, 26 and 51 • Change from baseline in Rapid Eye Movement Apnea-Hypopnea Index [REM AHI] at week 13, 26 and 51 (excluding participants whose PSG has <10 minutes of REM sleep) • Change from baseline in supine AHI4 [AHI4S] at week 13, 26 and 51 (excluding participants whose PSG has <10 minutes of supine sleep) • Change from baseline in Total sleep time (TST) and percentage of TST in sleep stages (sleep efficiency [SE]; wake after sleep onset [WASO]; sleep onset latency [SOL]; Stage N1% [N1P], Stage N2% [N2P], Stage N3% [N3P], Stage R% [RP]) • Change from baseline in Arousal Indices (Arousal Index - Respiratory [ARIR]; Arousal Index - total [ARI]) • Change from baseline in OSA severity category (None, Mild, Moderate and Severe) at week 13, 26 and 51 • Proportion of patients with loud breaths (i.e., snoring)
Safety Objectives Evaluate the safety and tolerability of treatment with AD109 in patients with mild to severe OSA	**Safety Assessments** • Physical exam, vital signs (including 24hr Ambulatory blood pressure monitoring [ABPM]), clinical laboratory assessment, ECG • Adverse events, including during the post-dosing period

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	• DSST • PVT • Verbal learning task • M-CSSA • MADRS-S • Spielberger
Abbreviations: ABPM = ambulatory blood pressure monitoring; AHI3a = apnea-hypopnea index based on 3% hypopnea desaturation plus arousals; AHI4 = apnea-hypopnea index based on 4% hypopnea desaturation; DSST = Digit Symbol Substitution Test; ECG = electrocardiogram; ESS = Epworth sleepiness Scale; HB4 = hypoxic burden based on 4% hypopnea desaturation; MADRS-S = self-reported Montgomery-Asberg depression rating scale; M-CSSA = Modified cocaine selective severity assessment; ODI3 = oxygen desaturation index based on 3% hypopnea desaturation; OSA = Obstructive Sleep Apnea; PGI-C = patient global impression change; PGI-S = patient global impression severity; PROMIS = Patient Reported Outcomes Measurement Information System; PSG = polysomnography; Spielberger = short version of Spielberger state-trait anxiety inventory	

3.1. Primary estimand

The primary clinical question of interest for the primary estimand is: what is the treatment effect of AD109 compared with placebo in participants with mild to severe OSA with respect to change from baseline in AHI4 at week 26 (and all secondary endpoints defined on a continuous scale), regardless of adherence to investigational product and irrespective of any changes in background therapy?

- Treatment condition: investigational treatment with AD109/Placebo regardless of adherence to investigational product and of any changes in background therapy (treatment policy strategy)
- Variable/endpoint:
  - Primary: change from baseline to week 26 in AHI4
  - Secondary:
    - Change from baseline to week 26 in ODI3, HB4, PROMIS-fatigue, PGI-S for fatigue
    - PGI-C scores at week 26
    - Change from baseline to week 26 in ESS, PROMIS sleep impairment and exploratory end point AHI3a
- Population of interest: participants with mild to severe OSA
- Intercurrent events:
  - Discontinuation of study treatment prior to week 26 due to any reason is handled by the treatment condition (treatment policy strategy).

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    - Change in background therapy (i.e., use of PAP or concomitant medications) is handled by the treatment condition (treatment policy strategy).
- Population-level summary measure: Difference in means between AD109 vs placebo estimated using a MMRM

Rationale for estimand: The primary estimand aims at reflecting how participants with mild to severe OSA are treated in clinical practice and considers both safety and efficacy.

For the secondary endpoint of 50% reduction in AHI4 at week 26, the clinical question of interest is: what is the treatment effect of AD109 compared with placebo in participants with mild to severe OSA with respect to achieving a 50% reduction in AHI4 at week 26, irrespective of adherence to investigational product and irrespective of any changes in background therapy?

- Treatment condition: investigational treatment with AD109/Placebo regardless of any changes in background therapy
- Variable/endpoint: Responder defined as achieving the following:
    - Achieved a ≥50% reduction from baseline in AHI4 at week 26
- Population of interest: participants with mild to severe OSA
- Intercurrent events:
    - Discontinuation of study treatment prior to week 26 due to any reason is handled by the treatment condition (treatment policy strategy).
    - Change in background therapy (i.e., use of PAP or concomitant medications) is handled by the treatment condition (treatment policy strategy).
- Population-level summary measure: Difference in response rates between AD109 vs placebo estimated using the stratified Cochran-Mantel Haenszel (CMH) approach

Rationale for estimand: The estimand aims at reflecting how participants with mild to severe OSA are treated in clinical practice and considers both safety/tolerability and efficacy.

3.2. Supportive estimands

The clinical question of interest for the supportive estimand is: what is the treatment effect of AD109 compared with placebo on primary and secondary endpoints in participants with mild to severe OSA, when participants are actively on study treatment?

- Treatment condition: AD109 versus placebo while participants remain on the assigned study treatment
- Variable/Endpoint:
    - Primary: change from baseline to week 26 in AHI4
    - Secondary:
        - Change from baseline to week 26 in ODI3, HB4, PROMIS-fatigue, PGI-S for fatigue
        - PGI-C scores at week 26

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        - Chang from baseline to week 26 in ESS, PROMIS sleep impairment and exploratory endpoint AHI3a
- Population of interest: participants with mild to severe OSA
- Intercurrent event:
    - Discontinuation of study treatment: Hypothetical strategy - data collected after treatment discontinuation will be excluded from analysis (set to missing).
    - Change in background therapy**:** Treatment policy strategy - data will be included regardless of changes in PAP use or concomitant medications.
- Population-level summary measure:
    - Difference in adjusted means between AD109 vs placebo estimated using a MMRM.

4. Study Details/Design

4.1. Brief Description

The LunAIRo Study (APC-APN-304) is a randomized, double blind, placebo-controlled, parallel-arm 1-year study of AD109 vs placebo in participants with mild to severe OSA who are intolerant of, or currently refuse, PAP. A screening visit and PSG will be conducted to establish, in combination with patient-reported outcomes assessments (PROs) and other criteria that each participant meets study enrollment criteria.

A screening/baseline PSG is conducted at V2 and is read by the central PSG reading center. For enrollment the AHI4 (hypopneas defined by 4% oxygen desaturation) of the V2 PSG must be >5, with ≤ 25% central or mixed apneas (as proportion of total apneas + hypopneas), and PLM arousal index ≤15.

Participants who meet all eligibility criteria will be randomized to one of 2 parallel treatment arms. Enrollment will be stratified, according to baseline AHI4 (<15, 15 to 30, >30) and PROMIS-Fatigue raw score (<25 vs ≥25), to ensure representative distribution of baseline AHI severity, the size of AHI4 strata will be controlled through enrollment limits, with AHI4 <15 representing ~20-40% of patients, AHI4 15 to 30 representing ~20-40% of patients, and AHI4 >30 representing ~20-40% of patients.

The first week of dosing will be with a lower dose of AD109 (run-in) or matched placebo, followed by the target dose taken for the duration of the study.

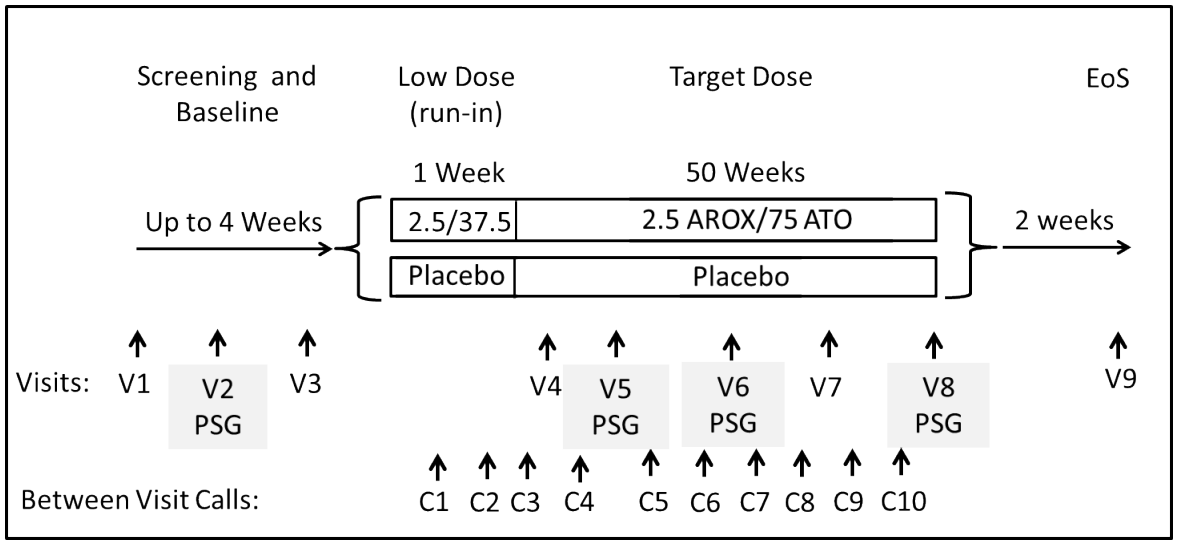
1. **Aroxybutynin 2.5 mg/Atomoxetine 75 mg tablet (n = 320)**
    - Week 1: aroxybutynin 2.5 mg/atomoxetine 37.5 mg tablet
    - Weeks 2-51: aroxybutynin 2.5 mg/atomoxetine 75 mg tablet
2. **Placebo tablet (n = 320)**
    - Week 1: matched placebo tablet
    - Weeks 2-51-: matched placebo tablet

Dose reduction is not permitted. Dosing is discontinued if the study drug to which the participant is randomized is not tolerated. Note that participants who discontinue dosing are encouraged to continue all other study activities for the full duration of the study.

A participant is considered to have completed the study if he/she has completed all phases of the study through the last scheduled procedure shown in the Schedule of Activities (SoA) in the protocol.

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Figure 1 Overview of Study Design



AROX = aroxybutynin; ATO = atomoxetine; C = contact/call; EoS = End of Study; PSG = polysomnogram; V = visit

4.2. Determination of Sample Size

A total sample size of approximately 640 participants (320/group) is planned. This sample size is based on the number of participants required to provide at least 90% power for the primary endpoint (change from baseline to week 26 in AHI4) and the key secondary endpoint (change from baseline to week 26 in PROMIS Fatigue T-score).

Change from baseline to week 26 in AHI4

In the previously conducted Phase 2 Mariposa study, the standard deviation of the placebo group change from baseline in AHI4 was approximately 9.0. Based on the observed dropout rates in Mariposa, it is assumed that the dropout rate in the placebo group will be 5% and the dropout rate in the AD109 group will be 25%. For the primary analysis, missing data will be handled under a missing not at random assumption by using multiple imputation from the control group. Based on the assumed standard deviation, anticipated dropout rates and planned method of handling missing data, the required sample size was estimated using simulation. A total of 640 participants (320/group) will provide >98% power to detect a treatment difference of ≥ 4 points between AD109 and Placebo for the change in AHI4.

Change from baseline to week 26 in PROMIS Fatigue T-score

In the Phase 2 Mariposa study, the standard deviation of the placebo group change from baseline in PROMIS Fatigue T-score was 8.6. Based on the observed dropout rates in Mariposa, it is assumed that the dropout rate in the placebo group will be 5% and the dropout rate in the AD109

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group will be 25%. For the primary analysis, missing data will be handled under a missing not at random assumption by using multiple imputation from the control group. Based on the assumed standard deviation, anticipated dropout rates and planned method of handling missing data, the required sample size was estimated using simulation. A total of 640 participants (320/group) will provide ~90% power to detect a treatment difference of 2.5 points and ~95% power to detect a treatment difference of 2.75 points.

4.3. Treatment Assignment and Blinding

Participants who meet all eligibility criteria will be randomized 1:1 to either AD109 or placebo, stratified by baseline AHI4 (<15, 15 to 30, >30) and PROMIS-Fatigue raw score (<25 vs ≥25).

Randomization will be centralized and will use Interactive Response Technology (IRT). Each participant will be assigned a unique randomization number that encodes the participant's assignment to 1 of the study arms, according to the randomization schedule.

The participants, site personnel, and investigators are masked to the randomized treatment assignment for the entire study duration. Also, the sponsor personnel and all CRO personnel will be masked to treatment assignment until database lock and unblinding has been declared, with the exception of those personnel required to be unblinded for specific reasons (e.g., drug packaging, preparation of unblinded DMC analyses, generation of randomization codes, etc.).

During the study period, unblinding of a participant's study treatment assignment is allowed if determined by the Investigator to be necessary to protect participant safety. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

Unblinding related to functions of the Data Monitoring Committee (DMC) is described separately in the DMC charter.

At the end of the study, the formal database lock will be declared after the completion of all procedures related to data cleaning, the medical review of the data, agreement of the final participant disposition, and agreement of the analysis populations upon review of all protocol deviations. Once database lock has been declared, the study will be unblinded and the participant's treatment assignments will be added to the clinical database for analysis. The sponsor/sponsor's designee will then be granted access to the unblinded database in order to analyze the data.

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5. Analysis Sets

5.1. Screened Set

The **Screened Set** will include all participants who signed the informed consent form (ICF), including screen failures.

5.2. Enrolled Set

The **Enrolled Set** will include all participants who signed the ICF and meet all eligibility criteria.

5.3. Full Analysis Set

The **Full Analysis Set (FAS)** consists of all participants who were randomized and received at least 1 dose of investigational medicinal product (IMP). All participants enrolled at Site 1308 will be excluded. The FAS Participants will be used for analyses of all efficacy endpoints according to the treatment group into which they are randomized.

5.4. Modified Intent to Treat Set

The Modified Intent to Treat (MITT) set for AHI consists of all participants and received at least 1 dose of IMP and had one post baseline on treatment PSG assessment. All participants enrolled at Site 1308 will be excluded. The MITT Participants will be used for the supportive analysis of selected efficacy endpoint, according to the treatment group into which they are randomized.

5.5. Safety Set

The **Safety Set (SS)** consists of all participants who are randomized and receive at least 1 dose of IMP. Participants will be analyzed according to treatment received. The SS will be used for all analyses of safety endpoints.

5.6. Per Protocol Set

Per Protocol Set for AHI4

The Per Protocol Set for AHI4 (PPS-A) consists of all participants in the FAS who completed the study treatment up to week 26 (i.e., visit 6) with at least 70% compliance of taking IMP and have non-missing AHI4 assessment at week 26, without any important protocol violations that could influence the efficacy assessments. All participants enrolled at Site 1308 will be excluded. The analyses using the PPS-A will be based upon the actual treatment assignment. Selected efficacy assessments related to AHI4, ODI3 and HB4 will be evaluated using the PPS-A.

The Per Protocol Set for PROMIS-Fatigue

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The Per Protocol Set for PROMIS-Fatigue (PPS-P) is defined in the same way as PPS-A except it requires non-missing PROMIS-Fatigue assessment at week 26 instead of AHI4. Selected efficacy assessment related to PROMIS-Fatigue will be evaluated using the PPS-P.

Criteria for exclusion from the PPS-A and PPS-P will be defined in the Protocol deviation and Non-compliance plan and will be determined at the Blinded Data Review Meeting (BDRM) before database lock and unblinding.

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6. General Aspects for Statistical Analysis

6.1. General Methods

- All analyses and summary outputs will be generated using SAS® version 9.4 or higher. All SAS programs used to generate analytical results will be developed and validated according to SYNH programming standards and SAS validation procedures.
- Unless otherwise specified, summaries will be presented for each treatment and overall and visit/time point where applicable.
- Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, interquartile range, minimum, and maximum. The minimum and maximum will be displayed to the precision with which the data were collected. The mean, median, and quartiles will be displayed to one additional decimal place and the SD will be displayed to two additional decimal places, where applicable. All CIs will be 2-sided 95% CIs unless otherwise specified.
- Categorical variables will be summarized using number of observations (n), frequency and percentages of participants in each group and visit/time point where applicable, where the denominator for percentages is the underlying analysis set, unless otherwise stated. All percentages will be presented with one decimal, unless otherwise specified. Percentages equal to 100 will be presented as "100", and percentages will not be presented for zero frequencies.
- Efficacy data will be listed, tabulated, and summarized graphically, as appropriate. In general, descriptive statistics for efficacy endpoints will be presented using the FAS, PPS and MITT population sets. Safety endpoints will be presented using the SS population.
- In general, participant data listings will be presented using the enrolled set or all randomized participants.

6.2. Key Definitions

6.2.1. Coding Dictionaries

Adverse events and medical history will be coded into Preferred Term (PT) and System Organ Class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 27.0 or higher.

Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD), Global B3 March 2023 or higher.

6.2.2. Study Day

The day of first dose of IMP is defined as Study Day 1.

Study day for an event or measurement occurring before the date of the first dose will be calculated as follows:

Study Day = (Event/Measurement Date – Date of First Dose)

Study day for an event or measurement occurring on the date of the first dose is 1. Study day for an event or measurement occurring on or after the date of the first dose to the date of the last dose will be calculated as follows:

Study Day = (Event/Measurement Date – Date of First Dose) +1

6.2.3. AHI4 Strata

AHI4 strata is defined as AHI4: <15, 15-<30 and ≥30 derived from AHI4 score at baseline.

6.2.4. Randomization Strata

Randomization strata is defined as AHI4: <15, 15-<30 and ≥30 derived from AHI4 score at baseline, and PROMS-Fatigue raw score: <25 vs ≥25 derived from PROMS-Fatigue scores at screening visit 1.

6.2.5. Baseline

In this study, baseline will be defined as the last non-missing value collected prior to the first IMP administration. This definition will be applied for all analyses. In case of randomized not treated participants, the last non-missing valid value prior to randomization is used.

6.2.6. Change and Percent Change from Baseline

The change and percent change from baseline will be calculated for each post-baseline assessment as:

Change = post-baseline value – baseline value

Percent change = 100 * change / baseline value

6.2.7. Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study through the last scheduled procedure shown in the Schedule of Activities (SoA) in the study protocol.

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6.2.8. Duration of Treatment

Total duration of treatment in days is defined as (last dose date – first dose date + 1), regardless of any temporary interruptions in study drug. If the last study drug dosing date is missing, the latest date among the study drug end date, clinical visit date, laboratory sample collection date, and vital signs assessment date that occurred during the on-treatment period will be used for participants included in the final analyses.

6.2.9. Treatment Emergent AEs (TEAEs)

TEAEs are defined as an AE with an onset (i.e., start date) on or after the first administration of IMP (or any worsening of a pre-existing medical condition on or after the first administration of IMP) and prior to the last date of administration of IMP plus 7 days. Incomplete start dates will be imputed as described in Section 6.3 and used equivalently.

6.3. Missing Data

Missing data will be maintained as missing unless otherwise specified. For all efficacy variables, methods to handle missing data are described in the analysis of the efficacy variable.

For missing/partial dates with respect to AEs and Medications, the following rules will be followed.

Algorithm for Treatment Emergent Determination of Adverse Events

START DATE	STOP DATE	ACTION
Known	Known	If start date < study medication start date or start date>study medication end date + 7 days, then not TEAE If study medication start date ⩽ start date ⩽ study medication end date + 7 days, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If start date < study med start date or start date>study med end date + 7 days, then not TEAE If study med start date ⩽start date ⩽ study med end date + 7 days, then TEAE
	Missing	If start date < study med start date or start date>study med end date + 7 days, then not TEAE If study med start date ⩽start date ⩽ study med end date + 7 days, then TEAE

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START DATE	STOP DATE	ACTION
Partial, but known components show that it cannot be on or after study medication start date or cannot be before study medication end date +7 days	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study medication start date but before study med end date +7 days	Known	If stop date < study med start date, then not TEAE If stop date ⩾ study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date ⩾ study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date ⩾ study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date ⩾ study med start date, then TEAE
	Missing	Assumed TEAE

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Algorithm for Prior / Concomitant Medications

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date ≥ study med start date and start date < study med start date, assign as prior concomitant If stop date ≥ study med start date and start date ≤ end of treatment, assign as concomitant If stop date ≥ study med start date and start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date ≥ study med start date and start date < study med start date, assign as prior concomitant If stop date ≥ study med start date and start date ≤ end of treatment, assign as concomitant If stop date ≥ study med start date and start date > end of treatment, assign as post study
	Missing	If stop date is missing could never be assumed a prior medication If start date ≤ end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date ≥ study med start date and start date < study med start date, assign as prior concomitant If stop date ≥ study med start date and start date ≤ end of treatment, assign as concomitant If stop date ≥ study med start date and start date > end of treatment, assign as post study

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START DATE	STOP DATE	ACTION
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date ≥ study med start date and start date < study med start date, assign as prior concomitant If stop date ≥ study med start date and start date ≤ end of treatment, assign as concomitant If stop date ≥ study med start date and start date > end of treatment, assign as post study
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date ≤ end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date ≥ study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date ≥ study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

6.4. Visit Windows

The Screening Period will last up to 4 weeks. Following the Screening Period, all eligible participants will be randomized on Visit 3 (Day 1), and then will be followed by a 1-week low dosing Run-in Period and 50-week target dosing period. The Dose Evaluation Period ends at Visit 8/Week 51. The End of Study Visit, Visit 9, occurs approximately 2 weeks following cessation of IMP by participants, at Day 374 ± 4.

The visit windows, defined below in Table 1a, 1b and

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Table 1, will be used to report by visit assessments for efficacy and safety displays. Except in the case of repeated labs, if two or more observations fall within the same visit window, the observation closest to the target day will be used in the analyses. If the observations are equidistant from the target day, the later observation will be used. If labs are repeated and both values fall within the visit window, the result from the repeated lab will be used. Nominal visit information will be displayed in the respective by participant listing.

Table 1a: Analysis Visit Windows for assessment with schedule visits at week 13, 26, 51 and 53

Scheduled Visit	**Target Day**	**Analysis Visit Window (day)**
Screening (Visit 1,2,3)	N/A	28 to 1
Visit 5/Week 13	90	[2,135]
Visit 6/Week 26	180	[136,270]
Visit 8/Week 51	360	≥ 271 (excluding EOS visit)
Visit 9/EOS Week 53	374	Nominal visit 9 as collected

Table 1b: Analysis Visit Windows for assessment with schedule visits at week 13, 26, 51 but not week 53

Scheduled Visit	**Target Day**	**Analysis Visit Window (day)**
Screening (Visit 1,2,3)	N/A	28 to 1
Visit 5/Week 13	90	[2,135]
Visit 6/Week 26	180	[136,270]
Visit 8/Week 51	360	≥271

Table 1c: Analysis Visit Windows for assessment with schedule visits at week 4, 13, 26, 39, and 51 and week 53.

Scheduled Visit	**Target Day**	**Analysis Visit Window (day)**
Screening (Visit 1,2,3)	N/A	28 to 1
Visit 4/Week 4	30	[2, 60]
Visit 5/Week 13	90	[61,135]
Visit 6/Week 26	180	[136,225]
Visit 7/Week 39	270	[226,315]
Visit 8/Week 51	360	≥ 316 (excluding EOS visit)
Visit 9/EOS Week 53	374	Nominal visit 9 as collected

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6.5. Pooling of Centers

Data from all sites will be pooled together for all analyses. Funnel plots will be used for the primary endpoint (AHI4) and the key secondary endpoints (ODI3, HB4, AHI4 responder and PROMIS Fatigue) to assess the influence of sites on the overall summary measures.

6.6. Outliers

All reported values will be included in the analyses. If any outliers are identified, analyses may be conducted both with and without the outliers. Any outliers will be flagged in the analysis dataset and identified prior to unbinding.

6.7. Subgroups

The following subgroups will be used for the analysis of the primary and first secondary endpoint based on the FAS and MITT:

- Age (< 65 vs ≥ 65)
- Gender
- Race (Asian, Black or African American, White, Other)
- Baseline AHI4 (<15, 15 to 30, ≥30)
- Baseline PROMIS-Fatigue Raw score (<25 vs ≥25)
- Baseline BMI (<18.5, 18.5-24.9, 25-29.9, 30-34.9, 35-39.9, ≥40 after rounding to 1 decimal place), <18.5 and 18.5-24.9 are combined for the purpose of subgroup analysis.
- Baseline ESS Total score (<10 vs ≥10)
- REM predominant OSA (Yes vs No)
    - REM predominant OSA is defined REM AHI4 / NREM AHI4 >2 and REM time >45 minutes

6.8. Multiplicity

As there is a single primary endpoint, with a single primary hypothesis test, no adjustment for multiplicity is needed for the primary hypothesis test, which will use a two-sided 5% significance level.

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Adjustment for multiplicity of the key secondary endpoints will be conducted through a closed testing approach, where each key secondary endpoint will be tested in pre-specified order as follows.

1. Change from baseline to week 26 in ODI3
2. Change from baseline to week 26 in HB4
3. Proportion of patients with ≥50% reduction in AHI4 at week 26
4. Change from baseline to week 26 in PROMIS-Fatigue

If the primary endpoint is statistically significant, then the first key secondary endpoint will be tested using a two-sided 5% significance level. If the first key secondary endpoint is significant, the second key secondary endpoint will be tested using a two-sided 5% significance level, and so on, until an endpoint is found to be not significant (using a two-sided 5% significance level), or all key secondary endpoints have been tested.

No adjustment for multiplicity will be made for the non-key secondary endpoints or tertiary endpoints or exploratory endpoints.

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7. Demographic, Other Baseline Characteristics and Medication

7.1. Participant Disposition and Withdrawals

All participants who provide informed consent will be accounted for in this study.

The number and percentage of participants screened, screen failed, reason for screen failure, randomized, included and excluded from each analysis set (including reasons for exclusion), completed study drug treatment, discontinued study drug treatment and reasons for discontinuation of study treatment, discontinued study drug treatment prior week 51 but are observed in the study until week 51, completed week 26 study drug treatment, discontinued study drug treatment prior week 26 and reasons for discontinuation of study treatment, discontinued study drug treatment prior week 26 but are observed in the study until week 26, and completed or prematurely discontinued the study, including reasons for discontinuation will be summarized for each treatment group and overall.

The duration on study will be summarized for each treatment group and overall.

A listing of participant disposition will also be presented using the Enrolled Set.

A listing of participants excluded from each analysis set will be presented using the Enrolled Set.

7.2. Protocol Deviations

A summary of important protocol deviations will be presented using the enrolled set for each treatment group and overall for the FAS. A listing of all important deviations will be provided for the Enrolled Set.

7.3. Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be listed and summarized by treatment group and overall using appropriate descriptive statistics for all randomized participants.

The demographic characteristics to be summarized include age (year), sex, race, ethnicity, baseline height (cm), weight (kg), and BMI (kg/m^2).

$$\text{BMI } (kg/m^2) = \text{Weight}(kg)/[\text{Height}(m)^2]$$

Age and BMI will be summarized both continuously and categorically. Age and BMI categories to be used are as follows:

- Age: <65, ≥65
- BMI: <18.5, 18.5-24.9, 25-29.9, 30-34.9, 35-39.9, ≥40

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Baseline characteristics include the following:

- Baseline AHI4 score and AHI4 group: <15, ≥ 15 to 30, > 30 to 50, ≥ 50
- Baseline OSA Severity: None=AHI4 <5, Mild=AHI4 5 to <15, Moderate=AHI4 15 to 30, and Severe=AHI4 ≥30.
- Baseline AHI3a
- Baseline ODI3
- Screening visit 1 PROMIS-Fatigue Raw score, and PROMIS-Fatigue Raw score group: <25 vs ≥25
- Baseline PROMIS-Fatigue Raw score, T-score and PROMIS-Fatigue Raw score group: <25 vs ≥25
- Baseline PROMIS-Sleep Impairment raw score and T-score
- Baseline PGI-S
- Baseline ESS
- Baseline HB4
- Baseline ESS Total score (<10 vs ≥10)
- REM predominant OSA: Yes vs. No.
    - REM predominant OSA is defined as REM AHI4 / NREM AHI4 >2 and REM time >45 minutes

7.4. Medical History and Concomitant Diseases

Medical history will be collected, including significant past and current medical conditions, especially autoimmune or inflammatory diseases; surgical history; and disease history, including date of diagnosis, prior treatment(s) and response(s), and notation of any remarkable toxicities. All medical history will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) Version 27.0 or higher.

Medical history will be summarized by MedDRA system organ class (SOC) and preferred term (PT) by treatment group and overall using the FAS. A participant who experienced more than one medical history within a given SOC and PT will be counted only once within that SOC and PT, respectively.

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Medical history findings will be listed chronologically by participant for all randomized participants.

7.5. Medications

7.5.1. Prior/Concomitant Medication

A prior medication is any medication taken prior to the first IMP administration. A concomitant medication is any medication that started or continued after the first IMP administration and on or before the end of study treatment (last dose of IMP).

Partial/Missing start and/or end dates will be handled as described in the section on missing data Session 6.3

All prior and concomitant medication will be classified using the Anatomical Therapeutic Chemical (ATC) classification codes level 4 (ATC 4) and preferred name (PT) from the World Health Organization Drug Dictionary (WHO-DD) Global B3, March 2023.

The prior and concomitant medications will be summarized by treatment group and overall for the FAS, using the ATC 4 level term as an upper classification level and the preferred drug name as a lower classification level. All medications will be summarized by descending frequency of ATC level 4 and PT within a given ATC level 4 term. The summary will include the number and percent of the participants who used the medication at least once by treatment group and total using the FAS.

For each participant, the medication will be counted only once within each level 4 ATC and only once within a given preferred drug name level. A participant may appear more than once if he/she has more than one medication coded under different ATC categories; however, the participant will be counted only once in the overall category.

A by-participant listing with coded terms will also be provided along with calculated study start and stop days for the all randomized participants.

7.6. Medical Device Use

A prior medical device is any device used prior to the first IMP administration. A concomitant medical device is any device that started or continued after the first IMP administration.

The prior and concomitant medical device will be classified by System Organ Class (SOC) and Preferred Term (PT) using MedDRA Version 27.0.

The prior and concomitant medical device use will be summarized by treatment group and overall for the FAS. The summary will include the number and percent of the participants who used medical device at least once by treatment group. For each participant, the medical device

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use will be counted only once within each level SOC and only once within a given preferred drug name level.

A summary of the number and percentage of participants who discontinued use of a PAP device, in those who were on a PAP device at study initiation will be provided.

A summary of the number and percentage of participants who initiated use of a PAP device, in those who were not on a PAP device at study initiation will be provided.

A by-participant listing with coded terms will also be provided along with calculated study start and stop days for all randomized participants.

7.7. Prior and Concomitant Medical or Surgical Procedure

A medical or surgical procedure is collected with an indication of adverse event, medical history, prophylaxis or other.

A prior procedure is any procedure used prior to the first IMP administration. A concomitant procedure is any procedure that started or continued to be used after the first IMP administration and on or before the end of study treatment (last dose of IMP).

The prior and concomitant procedure will be classified by System Organ Class (SOC) and Preferred Term (PT) using MedDRA Version 27.0 or higher.

The prior and concomitant procedure will be summarized by treatment group and overall for the FAS. The summary will include the number and percent of the participants who had procedure done at least once by treatment group. For each participant, procedure will be counted only once within each SOC and only once within a given preferred name level.

A by-participant procedure listing with coded terms will also be provided along with calculated study start and stop days for all randomized participants.

7.8. Extent of Exposure

The duration of treatment (days) defined in Section 6.2.88.

The duration of exposure (days) = duration of treatment - duration of interruption, where duration of interruption (days) = sum of (interruption end date - interruption start date + 1)

The actual number of doses taken is the sum of quantity dosed across all visits.

The treatment duration, duration of exposure, total number of doses received will be summarized as a continuous variable by treatment group for the SS.

A listing of participant drug administration will also be provided for the SS.

7.9. Treatment Compliance

The study drug dispensed, dosed, remaining or missing are recorded by the Interactive Response Technology (IRT) system.

The number of doses expected is calculated as:

Total number of doses expected (doses) = Duration of Exposure (day)*1(does/day)

The drug compliance is calculated as:

Overall treatment compliance = 100 * (Total number of doses received /Total number of doses expected)

The number and percent of participants with dose interruptions, reason for interruption, overdose, overall treatment compliance, categorical compliance (<50%, 50%-<60%, 60%-<70%, 70%-<80%, 80-100%, >100%-120%, >120%) will be summarized by treatment group and overall for the FAS and SS.

A listing of participant treatment compliance will be provided for the SS.

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8. Efficacy

All efficacy analyses will be based on the FAS. Supportive analyses will be based on the MITT set for AHI and PP sets (if applicable).

8.1. Primary Efficacy Estimand(s)/Endpoint(s) and Analysis

The primary efficacy endpoint is the change from baseline to week 26 in AHI4.

The apnea-hypopnea index (AHI) is a diagnostic tool for determining the presence and severity of obstructive sleep apnea (OSA). OSA participants experience a collapse of their airways during sleep. When this causes their breathing to completely stop or reduce to 10% of normal levels for at least 10 seconds, it is called an apnea. Hypopneas occur when the airways partially collapse, resulting in shallow breathing. If the airflow decreases by more than 30% for at least 10 seconds, it can be considered a hypopnea. The AHI represents the average number of apneas and hypopneas participant experienced each hour during sleep. Normal AHI is less than 5 events per hour, while mild AHI is at least five events per hour, but less than 15; moderate AHI is at least 15 events per hour, but less than or equal to 30; Severe AHI is equal to or more than 30 events per hour. AHI4 is AHI based on 4% hypopnea desaturation and collected at screening, week 13, 26 and 51 visits.

The primary hypothesis:

- H_0 (null hypothesis): $\Delta_{AD109} - \Delta_{Placebo} = 0$,
- H_1 (alternative hypothesis): $\Delta_{AD109} - \Delta_{Placebo} \neq 0$,

where Δ_{AD109} and $\Delta_{Placebo}$ are the corresponding mean change from baseline to week 26 for the AD109 and placebo groups, respectively.

Primary Analysis

The primary analysis methodology will utilize a restricted maximum likelihood (REML) based mixed model for repeated measurements (MMRM) in combination with the Newton Raphson Algorithm. Analyses will include treatment, AHI4 strata, time and the treatment by time interaction as fixed effects and baseline score as a covariate. An unstructured covariance matrix will be used to model the within participant error. If the model fails to converge with an unstructured covariance matrix, a compound symmetric covariance matrix will be used. In the case that a structured variance-covariance matrix is used to enable the model to converge, the "sandwich" estimator of the variance-covariance matrix will be employed. The Kenward-Roger approximation will be used to estimate the denominator, degrees of freedom. The analysis will be implemented using the MIXED procedure in SAS. The lsmeans, and treatment difference in lsmeans for week 13, 26 and 51 will be reported along with the corresponding 95% confidence intervals and the p-values for the treatment group comparisons at week 13, 26, and 51. The primary comparison will be the contrast between treatment groups at week 26.

All data collected up to week 51, regardless of adherence to investigational intervention, and initiation of PAP will be used in the analysis. While every effort will be made to retain participants who discontinue investigational intervention in the trial, it is expected that there will be some missing data for a small proportion of participants at week 51. Based on a previously conducted phase 2 study (Mariposa), we anticipate that up to 5% of placebo participants and 25% of AD109 participants may be missing their week 51 data due to early withdrawal from the trial prior to week 51. Given the anticipated unequal distribution of missing data between the AD109 and Placebo group, missing data will be assumed to be missing not at random (MNAR) and the endpoint will be analyzed using a pattern- mixture model using a control-based approach by means of sequential modelling with multiple imputation as described by O'Kelly (2014).

We distinguish between monotone and non-monotone missing values. Non-monotone missing values are values missing intermittently, where a participant may miss some assessments but has assessments for the same score later in time. Monotone missing values are such that once a value is missing for a given score, no subsequent values for this score are available.

Any given participant may have a combination of non-monotone and monotone missing values.

Non-monotone missing data will be imputed first, followed by the imputation of monotone missing data.

Non-monotone missing values are assumed MAR and will be imputed using a Markov Chain Monte Carlo (MCMC) method of Proc MI in SAS. The imputation model will include the following:

- Treatment arm (active or placebo)
- Baseline AHI4 score

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- Baseline PROMIS Fatigue Raw Score
- Age
- BMI

To impute monotone missing values, we define patterns depending on reason and timing of missingness as follows:

- **Pattern 1:** missing values before or at week 51 after treatment discontinuation due to AE.
- **Pattern 2:** missing values before or at week 51 due to missing/invalid outcome measure that is not in pattern 1.

The patterns are mutually disjointed, i.e., each participant with monotone missing data belongs only to one pattern.

The following assumptions will be made for the missing data in each pattern:

For **pattern 1**, control-based approach will be used for the active arm. For the placebo arm, multiple imputation under MAR assumption will be used.

For **pattern 2** data will be assumed to be MAR in both treatment arms.

The imputation of monotone missing data will be done sequentially for visit, k=1, 2, 3 (where 1 corresponds to week 13, 2 corresponds to week 26 and 3 corresponds to week 51) as follows:

a) For the pattern 1 AD109 participants only, impute the monotone missing values at visit k using the multiple imputation regression model including the effects for baseline covariates as listed for the imputation model of non-monotone missing data above and outcome measure values at each schedule assessment time point up to (k-1); at this step we will include all participants from the active arm with missing data at visit k, plus participants from the placebo arm with visit k data observed. We omit participants from the active arm with outcomes observed at visit k. Multiple imputation will now estimate regression parameters for visit k using data from the placebo arm only. The imputed data for visit k for a participant from the active arm will look like the imputed data for a similar participant from the placebo arm.

b) For pattern 2 and for pattern 1 placebo participants only, impute the monotone missing values at visit k using an MAR-based multiple imputation regression model (PROC MI option MONOTONE REG) including the effects for baseline covariates as listed for the imputation model of non-monotone missing data above and outcome measure values at each schedule assessment time point up to (k-1).

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The above steps (a)-(b) are performed for each visit k, before proceeding with the imputations of the next visit (k+1).

A total of M=100 imputed datasets will be created. The random number generator seed for the imputation of non-monotone missing values using MCMC will be 2717, and the random seed for imputation of monotone missing values will be 2717+k, for k=1, 2, ... for each sequential visit with monotone missing data. For monotone missing imputation, the specified seed will be used for the first dataset.

The MMRM modeling with the identical setup as described above will be performed for each imputed dataset.

The SAS MI Analyze procedure will be used to combine the results of these analyses for the imputations by using Rubin's rule.

Supportive Analyses

The following supportive analyses will be performed:

1) The analysis of the primary efficacy endpoint of change from baseline in AHI4 at week 26 will be repeated using FAS and MITT set and a while on treatment estimand approach under Hypothetical Strategy. For FAS analysis all data collected after a participant has discontinued treatment will be set to missing while for MITT analysis all data collected after a participant has discontinued treatment will be imputed by last available on treatment value. This analysis aims at estimating the effect of AD109 compared with placebo in participants with mild to severe OSA with respect to the change from baseline in AHI4 while on treatment. The same statistical method (i.e., MMRM) will be applied.
2) The analysis of the primary efficacy endpoint will be repeated using the PPS-A set using observed data.

Observed Data Summaries

A descriptive summary of the actual and change from baseline values will be provided for each scheduled visit by treatment group considering only the observed data, i.e., without any imputation for missing values.

Sub-group Analysis

The primary endpoint will also be reported by sub-groups of interest to verify consistency of results across sub-groups. Sub-group analyses will only include participants with known sub-group data and participants missing sub-group information will be excluded. Missing data will be imputed using the same MI approach as described above for the primary analysis. An assessment

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of consistency will be made by evaluating the lsmeans difference and associated 95% confidence interval of the difference across sub-groups. These estimates will be obtained by fitting the above MMRM model but including fixed effect terms for the sub-group and sub-group by treatment by visit interaction in the model. The lsmeans, and treatment difference in lsmeans for week 13, 26 and 51 will be reported along with the corresponding 95% confidence intervals for each sub-group. Results will be reported in both tabular format and graphically displayed using Forest plots.

Exploratory Analyses

An exploratory analysis of the primary efficacy endpoint, using the above methods will also be conducted as follows:

- At week 13 for the FAS, PPS-A and MITT set
- AHI4 and Relative Change at week 13 26 and 51 based on the natural log scale of AHI4 and results after back-transformation. If AHI4 is reported as 0, log(0.01) will be used in place of log(AHI4) .

8.2. Key Secondary Efficacy Estimand/Endpoint and Analyses

In this study, the key Secondary Efficacy Endpoints include the following:

- The change from baseline in ODI3 at 26 weeks
- The relative change from baseline in HB4 at 26 weeks (based on natural log scale of HB4)
- Proportion of participants with ≥50% reduction in AHI4 at week 26
- The change from baseline in PROMIS-Fatigue T-score at 26 weeks

8.2.1. Definition of the Continuous Key Secondary Efficacy Endpoints

In this study, ODI3 and HB4 are assessed at screening, week 13, 26 and 51 visits. PROMIS-Fatigue and PROMIS-Sleep Impairment are assessed at screening, week 4, 13, 26, 39, 51 and 53 visits.

ODI3: Oxygen desaturation index (ODI) based on 3% hypopnea desaturation measures the frequency of blood oxygen saturation decreases by 3% from baseline per hour of sleep.

HB4: Hypoxic burden is a measure to capture the total amount of respiratory event-related hypoxaemia over the sleep period. The hypoxic burden was defined as the total area under the respiratory event-related desaturation curve divided by the total area of the sleep duration, with the units of hypoxic burden being (%min)/h. HB4 will be analyzed on the natural log scale of

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HB4, i.e. log(HB4) and results will be back transformed. If HB4 is reported to be 0, log(0.01) will be used in place of log(HB4).

PROMIS-fatigue: PROMIS fatigue measures were developed with modern psychometric techniques including item response theory to assess various self-reported aspects of sleep and daytime impairment. Items are based on 5-point scales, either frequency or intensity, with higher scores corresponding to more severe or worse symptoms. The total raw score is the sum of all items.

The total raw score will be translated into a T-score by using standardized score with a mean of 50 and a standard deviation (SD) of 10 using scoring table for PROMIS Fatigue and Sleep Impairment, respectively.

8.2.2. Analyses of the Continuous Key Secondary Efficacy Endpoints

These key secondary endpoints will be analyzed using the FAS and MITT set.

These key secondary endpoints will be analyzed using the same methods as outlined for the primary endpoint, in Section 8.1, including the supportive, and sub-group analyses as well as the observed summaries.

In addition to an analysis at week 26, these endpoints will also be compared at weeks 4, 13, 39 (where applicable) and 51 as an exploratory analysis using the same analysis methods as applied to week 26. Week 53 EOS assessment, if collected, will be summarized by descriptive statistics and excluded from the MMRM analyses.

For PROMIS-Fatigue, responder analysis of meaningful within participant change (MWPC) will be provided for week 4, 13, 26, 39 and 51. Treatment groups will be compared at each post baseline time point using a stratified Cochran-Mantel Haenszel (CMH) test, controlling for randomization strata using the FAS set. Missing data will be imputed as non-responders. The adjusted risk difference of the response rates between AD109 vs placebo, along with the 2-sided 95% CI for the risk difference will be obtained using the Mantel-Haenszel estimate based on the Mantel-Haenszel stratum weights and the Sato variance estimator. The MWPC cut-offs will be defined after DB lock.

Cumulative distribution plot for the change from baseline in PROMIS-Fatigue T-score will be provided for week 4, 13, 26, 39 and 51.

8.2.3. Proportion of Participants with ≥50% Reduction in AHI4 at Week 26

The proportion of participants with ≥50% reduction in AHI4 at week 26 will be compared between treatment groups using the stratified Cochran-Mantel Haenszel procedure, controlling

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for randomization strata. An estimate of the unadjusted response rates in AD109 and placebo, the adjusted risk difference of the response rates between AD109 vs placebo, along with the 2- sided 95% CI for the risk difference will be presented. The Mantel-Haenszel estimate of the adjusted risk difference, and confidence limits for the adjusted risk difference will be based on the Mantel-Haenszel stratum weights (Mantel and Haenszel 1959) and the Sato variance estimator (Sato 1989).

All observed data will be used for analysis. Monotone missing data will be imputed as follows:

1) If a participant is missing data due to discontinuation as a result of an AE they will be considered as a non-responder for any timepoint after treatment discontinuation.

2) If a participant is missing data for other reasons their data will be imputed using MI assuming data is MAR.

For missing data we will distinguish between monotone and non-monotone missing values. Non-monotone missing values are values missing intermittently, where a participant may miss some assessments but has assessments for the same score later in time. Monotone missing values are such that once a value is missing for a given score, no subsequent values for this score are available. Any given participant may have a combination of non-monotone and monotone missing values.

Non-monotone missing data will be imputed first, followed by the imputation of monotone missing data.

Non-monotone missing values are assumed to be MAR and will be multiply imputed using a Markov Chain Monte Carlo (MCMC) method of Proc MI in SAS. The imputation model will include the following:

- Treatment arm (active or placebo)
- Baseline AHI4 score
- Baseline PROMIS Fatigue Raw Score
- Age
- BMI

The imputation of monotone missing data will be done sequentially for visit, k=1, 2, 3 (where 1 corresponds to week 13, 2 corresponds to week 26, and 3 corresponds to week 51 as follows:

1) Impute the monotone missing values at visit k using an MAR-based multiple imputation regression model (PROC MI option MONOTONE REG) including the effects for baseline covariates as listed for the imputation model of non-monotone missing data above and observed values at each schedule assessment time point up to (k-1).
2) Repeat the above step for each visit k, before proceeding with the imputations of the next visit (k+1).

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A total of *M*=100 imputed datasets will be created. The random number generator seed for the imputation of non-monotone missing values using MCMC will be 6879, and the random seed for imputation of monotone missing values will be 6879+*k*, for *k*=1, 2, ... for each sequential visit with monotone missing data. For monotone missing imputation, the specified seed will be used for the first dataset.

For each imputed dataset, a participant's response will be derived (i.e., ≥ 50% reduction in AHI4) and then each dataset will be analyzed using the stratified CMH test described above.

The individual results will then be combined using Rubin's rule (PROC MIANALYZE). The stratified risk difference is asymptotically normally distributed and can be combined using SAS PROC MIANALYZE directly. To obtain the combined p-value, as the CMH test statistic has a chi-square distribution, it will require transformation to normalize the CMH test statistic. The Wilson-Hilferty transformation will be used to normalize the CMH test statistic.

First, the following transformation will be done:

$$wh_cmh^{(m)} = \sqrt[3]{cmh^{(m)}/df}$$

Where *cmh(m)* is the CMH statistic computed from the *m*th imputed dataset, *df* is the number of degrees of freedom associated with the CMH statistic, and *wh_cmh(m)* is the transformed value. This transformed statistic is approximately normally distributed with mean 1-2/(9 x *df*) and variance 2/(9x *df*) under the null hypothesis. This value will then be standardized to have a mean of 0 and a variance of 1 as follows:

$$st_{wh_cmh^{(m)}} = \frac{\sqrt[3]{cmh^{(m)}/df} - \left(1 - \frac{2}{(9 * df)}\right)}{\sqrt[2]{\frac{2}{(9 * df)}}}$$

This final transformed variable will then be passed through SAS PROC MIANALYZE to obtain the combined CMH test. The p-value of the combined CMH test is then obtained as the upper tailed p-value from the normal test produced by SAS PROC MIANALYZE on the transformed variable.

Sub-group Analyses

This endpoint will also be reported by sub-groups of interest, using the FAS to verify consistency of results across sub-groups. An assessment of consistency will be made using a stratified CMH test, with sub-group as strata. The risk difference and associated two-sided 95% confidence interval (based on the Wald Method) will be reported for each sub-group. In these analyses, missing data for sub-group inclusion will be maintained as missing, and these participants will not be included. Missing data will be handled as outlined above. Results will be reported in both

tabular format and graphically displayed using Forest plots. The p-value from the Breslow-Day test of homogeneity will also be reported. As Breslow-Day test statistic has a chi-square distribution, similar approach as for CMH test will be used to calculate p-values based on MI data.

Supportive Analyses

The following supportive analyses will be performed:

- The analysis will be repeated using the MITT set and a while on treatment estimand approach. For this analysis all data collected after a participant has discontinued treatment will be set to missing and their last observation while on treatment will be carried forward. This analysis aims at estimating the effect of AD109 compared with placebo in participants with mild to severe OSA with respect to achieving a 50% reduction in AHI4 while on treatment. The same statistical method (i.e., CMH test) will be applied.
- Similar subgroup analysis as for FAS using the MITT set and while on treatment and LOCF approach.

Exploratory Analyses

An exploratory analysis using the above methods will also be conducted as follows:

- At week 13 and 51 for the FAS and MITT
- At week 13, 26 and 51 for PPS-A set

8.3. Other Secondary Efficacy Endpoints and Analyses

In this study, the other Secondary Efficacy Endpoints include the following:

- The change from baseline in PGI-S for Fatigue at 26 weeks
- PGI-C for Fatigue at 26 weeks
- The change from baseline in ESS at 26 weeks
- The change from baseline in PROMIS-Sleep Impairment T-score at 26 weeks

These endpoints will be analyzed using both the FAS and MITT.

8.3.1. Definition of Other Secondary Efficacy Endpoints

In this study, PGI-S for Fatigue and ESS are assessed at Screening, Week 4, 13, 26, 39, 51 and 53 visits. PGI-C for Fatigue is assessed at Week 4, 13, 26, 39, and 51 visits.

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PGI-S for Fatigue: PGI-S is a single-item scale of the patient's global, i.e., overall impression of severity of fatigue in the past 7 days. The response includes:

- None
- Mild
- Moderate
- Severe
- Very severe

For scoring PGI-S, set none=1, mild=2, moderate=3, severe=4 and very severe=5.

PGI-C for Fatigue: PGI-C for Fatigue is single-item scales of change in the severity of fatigue from pre-treatment to the time point measured. The response includes:

- Much better
- A little better
- No change
- A little worse
- Much worse

For scoring PGI-C, set much better=1, a little better=2, no change=3, a little worse=4 and much worse=5.

ESS score: The ESS is a self-administered questionnaire with 8 questions. Participants are asked to rate, on a 4-point scale (0-3), their usual chances of dozing off or falling asleep while engaged in 8 different activities in recent times. The ESS score (the sum of 8 item scores) can range from 0 to 24. The higher the ESS score, the higher that person's average sleep propensity in daily life, or their 'daytime sleepiness'.

PROMIS--Sleep Impairment: PROMIS Sleep Impairment measures were developed with modern psychometric techniques including item response theory to assess various self-reported aspects of sleep and daytime impairment. Items are based on 5-point scales, either frequency or intensity, with higher scores corresponding to more severe or worse symptoms. The total raw score is the sum of all items.

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The total raw score will be translated into a T-score by using standardized score with a mean of 50 and a standard deviation (SD) of 10 using scoring tables for PROMIS fatigue and sleep impairment, respectively.

8.3.2. Analyses of the Secondary Efficacy Endpoints

These endpoints will be analyzed using both the FAS and MITT set.

These secondary endpoints will be analyzed using the same methods as outlined for the key secondary endpoint in Section 8.2, including the supportive using MITT, and sub-group analyses as well as the observed summaries. Week 53 EOS assessment, if collected, will be summarized by descriptive statistics and excluded from MMRM analyses.

For the endpoint PGI-C, as no baseline score is collected for PGI-C, the baseline score for PGI-S will be included in the model.

For PROMIS-Sleep Impairment, responder analysis of meaningful within participant change (MWPC) will be provided for week 4, 13, 26, 39 and 51. Treatment groups will be compared at each post baseline time point using a stratified Cochran-Mantel Haenszel (CMH) test, controlling for randomization strata using the FAS set. Missing data will not be imputed, and patients with missing data will be imputed as non-responders. The adjusted risk difference of the response rates between AD109 vs placebo, along with the 2-sided 95% CI for the risk difference will be obtained using the Mantel-Haenszel estimate based on the Mantel-Haenszel stratum weights and the Sato variance estimator. The MWPC cut-offs will be defined after DB lock.

Cumulative distribution plots for the change from baseline in PROMIS-Sleep Impairment will be provided for week 4, 13, 26, 39 and 51.

In addition to an analysis at week 26, these endpoints will also be compared at week 4, 13, 39, 51 as an exploratory/tertiary analysis using the same analysis methods as applied to week 26.

8.4. Tertiary Efficacy Endpoints and Analyses

The tertiary endpoints include:

- Change from Baseline in ODI3 at 51 weeks
- Change from Baseline in natural log scale of HB4 at 51 weeks
- Proportion of participants with ≥50% reduction in AHI4 at 51 weeks
- Change from Baseline in PROMIS-Fatigue T-score at 51 weeks
- Change from Baseline in PGI-S for Fatigue at 51 weeks

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- PGI-C for fatigue at 51 weeks
- Change from Baseline in ESS at 51 weeks
- Change from Baseline in PROMIS-Sleep Impairment T-score at 51 weeks

The tertiary efficacy endpoints will be analyzed for the FAS and MITT, using the same methods as outlined for the primary endpoint as appropriate. Tertiary endpoints defined as a responder/non-responder will use the methods outlined for the key secondary endpoint defined as a proportion and tertiary endpoints that are continuous/ordinal will use the methods outlined for the primary endpoint.

A descriptive summary of the observed actual and change from baseline values will be provided for each of the tertiary efficacy endpoints at each scheduled visit by treatment group.

8.5. Exploratory Efficacy Endpoints and Analyses

These endpoints will be analyzed using the MITT analysis set for AHI as specified.

Percent of participants with AHI4<15, <10 and <5 at 13, 26 and 51 weeks,

Treatment groups will be compared at each post baseline time point for the MITT anlaysis set using a stratified Cochran-Mantel Haenszel (CMH) test, controlling for randomization strata. An estimate of the unadjusted response rates in AD109 and placebo, the adjusted risk difference of the response rates between AD109 vs placebo, along with the 2- sided 95% CI for the risk difference will be presented. The Mantel-Haenszel estimate of the adjusted risk difference, confidence limits, and test for the adjusted risk difference will be based on the Mantel-Haenszel stratum weights and the Sato variance estimator. For this analysis all data collected after a participant has discontinued treatment will be set to missing. Missing data will be imputed using Last Observation Carried Forward (LOCF) approach.

Cumulative distribution plots of the change from baseline by treatment group will also be produced for 13, 26 and 51 weeks for all participants.

Proportion of participants with AHI4 reduction of ≥ 30% to ≥ 90% by 10%

Treatment groups will be compared at each post baseline time point using a stratified Cochran-Mantel Haenszel (CMH) test, controlling for randomization strata using the FAS and MITT set respectively. For FAS, participants with missing data will be treated using the same MI approached as described in section 8.2.3, and for the MITT all data collected after a participant has discontinued treatment will be set to missing. Missing data will be imputed using LOCF The adjusted risk difference of the response rates between AD109 vs placebo, along with the 2- sided

95% CI for the risk difference will be using the Mantel-Haenszel estimate based on the Mantel-Haenszel stratum weights and the Sato variance estimator.

Change from baseline in AHI3a, at 13, 26 and 51 weeks

Change from baseline AHI3a will be analyzed using the same methods as outlined for the primary endpoint, in Section 8.1, including the supportive, and sub-group analyses as well as the observed summaries.

Change from baseline in HB3a and ODI4 at 13, 26 and 51 weeks

These endpoints will be analysed using the MITT set. Treatment groups will be compared at each post baseline time point utilizing a restricted maximum likelihood (REML) based mixed model for repeated measurements (MMRM) in combination with the Newton Raphson Algorithm. Analyses will include treatment, AHI4 strata (derived from AHI4 score at baseline), time and the treatment by time interaction as fixed effects and baseline score as a covariate. An unstructured covariance matrix will be used to model the within participant error. If the model fails to converge with an unstructured covariance matrix a compound symmetric covariance matrix will be used. In the case that a structured variance-covariance matrix is used to enable the model to converge, the "sandwich" estimator of the variance-covariance matrix will be employed. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The analysis will be implemented using the MIXED procedure in SAS. The lsmeans, and treatment difference in lsmeans for 13, 26 and 51 weeks will be reported along with the corresponding 95% confidence intervals and the p-values for the treatment group comparisons at 13, 26 and 51 weeks. Missing data will be assumed to be MAR and maintained as missing.

For HB3a, data will be analyzed on the natural log scale of HB3a and results will be back transformed. If HB3a is reported to be 0, log(0.01) will be used in place of log(HB3a).

Change from Baseline in Non-Rapid Eye Movement Apnea-Hypopnea Index [NREM AHI] at 13, 26 and 51 weeks

These endpoints will be analysed using the MITT set. Treatment groups will be compared at each post baseline time point utilizing a restricted maximum likelihood (REML) based mixed model for repeated measurements (MMRM) in combination with the Newton Raphson Algorithm. Analyses will include treatment, AHI4 strata, time and the treatment by time interaction as fixed effects and baseline score as a covariate. An unstructured covariance matrix will be used to model the within participant error. If the model fails to converge with an unstructured covariance matrix a compound symmetric covariance matrix will be used. In the case that a structured variance-covariance matrix is used to enable the model to converge, the "sandwich" estimator of the variance-covariance matrix will be employed. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The analysis will be

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implemented using the MIXED procedure in SAS. The lsmeans, and treatment difference in lsmeans for week 13, 26 and 51 will be reported along with the corresponding 95% confidence intervals and the p-values for the treatment group comparisons at weeks 13, 26 and 51. Missing data will be assumed to be MAR and maintained as missing.

Change from Baseline in Rapid Eye Movement Apnea-Hypopnea Index [REM AHI] at 13, 26 and 51 weeks (excluding participants whose PSG has <10 minutes of REM sleep)

These endpoints will be analysed using the MITT set. Treatment groups will be compared at each post baseline time point utilizing a restricted maximum likelihood (REML) based mixed model for repeated measurements (MMRM) in combination with the Newton Raphson Algorithm. Analyses will include treatment, AHI4 strata, time and the treatment by time interaction as fixed effects and baseline score as a covariate. An unstructured covariance matrix will be used to model the within participant error. If the model fails to converge with an unstructured covariance matrix a compound symmetric covariance matrix will be used. In the case that a structured variance-covariance matrix is used to enable the model to converge, the "sandwich" estimator of the variance-covariance matrix will be employed. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The analysis will be implemented using the MIXED procedure in SAS. The lsmeans, and treatment difference in lsmeans for week 13, 26 and 51 will be reported along with the corresponding 95% confidence intervals and the p-values for the treatment group comparisons at weeks 13, 26 and 51. Missing data will be assumed to be MAR and maintained as missing.

Change from baseline in supine AHI4 [AHI4S] at 13, 26 and 51 weeks (excluding participants whose PSG has <10 minutes of supine sleep)

These endpoints will be analysed using the MITT set. Treatment groups will be compared at each post baseline time point utilizing a restricted maximum likelihood (REML) based mixed model for repeated measurements (MMRM) in combination with the Newton Raphson Algorithm. Analyses will include treatment, AHI4 strata, time and the treatment by time interaction as fixed effects and baseline score as a covariate. An unstructured covariance matrix will be used to model the within participant error. If the model fails to converge with an unstructured covariance matrix a compound symmetric covariance matrix will be used. In the case that a structured variance-covariance matrix is used to enable the model to converge, the "sandwich" estimator of the variance-covariance matrix will be employed. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The analysis will be implemented using the MIXED procedure in SAS. The lsmeans, and treatment difference in lsmeans for week 13, 26 and 51 will be reported along with the corresponding 95% confidence intervals and the p-values for the treatment group comparisons at weeks 13, 26 and 51. Missing data will be assumed to be MAR and maintained as missing.

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Change from baseline in TST and percentage of TST in sleep stages (sleep efficiency [SE]; wake after sleep onset [WASO]; sleep onset latency [SOL]; Stage N1% [N1P], Stage N2% [N2P], Stage N3% [N3P], Stage R% [RP])

These endpoints will be analysed using the MITT set. Descriptive summary, including n, mean, median, SD, minimum and maximum of the observed actual and change from baseline values will be provided for SE, WASO, SOL, N1P, N2P, NP and RP at each scheduled visit by treatment group.

Change from baseline in Arousal Indices (Arousal Index - Respiratory [ARIR]; Arousal Index - total [ARI])

These endpoints will be analysed using the MITT set. Descriptive summary, including n, mean, median, SD, minimum and maximum of the observed actual and change from baseline values will be provided for ARIR and ARI at each scheduled visit by treatment group.

Change from baseline to 13, 26 and 51 weeks in OSA Severity (Mild, Moderate, Severe)

At baseline and each post baseline visit, the participant's OSA Severity will be categorized as either None, Mild, Moderate or Severe, based on their AHI4 score according the following definition: None: 1-AHI4 <5, 2-Mild: AHI4 5 to <15, 3-Moderate: AHI4 15 to <30, and 4-Severe: AHI4 ≥30.

For the change in OSA severity, a shift table from baseline to 13, 26 and 51 weeks in OSA severity will be provided. Treatment comparing for OSA severity will be performed using CMH (with Modified Ridit Scores) controlling for randomization strata. Coded OSA Severity score 1-4 will be used for this testing and p-value will be reported.

Change from baseline to 13, 26 and 51 weeks in OSA Severity will be analyzed using the FAS and MITT set. For analysis on FAS, missing AHI4 will be imputed using multiple imputation as described in SAP section 8.1 and the OSA Severity is derived based on imputed data. For analysis on MITT, only observed data will be used for analysis. If a participant is missing their AHI4 score, they will be categorized as missing. In addition, an exploratory analysis on MITT will be performed, in which missing data or data after treatment discontinuation are imputed using LOCF based on data prior to treatment.

Exploratory Analysis of Snoring

To examine the effect of AD109 on reducing the degree of snoring, exploratory analyses will be conducted to compare the proportion of loud breaths (i.e., snoring) recorded during the PSG assessment between treatment groups at week 26 using the MITT population. Data from study APC-APN-304 and APC-APN-305 will be combined for this analysis. Results from this analysis

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will be reported separately from the CSR, and data will not be included in the SDTM and ADaM datasets.

The sound level (i.e., the decibel increase above background noise) and the percentage of breaths recorded above a given sound level, will be used to select participants who are considered to snore at baseline. Given the absence of a standardized definition for snoring in participants, we will employ nine distinct criteria to identify moderate-to-loud snorers using baseline data from the MITT population.

1) ≥ 5% of breaths with >20 decibel increase from background

2) ≥ 10% of breaths with >20 decibel increase from background

3) ≥ 15% of breaths with >20 decibel increase from background

4) ≥ 5% of breaths with >25 decibel increase from background

5) ≥ 10% of breaths with >25 decibel increase from background

6) ≥ 15% of breaths with >25 decibel increase from background

7) ≥ 5% of breaths with >30 decibel increase from background

8) ≥ 10% of breaths with >30 decibel increase from background

9) ≥ 15% of breaths with >30 decibel increase from background

For each of these 9 cohorts the percentage of breaths above the decibel threshold used to select the cohort will be summarized at each post baseline time point using descriptive statistics. Treatment groups will be compared at Month 6 using an ANCOVA model that will include treatment, AHI strata, and study as fixed effects and baseline score as a covariate. The lsmeans, and treatment difference in lsmeans will be reported along with the corresponding 95% confidence interval and the p-values for the treatment group comparison. Missing data will be assumed to be MAR and maintained as missing.

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9. Safety

The population used for all safety analyses will be the Safety Set (SS). Safety will be assessed based on adverse event (AE), clinical laboratory data, ECG parameters, physical examinations, and vital signs. Safety data will be presented by treatment for all participants.

9.1. Adverse Events / Adverse Drug Reactions

All AEs will be coded and classified by System Organ Class (SOC) and Preferred Term (PT) using MedDRA Version 27.0 or higher. All AEs that occur after the first dose of IMP (i.e., date of onset is on or after the first dose of IMP) and on or before the end of treatment (last dose of blinded IMP) + 7 days will be considered treatment emergent adverse events (TEAEs) for the purpose of reporting and will be summarized using frequency counts and percentages. In addition, the number of events will also be provided. Summaries will be presented by treatment group and overall. All AEs will be provided in a data listing with an indication of if they are TEAEs. See Section 6.2.9 for determining if an AE is a TEAE based on partial/missing dates.

Summaries of TEAEs will be presented using the MedDRA level hierarchy (system organ class and preferred term) as follows:

- Overall (i.e., regardless of intensity or relationship to treatment)
- Most common (i.e., regardless of intensity or relationship to treatment) based on a frequency of ≥ 5% in the AD109 group and greater than placebo
- By intensity grade (mild, moderate, severe)
- By relationship to study medication (related, not-related)

Unless otherwise specified, at each level of participant summarization in reporting the incidence of the AEs, a participant will be counted once if the participant reported one or more events. If more than one occurrence of an event is reported, the event of the worst intensity will be summarized. The summaries will be presented by descending frequency by SOC and PT in the overall column and then alphabetically within PT.

TEAEs leading to premature discontinuation of IMP, TEAEs of primary reason to treatment discontinuation and serious TEAEs (SAEs) will also be summarized by treatment group and relationship. TEAEs leading to premature discontinuation of IMP will be defined as any TEAEs with an action taken regarding study medication equal to “permanently discontinued.”

The following adverse events of special interest (AESIs) have been pre-defined:

- Urinary Hesitation
- Urinary Retention
- Liver Injury
    - Hepatic Failure

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  - Hepatic Injury
- Cardiovascular
  - Hypotension Group
  - Palpitations Group
  - Myocardial Ischemia
  - Systemic Hypertension
  - Stroke and Transient Ischemic Attack (TIA)
- Suicidal Ideation
- Daytime Sleepiness
- Motor Vehicle Accidents
- Anticholinergic Effects
- Psychiatric disorders
  - Mania
  - Psychosis

Appendix 1 includes the list of FDA Medical Queries (FMQs) and/or consolidated PTs that will be used to identify the above AESIs. The checkbox on the AE eCRF will not be used to identify AESIs.

In addition, an overall summary table will be provided that includes the following:

- Any AE
- Any TEAE
- Any treatment-related TEAE
- Any serious TEAE
- Any TEAE leading to IMP discontinuation
- Any TEAE with outcome of death
- Any TEAESI

9.2. Laboratory Evaluations

In this study, serum and urine samples will be collected for hematology, clinical Chemistry and urinalysis, as described in **Table 1**, at screening visit, week 26 and 51 visit. The laboratory samples will be analyzed at a central laboratory facility and results will be transfer to the sponsor for data analysis.

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Table 1: 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 HbA1c	ALT AST Alkaline phosphatase Calcium Magnesium Total Protein	Glucose Total cholesterol HDL cholesterol LDL cholesterol Chloride Bicarbonate Uric acid
Routine Urinalysis	Specific gravity, bilirubin, color, appearance, leukocyte esterase, nitrite, pH, protein (albumin), glucose, ketones, occult blood, urobilinogen Microscopic examination (if positive protein, leukocyte esterase, blood or nitrite)		
Other Tests	• Serum hCG pregnancy test at screening. Additional testing may be performed if needed in WOCBP. • Urine test of drugs of abuse (marijuana, cocaine, amphetamine, methamphetamine, opiates, phencyclidine, barbiturates, benzodiazepines, propoxyphene); immunoassay with gas chromatography-mass spectrometry confirmation of positive results • FSH may be performed to aid in determination of menopausal status		

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; FSH = follicle stimulating hormone; HbA1c = hemoglobin A1c (glycated hemoglobin); hCG = human chorionic gonadotropin; RBC = red blood cell count; WBC= white blood cell; WOCBP = women of childbearing potential.

Results from the hematology, serum chemistry, and urinalysis will be summarized for each visit by treatment group and overall using the SS. Summaries will include the observed values and change from baseline values for numeric parameters (number of participants, mean, standard deviation, median, minimum, and maximum) and distribution of categories for categorical parameters (number and percentages).

In addition, shift tables with the categorization of low/normal/high based on the normal range will be provided showing the shift from baseline to each post-baseline visit.

By participant hematology, serum chemistry, and urinalysis results listings will be generated and flagged as abnormally high or low relative to the reference range, where applicable.

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Note:

1. All laboratory results will be summarized in tables and listings using SI units, with select labs using conventional units.
2. Laboratory reference ranges will be used to identify abnormalities with low, normal, or high values.
3. In the summary tables, missing lab results will not be imputed and will be maintained as missing in all descriptive summary statistics.
4. Analysis visit will be used in the summary tables. For each participant, a single result will be selected for each visit.
5. Laboratory tests will be listed in alphabetical order within their respective panels and categories. For example, all liver function tests will be presented together.

9.3. Vital Signs

In this study, the vital signs will be measured at clinic visit and recorded on the eCRF at the Screening visit, Baseline visit, Week 4, 13, 26, 39, 51 and EOS Week 53, also vital signs will be measured at 1 hour after end of PSG on day 2 of Week 13, 26 and 51, as outlined in the Schedule of Assessments in study Protocol Table 1. The Vital signs will include (Systolic and Diastolic Blood Pressure (mmHg), Heart Rate (bpm), Body Temperature (C), Respiratory Rate (breaths per minute), height (cm), body weight (kg) and BMI. The systolic and diastolic blood pressure will be measured in seated position after 5 minutes' rest and 3 readings will be collected at each visit. For analysis, the average of last 2 readings will be used for the summary analysis if multiple readings.

For participants who agree to ABPM, the Systolic and Diastolic Blood Pressure (mmHg), Heart Rate (beats/min), Mean Arterial Pressure (mmHg) and Pulse Pressure (mmHg) will be measured for 24 hours at Baseline visit and Week 4. The average of the measurements during the 24 Hours, Daytime from the hours between 9 am to 9 pm, and Nighttime from the hours between 1 am and 6 am will be calculated and used for the summary analysis. Vital sign and ABPM data will be summarized for each nominal visit by treatment group and overall using the SS. Summaries will include the observed values and change from baseline values for numeric parameters (number of participants, mean, standard deviation, median, minimum, and maximum).

Vital sign and ABPM data will be listed chronologically by participant and visit for each vital sign parameter.

Note:

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1. In the summary tables, missing vital sign results will not be imputed and will not be counted in the descriptive summary statistics.

2. Nominal visit as collected will be used in the summary tables, i.e. visit window is not applicable. For each participant, a single result will be selected for each visit.

   The nominal visits for vital signs are:

   - Baseline – Day 1 (Evening before PSG)
   - Baseline – Day 2 (Morning after PSG)
   - Baseline V3
   - Week 4
   - Week 13 – Day 1
   - Week 13 – Day 2 (Post PSG)
   - Week 26 – Day 1
   - Week 26 – Day 2 (Post PSG)
   - Week 39
   - Week 51 – Day 1
   - Week 51 – Day 2 (Post PSG)
   - EOS Week 53

   The following table shows the baseline vital signs value to use in deriving the change from baseline for each post baseline nominal visit.

Post Baseline Visit	Baseline Value for deriving Change
Week 13 - Day 1 (Evening before PSG) Week 26 - Day 1 (Evening before PSG) Week 51- Day 1 (Evening before PSG)	Baseline – Day 1 (Evening before PSG)
Week 13 - Day 2 (Post PSG) Week 26 –Day 2 (Post PSG) Week 51 - Day 2 (Post PSG)	Baseline – Day 2 (Morning after PSG)
Week 4 Week 39 EOS Week 53	Baseline – Visit 3 (V3)

   The nominal visits for ABPM are: Baseline and Week 4.

9.4. ECG

In this study, a standard 12-lead ECG will be performed locally at the site and recorded on eCRF at the Screening visit, Week 26 and 53, as outlined in the Schedule of Assessments in study Protocol Table 1, using an ECG machine that automatically calculates the heart rate (beats/min)

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and measures PR interval (msec), QRS duration (msec), QT interval (msec), QTcF interval (msec). In addition, the overall ECG interpretation (normal, abnormal CG, abnormal NCG, unable to evaluate) will be assessed.

ECG data will be summarized for each visit by treatment group and overall using the SS. Summaries will include the observed values and change from baseline values for heart rate, PR, QRS, QT, QTcF (number of participants, mean, standard deviation, median, minimum, and maximum) and distribution of overall ECG interpretation (number and percentages)

Additionally, the numbers and percentages of participants with ECG abnormalities at each visit will be presented. The parameters and abnormality criteria are specified in the table below.

Parameter	**Abnormality Criterion**
PR interval	<110 msec
	>300 msec
QRS interval	≥120 msec
QTcF	<350 msec
	>450msec
	>500msec
	>550msec
Δ QTcF*	>30msec
	>60msec
Heart rate	<50 bpm
	>110 bpm

* Change from baseline in QTcF.

Shift tables will also be used to show the changes from baseline to each post baseline time point based on the above abnormality criteria (with the exception of Δ QTcF).

ECG data will be listed chronologically by participant and visit for each parameter: heart rate, PR, QRS, QT, QTcF and overall ECG interpretation.

Note:

1. In the summary tables, missing ECG results will not be imputed and will not be counted in the descriptive summary statistics.
2. Nominal visit will be used in the summary tables. For each participant, a single result will be selected for each visit. If multiple results are available for the same visit, the results closest to the target visit day will be selected. If more than one result are available for the same day, the first one will be selected.

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9.5. Physical Examination

In this study, a full comprehensive physical examination will be performed at the Screening Visit, which includes the assessment for the following body systems: general Appearance, dermatologic, Head, Eyes, Ears, Nose, Mouth/Throat/Neck, Thyroid, Lymph Nodes, Respiratory, Cardiovascular, Gastrointestinal, Extremities, Musculoskeletal, Neurologic, Psychiatric, Other.

Participants with abnormal physical examination will be summarized by treatment group and overall using the SS. Summaries will include the number and percentage of participants with abnormal physical examination in organ or body system.

Physical examination data will be listed by participant and body system.

9.6. Other Safety

The Other safety endpoints include the followings:

- Digit Symbol Substitution Test (DSST)
- Psychomotor Vigilance Test (PVT)
- Verbal learning task (VLT)
- Modified cocaine selective severity assessment (M-CSSA)
- Self-reported Montgomery-Asberg depression rating scale (MADRS-S)
- Spielberger Anxiety Inventory (STAI) - short form

DSST: The DSST measures a range of cognitive and motor operations including motor speed, attention, visuo-perceptual functions, and some aspects of associative learning. In this study, the DSST is used as a safety measure for psychomotor impairment related to residual next-day effects of IMP dosed at bedtime. The DSST is a key of nine digit-symbol pairs and a test set of ten digits with empty spaces below them. The individual is instructed to match each digit to its corresponding symbol. When all ten digits of the test set have been matched, a new test set is presented. Individuals are instructed to complete as many digit-symbol matches as possible within 60 seconds. The score is the number of correct symbols filled in within the time limit. Higher scores indicate better cognitive performance. Errors are typically not penalized directly, but they do reduce the total number of correct items completed, affecting the overall score. In addition to the number of slots correct, the accuracy rate (defined as the number of matches correct divided by the total number of matches; correct, incorrect and skips) will be reported.

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PVT: The PVT measures sustained attention and reaction time. In addition to reaction time, the test records lapse, in which the screen is not pressed in response to a cue, and false-positives in which the screen is pressed prior to appearance of the cue. The following endpoints will be derived:

- Accuracy Rate is the percentage of correct responses
- Mean and Median Response Time (ms)
- No Response Rate is the percentage of no responses
- False Response Rate is the percentage of early responses
- Count of Lapses is number of no responses or responses with reaction time > 500 ms
- PVT Performance is percent of correct responses with reaction time ≤ 500 ms out of all correct and incorrect responses.

VLT: The VLT measures the ability to store words in working memory and long-term memory.

The test has two phases, the learning phase (working memory) and the recall phase (long term memory). In the learning phase, participants are instructed to pay attention to a list of 12 spoken words that are visually presented simultaneously on the screen, and to verbally repeat as many words as they can remember from the list. This cycle of presenting and repeating the same words is repeated three times. The recall phase is done after a prescribed delay and divided into the free recall task and the recognition task. During the free recall task, participants are asked to verbally recall as many of the words as they can remember from the original list of words presented during the learning phase. During the subsequent recognition task, participants are sequentially presented with 24 words, which consist of words from the original list and new words (distractors), and are then instructed to respond as to whether that word was one they had heard before or not. There is no single overall summary score. The following domain scores will be provided:

- VLT Learning
    - Immediate Recall in the1st Trial
        - Immediate Recall 1: number of correct words for first reading of word list
    - Immediate Recall in the 3rd Trial
        - Immediate Recall 3: number correct words for last reading of word list
    - Learning Rate, defined as the number of correct words in the 3rd trial minus the number of correct words in the 1st trial) / (number of trails -1)
- VLT-Recall
    - Delayed Recall

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        - Delayed Recall: number of correct words during the free recall phase (only first row for given block will have this value)
    - Recognition Accuracy
        - Recognition Accuracy: average accuracy value for all recognition trials (all rows except for first row for a given block). This is the proportion of target words and distractor words that were correctly identified.

M-CSSA: the CSSA was originally designed to measure the signs and symptoms of cocaine withdrawal. In this study, the CSSA is used as a safety measure for withdrawal symptoms that might be caused by AD109, particularly the atomoxetine component, which affects the norepinephrine system, a system also affected by cocaine. The following 17 symptoms are assessed: hyperphagia, hypophagia, carbohydrate craving, study drug craving, study drug craving frequency, sleeping less, sleeping more, anxiety, energy level, activity level, tension attention, paranoid ideation, anhedonia, depression, suicidality, irritability. Each item of the M-CSSA is scored on a 0-7 Likert scale. A higher score indicates greater severity of each symptom. Summaries will be provided by symptom.

MADRS-S: the Montgomery Asberg Depression Rating Scale - Self Assessment (MADRS-S) is a 9-item diagnostic questionnaire used to measure the severity of depressive symptoms. The following symptoms are assessed; mood, feelings of unease, sleep, appetite, ability to concentrate, initiative, emotional involvement, pessimism and zest for life. Each item is based on a 6-point scale (scored 0, 0.5, 1, 1.5, 2, 2.5, 3), with the overall score ranging from 0-27. Higher scores indicate more severe depression. Question 9 (zest for life) of the MADRS-S deals with suicidality and will be also be reported separately.

STAI: the STAI is a self-completed questionnaire that aims to assess separately state anxiety (a temporary state influenced by the current situation where the respondent notes how participant feels right now at this moment) and trait anxiety (a general propensity to be anxious where the respondent. The STAI short form is scored by summing responses to 6 items (each scored on a 4-point Likert Scale from 1 to 4), yielding scores that reflect the level of anxiety experienced in the moment. The 6 items scored relate to feeling: calm, tense, upset, relaxed, content and worried.

To calculate the total STAI score (which ranges from 20-80) based on the STAI short form the following steps are taken:

1) reverse score the positive items: calm, relaxed and content are reverse scored (i.e., 1=4, 2=3, 3=2 and 4=1)

2) sum all six scores

3) multiply the total score by 20/6 to get the total score, with higher scores representing greater anxiety.

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The above safety endpoints will be summarized for each visit by treatment group and overall using the SS. The summaries will include the appropriate descriptive statistics based on the endpoint. For count data, counts and percentages will be provided. For continuous data the absolute value and the change from baseline values will be summarized.

By participant list for DSST, PVT, VLT, M-CSSA, MADRS-A and STAI will be generated, including visit, data/time, itemized response and overall score, where applicable.

This document is confidential.

10. Interim Analyses

No interim analysis is planned.

11. Changes from Analysis Planned in Protocol

Change from baseline in AHI4 is updated to the primary efficacy endpoint.

Additional analyses for AHI3a have been added in the same way as AHI4.

The following endpoints are added to the Section 8.5, Exploratory Efficacy Endpoints and Analyses, which are not included in the protocol.

- Percent of participants with AHI4<15, <10 and <5 at 13, 26 and 51 weeks.
- Proportion of participants with AHI4 reduction of ≥ 30% to ≥ 90% by 10% increments
- Change from baseline in AHI4, AHI3a, HB3a and ODI4 at 13, 26 and 51 weeks (where applicable)
- Change from baseline in Non-Rapid Eye Movement Apnea-Hypopnea Index [NREM AHI] at 13, 26 and 51 weeks.
- Change from baseline in Rapid Eye Movement Apnea-Hypopnea Index [REM AHI] at 13, 26 and 51 weeks (excluding participants whose PSG has <10 minutes of supine sleep).
- Change from baseline in supine AHI4 [AHIS] at 13, 26 and 51 weeks (excluding participants whose PSG has <10 minutes of REM sleep).
- Change from baseline in TST and percentage of TST in sleep stages (sleep efficiency [SE]; wake after sleep onset [WASO]; sleep onset latency [SOL]; Stage N1% [N1P], Stage N2% [N2P], Stage N3% [N3P], Stage R% [RP]).
- Change from baseline in Arousal Indices (Arousal Index - Respiratory [ARIR]; Arousal Index - total [ARI]).
- Proportion of participants with ≥50% reduction in AHI4 at 13 and 51 weeks
- Change from baseline to 13, 26 and 51 weeks in OSA severity category (None, Mild, Moderate and Severe).
- Proportion of patients with a reduction in loud breaths (i.e., Snoring)

The following endpoints have been removed due to redundancy.

- Proportion of participants with ≥50% reduction at 13 and 26 weeks for AHI3a, ODI3.

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12. Reference list

- O'Kelly, M and Ratitch, B. 2014. *Clinical Trial with Missing Data A Guide for Practitioners* (1st ed.). John Wiley & Sons https://doi.org/10.1002/9781118762516
- Mantel, N., and Haenszel, W. (1959). "Statistical Aspects of Analysis of Data from Retrospective Studies of Disease." Journal of the National Cancer Institute 22:719–748.
- Sato, T. (1989). "On the Variance Estimator of the Mantel-Haenszel Risk Difference." Biometrics 45:1323–1324. Letter to the editor.

This document is confidential.

13. Programming Considerations

Programming considerations are presented in TFL shell document.

14. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health SAS Programming and Validation Plan SOP (3920).

Syneos Health End-to-End Process of the Production of Study Data Tabulation Model (SDTM) (3921) and End-to-End Process of Analysis Datasets (ADs) and Tables, Figures and Listings (TFLs) SOPs (3922) and the SAS Programming and Validation Plan describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

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15. Example SAS Code for the Primary and Key Secondary Endpoint Analyses

15.1. Imputation Procedures

The following sample codes are for imputing the numerical endpoint PROMIS-Fatigue, which is assessed at week 4 (M1), 13 (M3), 26 (M6), 36 (M9) and 51 (M12). Similar sample codes can be applied to primary endpoint AHI4 that is collected at week 13 (M3), 26 (M6) and 51(M12) by using 3 visits.

15.1.1. Non-monotone missing imputation

```
proc mi data= xxx1 seed=2717 nimpute=100 out=xxx2;
   by TRTP;
   mcmc impute=monotone;
   var AHIBL PRFATBL AGE BMIBL M1 M3 M6 M9 M12;
run;
```

TRTP=Treatment arm (active or placebo), AHIBL= Baseline AHI4 score, PRFATBL Baseline PROMIS Fatigue Raw Score, AGE=Age, BMI = Body Mass Index, M1/M3/M6/M9/M12 = PROMIS Fatigue Raw Score at Week 4/13/26/39/51, respectively.

15.1.2. Monotone Missing imputation

Step 1: Impute missing value for M1

AD109 Pattern 1 (dataset xxx2a): Keep all AD109 participants with missing M1 with pattern 1 and all Placebo participants with complete data M1.

```
proc mi data= xxx2a seed=2718 nimpute=1 out=  ixxx2a ;
   by _Imputation;
   class TRTP;
   var AHIBL PRFATBL AGE BMIBL M1;
   monotone reg(M1= AHIBL PRFATBL AGE BMIBL);
   mnar model(M1/modelobs= (TRTP='placebo'));
run;
```

AD109 Pattern 2 and Placebo Pattern1 (dataset xxx2b)**:** Keep all except AD109 Pattern 1 missing M1.

```
proc mi data= xxx2b _b seed=2719 nimpute=1 out=ixxx2b;
   by _Imputation_;
   class TRTP;
   var M1 TRTP AHIBL PRFATBL AGE BMIBL;
   monotone reg(M1= TRTP AHIBL PRFATBL AGE BMIBL);
run;
```

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xxx3 is the combined data set ixxx2a (where TRTP='AD109') and ixxx2b;

Step 2: Impute missing value for M3

AD109 Pattern 1 (dataset xxx3a): Keep all AD109 participants from xxx3 with missing M3 with pattern 1 and all Placebo participants with non-missing M3.

```
proc mi data=xxx3a seed=2720 nimpute=1 out=ixxx3a;
   by _Imputation_;
   class TRTP;
   monotone reg(M3= AHIBL PRFATBL AGE BMIBL M1);
   mnar model(M3/modelobs= (TRTP='placebo'));
   var AHIBL PRFATBL AGE BMIBL M1 M3;
run;
```

AD109 Pattern 2 and Placebo Pattern 1 (dataset xxx3b): Keep all except AD109 Pattern 1 missing M3.

```
proc mi data=xxx3b seed=2721 nimpute=1 out=ixxx3b;
   by _Imputation_;
   class TRTP;
   monotone reg(M3= TRTP AHIBL PRFATBL AGE BMIBL M1);
   var TRTP AHIBL PRFATBL AGE BMIBL M1 M3;
run;
```

xxx4 is the combined data set ixxx3a (where TRTP='AD109') and ixxx3b;

Step 3: Impute missing value for M6:

AD109 Pattern 1 (dataset xxx4a): Keep all AD109 participants from xxx4 with missing M6 with pattern 1 and all Placebo participants with non-missing M6.

```
proc mi data=xxx4a seed=2722 nimpute=1 out=ixxx4a;
   by _Imputation_;
   class TRTP;
   monotone reg(M6= AHIBL PRFATBL AGE BMIBL M1 M3);
   mnar model(M6/modelobs= (TRTP='placebo'));
   var AHIBL PRFATBL AGE BMIBL M1 M3 M6;
run;
```

AD109 Pattern 2 and Placebo Pattern 1 (dataset xxx4b): Keep all except AD109 Pattern 1 missing M6.

```
proc mi data=xxx4b seed=2723 nimpute=1 out=ixxx4b;
   by _Imputation_;
```

This document is confidential.

```
    class TRTP;
    monotone reg(M6= TRTP AHIBL PRFATBL AGE BMIBL M1 M3);
    var TRTP AHIBL PRFATBL AGE BMIBL M1 M3 M6;
run;
```

xxx5 is the combined data set ixxx4a (where TRTP='AD109') and ixxx4b;

Step 4: Impute missing value for M9: **AD109 Pattern 1** (dataset xxx5a): Keep all AD109 participants from xxx5 with missing M9 with pattern 1 and all Placebo participants with non-missing M9

```
proc mi data=xxx5a seed=2724 nimpute=1 out=ixxx5a;
    by _Imputation_;
    class TRTP;
    monotone reg(M9= AHIBL PRFATBL AGE BMIBL M1 M3 M6);
    mnar model(M9/modelobs= (TRTP='placebo'));
    var AHIBL PRFATBL AGE BMIBL M1 M3 M6 M9;
run;
```

AD109 Pattern 2 and Placebo Pattern 1 (dataset xxx4b): Keep all except AD109 Pattern 1 missing M9.

```
proc mi data=xxx5b seed=2725 nimpute=1 out=ixxx5b;
    by _Imputation_;
    class TRTP;
    monotone reg(M9= TRTP AHIBL PRFATBL AGE BMIBL M1 M3 M6);
    var TRTP AHIBL PRFATBL AGE BMIBL M1 M3 M6 M9;
run;
```

xxx6 is the combined data set ixxx5a (where TRTP='AD109') and ixxx5b;

Step 5 Impute missing value for M12:

AD109 Pattern 1 (dataset xxx6a): Keep all AD109 participants from xxx6 with missing M12 with pattern 1 and all Placebo participants with non-missing M12.

```
proc mi data=xxx6a seed=2726 nimpute=1 out=ixxx6a;
    by _Imputation_;
    class TRTP;
    monotone reg(M12= AHIBL PRFATBL AGE BMIBL M1 M3 M6 M9);
    mnar model(M12/modelobs= (TRTP='placebo'));
    var AHIBL PRFATBL AGE BMIBL M1 M3 M6 M9 M12;
run;
```

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AD109 Pattern 2 and Placebo Pattern 1 (dataset xxx6b): Keep all except AD109 Pattern 1 missing M12.

```
proc mi data=xxx6b seed=2727 nimpute=1 out=ixxx6b;
   by _Imputation_;
   class TRTP;
   monotone reg(M1= TRTP AHIBL PRFATBL AGE BMIBL M1 M3 M6 M9);
   var TRTP AHIBL PRFATBL AGE BMIBL M1 M3 M6 M9 M12;
run;
```

xxx7 is the combined data set ixxx6a (where TRTP='AD109') and ixxx6b;

15.2. Analysis Procedure for primary endpoint (AHI4)

```
ods output lsmeans=ls diffs=diff;
proc mixed data= DATAMI Method=REML Empirical;
   by _imputation_;
   CLASS TRTP (ref="Placebo") USUBJID AHIGP AVISITN;
   MODEL CHG= TRTP AVISITN TRTP*AVISITN BASE AHIGP / s covb
ddfm=kr;
   REPEATED AVISITN/ SUBJECT = USUBJID TYPE=UN;
   LSMEANS TRTP *AVISITN/DIFF CL;
run;
```

Note: AHIGP is AHI strata and BASE is baseline for the variable being analyzed.
Add option Empiracal only (sandwich estiamtor') in case that TYPE=UN is not converge and TYPE=CS is used

```
*ls means;
proc sort data=ls; by EFFECT AVISITN TRT01PN; run;
ods output parameterestimates=rst_ls;
proc mianalyze data=ls;
   by  EFFECT AVISITN TRTP;
   modeleffects Estimate;
   stderr stderr;
run;


*ls mean diff and p-value;
proc sort data=diff; by  EFFECT AVISITN TRTP; run;
ods output parameterestimates=rst_diff;
proc mianalyze data=diff;
   by EFFECT AVISITN TRTP;
   modeleffects Estimate;
   stderr stderr;
run;
```

16. Example SAS Code for AHI4 Responder

16.1. Imputation Procedures

16.1.1. Non-monotone missing imputation

```
proc mi data=xxx1 seed=6879 nimpute=100 out=xxx2;
   mcmc impute=monotone;
   var TRTP AHIBL PRFATBL AGE BMIBL M3 M6 M12;
run;
```

TRTP=Treatment arm (active or placebo), AHIBL= Baseline AHI4 score, PRFATBL Baseline PROMIS Fatigue Raw Score, AGE=Age, BMI = Body Mass Index, M3/M6/M12 = AHI4 at Week 13, 26 and 51, respectively.

16.1.2. Monotone Missing imputation

Note: _imputation_ is imputation dataset reference ID created from Non-monotone imputation.

```
proc mi data=xxx2 seed=6880 nimpute=1 out=xxx3;
        by _Imputation_;
        class TRTP;
        monotone reg(M3= TRTP AHIBL PRFATBL AGE BMIBL);
       var TRTP AHIBL PRFATBL AGE BMIBL M3;
run;

proc mi data=xxx3 seed=6881 nimpute=1 out=xxx4;
        by _Imputation_;
        class TRTP;
        monotone reg(M6= TRTP AHIBL PRFATBL AGE BMIBL M3);
       var TRTP AHIBL PRFATBL AGE BMIBL M3 M6;
run;
proc mi data=xxx4 seed=6882 nimpute=1 out=xxx5;
        by _Imputation_;
        class TRTP;
        monotone reg(M12= TRTP AHIBL PRFATBL AGE BMIBL M3 M6);
        var TRTP AHIBL PRFATBL AGE BMIBL M3 M6 M12;
run;
```

16.2. Analysis Procedure

```
*calculate the of responder;
Data temp;
        Set yyy;
        if PCHG^=.  then do;
                if PCHG<-50 then RESPNDEF=1;
```

```
        else RESPNDEF=2;
        end;
run;

*calculate the proportion of responder with 95% CI for each group;
proc freq data=temp;
   by _imputation_ TRTP;
   tables RESPNDEF /cl binomial(level=1);
   ods output Binomial=prop;
run;

data prop_trt;
   merge prop ( where=(label1="Proportion") keep = _imputation_ TRTP
NVALUE1 label1 rename=(NVALUE1=prop))
            prop( where=(label1="ASE") keep =_imputation_ TRTP NVALUE1
label1 rename=(NVALUE1=prop_se));
   by _imputation_ TRTP;
run;
proc sort data=prop_trt; by TRTP _imputation_; run;
proc mianalyze  data=prop_trt;
   modeleffects prop;
   stderr prop_se;
   by TRTP;
   ods output parameterestimates =rst_prop;
run;


*calculate the difference with 95% CI of responder proportion between AD107 vs
Placebo;
proc freq data=temp;
   by _imputation_;
   tables STRATUM *TRTP* RESPNDEF /cmh  RISKDIFF(COMMON
Column=2);
   ods output CommonPdiff=PdiffCMH=cmh;
run;
```

Note: need to specify column=2 if responder is the 2nd value of RESPNDEF (eg. Y vs N).

```
* Combined adjusted proportion difference from 100 imputed outputs;
proc mianalyze  data= Pdiff (where=(METHOD =" Mantel-Haenszel"));
   modeleffects VALUE;
   stderr STDERR;
   ods output parameterestimates =rst_prop_diff_adj;
run;
```

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```
*Combined P value;
data cmh_wh;
    SET cmh(WHERE=(AltHypothesis="General Association"));
    cmh_value_wh=((VALUE/DF)**(1/3) - (1-2/(9*DF)))/SQRT(2/(9*DF));
    cmh_sterr_wh = 1.0;
run;

proc mianalyze data=cmh_wh;
 modeleffects cmh_value_wh;
 stderr cmh_sterr_wh;
 ods output parameterestimates =p_value;
run;
```

17. Appendix 1: Adverse Event of Special Interest List of FMQs and PTs

	Search Strategy			
AESI	**FMQs[1]**	**Customized Medical Query (CMQ)**	**Single Preferred Term**	**Comments**
Urinary hesitation	NA	Propose to group the following 3 PTs: • Urinary hesitation • Urine flow decreased • Urine output decreased	NA	Urinary retention is clinically different from urinary hesitation and the Sponsor proposes not to combine and to present AE data separately
Urinary retention	• Urinary retention (narrow and broad)		NA	
Liver Injury	• Hepatic Failure (narrow and board) • Hepatic Injury (narrow and board)			The Sponsor is including these FMQs per FDA ISS Type C Meeting written response dated 08Jan2025
Cardiovascular	• Hypotension Group includes the following FMQs: ○ Syncope (narrow and broad) ○ dizziness (narrow) ○ hypotension (narrow) • Palpitations Group includes the following FMQs: ○ palpitations (narrow) ○ Tachycardia (narrow)	NA	NA	

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	Search Strategy			
AESI	**FMQs[1]**	**Customized Medical Query (CMQ)**	**Single Preferred Term**	**Comments**
	• Myocardial ischemia (narrow and broad) • Systemic Hypertension (narrow) • Stroke and TIA (narrow)			
Suicidal ideation	• Self-harm (narrow and broad)	NA	NA	
Daytime sleepiness	• Somnolence (Narrow and broad)	NA	NA	
Motor vehicle accidents	NA	NA	Road Traffic Accident	
Anticholinergic effects	NA	4 FMQs • Confusional state (narrow), • constipation (narrow and broad), • psychosis (narrow and broad), • nausea (narrow) PTs • blurred vision • memory impairment	NA	The Sponsor is proposing to combine 4 FMQs and 2 PTs to represent the medical concept of anticholinergic effects that are not cardiac in nature
Psychiatric disorders	• mania (narrow and broad) • psychosis (narrow and broad)			

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[1] FMQs are based on the 2022 FDA list (https://downloads.regulations.gov/FDA-2022-N-1961-0001/attachment_1.xlsm)

Some AE terms are counted to 2 FMQs in below tables, the terms in green box will be considered when assigning AESI categories:

	AEDECOD	CMQ	_NAME_	FMQ01	FMQ02
1	Delirium	Anticholinergic effects	FMQ	Confusional State (narrow)	Psychosis (narrow and broad)
2	Dizziness	Cardiovascular	FMQ	Dizziness (narrow)	Syncope (narrow and broad)
3	Hypotension	Cardiovascular	FMQ	Hypotension (narrow)	Syncope (narrow and broad)
4	Hypotension postural aggravated	Cardiovascular	FMQ	Hypotension (narrow)	Syncope (narrow and broad)
5	Intensive care unit delirium	Anticholinergic effects	FMQ	Confusional State (narrow)	Psychosis (narrow and broad)
6	Neonatal hypotension	Cardiovascular	FMQ	Hypotension (narrow)	Syncope (narrow and broad)
7	Orthostatic hypotension	Cardiovascular	FMQ	Hypotension (narrow)	Syncope (narrow and broad)
8	Postural hypotension	Cardiovascular	FMQ	Hypotension (narrow)	Syncope (narrow and broad)
9	Presyncope	Cardiovascular	FMQ	Dizziness (narrow)	Syncope (narrow and broad)
10	Procedural hypotension	Cardiovascular	FMQ	Hypotension (narrow)	Syncope (narrow and broad)
11	Vasovagal attack	Cardiovascular	FMQ	Dizziness (narrow)	Syncope (narrow and broad)
12	Ventricular tachycardia	Cardiovascular	FMQ	Myocardial Ischemia (narrow and broad)	Tachycardia (narrow)

APC-APN-304_Statistical Analysis Plan_v1.0_11Jun2025

Final Audit Report 2025-06-11

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Challenge: The user opened the agreement.
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Agreement viewed by Ron Farkas (rfarkas@apnimed.com)
Documents: APC-APN-304_Statistical Analysis Plan_v1.0_11Jun2025.pdf
2025-06-11 - 5:23:08 PM GMT- IP address: 100.18.7.250

Email viewed by Shuhong Zhao (shuhong.zhao@syneoshealth.com)
2025-06-11 - 5:23:25 PM GMT- IP address: 104.47.74.126

Agreement viewed by Shuhong Zhao (shuhong.zhao@syneoshealth.com)
Documents: APC-APN-304_Statistical Analysis Plan_v1.0_11Jun2025.pdf
2025-06-11 - 5:23:47 PM GMT- IP address: 136.226.65.75

Shuhong Zhao (shuhong.zhao@syneoshealth.com) authenticated with Adobe Acrobat Sign.
Challenge: The user completed the signing ceremony.
2025-06-11 - 5:24:43 PM GMT

Document e-signed by Shuhong Zhao (shuhong.zhao@syneoshealth.com)
Documents: APC-APN-304_Statistical Analysis Plan_v1.0_11Jun2025.pdf
Signing reason: I am the reviewer
Signature Date: 2025-06-11 - 5:24:44 PM GMT - Time Source: server- IP address: 136.226.65.75

Ron Farkas (rfarkas@apnimed.com) authenticated with Adobe Acrobat Sign.
Challenge: The user completed the signing ceremony.
2025-06-11 - 5:27:18 PM GMT

Ron Farkas (rfarkas@apnimed.com) authenticated with Adobe Acrobat Sign.
Challenge: The user completed the signing ceremony.
2025-06-11 - 5:27:39 PM GMT

Ron Farkas (rfarkas@apnimed.com) authenticated with Adobe Acrobat Sign.

Challenge: The user completed the signing ceremony.

2025-06-11 - 5:28:14 PM GMT

Document e-signed by Ron Farkas (rfarkas@apnimed.com)

Documents: APC-APN-304_Statistical Analysis Plan_v1.0_11Jun2025.pdf

Signing reason: I am the approver

Signature Date: 2025-06-11 - 5:28:15 PM GMT - Time Source: server- IP address: 100.18.7.250

Email viewed by Brian Mangal (bmangal@gmail.com)

2025-06-11 - 5:32:35 PM GMT- IP address: 66.249.84.9

Brian Mangal (bmangal@gmail.com) authenticated with Adobe Acrobat Sign.

Challenge: The user opened the agreement.

2025-06-11 - 5:32:51 PM GMT

Agreement viewed by Brian Mangal (bmangal@gmail.com)

Documents: APC-APN-304_Statistical Analysis Plan_v1.0_11Jun2025.pdf

2025-06-11 - 5:32:52 PM GMT- IP address: 173.180.25.216

Brian Mangal (bmangal@gmail.com) authenticated with Adobe Acrobat Sign.

Challenge: The user completed the signing ceremony.

2025-06-11 - 5:33:22 PM GMT

Document e-signed by Brian Mangal (bmangal@gmail.com)

Documents: APC-APN-304_Statistical Analysis Plan_v1.0_11Jun2025.pdf

Signing reason: I am the approver

Signature Date: 2025-06-11 - 5:33:23 PM GMT - Time Source: server- IP address: 173.180.25.216

Luigi Taranto Montemurro (ltaranto@apnimed.com) authenticated with Adobe Acrobat Sign.

Challenge: The user opened the agreement.

2025-06-11 - 6:09:20 PM GMT

Agreement viewed by Luigi Taranto Montemurro (ltaranto@apnimed.com)

Documents: APC-APN-304_Statistical Analysis Plan_v1.0_11Jun2025.pdf

2025-06-11 - 6:09:24 PM GMT- IP address: 2.36.53.244

Luigi Taranto Montemurro (ltaranto@apnimed.com) authenticated with Adobe Acrobat Sign.

Challenge: The user completed the signing ceremony.

2025-06-11 - 6:10:26 PM GMT

Document e-signed by Luigi Taranto Montemurro (ltaranto@apnimed.com)

Documents: APC-APN-304_Statistical Analysis Plan_v1.0_11Jun2025.pdf

Signing reason: I am the approver

Signature Date: 2025-06-11 - 6:10:27 PM GMT - Time Source: server- IP address: 2.36.53.244

Agreement completed.

2025-06-11 - 6:10:27 PM GMT

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