Statistical Analysis Plan (SAP)

Protocol Title: A Phase 2, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of 2 mg and 4 mg SUVN-G3031 Compared to Placebo in Patients with Narcolepsy with and without Cataplexy

Protocol Number: CTP2S13031H3

NCT04072380

Date: 05 September 2023

Statistical Analysis Plan

Version 5.0 – 05Sep2023

Sponsor Name: Suven Life Sciences

Protocol Number: CTP2S13031H3

Protocol Title: A Phase 2, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of 2 mg and 4 mg SUVN-G3031 Compared to Placebo in Patients with Narcolepsy with and without Cataplexy

Protocol Version and Date: Version 4.0 – 16 Aug 2023

[redacted]

Notice of Confidential and Proprietary Information:

The information contained in this document is confidential belonging to Suven Life Sciences. Acceptance of this document constitutes agreement by the recipient that no information contained herein will be published or disclosed without prior written authorization from an official of Suven Life Sciences. However, this document may be disclosed to appropriate Institutional Review Board and Ethics Committees or duly authorized representatives of a national regulatory authority under the condition that they are requested to keep it confidential. In the event of an actual or suspected breach of this obligation, [redacted] should be notified promptly.

Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.0	11-Feb-2020	[redacted]	Initial Release Version
2.0	05-Mar-2021	[redacted]	– [redacted] – [redacted] – Updated the baseline missing value imputation – Changed the approach to imputing missing dates for TEAE and prior/concomitant medication
3.0	09-Nov-2022	[redacted]	[redacted] 2. Additionally below changes are made. • Startification criteria based on Na1 and Na2 proportiion has been modified (Section 3.6) • [redacted] • Exploratory analysis of all endpoints to evaluate the combined SUVN-G3031 doses (2 mg and 4 mg) compared to placebo (Section 4.3, 8.5) • Proportion of subjects reporting CGI-C scores of 1 or 2 or 3 at Day 7 and Day 14 (EDS) (Section 4.3, 8.5) • Proportion of subjects reporting CGI-S scores related to EDS of 1 or 2 or 3 at Day 7 and Day 14 (Section 4.3, 8.5) • Proportion of subjects reporting CGI-C scores of 1 or 2 at Day 7 and Day 14 (EDS) (Section 4.3, 8.5) (only Day 7 added)

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
4.0	15-Mar-2023	[redacted]	As per comments from Agency below changes are made: 1. Section 8.1, Primary Efficacy Endpoint and Analysis (Primary Estimand) is updated for Estimand and got modified. 2. Section 8.4, Secondory efficacy Endpoint (s) and Analysis (Secondary Estimand) is updated for confirmatory and exploratory testing approach. 3. SAS program codes are provided in appendix1 (Section 19) for handling missing data. 4. Section 11.2 (Brief Description of CHW) is modified and explained in detail.
5.0	05-Sep-2023	[redacted]	1. Section 6.2.9 removed, as it is out of use. 2. Section 6.2.10 updated. 3. Section 7.4, Prior and Concomitant medication table updated. [redacted] 5. Section 9, 11.2 and 11.4 updated. [redacted]

Approvals

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

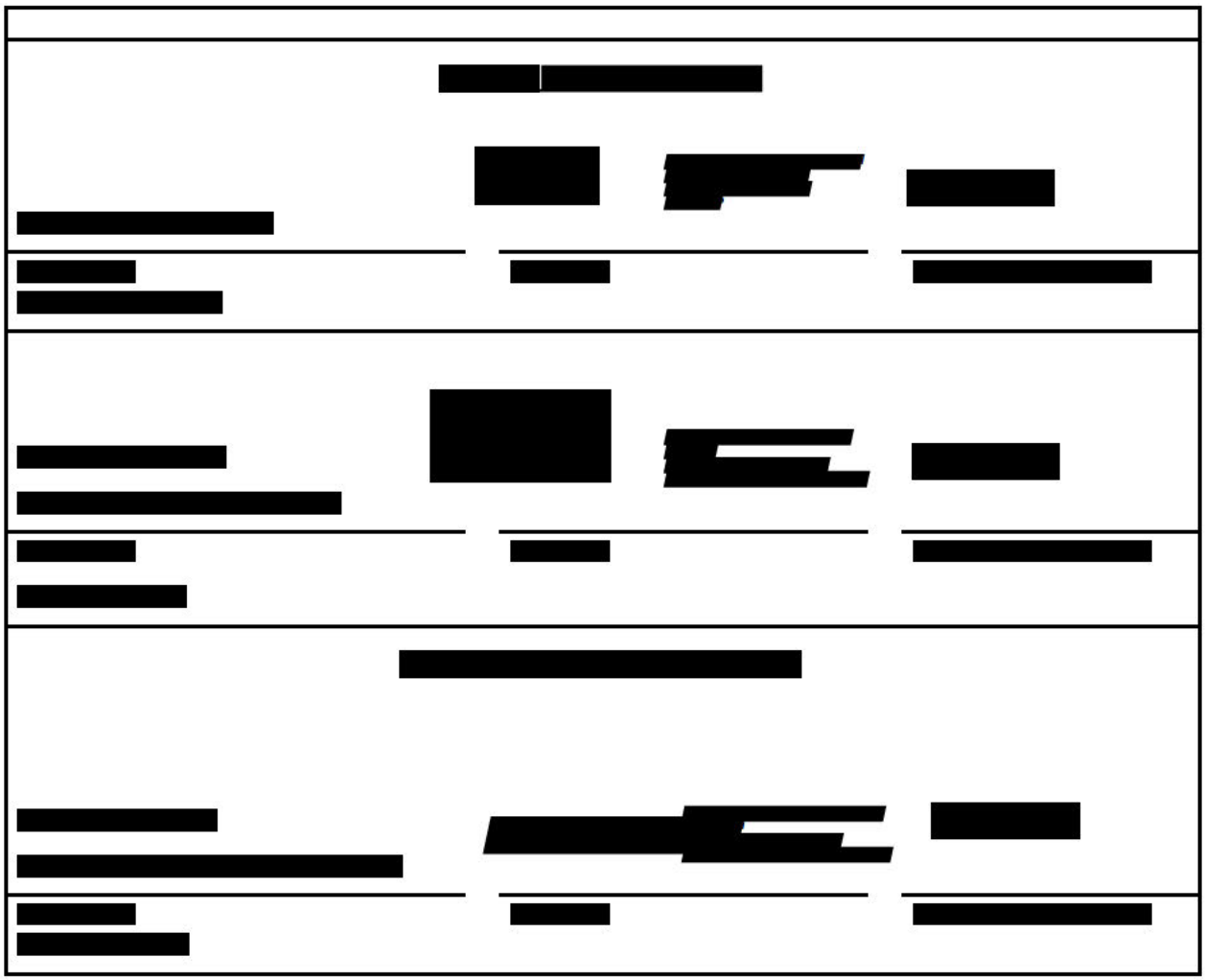


Table of Contents

1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
AESIs	Adverse events of Special Interest
ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass index
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CHW	Cui, Hung, Wang test-statistic
CI	Confidence Interval
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	Data Monitoring Committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDS	Excessive Daytime Sleepiness
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IP	Investigational Product
ITT	Intent–to-treat
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MSLT	Multiple Sleep Latency Test
MWT	Maintenance of Wakefulness Test
N/A	Not Applicable
PGI-C	Patient Global Impression – Change
PK	Pharmacokinetic
PSG	Polysomnography

Abbreviation	Description
PT	Preferred Term
QC	Quality Control
QTc	Corrected QT Interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
SOREMP	Sleep Onset Rapid Eye Movement Period
TEAE	Treatment Emergent Adverse Event
TFL	Table, Figure and Listing
WHO	World Health Organization

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to draw valid conclusions regarding the study objectives described under Suven Life Sciences Protocol CTP2S13031H3 titled "A Phase 2, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of 2 mg and 4 mg SUVN-G3031 Compared to Placebo in Patients with Narcolepsy with and without Cataplexy", Version 4.0 dated 16 Aug 2023.

2.1. Responsibilities

[redacted] 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

The final analysis of safety and efficacy is planned after all subjects complete the final study visit or terminate early from the study for the respective part. Unless otherwise specified, the analysis includes all data collected in the database through the time of the database lock.

An independent Data Monitoring Committee (DMC) will review descriptive summaries of accumulating safety and subject disposition data after 25%, and 50% of subjects have been completed treatment. Further description of the DMC analyses can be found in the DMC charter Version 1.0 dated 30-Sep-2019. [redacted]

Ad hoc meetings will be at the discretion of the committee or Suven (e.g. in the event of unexpected SAEs or if consultation with additional expert consultants is required).

An interim analysis to evaluate sample size assumptions will be conducted when approximately 50% of subjects have completed 14 days of treatment. Sample size re-estimation will be performed as part of the interim analysis. An unblinded team from [redacted] biostatistics will perform the analyses as described in Section 11.1 of this SAP to maintain the blinding of the study.

[redacted]

[redacted]

[redacted]

3. Study Objectives

3.1. Primary Objective

To evaluate the efficacy of SUVN-G3031 compared with placebo as measured by the change in total Epworth Sleepiness Scale (ESS) score.

3.2. Secondary Objective(s)

To evaluate the efficacy of SUVN-G3031 compared with placebo as measured by an improvement in the Clinical Global Impression of Severity (CGI-S) score related to excessive daytime sleepiness (EDS) and Maintenance of Wakefulness Test (MWT) score.

3.3. Exploratory Objective(s)

- To evaluate the efficacy of SUVN-G3031 compared with placebo as measured by an improvement in the MWT score, at each of 4 planned 30-minute sessions per test day
- To evaluate the change in Clinical Global Impression of Change (CGI-C) score with regard to EDS
- To evaluate the change in CGI-S score with regard to EDS
- To evaluate the change in Patient Global Impression – Change (PGI-C) score
- To evaluate the change in Daily Sleep Diary
- To evaluate the change in nocturnal overnight polysomnography (PSG) assessments
- To evaluate the change in total ESS score

3.4. Brief Description

This is a Phase 2, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety, tolerability, PK, and efficacy of 2 mg and 4 mg SUVN-G3031 compared with placebo in subjects with narcolepsy with and without cataplexy. Subjects will be randomized at a ratio of 1:1:1 to 2 mg SUVN-G3031, 4 mg SUVN-G3031, or placebo. Subjects will be stratified based on whether they have narcolepsy with or without cataplexy (Na-1 or Na-2, respectively).

Each subject will receive study drug once daily, in a tablet formulation, for 14 days. Enough subjects will be screened to enable 114 subjects to be enrolled (38 per treatment group). A single, unblinded, interim analysis will be undertaken when approximately 50% of subjects have completed 14 days of treatment; this analysis will enable sample size re-estimation to occur if appropriate. A maximum of 57 additional subjects (19 subjects per treatment arm) will be enrolled to generate a total maximum study population of 171 subjects.

Subjects will be enrolled at approximately 65 sites in the United States and Canada. It is anticipated it will take 12 months to complete enrollment and 13 months to complete the entire study.

Each subject will complete 3 periods: Screening, Dosing Period and Safety Follow-up.

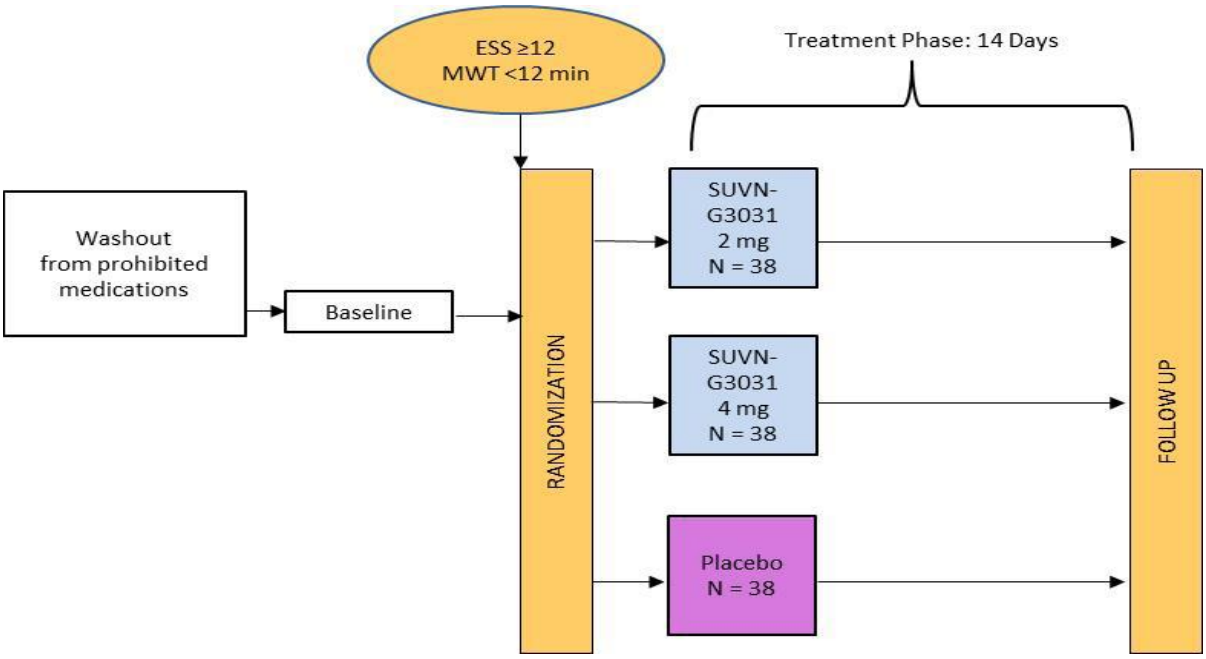
Screening: Subjects who have provided written informed consent will be screened up to 28 days

before enrollment. Eligible subjects will complete a washout period of ≥ 14 days for all agents targeting cataplexy and ≥ 7 days for all stimulants targeting EDS.

Dosing Period: Once these washout periods have been completed, subjects will attend the clinic for randomization and baseline (Day 0) assessments; subjects will provide a blood sample for PK analysis. Following completion of baseline (Day 0) assessments, study drug will be dispensed to subjects and they will take their first dose the next day (Day 1); subjects will receive enough study drug to last until the next visit at Day 7. On Day 7 (±1 day), subjects will attend the clinic for an outpatient visit, when efficacy and safety assessments will be undertaken. Subjects will provide a blood sample for PK analysis at the estimated trough (just prior to dosing) and at the estimated maximum plasma concentration of SUVN-G3031 (3 ± 0.5 hours post-dosing). Subjects will be dispensed enough study drug to last until the next visit at Day 14. On Day 14 (±1 day), subjects will attend the clinic for an outpatient visit, where efficacy and safety assessments will be undertaken. They will provide a sample for PK analysis as per the Day 7 visit.

Safety Follow-up: A final safety follow-up visit will be performed at Day 21 (±1 day). All visits will be outpatient visits and subjects will be enrolled in the study for a maximum of 49 days (7 weeks) from the start of the screening period.

Flowchart: A study schematic can be seen below.



Abbreviations: ESS, Epworth Sleepiness Scale; MWT, Maintenance of Wakefulness Test.

3.5. Subject Selection

3.5.1. Inclusion Criteria

Individuals must meet all of the following criteria to be included in the study:

1. Must be between the ages of 18 to 65 years (adult), inclusive.

2. Have narcolepsy with or without cataplexy (Na-1 or Na-2) based on the International Classification of Sleep Disorders (3rd Edition) criteria for the diagnosis of narcolepsy (new or previously diagnosed).
3. Have undergone an Multiple Sleep Latency Test (MSLT) study showing an MSLT of ≤ 8 minutes with 2 or more SOREMPs performed according to standard techniques, with substitution of 1 of the required SOREMPs on MSLT with 1 obtained from the preceding nocturnal PSG, performed at the time of diagnosis. No other potential cause for EDS must have been identified during the preceding nocturnal PSG. If the study site is unable to obtain the MSLT diagnoses, the MSLT may be performed to confirm diagnoses upon Sponsor and medical monitor approval.
4. An ESS score of ≥ 12; and mean MWT time of < 12 minutes across the first 4 sessions at baseline. An ESS score of ≥ 12 for eligibility is only required at the Baseline visit. An ESS score of < 12 at Screening due to concomitant medications will be subjected to PI's discretion for eligibility.
5. Must have a body mass index ranging from 18 to < 45 kg/m2.
6. Negative urine drug screen (UDS) at the Screening and Baseline (Visit 1) visits.
   - A positive UDS at Screening can be repeated up to Day -1; however, a negative UDS is required prior to Day 0 (Baseline visit), and a second negative UDS is required on Day 0 (Baseline visit).
   - A positive UDS at Screening due to concomitant medications will be subject to PI's discretion for eligibility.
7. All patients must agree to remain free of alcohol and illicit drugs from Screening and until the Safety Follow-up visit.
8. All male subjects who are sexually active and not surgically sterilized must agree to use a condom with or without spermicide, in addition to any birth control used by their partner during the study until 1 month after the final dose of investigational product (IP).
9. Before randomization, a woman must be either not of childbearing potential or of childbearing potential practicing highly effective methods of birth control.

   - "Not of childbearing potential" is defined as a subject who is postmenopausal (> 45 years of age with amenorrhea for at least 12 months); permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy); or otherwise is incapable of pregnancy, and müllerian agenesis).

   - "Of childbearing potential" and practicing a highly effective method of birth control is defined as a subject following regulations consistent with the use of birth control methods for subjects participating in clinical studies. A highly effective method of birth control is a method with low user dependency that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. No exhaustive examples of highly effective methods include: e.g., established use of oral, injected, or implanted hormonal methods of contraception; placement of an intrauterine device or intrauterine system; barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; male partner sterilization (the vasectomized partner should be the sole partner for that subject), or male partner is using condoms with spermicide; practicing true abstinence (the preferred and usual lifestyle of the subject). Two forms of effective methods of birth control must be used during the study and for 1 month after the last dose of IP.

10. Willingness to complete the study protocol with full compliance with procedures and sign an informed consent form (ICF).

3.5.2. Exclusion Criteria

Individuals meeting any of the following criteria at Screening or baseline are ineligible to participate in this study:

1. Habitual wake-up time after 8 AM as assessed by sleep diary, habitual sleep time of < 6 h and habitual bedtime past 1 AM as determined by sleep diary entries.
2. Use of any investigational therapy within the 30-day period prior to enrollment.
3. Excessive caffeine (defined as > 600 mg/per day) use at least 1 week prior to baseline assessments and during the course of the trial. (See protocol APPENDIX 3 for caffeine dosage definitions).
4. Nicotine dependence that has an effect on sleep (e.g., a subject who routinely awakens at night to smoke).
5. Use of concurrent medications prescribed to treat narcolepsy or any indication as specified including stimulants, antidepressants and sodium oxybate before Baseline and until the Safety Follow-up visit, as specified in protocol APPENDIX 2.
6. Current diagnosis of or past treatment for syndromes known to cause sleep disruption or any other cause of daytime sleepiness. If Investigator confirms that any of the following syndromes are not clinically significant to the extent that it is causing sleep disturbance, this subject may be permitted at the Investigator's discretion.

    - Obstructive sleep apnea, or individuals requiring continuous positive airway pressure (obstructive sleep apnea noted during nocturnal PSG should be queried).
    - Periodic limb movement disorder (periodic limb movements noted during nocturnal PSG should be queried).
    - Other clinically significant disorders which cause sleep disruption (e.g., chronic pain disorder, chronic or untreated insomnia, clinically significant levels of gastroesophageal reflux disease, asthma, neuropathy, or other chronic pain disorders such as osteoarthritis or degenerative joint disease).
    - Hypothyroidism requires Investigator assessment to determine whether it contributes to interrupted or poor sleep, (i.e., causing daytime somnolence).
    - Parasomnias.
    - Significant nocturia.

7. Clinically significant ECG abnormalities. Subjects are excluded with a screening ECG PR interval of ≥ 300 msec, QRS interval ≥ 200 msec, or Fridericia's correction of QT interval ≥ 450 msec for men and ≥ 470 msec for women obtained after 3-minute rest in a supine position using a digital ECG. Abnormal results for ECGs should be repeated once at screening with 3 consecutive ECG recordings to ensure reproducibility of the abnormality before excluding a subject based on the exclusion criteria. Each ECG recording should be taken approximately 5 minutes apart (the ECG result reported would be evaluated at each time point). A subject will be excluded if the QTcF is ≥450 msec in men and ≥470 msec in women for 2 of the 3 time points of the ECGs done, unless due to ventricular pacing. If only 1 ECG time point has a QTcF of ≥450 msec in men and ≥470 msec in women, and this is not reproduced at either of the other 2 time points, the subject can be included in the trial.
8. Concurrent use of sedating agents such as hypnotics, tranquilizers, sedating antihistamines, antipsychotics, benzodiazepines, anticonvulsants, clonidine or tricyclic antidepressants which have H1-antihistamine properties (clomipramine, protriptyline) before Baseline and until the Safety Follow-up visit, as specified in protocol APPENDIX 2.

9. History of (within past 3 months) or current substance use disorder involving illicit drugs, alcohol, or marijuana, as per Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria and non-disordered use of alcohol and recreational drugs.
10. History or presence of any unstable medical condition or neurological disorder which may affect the subject's safety or stability (such as serious cardiovascular disorder, moderate or severe gastrointestinal abnormalities, hepatic disorder or renal abnormalities, hepatitis C, hepatitis B, human immunodeficiency virus positive status, history of epilepsy, significant head injury, history of intracranial surgery, or malignancy in past 5 years).
11. Subjects with preplanned surgeries requiring general anesthesia throughout the duration of the trial.
12. Severe, unstable psychiatric illness including a diagnosis of bipolar disorder, schizophrenia or psychotic disorder in the subject's lifetime, according to DSM-5 criteria. Subjects with severe or uncontrolled depression that, in the judgment of the Investigator, makes the subject inappropriate for entry into the study or which will require new onset of treatment during the course of the trial. Subjects who are at significant potential suicidal risk are determined by:

    - Subjects who answer "Yes" on the C-SSRS Suicidal Ideation Item 4 (active suicidal ideation with some intent to act, without specific plan) and whose most recent episode meeting criteria for this C-SSRS Item 4 occurred within the last 6 months; or
    - Subjects who answer "Yes" on the C-SSRS Suicidal Ideation Item 5 (active suicidal ideation with specific plan and intent) and whose most recent episode meeting criteria for this C-SSRS Item 5 occurred within the last 6 months; or
    - Subjects who answer "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) and whose most recent episode meeting criteria for any of these 5 C-SSRS Suicidal Behavior Items occurred within the last 2 years; or
    - Subjects who, in the opinion of the investigator, present a serious risk of suicide.

13. An occupation requiring variable shift work, night shifts, or frequent overnight travel which disrupts sleep patterns.
14. In the opinion of the Investigator, it would be unsafe for a subject to stop taking any wake promoting agent for more than 4 weeks. The subject's occupation (e.g., requirement for driving) may need to be considered.

3.6. Determination of Sample Size

Sample size for the MWT which was the primary efficacy in the study until the change in primary efficacy endpoint (refer to section 2.3): This study plans to randomize 114 subjects, using 1:1:1 treatment allocation (stratified by atleast 30% each by reported cataplexy subject history, Na-1 or Na-2 respectively), 38 to each treatment group. Using an SD of 5.0, N = 38 randomized subjects per group will provide 80% power, to detect a treatment difference over placebo of 3.5 points or greater on the MWT at a 2-sided Type I error level of 0.05, assuming a dropout rate of 10%.

Because of the unknown prognostic importance of a history of cataplexy with EDS on study outcome, a stratification factor will be included based upon that clinical presentation. Stratification would be applied across the entire study, and not within an individual center, and will be reflected in the analytic model. The purpose of the a priori defined subgroup is for hypothesis generation.

Based on the unblinded interim analysis results sample size was re-calculated to maximum of 171 subjects (57 to each treatment group) on mean MWT as primary efficacy endpoint.

[redacted]

3.7. Treatment Assignment and Blinding

Subjects will be randomized to the 3 study treatments (2 mg SUVN-G3031, 4 mg SUVN-G3031 and Placebo) in a 1:1:1 ratio. This randomization will be stratified based on whether they have narcolepsy with or without cataplexy (Na-1 or Na-2), respectively.

Subjects will be randomized using an interactive response technology (IRT). The randomization number generated should be entered into the eCRF.

This is a double-blind study. Tablets will be provided, pre-dispensed in blinded study kits. All tablets will be identical in appearance and size.

According to the randomization schedule as indicated in the Schedule of Assessments Table 1 and in accordance with the Pharmacy Manual, the Investigator or designee will obtain the kit number from the IRT for the subject and the kit number will be provided to the blinded pharmacist or designee at the study center who is responsible for the preparation of study drug. The blinded pharmacist will then dispense the correct kit number to the subject.

Each subject will receive 2 kits: the first for Days 1 to 7 and the second for Days 8 to 14. The kits numbers should be recorded in the eCRF and in the pharmacy dispensing logs.

If an Investigator becomes unblinded to a given subject's study treatment that subject will be discontinued from the study unless there are ethical reasons for that subject not to be discontinued; approval from the Sponsor's medical monitor must be obtained in such instances.

In the event that emergency unblinding is required for a given subject because of AEs or concerns for the subject's safety or wellbeing, the Investigator may break the randomization code for the subject via the IRT, by which system the unblinding will be captured. The Investigator is responsible for notifying the medical monitor and/or Sponsor of such an event as soon as possible. The unblinding and its cause will also be documented in the eCRF.

3.8. Administration of Study Medication

The study treatments to be used in this study are:

- 2 mg SUVN-G3031
- 4 mg SUVN-G3031
- Placebo

Subjects should take 1 tablet per day in the morning, as soon as they wake up, with approximately 250 mL water. Dosing may occur with or without food. Subjects will be dosed for 14 days.

If a subject forgets to take their morning dose and remembers before 1:00 PM, then they should take it as soon as they remember. If a subject forgets to take their morning dose and remembers after 1:00 PM, then they should skip the day's dose and take the next scheduled dose the next morning. If the subject has missed more than 1 dose, then they should only take the most recent forgotten dose.

3.9. Study Procedures

Subjects will be enrolled at approximately 65 sites in the United States and Canada. Each subject will receive study drug once daily, in a tablet formulation, for 14 days. It is anticipated it will take 12 months to complete enrollment and 13 months to complete the entire study.

Table 1: Schedule of Assessments

Visit	**Screening**	**Visit 1**	**Visit 2**	**Visit 3**	**Safety Follow-up**
Study Day	**Day -28 to Day -1**	**Baseline (Day 0)**	**Day 7**	**Day 14**	**Day 21**
Window			**±1 day**	**±1 day**	**±1 day**
Informed consent	X				
Demographic information	X				
Medical History and Disease History	X				
Virology/Serology[a]	X				
Inclusion/exclusion criteria	X	X			
Physical examination	X	X		X	X
Vital signs[b]	X	X	X	X	X
ECG	X	X[c]	X[c]	X[c]	X
Hematology[d]	X	X		X	X
Serum chemistry[d]	X	X		X	X
Pharmacokinetic sample[e]		X	X	X	
Urinalysis[d]	X	X		X	X
Pregnancy test[f]	X	X	X	X	X
UDS[g]	X	X	X	X	
Nocturnal overnight PSG[h]		X	X	X	
MWT[i]		X	X	X	
CGI-S[j]		X	X	X	
CGI-C[j]			X	X	
ESS[k]	X	X	X	X	
C-SSRS[k]	X	X	X	X	X
PGI-C[k,l]		X	X	X	
Diary dispensing[m]	X	X	X	X	
Washout from EDS/cataplexy medications[n]	X				
Assign/randomize to IP		X			

Visit	**Screening**	**Visit 1**	**Visit 2**	**Visit 3**	**Safety Follow-up**
Study Day	**Day -28 to Day -1**	**Baseline (Day 0)**	**Day 7**	**Day 14**	**Day 21**
Window			**±1 day**	**±1 day**	**±1 day**
Dispense IP		X	X		
Collect IP[o]			X	X	
IP accountability[o]			X	X	
Prior medications/concomitant medications[o,p]	X	X	X	X	X
AEs including AESIs[o,p]	X	X	X	X	X

Abbreviations: AE, adverse event; AESI, adverse event of special interest; CGI-C, Change in Clinical Global Impression of Change; CGI-S, Clinical Global Impression of Severity; C-SSRS, Columbia Suicide Severity Rating Scale; ECG, electrocardiogram; ESS, Epworth Sleepiness Scale; IP, investigational product; MWT, Maintenance of Wakefulness Test; PGI-C, Patient Global Impression – Change; UDS, Urine Drug Screen.

[a] Virology and Serology laboratory tests (i.e., Hepatitis B, Hepatitis C, and human immunodeficiency virus) will be completed at Screening.

[b] Vital signs (i.e., SBP, DBP, body temperature, pulse, and respiratory rate) to be obtained after subject has been sitting for at least 5 min. The method of obtaining body temperature will be per sites standard practice but should be obtained by the same method for a given subject throughout the study. Vital signs may be collected prior to the PSG and the first MWT.

[c] Electrocardiograms should be obtained after the subject has been quiet and supine for approximately 3 minutes. An ECG will be captured at baseline (Day 0, Visit 1), and 3 h (±30 min) post dose on Days 7 and 14.

[d] Laboratory assessments are listed in protocol Table 2.

[e] Venipuncture for point estimates of the plasma concentration of SUVN-G3031 will be obtained at baseline (Day 0; blank), and on Day 7 (Visit 2) and Day 14 (Visit 3) at the estimated trough just prior to dosing and at the estimated maximum plasma concentration of SUVN-G3031 (3 ± 0.5 hours post dosing on Day 7 and Day 14) for a total of 5 samples.

[f] A serum pregnancy test will be completed at baseline (Day 0; Visit 1). Urine pregnancy tests will be completed at Screening, Baseline (Visit 1), Day 7 (Visit 2), Day 14 (Visit 3), and Day 21 (Safety Follow-up visit).

[g] A positive UDS at Screening can be repeated up to Day -1; however, a negative UDS is required prior to Day 0 (Baseline visit), and a second negative UDS is required on Day 0 (Baseline visit).

[h] Within the current study nocturnal overnight PSG will be completed at baseline (Day 0; Visit 1), Day 7 (Visit 2), and at Day 14 (Visit 3). Variables to be collected will include latency to persistent sleep in minutes (latency from lights-off to the first epoch of 20 consecutive epochs of any stage of sleep), number of arousals, number of awakenings, sleep efficiency, total sleep time in minutes, wake after sleep onset in minutes, percentage of time in stage 1, 2, 3, 4, REM sleep percentage, REM sleep latency in minutes and periodically movements during sleep (N).

[i] The [redacted] MWT will be utilized within this study and will be performed after a nocturnal overnight PSG at baseline (Day 0), Day 7, and at Day 14 according to validated standards. The MWT will begin at approximately 2 hours after awakening (4 total MWT sessions will be performed at 2 hour intervals). Subjects will be required to recline in a quiet, dimly lit bedroom and instructed to remain awake for as long as possible. Each MWT session will be stopped after the onset of sleep or after [redacted] if sleep did not occur. The onset of sleep will be evaluated using a standard PSG montage and defined as 3 consecutive 30-second epochs of stage 1 sleep or 30 seconds of sleep stage 2, 3, 4, or rapid eye movement sleep.

[j] Physicians will complete a CGI-S and CGI-C assessments for EDS rather than totally of illness. The CGI-S assessment will be completed first followed by CGI-C evaluation. The administrator of the CGI-S and CGI-C should remain consistent for each subject at each visit.

[k] ESS, PGI-C, C-SSRS assessments will be completed in this order at the beginning of each evaluation day prior to start of first MWT session. Note: 2 distinct forms of C-SSRS will be used: “Baseline-Screening” form will be used at Screening and “Since Last Visit” form will be used at subsequent visits.

[l] For the PGI-C, the subject will be asked to address the totality of experience on study medication, without attempts to demarcate between excessive daytime somnolence versus cataplexy.

[m] Sleep diary is collected nightly by the subject from Screening through Visit 3. The subject will provide the sleep diary from the preceding week at the beginning of each visit. In addition, dosing data will be collected in the diary.

[n] Washout period will occur within a maximum 28-day Screening period to allow for minimum drug free period of ≥ 7 days for all stimulants targeting EDS, and ≥ 14 days for all agents targeting cataplexy prior to randomization and baseline (Day 0) assessments.

[o] At the start of each visit as indicated, the subject will return IP that has not been used, provide sleep diary, report any modification in concomitant medication dosage or regimen, and research personnel will complete a nondirected inquiry for the detection of AEs. Safety assessments completed by the Investigator precede the efficacy assessments.

[p] Concomitant medications and AEs may be collected prior to the PSG and the first MWT.

4. Study Endpoints

4.1. Primary Efficacy Endpoint

- Primary endpoint: Change from baseline in the mean total ESS score at Day 14

4.2. Secondary Efficacy Endpoints

- Change from baseline in the mean CGI-S score related to EDS at Day 14
- Change from baseline in the mean MWT score at Day 14

4.3. Exploratory Endpoints

- Change from baseline in the mean total ESS score at Day 7
- Change in MWT score, within each of the 4 MWT sessions within a single day (Day 7 and Day 14)
- Proportion of subjects reporting CGI-C scores of 1 or 2 at Day 7 and Day 14 (EDS)
- Proportion of subjects reporting CGI-C scores of 1 or 2 or 3 at Day 7 and Day 14 (EDS)
- Proportion of subjects reporting CGI-S scores related to EDS of 1 or 2 at Day 7 and Day 14
- Proportion of subjects reporting CGI-S scores related to EDS of 1 or 2 or 3 at Day 7 and Day 14
- Proportion of subjects with improvement in the PGI-C score from baseline to Day 7 and Day 14
- Change from baseline in the behavior of Sleep Diary parameters at Day 7 and Day 14 (7-day average)
- Change from baseline in the mean CGI-S score related to EDS at Day 7
- Changes in the behavior of the nocturnal overnight PSG assessments at Day 7 and Day 14
- Change from baseline in the mean MWT score at Day 7
- Analysis of all endpoints (except Sleep Diary parameters and nocturnal overnight PSG assessments) evaluating SUVN-G3031 doses (2 mg and 4 mg) compared to placebo.

4.4. Pharmacokinetic Endpoints

Not applicable for this study.

The plasma concentration data will be summarized using descriptive statistics and all plasma concentration data will be listed using the PK population.

4.5. Pharmacodynamic Endpoints

No Pharmacodynamic assessments performed for this study.

4.6. Safety Endpoints

- Physical examination
- Vital signs
- Laboratory assessments (blood and urine)
- Electrocardiogram (ECG)
- Adverse events (AEs)
- Adverse events of Special Interest (AESIs)
- Columbia-Suicide Severity Rating Scale (C-SSRS)

4.7. Health-economics Endpoints

Not applicable for this study.

4.8. Other Endpoints

Not applicable for this study.

5. Analysis Population

5.1. Safety Population

The safety population will include all randomized subjects who receive at least 1 dose of study treatment. The treatment group assignment in this population will be defined by the treatment actually received. This population will be used for the analysis of safety.

5.2. ITT Population

The intent-to-treat (ITT) population will include all subjects who were randomized, received at least one dose of study treatment drug, and had baseline and at least one post-baseline primary efficacy assessment. This population will be used for the analysis of efficacy.

5.3. Per Protocol (PP) Population

The Per Protocol (PP) population will be a subset of ITT population consisting of those subjects who complete 14 days treatment and had no major protocol deviation affecting the primary efficacy variable. All protocol deviations will be assessed and documented on a case-by-case basis before the database lock, and deviations considered to have a serious impact on the efficacy results will lead to the relevant subject being excluded from the PP population. Before database lock, potential subject exclusions from PP population will be reviewed by the Sponsor and documented in a subject evaluability document.

5.4. Pharmacokinetic (PK) Population

The PK population will include all subjects who receive at least 1 dose of study treatment with sufficient post dose plasma concentration data. This population will be used for PK analysis, summaries will be provided by actual treatment received.

5.5. Pharmacodynamic Population

Not applicable for this study.

5.6. Other Analysis Population

Not applicable for this study.

5.7. Protocol Deviations

All subjects protocol deviations will be summarized with number and percentage by treatment group: Protocol deviations data will be summarized on all randomized subjects.

A listing will be produced containing the following information:

- Date
- Minor or Major deviation
- Category of deviation
- Description of deviation

The listing will be presented for the all randomized subjects.

6. General Aspects for Statistical Analysis

6.1. General Methods

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables and figures will be provided.

- Summary tables will be organized by treatment group. Descriptive statistics for continuous variables will include number of subjects (n), mean, standard deviation, median, minimum, and maximum, unless otherwise noted. Frequency and percentage will be calculated for categorical variables. Unless stated otherwise, all summary tables will present descriptive statistics and/or frequencies by treatment.

- All data listings will be sorted by treatment and subject number. Data listing will be provided for all randomized subjects with exception of few listings which will be provided for all enrolled subjects.

- Unscheduled assessments will not be included in summary tables unless specified otherwise but will be included in the subject listings.

6.2. Key Definitions

6.2.1. Baseline

In general, the last non-missing valid observation before first dose of study drug will serve as the baseline measurement.

6.2.2. Body Mass Index

The BMI of a subject will be calculated in kg/m² as BMI = body weight [kg] / (height [m])².

6.2.3. Change from Baseline

Change = Post-baseline value – Value at baseline.

Relative change = [(Post-baseline value – Value at baseline)/ Value at baseline] x100.

6.2.4. Treatment Accountability and Compliance

The pharmacist or other designated individual will maintain records of study treatment delivered to the study site, the inventory at the study site, the distribution to and use by each subject and the return of any required materials to the Sponsor. Study sites will be responsible for disposal of study treatment. Records should include dates, quantities, batch/serial numbers, expiration dates, in-clinic temperature log, and unique code numbers assigned to the product and study subjects.

At each visit after initiation of treatment, study site personnel will record compliance of the subject with the subject's assigned regimen. Subjects will be instructed to bring their sleep diaries and unused/partially used/empty bottles back for inspection at each study visit. Subjects are to be reminded of the importance of compliance with their assigned regimen, with an emphasis on taking their study drug on schedule and maintaining the prescribed interval between doses.

Subjects with missing sleep diaries or with missing entries in sleep diaries for dosing will be considered as treated if number of tablets returned at post baseline visit are less than the number of tablets dispensed at baseline visit.

Investigators will maintain records that adequately document that the subjects were provided with the correct study treatment kits and reconcile the products received from the drug dispensing center. Investigational product will not be disposed until accountability has been fully monitored.

Medication containers must be returned at each visit, as compliance will be assessed by tablet counts. Noncompliance is defined as taking less than <80% or more than 120% of study drug during any outpatient evaluation period (visit to visit). Discontinuation for noncompliance is at the Investigator's discretion and is to be noted on the eCRF.

Compliance until Day 7 visit, Compliance between Day 7 and Day 14 visit and Overall Treatment Compliance will be present in continuous summary (Number, Mean (SD), Median and Min, Max)

Categorized Overall Compliance [n (%)]

- < 80%
- 80% - 120%
- >120%

6.2.5. Days of Study Termination

Days of study termination = End of study date – Randomization date + 1.

6.2.6. Study Completion

A subject will be defined as "completed" if she/he remained in the study up to End of study (see End of study CRF). Termination at a time point and prior to this will be considered as discontinuation.

6.2.7. Duration of AE

Duration of AE [days] = Date of stop of AE – Date of start of AE + 1.

6.2.8. Prior/Concomitant Medication

A medication is regarded as 'prior' if the stop date of the event is prior to the first dose of study drug, irrespective of the start date.

A medication is regarded as 'concomitant' if it is not 'prior' and the start date or stop date is between the date of first dose of study drug (included) and the End of study date (included).

A medication is regarded as 'concomitant' if ticked as ongoing on the CRF.

6.2.9. Study Day 1

Study day 1 will be the first day of study drug administration.

First day of study drug administration is defined as first dispensation date + 1.

6.3. Missing Data

6.3.1. Missing Dates

No missing date will be imputed.

6.3.2. Missing values

Efficacy - Missing Values at Baseline: If a value is missing at baseline but there are non-missing post-baseline values, the missing baseline will be imputed as the first post-baseline non-missing assessment of the subject.

6.4. Visit Windows

All assessments will be included in the listings. No visit windows will be applied to assessments.

6.5. Pooling of Centers

Data from all centers/sites will be pooled together.

[redacted]

7. Demographic, Other Baseline Characteristics and Medication

7.1. Subject Disposition and Withdrawals

Study completion and withdrawals (with reasons) will be summarized for the all enrolled subjects.

Inclusion in each analysis population will be summarized, along with reasons for exclusion.

7.2. Demographic and Other Baseline Characteristics

Demographic and baseline characteristics (cataplexy, without cataplexy, duration of narcolepsy, baseline data of MWT, ESS, CGI-S, PGI-C) will be summarized using descriptive statistics. Demographics and informed consent data will be listed for all randomized subjects.

Age at date of informed consent= (date of informed consent- date of birth + 1) / 365.25 and truncated to complete years.

7.3. Medical History and Disease History

Medical history will be coded by System Organ Class (SOC) and Preferred Term (PT) using MedDRA version 22.0 (or) higher version.

Medical history will be summarized by treatment group and overall, and sorted by frequency (descending order based on overall totals) by SOC and PT.

Separate Summaries will be performed for Medical History and Disease History on the Safety Population. All available medical history information will be listed on all randomized subjects.

7.4. Prior and Concomitant medication

All non-study medications will be classified using the dynamic version of the World Health Organization Drug Dictionary (WHODD) coding dictionary version Global B3 March 2019 or higher version. Coding includes the Anatomical Therapeutic Chemical (ATC) classification levels 1 and 2 and preferred term.

Any medication which started before the first dose of study medication will be categorized as Prior Medication. Any medication continued or started after the first dose of study medication will be categorized as concomitant medication.

Concomitant medications will be summarized by the ATC levels and preferred term. All non-study medications will be listed.

Missing dates will not be imputed. However the following table will be utilized to categorize prior and concomitant medication.

Medication start (↓) /end (→) date		< baseline visit	≥ baseline visit		**All cases where year is missing or ongoing is ticked**	**Month and Day is missing**		**Only Day is missing**	
						Year of Medication < Year of baseline visit	Year of Medication ≥ Year of baseline visit	Month-Year of Medication < Month-Year of baseline visit	Month-Year of Medication ≥ Month-Year of baseline visit
< baseline visit		P	PC		PC	P	PC	P	PC
≥ baseline visit			C		C		C		C
All cases where year is missing		P	PC		PC	P	PC	P	PC
Month	Year of	P	PC		PC	P	PC	P	PC

Medication start (↓) /end (→) date		< baseline visit	≥ baseline visit		All cases where year is missing or ongoing is ticked	Month and Day is missing		Only Day is missing	
						Year of Medication < Year of baseline visit	Year of Medication ≥ Year of baseline visit	Month-Year of Medication < Month-Year of baseline visit	Month-Year of Medication ≥ Month-Year of baseline visit
and Day is missing	Medication < Year of baseline visit								
	Year of Medication ≥ Year of baseline visit	P	C		C		C	P	C
Only Day is missing	Month-Year of Medication < Month-Year of baseline visit	P	PC		PC	P	PC	P	PC
	Month-Year of Medication ≥ Month-Year of baseline visit	P	C		C		C		C

Abbreviations: P=Prior, C=Concomitant, PC=Prior and Concomitant.

8. Efficacy Evaluation

The primary testing approach for efficacy is the statistical comparison of the pooled active SUVN-G3031 dose groups (2 mg/day and 4 mg/day) versus placebo. Additionally, each active dose will be tested against placebo. All statistical tests will be performed at alpha=5% for the two-sided test.

8.1. Primary Efficacy Endpoint and Analysis (Primary Estimand)

The null (H0) and alternative (H1) hypotheses of the study are as follows:

H0: SUVN-G3031 and placebo do not differ in their change from baseline in the mean total ESS score at Day 14.

H1: SUVN-G3031 and placebo differ in their change from baseline in the mean total ESS score at Day 14.

The primary estimand is defined with the following 5 attributes:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

The primary analysis approach will be performed using a mixed model repeated measures (MMRM) analysis. This model considers all observed post-baseline assessments of both post-baseline visits (Day 7 and Day 14), in case of death, the visits after the death will be filled with the worst observed value post-baseline, prior to entering the MMRM. In the MMRM all missing values will be imputed via direct likelihood based on the assumption of missing at random.

The MMRM model will include randomized treatment (for the pooled analysis, both active treatments will be combined), visit and treatment (for the pooled analysis, both active treatments will be combined) by visit interaction as explanatory variables, stratification factor for cataplexy subject history (presence or absence) and baseline MWT score as continuous covariates. An unstructured covariance structure will be assumed. Least square mean changes will be estimated for each single treatment and the difference of each SUVN-G3031 dose versus placebo. Results of comparison of pooled active treatment groups versus placebo will be presented. Additionally, the analysis will be repeated with consideration of single treatment groups.

If the assumptions underpinning the MMRM are found to be violated, either a log transform or an analysis based on ranked data will be performed as appropriate and least squares means, 95% confidence intervals, and p-values of the treatment comparisons (across visits and within visits) for descriptive purposes along with basic arithmetic summary statistics (mean, median, SD, standard error of the mean, min, and max) will be provided.

If the statistical comparison of pooled active dose group versus placebo results in superiority with p-values less or equal to 5% then SUVN-G3031 can be considered as superior to placebo in a confirmatory way. Otherwise result will be interpreted in an exploratory way.

[redacted]

[redacted]

8.4. Secondary Efficacy Endpoint(s) and Analyses (Secondary Estimands)

The secondary efficacy endpoints for this study are:

- Change from baseline in the mean CGI-S score related to EDS at Day 14
- Change from baseline in the mean MWT score at Day 14

The two secondary estimands investigate the efficacy endpoints 'Difference to placebo in the change from baseline in the CGI-S score related to EDS at Day 14' on the ITT population using a MMRM analysis, and the 'Difference to placebo in the Change from baseline in the MWT score at Day 14' on the ITT population using a MMRM analysis. MMRM considers all observed post-baseline assessments of both post-baseline visits (Day 7 and Day 14), , in case of death, the visits after the death will be filled with the worst observed value post-baseline from all subjects, prior to entering the MMRM In the MMRM all missing values will be imputed via direct likelihood based on the assumption of missing at random.

The approaches to handle intercurrent events for secondary endpoints will be consistent with those for the primary endpoint.

The testing of secondary endpoints will be controlled using hierarchical testing methods. The testing of the first secondary efficacy endpoint will be performed in a confirmatory way only, if for the primary efficacy of pooled treatment is significant versus placebo. The confirmatory testing approach will proceed to the second secondary efficacy endpoint only, if pooled active treatment comparison versus placebo is significant for the first secondary efficacy endpoint.Otherwise the results will be considered as exploratory only.

The secondary endpoints will be analyzed similar to the primary efficacy endpoint: using MMRM with multiple imputation and an ANCOVA of Day 7 and Day 14 data with multiple imputation as sensitivity analyses, and by repeating the analyses on PP as supportive analyses.

The time course (Baseline, Day 7, Day 14) of mean values of CGI-S and MWT, respectively, together with +/- standard error of mean will be presented in figures for the ITT and PP populations.

Summary tables by visit by treatment with actual and changes from baseline (if applicable) will be provided for the ITT and PP population.

8.5. Analysis of Exploratory Endpoints

Summary tables with actual and changes from baseline (if applicable) will be provided for the continuous exploratory endpoints (listed below), and they will be analyzed in a similar fashion as the primary endpoint, i.e., an MMRM using the ITT population and PP population. No imputations will be applied in the analysis of exploratory endpoints except total ESS score at Day 7, CGI-S score at Day 7 and MWT score at Day 7.

- Change from baseline in the mean total ESS score at Day 7
- Change from baseline in the mean CGI-S score related to EDS at Day 7
- Change from baseline in the mean MWT score at Day 7
- Change from baseline in the behavior of Sleep Diary parameters at Day 7 and Day 14 (7-day average)
- Changes in the behavior of the nocturnal overnight PSG assessments at Day 7 and Day 14
- Change in MWT score, within each of the 4 MWT sessions within a single day (Day 7 and Day 14)

Frequency tables will be provided. For binary assessments (listed below), a repeated measures responder analyses will use a generalized estimating equations with a logit link function and starting with an unstructured working correlation matrix. No imputations will be applied in the analysis of below endpoints.

- The proportion of subjects reporting CGI-C scores of 1 or 2 at Day 7 and Day 14 (EDS)
- Proportion of subjects reporting CGI-C scores of 1 or 2 or 3 at Day 7 and Day 14 (EDS)
- The proportion of subjects reporting CGI-S scores related to EDS of 1 or 2 at Day 7 and Day 14
- Proportion of subjects reporting CGI-S scores related to EDS of 1 or 2 or 3 at Day 7 and Day 14
- Proportion of subjects with improvement in the PGI-C score from baseline to Day 7 and Day 14
- Analysis of all endpoints (except Sleep Diary parameters and nocturnal overnight PSG assessments) evaluating SUVN-G3031 2 mg or 4 mg compared with placebo.

Factors included in the model will be treatment group, a stratification factor for cataplexy subject history, visit, treatment-by-visit interaction, and baseline value as a covariate. Model estimates will be based on Wald statistics.

Sleep diary and measures collected as part of the nocturnal overnight PSG assessments at Day 7 and Day 14 will be summarized using descriptive statistics.

Further exploratory analyses will include each individual MWT session throughout the day in comparison to matched baseline sessions (morning, afternoon, or evening testing periods as defined within the protocol).

9. Analysis of Pharmacokinetics

Individual SUVN-G3031 plasma concentrations versus time at pre-dose on baseline (day 0), at pre-dose and post dose (3 ± 0.5 h) on day 7 day 14 will be summarized versus time points of collection and by treatment dose using descriptive statistics of the PK profile.

The following descriptive statistics (number of subjects, arithmetic and geometric mean, SD, % coefficient of variation, % Geometric coefficient of variation, minimum, maximum, and median) of the plasma concentrations versus time will also be presented on PK population.

The concentration data will also be listed by time points of collection.

Figures:

Summarized (Mean ± SD, N) SUVN-G3031 plasma concentrations versus time at pre-dose on baseline (day 0), at pre-dose and post dose (3 ± 0.5 h) on day 7 and day 14 by treatment will be presented on a linear scale.

Summarized (Mean ± SD, N) SUVN-G3031 plasma concentrations versus time at pre-dose on baseline (day 0), at pre-dose and post dose (3 ± 0.5 h) on day 7 and day 14 by treatment will be presented on a log scale.

10. Safety Evaluation

The population used for safety analyses will be the Safety Population. Safety will be assessed on the basis of adverse event (AE), clinical laboratory data, ECG parameters, physical examinations, vital signs, and C-SSRS.

Partial or missing dates of safety data will be imputed according to the most conservative approach.

The imputation would be applicable to only assigning the event. Eg. If AE start date is incomplete then date or month will be imputed just to assign if AE is treatment emergent or not. In listing all incomplete or partial dates will be presented and not imputed.

10.1. Extent of Exposure

Study Drug Exposure, study duration and cumulative dose will be summarized for each treatment group and overall, and will also be listed.

10.2. Treatment Compliance

Overall treatment compliance (%) is defined as number of tablets taken during the complete treatment period / number of tablets expected to be taken during the complete treatment period * 100. Overall compliance (%) and classified overall compliance (<80%, 80-120%, >120%) will be summarized. The number of tablets (study medication) dispensed, returned, lost/damaged/missed, overall compliance and overall classified compliance will be listed.

10.3. Adverse Events (AEs)

All reported AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). The incidence of TEAEs (events with onset dates on or after the start of the study drug) will be included in incidence tables. Events with missing onset dates will be included as treatment-emergent unless an incomplete date clearly indicates that the event started prior to the first study drug administration. If a subject experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug will be used in the summary tables. Serious AEs, AEs causing discontinuation and AESIs will be tabulated. All AEs will be listed by subject, along with information regarding onset, duration, relationship and severity to study drug, action taken with study drug, treatment of event, and outcome.

Adverse events (AEs) will be coded using MedDRA 22.0 or higher version.

Events that occur after a subject provides informed consent but before the time of the first dose of study drug will be considered non treatment-emergent AEs. Treatment-emergent AEs are defined as events that are newly occurring or worsening from the time of the first dose of study drug.

Missing dates will not be imputed. However, the following table will be utilized to categorize TEAEs.

AE Start Date	AE End Date	Rule on AE End Date	Rule on AE Start Date	TEAE
Not missing			AE Start Date < Treatment Start Date	N
			AE Start Date ≥ Treatment Start Date	Y
Partly missing	Not missing	AE End Date < Treatment Start Date		N
		AE End Date ≥ Treatment Start Date	non missing part of AE Start Date < Treatment Start Date	N
			non missing part of AE Start Date	Y

AE Start Date	AE End Date	Rule on AE End Date	Rule on AE Start Date	TEAE
			≥ Treatment Start Date	
	Partly missing	non missing part of AE End Date < Treatment Start Date		N
		non missing part of AE End Date ≥ Treatment Start Date	non missing part of AE Start Date < Treatment Start Date	N
			non missing part of AE Start Date ≥ Treatment Start Date	Y
	Totally Missing or Ongoing		non missing part of AE Start Date < Treatment Start Date	N
			non missing part of AE Start Date ≥ Treatment Start Date	Y
Totally Missing	Not missing	AE End Date < Treatment Start Date		N
		AE End Date ≥ Treatment Start Date		Y
	Partly missing	non missing part of AE End Date < Treatment Start Date		N
		non missing part of AE End Date ≥ Treatment Start Date		Y
	Totally Missing or Ongoing			Y

An overall summary of AEs and TEAEs will show the number and percentage of subjects (and the corresponding number of TEAEs) by treatment group

- any AEs
- any TEAE
- any TEAE by severity
- any related TEAE
- any TEAE leading to treatment discontinuation
- any SAE
- any related SAEs
- any AESIs
- any TEAE leading to death

Summary tables by system organ class and preferred term will be provided for treatment group and overall for

- TEAEs
- TEAEs by maximum severity
- TEAEs by maximum relationship to study treatment
- Treatment-related TEAEs
- Serious TEAEs
- TEAEs leading to withdrawal
- AEs of special interest (AESI)

As AESI the following AEs (after start of study treatment) will be considered:

- Vivid and/or unpleasant dreams
- Difficulty initiating or maintaining sleep

The summaries will be produced on the Safety Analysis Population.

Separate listings will be provided in the tables section for

- any SAE

- any fatal AE
- any AE leading to treatment discontinuation

All TEAEs for each subject, including multiple occurrences of the same event, will be presented for all randomized subjects. In a separate listing all non-TEAEs of randomized subjects will be provided.

10.4. Laboratory Evaluations

Descriptive statistics will be performed for those laboratory parameters on a continuous scale for actual values and change from baseline at each visit, by treatment. Categorical results for urinalysis will be summarized using frequency tabulations. Abnormal values for each analyte will be determined using reference ranges provided by the central laboratory. All laboratory results will be listed including unscheduled visits. Additionally, shift table of post-baseline to baseline of the values below normal range, within normal range and above normal range will be provided.

Dipstick urinalysis results evaluation (Normal, Abnormal Not Clinically Significant and Abnormal Clinically Significant) will be summarized at each protocol scheduled time point by treatment group using frequency tabulations. All abnormal laboratory values will be flagged in the listings.

The following table summarizes all laboratory parameters which will be assessed in the study.

Hematology	**Serum Chemistry**	**Urine Analysis (Dipstick)**
Hematocrit Hemoglobin Red blood cell count White blood cell count with differential Platelets Red blood cell indices	Albumin Alanine aminotransferase Alkaline phosphatase Aspartate aminotransferase Blood urea nitrogen or urea Creatinine Electrolytes (sodium, potassium, chloride, calcium) Gamma glutamyltransferase Glucose Lactate dehydrogenase Total bilirubin Direct bilirubin Uric acid Follicle-stimulating hormone[a] Thyroid stimulating hormone[b]	Appearance pH Protein Glucose Ketone bodies Indicators of blood and white blood cells Specific gravity Urobilinogen Microscopic analysis will occur when dipstick indicates clinically significant changes in one of the above.
Virology/Serology tests: Virology and Serology laboratory tests (i.e., Hepatitis B, Hepatitis C, and human immunodeficiency virus) will be completed at Screening.		
Pregnancy test: A pregnancy test will be performed on all women of childbearing potential at Screening, baseline, Day 7, Day 14, and follow-up. Additionally, a serum pregnancy test will also be performed at baseline.		
Urine drug screen: The following drugs will be tested for: barbiturates, benzodiazepines, cocaine, cannabinoids, methadone, methamphetamines, morphine/opiates, phencyclidine, and tricyclic antidepressants.		

[a] Serum follicle-stimulating hormone tests will be completed as necessary.

[b] Thyroid stimulating hormone tests will be completed at Investigator's discretion.

Women of childbearing potential (WOCBP) must have a negative pregnancy test at Screening, Baseline, and follow-up. After administration of study drug, any known cases of pregnancy in female subjects or female partners of male subjects will be reported until the subject completes or withdraws from the study.

A listing with pregnancy test results will be summarized for all randomized female subjects.

10.5. Vital Signs

Vital signs (body temperature, respiration rate, heart rate, and systolic and diastolic blood pressure measurements) will be evaluated at the visits indicated in the Schedule of Assessments. All vital signs will be measured after the subject has been resting in a sitting position for at least 5 minutes. Blood pressure measurements are to be taken in the same arm for the duration of the study. Body weight (without shoes) will be recorded whenever vital signs are recorded; height (without shoes) will be recorded at Screening only.

Vital signs and body weight will be summarised at each protocol scheduled time point by treatment group. Actual values and changes from baseline will be presented. Vital signs and body weight will be listed for all randomized subjects.

10.6. Electrocardiogram (ECG)

A frequency tabulation of ECG results evaluation (Normal, Abnormal Not Clinically Significant or Abnormal Clinically Significant) will be presented at each protocol scheduled time point, by treatment group at each time point. Additionally, a shift table of the overall ECG evaluation at the post-baseline visits compared to baseline will be provided.

10.7. Physical Examination

Physical examination data (Normal/Abnormal) at each visit will be listed by body system for all randomized subjects.

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

Two versions of the C-SSRS are to be used in the study: The first is to be used at Screening and will assess lifetime suicidal ideation and behavior until that point (Baseline-Screening Form). Identification of active suicidal ideation will exclude the subject from enrollment in the study. At each subsequent visit, the follow-up C-SSRS is used (Since Last Visit form) to assess suicidal ideation and behavior since the last visit.

The C-SSRS data, i.e. suicidal ideation severity, suicidal ideation intensity, suicidal behavior, non-suicidal self-injuries behavior and lethality, will be summarized by treatment arm and visit for the Safety Population. Additionally, a frequency table of subjects answering Yes to questions of C-SSRS form by any question will be provided by treatment arm for the Safety Analysis Set. A listing of all randomized subjects will be provided.

[redacted]

[redacted]

11.2. Brief Description of CHW

The Cui, Hung, Wang (CHW; Cui, Hung et al. 1999) weighted test statistic to analyze the primary and secondary efficacy endpoint (i.e., for total ESS and mean MWT) at the end of the study is described below and it preserves the type 1 error in case of updated sample size:

Cui-Hung-Wang (CHW) approach defines a weighted statistic (Z), data from the 2-stages (stage 1 uses all data until interim analysis, stage 2 uses all data after interim analysis) by weighting the stage wise Wald test statistics

Wald Test Statistic under $H_0: \delta = 0$, is defined as

$$\text{Stage 1: } Z_1 = (\widehat{\delta_1} - \delta)/SE(\widehat{\delta_1})$$

$$\text{Stage 2: } Z_2 = (\widehat{\delta_2} - \delta)/SE(\widehat{\delta_2})$$

Where $\widehat{\delta_1}$ is difference in sample means at stage 1. Similarly, $\widehat{\delta_2}$ is the difference in sample means at stage 2. $SE(\widehat{\delta_1})$ is standard error for $\widehat{\delta_1}$ at stage 1. Similarly, $SE(\widehat{\delta_2})$ is standard error for $\widehat{\delta_2}$ at stage 2.

The CHW pooled test statistic combines the two stages statistics together and applies the weighting,

$$Z = \sqrt{W_1} Z_1 + \sqrt{1 - W_1} Z_2$$

Confidence interval and point estimate:

A 100(1-α)% Confidence Interval;

$$\frac{W_1 \widehat{\delta_1} + \sqrt{1 - W_1}\sqrt{W^* - W_1}\,\widehat{\delta_2} \pm K^{-1} z_{\alpha/2}}{W_1 + \sqrt{1 - W_1}\sqrt{W^* - W_1}}$$

Point Estimate, $\widehat{\delta}$;

$$\widehat{\delta} = \frac{W_1 \widehat{\delta_1} + \sqrt{1 - W_1}\sqrt{W^* - W_1}\,\widehat{\delta_2}}{W_1 + \sqrt{1 - W_1}\sqrt{W^* - W_1}}$$

Where W1 is time measured on information scale and will be around 50%, W* is time measured after doing possible adjustment to initial maximum information ($W^* > W_1$). Please note, Time is measured on the information scale and is rescaled so that the study as originally planned will have maximum information equal to one. K^{-1} = S*sqrt((1/n1)+(1/n2)), is constant and depends on initial maximum information, where S is square root of poolled variance.

Deriving a point estimate and confidence interval will be aligned with the CHW test statistic (Lawrence & Hung, 2003). These point estimates will be used for MWT and ESS.

11.3. Conditional Power

The conditional power (CP) at the IA is calculated assuming that the estimated treatment difference is the true effect. Thus, CP can be obtained with (Mehta & Pocock, 2011):

$$CP = 1 - \Phi\left(\frac{z_\alpha\sqrt{n_2} - z_1\sqrt{n_1}}{\sqrt{\tilde{n}_2}} - \frac{z_1\sqrt{\tilde{n}_2}}{\sqrt{n_1}}\right)$$

Where:

- n_1 represents the number of subjects needed to perform the interim analysis, n2 the number of subjects needed to perform the final analysis, and $\tilde{n}_2$ represents the increment of subjects between the IA and the final analysis (i.e., $n_2 = n_1 + \tilde{n}_2$).
- z is the test statistic calculated from the observed data up to the interim analysis (z_1) or under a significance level of alpha.

[redacted]

[redacted]

[redacted]

13. Reference List

1) *For missing data assumptions refer to the ICH E9(R1) draft guidance on https://www.fda.gov/media/108698/download.*

2) *Lu Cui, H. M. James Hung,' and Sue-Jane Wang (1999): Modification of Sample Size in Group Sequential Clinical Trials. BIOMETRICS 55, 853-857.*

3) *Cyrus R. Mehta, and Stuart J. Pocock (2011): Adaptive increase in sample size when interim results are promising: a practical guide with examples. Stat Med 30(28): 3267-3284.*

4) *Ping Gao, James H. Ware, Cyrus Mehta (2008): Sample size re-estimation for adaptive sequential design in clinical trials. Journal of Biopharmaceutical Statistics, 18: 1184–1196.*

5) *W. Joseph Herring, Kenneth Liu, Jill Hutzelmann, Duane Snavely, Ellen Snyder, Paulette Ceesay, Christopher Lines, David Michelson, Thomas Roth(2013): Alertness and psychomotor performance effects of the histamine-3 inverse agonist MK-0249 in obstructive sleep apnea patients on continuous positive airway pressure therapy with excessive daytime sleepiness: a randomized adaptive crossover study, Sleep Medicine 14 (2013) 955–963.*

6) *Terri E. Weaver, Susan D. Mathias, Ross D. Crosby, Morgan Bron, Shay Bujanover, Diane Menno, Kathleen F. Villa, Christopher Drake (2020): Relationship between sleep efficacy endpoints and measures of functional status and health-related quality of life in participants with narcolepsy or obstructive sleep apnea treated for excessive daytime sleepiness, J. Sleep Res.. 2020;00:e13210.*

7) *Lawrence, J. and Hung, H.J. (2003), Estimation and Confidence Intervals after Adjusting the Maximum Information. Biom. J., 45: 143-152.*

8) *van der Heide A, van Schie MK, Lammers GJ, Dauvilliers Y, Arnulf I, Mayer G, Bassetti CL, Ding CL, Lehert P, van Dijk JG. Comparing Treatment Effect Measurements in Narcolepsy: The Sustained Attention to Response Task, Epworth Sleepiness Scale and Maintenance of Wakefulness Test. Sleep. 2015;38(7):1051-8.*

9) *Inoue, Y., Uchiyama, M., Umeuchi, H., Onishi, K., Ogo, H., Kitajima, I., Matsushita, I., Nishino, I., & Uchimura, N. (2022). Optimal dose determination of enerisant (TS-091) for patients with narcolepsy: two randomized, double-blind, placebo-controlled trials. BMC psychiatry, 22(1), 141.*

14. Programming Considerations

All statistical computations and construction of tables, listings and figures will be performed using SAS® for Windows Version 9.4 or higher (SAS® Institute Inc., Cary, NC, USA). Pharmacokinetic calculations will be performed using Pheonix™ WinNonlin® (Version 8.0 or higher, Pharsight Corporation) and/or SAS® (Version 9.4 or higher, SAS® Institute Inc.).

The format of the table shells will be followed as closely as possible; however, in the course of programming and familiarization with the database, some changes may become necessary. All changes will be documented. Major changes will be documented through a formal amendment to this document.

SDTM datasets will be created from the clinical database and external data, following the Study Data Tabulation Model Implementation Guide Version 3.2 or latest version. Analysis will be based on ADaM datasets created from the SDTM datasets.

The below programming considerations will be followed unless already specified in the above text.

14.1. General Considerations

- One SAS program may create several outputs.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format.
- Numbering of TFLs will follow International Conference on Harmonisation (ICH) E3 guidance

14.2. Table, Listing, and Figure Format

14.3. General

- All TFLs will be produced in landscape format, unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified. Colors may be used in figures.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

14.3.1. Headers

- All outputs should have the following header at the top left of each page:

Suven Life Sciences
Protocol No: CTP2S13031H3
Draft/Final Run

- All outputs should have “Page n of N” at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

14.3.2. Display Titles

- Each TFL will be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering will be followed. A decimal system (x.y and x.y.z) is used to identify TFLs with related contents. The title is centered. The analysis Population is identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(Mock Shells specified Analysis Population)

14.3.3. Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis Population sizes will be presented in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis Population.

14.3.4. Body of the Data Display

14.3.4.1. General Conventions

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;
- Whole numbers (e.g., counts) are right-justified; and
- Numbers containing fractional portions are decimal aligned.

14.3.4.2. Table Conventions

- Units will be included where available.
- If the categories of a parameter are ordered, then all categories between the minimum and maximum category are presented in the table, even if n=0 for in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
Mild	3
moderate	8
Severe	0

The same convention will be followed for data where categories are not ordered (e.g., Reasons for Discontinuation from the Study, etc.) i.e. all possible responses available on the CRF will be presented in the table even if there are one or more categories with n = 0 for all treatment groups.

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- An Unknown or Missing category will be added to each parameter for which information is not available for 1 or more subjects.

- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean (SD)	XXX.X (X.XX)
Median	XXX.X
Min, Max	XX, XXX

- P-values are output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value is less than 0.0001, then it will be presented as <0.0001. If the p-value is returned as >0.999, then it will be presented as >0.999.

- Percentage values will be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Unless otherwise noted, for all percentages, the number of subjects in the analysis Population who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data will be presented by the body system or SOC with the highest occurrence in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) are displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated will be reported as “-”.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, a footnote or programming note will be used to explain

if the subject is included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, the subheading followed by "(cont)" will be printed at the top of each subsequent page. The overall summary statistics for the subheading will only be displayed on the first relevant page.

14.3.4.3. Listing Conventions

- Listings will be sorted for presentation in order of subject number, visit/collection day, and visit/collection time.
- Missing data will be represented on listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates will be printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates will be represented on data listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject will be output as "N/A", unless otherwise specified.
- All observed time values are to be presented using a 24-hour clock HH:MM:SS or HH:MM format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included wherever available

14.3.4.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

14.3.4.5. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Subject specific footnotes will be avoided, wherever possible.
- Footnotes will be used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page will be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.

- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display and the date the program was run (i.e., 'Program: myprogram.sas Date generated: ddMMMyyyy).

15. 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 [redacted] SOP Developing Statistical Programs [redacted]

[redacted] SOPs Developing Statistical Programs [redacted] and Conducting the Transfer of Bio statistical Deliverables [redacted]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."

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

17. Index of Listings

Mock Listings Titles

1. Listing 16.2.1.7 Randomization Scheme and Treatment Assigned Randomized Subjects
2. Listing 16.2.1.1 Subject Disposition Randomized Subjects
3. Listing 16.2.1.2 Screening Failures Enrolled Subjects
4. Listing 16.2.2 Protocol Deviations Randomized Subjects
5. Listing 16.2.3 Exclusions from Populations Enrolled Subjects
6. Listing 16.2.4.1 Demographic and Baseline Characteristics Randomized Subjects
7. Listing 16.2.4.2.1 Medical History Randomized Subjects
8. Listing 16.2.4.2.2 Disease History Randomized Subjects
9. Listing 16.2.4.3 Prior and Concomitant Medications Randomized Subjects
10. Listing 16.2.5.1 Study Drug Exposure Randomized Subjects
11. Listing 16.2.5.2 Study Drug Accountability and Compliance Randomized Subjects
12. Listing 16.2.5.3 Pharmacokinetic Blood Sample Collection Times and Concentration Data Randomized Subjects
13. Listing 16.2.6.1 Epworth Sleepiness Scale (ESS) Randomized Subjects
14. Listing 16.2.6.2 Clinical Global Impression of Severity (CGI-S) Related to EDS Randomized Subjects
15. Listing 16.2.6.3 Maintenance of Wakefulness Test (MWT) Randomized Subjects
16. Listing 16.2.6.4 Clinical Global Impression of Change (CGI-C) Related to EDS Randomized Subjects
17. Listing 16.2.6.5 Patient Global Impression of Change (PGI-C) Related to EDS Randomized Subjects
18. Listing 16.2.6.6 Sleep Diary Randomized Subjects
19. Listing 16.2.6.7 Polysomnography (PSG) Test Randomized Subjects
20. Listing 16.2.7.1 Treatment-Emergent Adverse Events Randomized Subjects
21. Listing 16.2.7.2 Non-Treatment-Emergent Adverse Events Randomized Subjects
22. Listing 16.2.8.1.1 Hematology Randomized Subjects
23. Listing 16.2.8.1.2 Serum Chemistry Randomized Subjects
24. Listing 16.2.8.1.3 Urinalysis Randomized Subjects
25. Listing 16.2.8.1.4 Urine Pregnancy Test Randomized Subjects- Female Subgroup
26. Listing 16.2.8.1.5 Urine Drug Screen Randomized Subjects
27. Listing 16.2.8.1.6 Serology/Virology Screened Subjects
28. Listing 16.2.8.2.1 Vital Signs Randomized Subjects
29. Listing 16.2.8.2.2 Electrocardiogram (ECG) Randomized Subjects
30. Listing 16.2.8.2.3 Physical Examination Randomized Subjects

31. Listing 16.2.8.2.4.1 Suicidal Ideation based on C-SSRS: Questions Randomized Subjects
32. Listing 16.2.8.2.4.2 Subjects with Suicidal Ideation based on C-SSRS: Intensity of Ideation Randomized Subjects
33. Listing 16.2.8.2.4.3 Suicidal Behavior based on C-SSRS Randomized Subjects
34. Listing 16.2.8.2.4.4 Subjects with Suicidal Behavior based on C-SSRS: Lethality Randomized Subjects

18. Shells

Mock shells for tables, listings and figures will be created in a separate document as an attachment to the SAP which may be updated, revised and finalized separately from the SAP.

19. Appendices

[redacted]

[redacted]

[redacted]