Clinical Study Protocol

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: 16 August 2023

1 FINAL CLINICAL STUDY PROTOCOL

Suven Life Sciences

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Protocol Number: CTP2S13031H3

Short Title: Phase 2 DBPC Narcolepsy

[redacted] [redacted]

EudraCT Number:	Not applicable
Name of Investigational Product:	SUVN-G3031
Phase of Development:	2
Indication:	Narcolepsy with and without cataplexy
[redacted]	[redacted]
Protocol Version:	4.0 Final
Protocol Date:	16 Aug 2023

PROTOCOL APPROVAL SIGNATURES

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

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP), and applicable regulatory requirements.

INVESTIGATOR SIGNATURE PAGE

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

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Confidentiality and Current Good Clinical Practice (GCP)/E6(R2) Compliance Statement)

- I, the undersigned, have reviewed this protocol, including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant International Council for Harmonisation (ICH) guidelines.
- I am thoroughly familiar with the appropriate use of the study drug, as described in this protocol and any other information provided by Suven Life Sciences including, but not limited to, the current Investigator's Brochure.
- Once the protocol has been approved by the Institutional Review Board (IRB), I will not modify this protocol without obtaining prior approval of Suven Life Sciences and of the IRB. I will submit the protocol amendments and/or any informed consent form modifications to Suven Life Sciences and the IRB, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or party assisting me with the study are adequately qualified and informed about the Suven Life Sciences study drug and of their delegated study-related duties and functions as described in the protocol.
- I ensure that source documents and trial records that include all pertinent observations on each of the site's trial patients will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study with regard to the patients' state of health will be regarded as confidential. No patients' names will be disclosed. All patients will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the patient before disclosure of patient information to a third party.
- Information developed in this clinical study may be disclosed by Suven Life Sciences to other clinical Investigators, regulatory agencies, or other health authority or government agencies as required.

<Name>
<Title>

Investigator Signature

Date (DD-Mmm-YYYY)

Institution

2 SYNOPSIS

Title of Study:	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
Investigators/Study Sites:	Approximately 65 sites in the United States and Canada
Phase of Development:	Phase 2
Objectives:	Primary objective: To evaluate the effectiveness of SUVN-G3031 compared with placebo as measured by the change in total Epworth Sleepiness Scale (ESS) score. Secondary objectives: To evaluate the effectiveness 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 the Maintenance of Wakefulness Test (MWT) score. Exploratory objectives: • To evaluate the effectiveness of SUVN-G3031 compared with placebo as measured by an improvement in the MWT score, [redacted] • 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
Study Endpoints:	Primary endpoint: Change from baseline in the mean total ESS score at Day 14 Secondary 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 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 (CSSRS) 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 patients reporting CGI-C scores of 1 or 2 at Day 14 (EDS) • Proportion of patients reporting CGI-S scores related to EDS of 1 or 2 at Day 7 and Day 14

	• Proportion of patients 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 2 mg or 4 mg compared with placebo • Additional exploratory endpoints may be included in the statistical analysis plan (SAP)
Study Design:	This is a Phase 2, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety, tolerability, pharmacokinetics (PK), and efficacy of 2 mg and 4 mg SUVN-G3031 compared with placebo in patients with narcolepsy with and without cataplexy. Patients will be randomized at a ratio of 1:1:1 to 2 mg SUVN-G3031, 4 mg SUVN-G3031, or placebo. Patients will be stratified by at least 30% each based on whether they have narcolepsy with or without cataplexy (Na-1 or Na-2, respectively). Each patient will receive study drug once daily, in a tablet formulation, for 14 days. Enough patients will be screened to enable 114 patients to be enrolled (38 per treatment group). A single, unblinded, interim analysis will be undertaken when approximately 50% of patients have completed 14 days of treatment; this analysis will enable sample size re-estimation to occur if appropriate. A maximum of 57 additional patients (19 patients per treatment arm) will be enrolled to generate a total maximum study population of 171 patients. Patients, who have provided written informed consent, will be screened up to 28 days prior to enrollment. Eligible patients will complete a washout period of ≥ 14 days for all agents targeting cataplexy and ≥ 7 days for all stimulants targeting EDS. Sleep diaries will be distributed to eligible patients during the screening window and patients will start to record their sleep evaluations in it immediately. Diary entries will be reviewed at baseline and all subsequent visits. Once these washout periods have been completed patients will attend the clinic for randomization and baseline (Day 0) assessments; patients will provide a blood sample for analysis of plasma PK. After completion of baseline assessments, study drug will be dispensed to patients and they will take their first dose the next day (Day 1); patients will receive enough study drug to last until the next visit at Day 7. On Day 7 (±1 day) patients will attend the clinic for an outpatient visit, when efficacy and safety assessments will be undertaken. Patients 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 postdosing). Patients will be dispensed enough study drug to last until the next visit at Day 14. On Day 14 (±1 day) patients 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. A final safety follow-up visit will be performed at Day 21 (±1 day). All visits will be outpatient visits and patients will be enrolled in the study for a maximum of 49 days (7 weeks).

Selection of Patients:	Inclusion Criteria: 1. Must be between the ages of 18 to 65 years, 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 a Multiple Sleep Latency Test (MSLT) study showing an MSLT of ≤ 8 minutes with 2 or more sleep onset rapid eye movement periods (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/m^2. 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 patients who are sexually active and <u>not</u> 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 patient 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 (due to reasons including bilateral blocked fallopian tubes, bilateral oophorectomy, androgen insensitivity syndrome, and Müllerian agenesis). • "Of childbearing potential" and practicing a highly effective method of birth control is defined as a patient following regulations consistent with the use of birth control methods for patients 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. Nonexhaustive 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 patient), or male partner is using condoms with spermicide;

	practicing true abstinence (the preferred and usual lifestyle of the patient). 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. Exclusion Criteria: 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 1week prior to baseline assessments and during the course of the trial. 4. Nicotine dependence that has an effect on sleep (e.g., a patient 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. 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 patient 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. Patients 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. 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 patient'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. Patients 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 patient's lifetime, according to DSM-5 criteria. Patients with severe or uncontrolled depression that, in the judgment of the Investigator, makes the patient 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: • Patients who answer "Yes" on the CSSRS Suicidal Ideation Item 4 (active suicidal ideation with some intent to act, without specific plan) and whose most recent episode meeting criteria for this CSSRS Item 4 occurred within the last 6 months; or • Patients who answer "Yes" on the CSSRS Suicidal Ideation Item 5 (active suicidal ideation with specific plan and intent) and whose most recent episode meeting criteria for this CSSRS Item 5 occurred within the last 6 months; or • Patients who answer "Yes" on any of the 5 CSSRS 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 CSSRS Suicidal Behavior Items occurred within the last 2 years; or • Patients 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 patient to stop taking any wake promoting agent for more than 4 weeks. The patient's occupation (e.g., requirement for driving) may need to be considered.
Withdrawal Criteria:	• Unacceptable toxicity or AE. • Clinically significant abnormal lab values: o Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 8x upper limit of normal (ULN); o ALT or AST ≥ 3x ULN and total bilirubin ≥ 2x ULN at the same visit; o ALT or AST ≥ 3x ULN with the appearance of symptoms indicating hepatitis (e.g., worsening fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia).

	• QT syndrome, Fridericia's formula corrected QT (QTcF) interval ≥ 470 ms (for male subjects) or ≥ 480 ms (for female subjects), or torsades de pointes. • A positive urinary drug screen at any visit. • Patient withdrawal of consent: at any time, a patient's participation in the study may be terminated at his/her request or on the basis of the Investigator's clinical judgment. The reason for patient withdrawal will be noted on the electronic case report form (eCRF). • Intercurrent illness: a condition, injury, or disease unrelated to the primary diagnosis that became apparent during treatment and necessitated the patient's termination from the study. • General or specific changes in the patient's condition that renders him/her ineligible for further treatment according to the inclusion/exclusion criteria. • Patient fails to adhere to the protocol requirements (e.g., drug noncompliance, failure to return for defined number of visits). • Lost to follow-up: the patient stopped coming for visits, and study personnel were unable to contact the patient. • Pregnancy.
Planned Sample Size:	114 patients (38 per treatment group). This may be increased following a sample size re-estimation up to a maximum of 171 patients.
Investigational Therapy:	• 2 mg SUVN-G3031 • 4 mg SUVN-G3031
Reference Therapy:	Placebo
Treatment Duration:	Each patient will be dosed for 14 days. The study is expected to last a total of 13 months.
Efficacy:	Efficacy assessments include MWT, CGI-S, ESS, CGI-C, PGI-C, nocturnal overnight PSG, and sleep diary.
Safety:	Safety assessments include vital signs, physical examinations, ECGs, laboratory assessments, CSSRS and AEs.
Pharmacokinetics:	Blood samples will be collected for analysis of plasma PK.
Statistical Methods and Planned Analyses:	Summary tables will be organized by treatment group. Descriptive statistics for continuous variables will include number of patients (n), mean, standard deviation, standard error of mean, 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 study part and treatment. All data listings will be sorted by treatment and patient number. All data collected during the study will be analyzed and reported unless stated otherwise. The intent-to-treat (ITT) population will include all patients who were randomized, received at least one dose of study drug, and had baseline and at least one post-baseline primary efficacy assessment. The Safety population will include all randomized patients who receive at least 1 dose of study treatment. This population will be used for the analysis of safety. The Per Protocol (PP) population will be a subset of ITT population consisting of those patients 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 patient being excluded from the PP set. Before database lock,

	potential patient exclusions from PP population will be reviewed by the Sponsor and documented in a patient evaluability document. The PK population will include all patients who receive at least 1 dose of study treatment with sufficient postdose plasma concentration data. This population will be used for PK analysis. All patients who discontinued from treatment will be listed and the reasons for discontinuation will be tabulated. Baseline and demographic characteristics will be summarized for each treatment group. The primary efficacy endpoint is the change from baseline in the mean total ESS score at Day 14. A successful study requires demonstration of statistically significant differences between the combined SUVN-G3031 doses (2 mg and 4 mg) group and the placebo group at endpoint for the ESS. The primary endpoint will be analyzed using a mixed model repeated measures (MMRM) analysis that includes the mean total ESS score from baseline to 7 days through to 14 days. The model will include randomized treatment, visit and treatment-by-visit interaction as explanatory variables, [redacted] The main comparison will be a contrast between treatment groups at 14 days. Least square mean changes will be estimated for SUVN-G3031 and placebo. The primary analysis will be performed using the ITT population. Analysis of the secondary endpoints will be analyzed analogous to the principal analysis of the primary efficacy endpoint only if the primary endpoint is statistically significant. Continuous exploratory efficacy endpoints will be analyzed in a similar fashion as the primary endpoint. For binary assessments, a repeated measures responder analysis will use a generalized estimating equation with a logit link function and starting with an unstructured working correlation matrix. The evaluation of associated features of narcolepsy through a sleep diary and measures collected as part of the nocturnal overnight PSG assessments at Day 7 and Day 14 will be carried out using descriptive statistics. In addition, 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). Any AEs will be classified as treatment-emergent AEs (TEAEs) if they start on or after the date of first dose of study medication. The incidence of TEAEs will be included in incidence tables. Serious AEs, AEs causing discontinuation and AESIs will be summarized. The corresponding listings will be provided. Descriptive statistics will be performed for those laboratory parameters on a continuous scale for the raw scores and change from baseline at each visit. Categorical results for urinalysis will be summarized using frequency tabulations. All laboratory results will be listed including unscheduled visits. Actual and change from baseline values in vital signs and body weight will be summarized for each scheduled visit. The corresponding listing will be provided. Change from baseline in the 12-Lead ECG results will be calculated and summarized along with the actual results for each scheduled visit. Electrocardiogram data will also be listed. Concomitant medications will be summarized by the Anatomical Therapeutic Chemical levels and preferred term. All nonstudy medications will be listed. Physical examination data (Normal/Abnormal) at each visit will be listed by body system. The CSSRS data will be listed for all patients.

3 TABLE OF CONTENTS

3.1 List of In-text Tables

3.2 List of In-text Figures

4 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CSD	Consensus Sleep Diary
CSF	cerebrospinal fluid
CSSRS	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
EDC	electronic data capture
EDS	excessive daytime sleepiness
ESS	Epworth Sleepiness Scale
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
H3R	histamine H3 receptor
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonisation
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
MMRM	mixed model repeated measures
MSLT	Multiple Sleep Latency Test
MWT	Maintenance of Wakefulness Test
Na-1	narcolepsy with cataplexy
Na-2	narcolepsy without cataplexy
PGI	Patient Global Impression
PGI-C	Patient Global Impression - Change
PI	Principal Investigator
PK	pharmacokinetic(s)
PO	oral
PP	per protocol

Abbreviation	Definition
PSG	polysomnography
REM	rapid eye movement
RT	reaction time
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOL	sleep onset latency
SOREMP	sleep onset rapid eye movement period
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
UDS	urine drug screen
ULN	upper limit of normal
US	United States
WASO	wake after sleep onset
WOCBP	women of childbearing potential

5 INTRODUCTION

5.1 Background on Narcolepsy

Narcolepsy is a long-term neurological disorder that specifically affects the regulation of sleep-wake cycles. The disorder affects males and females equally with symptoms often starting in childhood, adolescence, or young adulthood (ages 7 to 25 years). It is estimated that anywhere from 135,000 to 200,000 people in the United States (US) have narcolepsy [National Institute of Neurological Disorders and Stroke, 2018]; however, because the condition often goes undiagnosed, the prevalence could be higher. People with narcolepsy are often misdiagnosed with other conditions, such as psychiatric disorders or medical disorders, delaying proper diagnosis and treatment for years.

The cardinal symptom of narcolepsy is excessive daytime sleepiness (EDS) [Nishino, 2007]. Excessive daytime sleepiness is characterized by persistent sleepiness, regardless of nighttime sleep accrual, and is often described as a “sleep attack” where patients experience a sudden and overwhelming sense of sleepiness [National Institute of Neurological Disorders and Stroke, 2018]. In between sleep attacks, however, patients with narcolepsy experience normal levels of alertness.

Narcolepsy may be further defined by the presence or absence of cataplexy. Approximately 70% of patients with narcolepsy experience cataplexy characterized by recurrent episodes of sudden loss of muscle strength accompanied by full conscious awareness [Wozniak and Quinell, 2015]. Narcolepsy with cataplexy (narcolepsy-cataplexy; hypocretin deficiency syndrome) is referred to as Narcolepsy Type 1 (Na-1). Cataplexy attacks in patients with Na-1 are typically triggered by negative and positive emotions [Calik, 2017] and vary in frequency, character, and severity. Severe attacks can result in a total body collapse during which patients are unable to move, speak, or keep their eyes open [National Institute of Health, 2017]. Narcolepsy without cataplexy is referred to as Narcolepsy Type 2 (Na-2).

Additional symptoms of narcolepsy experienced in both patients with Na-1 and patients with Na-2 at differing intensities and frequencies include hypnagogic hallucinations, sleep paralysis, and automatic behavior [Sturzenegger and Bassetti, 2004]. All symptoms of narcolepsy result in a decreased quality of life compared with the general population [Bogan et al, 2016]. A biological substrate has been suggested in that Na-1 is caused by a deficiency of hypothalamic hypocretin (levels $\leq$ 110 pg/mL). Little is known about the underlying causes of Na-2 [Baumann et al,2014]. However, evidence from animal models indicates that deficient orexin transmission is involved in the Na-2 pathophysiology. Lack of orexin could be circumvented by activating histaminergic neurons.

Until recently, therapy for narcolepsy consisted primarily of amphetamines and related stimulants, including methylphenidate and dextroamphetamine, to increase alertness and improve daytime performance [Zwicker, 1995; Smith et al, 2016]. Although studies show a moderate improvement in alertness levels (to approximately 70% of normal individuals), common adverse effects including headaches, nervousness, irritability, tremor, insomnia,

anorexia, and palpitations, limit utility of these therapies. Additionally, tolerance to the alerting effect of these drugs develops in up to 30% of patients using these medications [Mitler et al, 1994].

The standard of care for the treatment of EDS in patients with narcolepsy is modafinil or its enantiomer, armodafinil (although a number of products generally subsumed under the category of "stimulants" are available) [Billiard, 2008]. Chemically distinct and to some extent pharmacologically unrelated to other stimulants, modafinil has an improved safety profile and lower abuse potential, compared with older stimulants; however, it usually does not reduce EDS to normal levels [Wise et al, 2007] and provides no benefit for cataplexy or disrupted nighttime sleep, necessitating the use of other drugs for these symptoms. For cataplexy, venlafaxine, fluoxetine, clomipramine, and sodium oxybate customarily are employed.

In 2002, sodium oxybate was approved by the US Food and Drug Administration for the treatment of cataplexy and EDS in adults with narcolepsy (Xyrem®, Jazz Pharmaceuticals plc.). Although the drug has advantages over previously used cataplexy therapies in that it targets both EDS and cataplexy, it requires titration to an optimal dose, and must be administered under a Risk Evaluation and Mitigation Strategies mandate in the United States through a central pharmacy in conjunction with step therapy. Co-administration of sodium oxybate with modafinil was shown to provide improved beneficial effects on EDS compared with the administration of either medication alone, as might be anticipated by the mechanisms of action for each agent [Black and Houghton, 2006]. However, a single safe and effective therapeutic agent for the treatment of multiple symptoms is still unavailable and would represent a significant advancement in treatment options.

To address this unmet need, Suven is developing SUVN-G3031, an orally active inverse agonist of the human histamine H3 receptors (H3R). Histaminergic neurons are mainly located in the posterior hypothalamus and play a role in arousal mechanisms. It has been demonstrated that the H3R inverse agonists are able to promote activation of cerebral histamine neurons. SUVN-G3031 enhances the histaminergic transmissions in brain, acetylcholine release in prefrontal cortex and hippocampus, and dopamine release in prefrontal cortex (but not in striatum and nucleus accumbens).

5.2 Background on SUVN-G3031

SUVN-G3031 emerges as a potent, selective, orally bioavailable, brain-penetrating, H3R-inverse agonist with dose-dependent receptor occupancy implicated in the regulation of sleep/wake cycles. SUVN-G3031 increased wakefulness in rodents providing the evidence for treatment of sleep-related disorders. In rodent models of cognition, a procognitive effect has been demonstrated and SUVN-G3031 enhanced neurotransmitters responsible for procognitive properties. In wild type and orexin knockout mice, the selective H3R antagonist GSK189254 increased wakefulness, and decreased slow wave sleep and paradoxical sleep, supporting the potential use of H3R antagonist/inverse agonist for the treatment of narcolepsy in EDS [Guo et al, 2009].

5.2.1 Nonclinical Studies

Six-month oral toxicity studies of SUVN-G3031 in rats, and 9-month oral toxicity studies in dogs have been completed along with genotoxicity, fertility studies in rats, and fetal development toxicity studies in rat and rabbit embryo. Overall, the single-dose, repeat-dose, genotoxicity and reproduction and developmental toxicity studies completed support conduct of the Investigational New Drug Phase 2 study in patients with narcolepsy at the dosage levels and durations of exposures proposed. Clinical observations, within in vivo models reported, are related to the pharmacological effects of this class of compound. These observations, as well as those obtained from regulatory mandated evaluations of safety (cardiovascular, respiratory, and central nervous system) suggest standard methods of surveillance are sufficient at dosage levels proposed for clinical use.

Further information on nonclinical studies can be found in the Investigator's Brochure.

5.2.2 Clinical Studies

The SUVN-G3031 Phase 1 program included 72 healthy volunteers and provided preliminary clinical safety and pharmacokinetic (PK) data. SUVN-G3031 was well tolerated in both single-dose (up to 20 mg oral [PO]) and multiple-dose administrations (up to 6 mg PO for 14 days). There were no deaths, serious adverse events (SAEs), or treatment-emergent adverse events (TEAEs) leading to discontinuation from the Phase 1 program. The most frequently reported TEAE preferred terms were dyssomnia (33.3%) followed by abnormal dreams (27.8%), and TEAEs that occurred most frequently were in the System Organ Class, Psychiatric Disorders.

A maximum tolerated single dose (20 mg PO) and maximally well tolerated multiple doses of 6 mg/day PO for 14 days were established using a sequential dose-escalation paradigm. Specifically, no significant changes in safety parameters including laboratory results, physical examinations, vital signs, fluid balance, suicidal ideation, and electrocardiogram (ECG) parameters were noted. Pharmacokinetic data suggest dose proportionality across a range from 0.1 mg to 20 mg after single administration of SUVN-G3031 PO, with the main terminal half-life of approximately 23 to 34 hours across dosages evaluated. Multiple oral administration exhibited dose-proportional increases in exposures across 1 mg to 6 mg dose range with steady state achieved in approximately 5 days. Approximately 55% to 60% of the administered dose was excreted via the urinary route. Food, gender, and age had no appreciable effect on the PK profile of SUVN-G3031.

SUVN-G3031 may be used adjunctively with a variety of compounds affecting EDS or cataplexy in patients with narcolepsy as outlined in the Investigator's Brochure. However, SUVN-G3031 is being evaluated as a monotherapy in the current protocol and all adjunctively used compounds affecting EDS or cataplexy in patients with narcolepsy are prohibited.

Further information on clinical studies can be found in the Investigator's Brochure.

5.3 Clinical Risks/Benefits of SUVN-G3031

5.3.1 Risks

This is the first study to be performed using SUVN-G3031 in patients with narcolepsy. As such there may be risks to the enrolled patients that cannot be identified at this stage.

Based on clinical trials in healthy subjects, there are no expected adverse reactions. The most frequently reported TEAE preferred terms in healthy subject trials were dyssomnia (33.3%) followed by abnormal dreams (27.8%), and the TEAEs that occurred most frequently were in the System Organ Class, Psychiatric Disorders.

5.3.2 Benefits

Due to the short treatment period in this study (14 days), patients are unlikely to experience any benefit from enrollment in this study. However, results from this study will be used to advance the development of SUVN-G3031; therefore, potentially benefitting this population in the future.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

6.1.1 Primary Objective

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

6.1.2 Secondary Objectives

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

6.1.3 Exploratory Objectives

- To evaluate the effectiveness of SUVN-G3031 compared with placebo as measured by an improvement in the MWT score, [redacted]
- 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

6.2 Study Endpoints

6.2.1 Primary Endpoint

The primary endpoint of this study is the change from baseline in the mean total ESS score at Day 14.

6.2.2 Secondary Endpoints

The secondary endpoints in this study are as follows:

- 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

6.2.3 Safety Endpoints

The safety endpoints in this study are as follows:

- Physical examination
- Vital signs
- Laboratory assessments (blood and urine)

- Electrocardiogram
- Adverse events (AEs)
- AEs of special interest (AESIs)
- Columbia Suicide Severity Rating Scale (CSSRS)

6.2.4 Exploratory Endpoints

The exploratory endpoints of this study are as follows:

- 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 patients reporting CGI-C scores of 1 or 2 at Day 14 (EDS)
- Proportion of patients reporting CGI-S scores related to EDS of 1 or 2 at Day 7 and Day 14
- Proportion of patients 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 2 mg or 4 mg compared with placebo
- Additional exploratory endpoints may be included in the statistical analysis plan (SAP)

7 INVESTIGATIONAL PLAN

7.1 Description of Overall Study Design and Plan

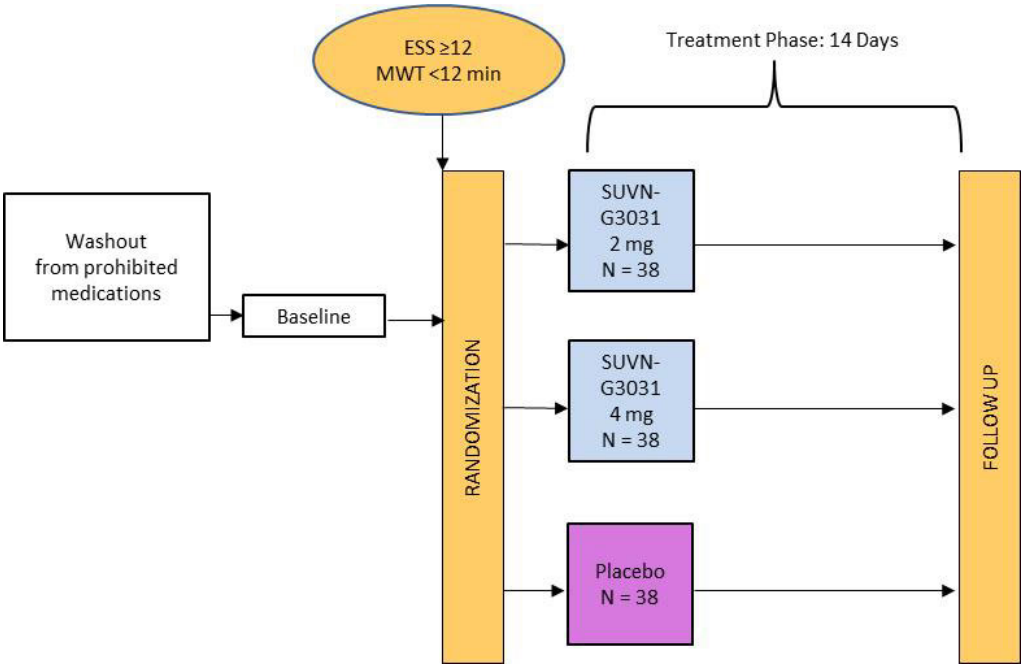
This is a Phase 2, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety, tolerability, PK, and efficacy of 2 mg and 4 mg SUVN-G3031 compared with placebo in patients with narcolepsy with and without cataplexy. Patients will be randomized at a ratio of 1:1:1 to 2 mg SUVN-G3031, 4 mg SUVN-G3031, or placebo. Patients will be stratified by at least 30% each based on whether they have narcolepsy with or without cataplexy (Na-1 or Na-2, respectively).

Each patient will receive study drug once daily, in a tablet formulation, for 14 days. Sufficient patients will be screened to enable 114 patients to be enrolled (38 per treatment group). Further details on the sample size calculations can be found in Section 14.1. A single, unblinded, interim analysis will be undertaken when approximately 50% of patients have completed 14 days of treatment; this analysis will enable sample size re-estimation to occur if appropriate. A maximum of 57 additional patients (19 patients per treatment arm) will be enrolled to generate a total maximum study population of 171 patients. Further details on the interim analysis can be found in Section 14.6.

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

A study schematic can be seen in Figure 1.

Figure 1. Study Design



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

7.1.1 Screening

Patients who have provided written informed consent will be screened up to 28 days before enrollment. Eligible patients will complete a washout period of ≥ 14 days for all agents targeting cataplexy and ≥ 7 days for all stimulants targeting EDS.

7.1.2 Dosing Period

Once these washout periods have been completed, patients will attend the clinic for randomization and baseline (Day 0) assessments; patients will provide a blood sample for PK analysis. After completion of baseline (Day 0) assessments, study drug will be dispensed to patients and they will take their first dose the next day (Day 1); patients will receive enough study drug to last until the next visit at Day 7. On Day 7 (±1 day), patients will attend the clinic for an outpatient visit, when efficacy and safety assessments will be undertaken. Patients 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 postdosing). Patients will be dispensed enough study drug to last until the next visit at Day 14. On Day 14 (±1 day), patients 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.

7.1.3 Safety Follow-up

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

7.1.4 Data Monitoring Committee

The data monitoring committee (DMC) will be established and the charter, composition, and methods of analysis and review will be presented separately prior to study initiation. [redacted]

7.2 Discussion of Study Design

7.2.1 Eligibility Criteria

The primary objective of this study is to evaluate the impact of SUVN-G3031 on EDS associated with narcolepsy in adult patients aged 18 to 65 years. Patients must present with an established diagnosis of Na-1 or Na-2 to be considered eligible for enrollment consistent with the American Academy of Sleep Medicine, International Classification of Sleep Disorders, 3rd Edition. The randomization is not constrained upon subtype, although stratification based upon the diagnosis of Na-1 or Na-2 is included.

As the primary objective of this study is to evaluate the impact of SUVN-G3031 on EDS associated with narcolepsy, minimum thresholds of severity of EDS will be required. The minimum threshold of severity of EDS will be defined using key eligibility criteria of MWT

mean time of < 12 minutes across the first 4 sessions at baseline [Schwartz et al, 2004] and ESS score of ≥ 12 [Szakacs et al, 2017].

Patients with Na-1 must have a documented history of irrepressible need to sleep or daytime lapses into sleep for at least 3 months, and the presence of cataplexy with previously confirmed Multiple Sleep Latency Test (MSLT) ≤8 minutes with 2 or more sleep onset rapid eye movement periods (SOREMPs) performed according to standard techniques. Substitution of 1 of the required SOREMPs on MSLT with 1 obtained from the preceding nocturnal PSG, obtained at the time of diagnosis, is permitted. Alternatively, previously obtained cerebrospinal fluid (CSF) hypocretin-1 concentrations may also be used to support the diagnosis in the absence of clinical cataplexy assuming acceptable MSLT findings [Scammell, 2003].

Compliance with a uniform operational definition of cataplexy is not mandated by protocol because cataplexy phenotype and frequency may differ widely across patients [Pillen et al, 2017] (frequent attacks of collapse, sporadic partial attacks, etc) and because modification of cataplexy after pharmacotherapy is not a principal hypothesis of the study.

Patients with Na-2 must have a comparable history of irrepressible need to sleep or daytime lapses into sleep for at least 3 months, identical criteria based upon MSLT and nocturnal PSG, but do not have a clinical history of cataplexy or data based upon CSF hypocretin-1 concentrations which are incompatible with the diagnosis. For both conditions, eligibility criteria mimic those frequently associated with interventional studies in narcolepsy and reduce diagnostic confounders related to medical condition such as obstructive sleep apnea, and psychiatric disorders including chronic fatigue syndrome, depression, bipolar affective disorder, malingering, and substance use disorder. Idiopathic hypersomnia must be excluded by the pre-existing diagnostic evaluation [Broughton et al, 1997].

SUVN-G3031 in this study is being evaluated as a monotherapy; patients will require washout from current narcolepsy therapies for both EDS and cataplexy. 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 assessments. The 28-day screening period allows a window of drug withdraw to be completed safely at the discretion of the Investigator.

7.2.2 Assessments

7.2.2.1 Primary Outcome Measure

The primary objective pivots upon changes in EDS in patients with Na-1 and Na-2. The primary outcome measure, the change in total ESS scores from baseline, is used to derive the primary dependent variable. A successful study requires demonstration of a statistically significant difference between treatment groups based upon the ESS as a single primary endpoint, using a prespecified analytic model and an intent-to-treat (ITT) dataset.

The ESS consists of 8 questions chosen on a priori grounds to represent activities with a wide range of different somnificities.

The ESS is a self-administered questionnaire wherein respondents 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 (see Section 11.3). It is important that participants answer every question, as there is no method for interpolating item scores and a missed question results in an invalid test. Most people engage in the activities in the test at least occasionally, although not necessarily every day. The recall period for the test asks subjects to rate experiences taking place "in recent times," which is purposefully vague and is meant to represent a few weeks to a few months. Within the study, the ESS will be completed weekly, consistent with the recall period. The ESS score (the sum of 8 item scores, 0–3) can range from 0 to 24. The higher the ESS score, the higher the person's average sleep propensity in daily life, or their "daytime sleepiness." The questionnaire takes no more than 2 or 3 minutes to answer. The ESS can be interpreted per the bullets below:

- 0 to 5 Lower Normal Daytime Sleepiness
- 6 to 10 Higher Normal Daytime Sleepiness
- 11 to 12 Mild EDS
- 13 to 15 Moderate EDS
- 16 to 24 Severe EDS

In contrast to other sleep scales, the ESS has been designed to use the questions above based on subject reports to determine sleep propensity or EDS [Johns, 2000]. As a result, the test can measure a subject's high sleep propensity or history of dozing in situations that are low soporific in nature and during which normal subjects would be unlikely to fall asleep [Johns, 2000; Herring et al, 2013; Van der Heid et al, 2015; Weaver et al, 2020]. Furthermore, a recent publication emphasized that ESS could be a reliable measure to evaluate daytime sleepiness in clinical trials with histamine 3 receptor antagonists [Inoue et al, 2022]. Thus, the ESS is a useful test to determine improvement in sleep propensity in patients with narcolepsy treated with targeted therapeutic agents.

7.2.2.2 Secondary Outcome Measures

The secondary measures include the change from baseline in the clinician-derived CGI-S related to EDS [Dauvilliers et al, 2013; Szakacs et al, 2017] and the change in MWT score from baseline. Appropriate methods for control of multiplicity will be employed for analysis of secondary endpoints (see Section 14.3.2).

7.2.2.2.1 Clinical Global Impression of Severity

The CGI was developed for use in National Institute of Mental Health-sponsored clinical studies to provide a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating a study medication. The CGI provides an overall clinician-determined summary measure that takes into account all available information, including a knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function. In all of its applications, it

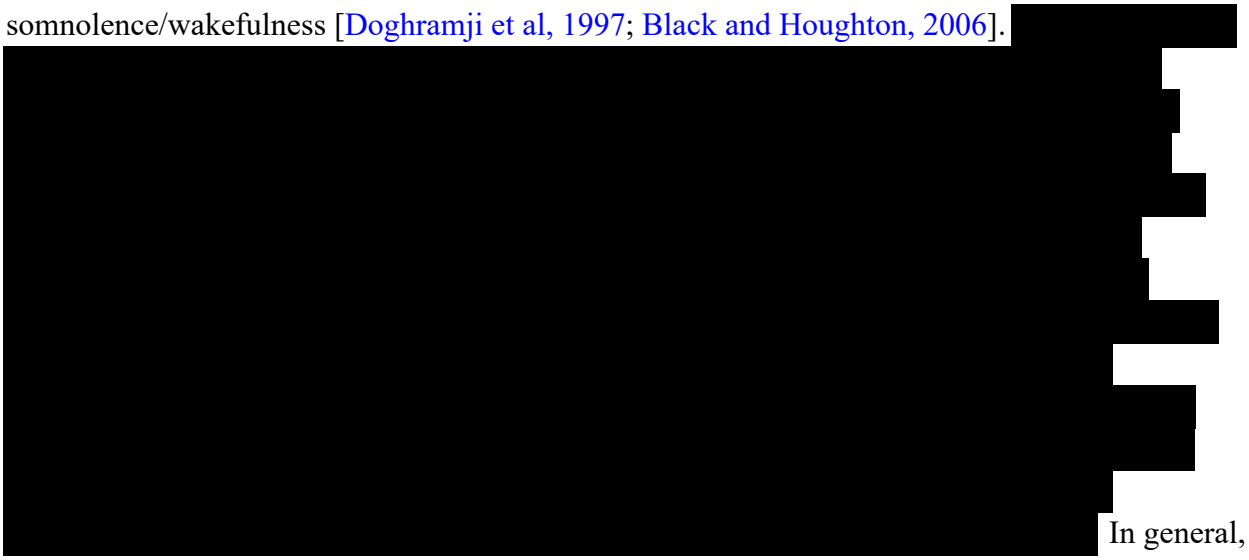
functions as a corroborating "clinically relevant" assessment of disease severity, independently of assessments which are more specific to the disease under evaluation.

The CGI can be completed in less than a minute, captures clinical impressions and can track clinical progress across time. It is administered by an experienced clinician who is familiar with the disease and the potential impact of treatment. The CGI rater can make an expert clinical global judgment about the severity of the illness across various time points within the context of that clinical experience [Busner and Targum, 2007]. The CGI has 2 established components, the CGI-S, which rates illness severity, and the CGI-C, which rates change from the initiation (baseline) of treatment. Both measures have been employed in the evaluation of investigational therapeutic agents for treatment of narcolepsy and both will be used within this proposed study.

The CGI-S within this protocol will be used to rate the severity of the patient's illness related to EDS symptoms, on a 7-point scale [Busner and Targum, 2007].These ratings are based on the clinician's experience of patient's suffering from the same condition [Berk et al, 2008]. This scale has classically been utilized in clinical research of a number of indications to observe and report average symptoms, behavior, and function over a 7-day period [Busner and Targum, 2007], in essence amalgamating the totality of a patient's presentation into 1 score based upon physician's judgments of clinical severity. Within this study, the CGI-S assessments will be based on severity related to EDS rather than on the totality of the disease [Szakacs et al, 2017; Dauvilliers et al, 2013].

7.2.2.2.2 Maintenance of Wakefulness Test

The MWT is a common test used to measure latency to sleep onset/daytime somnolence/wakefulness [Doghramji et al, 1997; Black and Houghton, 2006].



In general, the MWT has been extensively used for the clinical evaluation of sleep latency both in normal subjects as well as in patients with disease states such as narcolepsy, EDS, and obstructive sleep apnea.

[redacted]

7.2.2.3 Exploratory Outcome Measures

Given the need for hypothesis generation, exploratory measures have been included acknowledging that neither the patient phenotype, sample size, nor the duration of exposure may be adequate for definitive biostatistical contrasts. Exploratory measures include the evaluation of associated features of narcolepsy through a sleep diary (sleep attacks, severe sleepiness, cataplexy attacks, hypnagogic or hypnopompic hallucinations, sleep paralysis, nocturnal awakening, and nocturnal sleep time – all presented descriptively), changes in nocturnal overnight PSG, subjective assessments of EDS obtained through the ESS as an operationally defined responder analysis, CGI-C, and PGI-C.

Additionally, exploratory analyses evaluate the impact of treatment on symptoms of EDS within each of the 4 MWT sessions within a single day (Day 7, Day 14). Specifically, the [redacted] MWT will be performed after a nocturnal overnight PSG at baseline prior to the first dose of study medication, Day 7 (Visit 2), and Day 14 (Visit 3) according to validated standards. The first MWT session will occur at approximately 2 hours after awakening.

There is no attempt to evaluate the occurrence of a discontinuation phenomenon at the end of double-blind treatment given the duration of the study and the pharmacological properties of SUVN-G3031 either through self-assessments, or clinician-based interview [Dauvilliers et al, 2013]. However, the occurrence of 2 AESIs during therapy, described as vivid and unpleasant dreams and difficulty initiating or maintaining sleep, will be monitored (see Section 12.7.2).

7.2.2.3.1 Clinical Global Impression of Change

The CGI-C will be used in this study to evaluate patient improvement related to EDS symptoms. The CGI-C is used by the physician to compare change in the patient's clinical condition at each visit after initiation of treatment to an established baseline taken prior to study treatment. The CGI-C is based on a 7-point scale, where at each visit the physician will rate the change from baseline [Busner and Targum, 2007]. Within this study, the CGI-C assessment will be based on change observed from baseline related to EDS.

7.2.2.3.2 Nocturnal Overnight Polysomnography

Although PSG is not always required during the evening prior to an MWT assessment, it has been used to objectively demonstrate a lack of sleep disruption by residual effects of test product and is commonly used before MWT testing within the narcolepsy literature. For example, Harsh et al (2006) used PSG variables that included latency to persistent sleep in minutes (time from lights out to the first of 3 consecutive epoch of stage 1 sleep, or 1 epoch of any other sleep stage), number of arousals, number of awakenings, sleep efficiency, total sleep time in minutes, wake after sleep onset (WASO) in minutes, percentage of time in stage 1, 2, 3, 4, rapid eye movement (REM) sleep percentage, and REM sleep latency in minutes. Similarly, the US

Modafinil in Narcolepsy Multicenter Study Group PSG variables included total sleep time in minutes; sleep efficiency; percentage (sleep time/time in bed); percentage of time in stages 1, 2, 3, 4; REM; sleep latency, minutes; REM latency, minutes; and periodically movements during sleep (N) [US Modafinil in Narcolepsy Multicenter Study Group, 2000].

7.2.2.3.3 Patient Global Impression

The Patient Global Impression (PGI) is a self-assessed, single-item questionnaire typically with a 7-point Likert-type scale a patient can select. There are 2 versions: a PGI-S to measure impression of disease severity at a single point in time, and a PGI-C to measure improvement or change based on a baseline state. For the proposed investigation, the PGI-C will be employed. The patient will be asked to address the totality of experience on study medication, without attempts to demarcate between excessive daytime somnolence and cataplexy. The PGI-C has categories regarding the condition being measured, from 1 (very much better) to 7 (very much worse).

The PGI-C is a simple, direct, easy-to-use scale that is intuitively understandable to patients. The improvement scale aims to evaluate all aspects of patient's health and determine if there has been an improvement or not compared with a point in time. Customarily, this is the pretreatment (baseline) condition of the patient prior to administration of study medication. Although it is generally used as a global assessment, the measure can be tailored to discrete symptoms within a clinical condition. The patient selects 1 response from the options that gives the most accurate description of his/her overall state of health.

The test-retest reliability of the PGI-C was found to be excellent based on Cronbach's alpha analysis of responses (0.849) at 6 months and 1 year in women undergoing surgery for urogenital prolapse [Srikrishna et al, 2010]. The PGI-C has been utilized as often as weekly in a number of indications [Ruoff et al, 2016].

The PGI has historical precedent for use in narcolepsy trials. A survey of 35 interventional studies in narcolepsy since 1994 suggests that approximately 3% employed a PGI rating of change as a primary or secondary outcome measure. For example, the PGI-C was a secondary endpoint in a Phase 2b study to evaluate the efficacy and safety of JZP-110 on wakefulness and sleepiness in adults with narcolepsy [Ruoff et al, 2016]. The PGI-C was administered at 1, 2, 4, 6, 8, and 12 weeks, with the evaluation anchored to baseline condition. Significant benefits of JZP-110 relative to placebo were observed on the PGI-C as early as 1 week after treatment.

7.2.2.3.4 Sleep Diary

A sleep diary can be designed to document across a variety of associated signs or symptoms in narcolepsy: from time spent asleep to how many cataplectic attacks occur each day and how they manifest themselves. Subjects are generally instructed to try to keep track of the day's events with notes and to fill out the diary regularly, at minimum once daily, and data can be captured electronically or on paper.

There is no single standard for the structure of a sleep diary. Review of existing literature indicates considerable heterogeneity in the signs/symptoms associated with narcolepsy which have been assessed, consistent with hypotheses and patient populations evaluated. The sleep diary used by the Harvard Medical School – Division of Sleep Medicine will be used in this study. Further details can be found in Section 11.7.

A 2017 study analyzed how many nights of sleep diary entries were required for reliable estimates of 5 sleep-related outcomes (bedtime, wake time, SOL, sleep duration, and WASO) in adolescents. Participants completed a pencil and paper sleep diary across 1 week during the school term. Variables included bedtime ("Went to bed last night at"), SOL ("Minutes until fell asleep"), sleep duration ("Slept this much last night"), WASO ("After you fell asleep, what is the total amount of time you spent awake during any nighttime awakenings?"), and wake time ("Finally woke at"). For each item, adolescents were instructed to answer with a specific time (e.g., 9:35 pm) or duration (e.g., 12 minutes). Participants also concurrently wore wrist actigraphs (Mini-motionlogger; Ambulatory Monitoring Inc. [Ardsley, NY]) and called a time-stamped answering machine before bedtime and after they woke each day [Short et al, 2017].

A 2010 paper discussed the development of an online sleep diary. It included bedtime, time the subject went to bed, time they settled for sleep, and an estimate of how long it took them to go to sleep. It also included wake time, time to get out of bed, number of awakenings during the night, and estimated time awake. It also included checkboxes for reasons the subject awoke, and whether anything kept them awake. Finally, it evaluated sleep quality by asking subjects how they felt on a 4-point scale and their mood on a 4-point scale [Blake and Kerr, 2010].

A 2012 study compared sleep diaries from an expert panel of 25 attendees of a Pittsburgh Assessment Conference. A smaller subset of experts formed a committee and reviewed the compiled diaries. Items deemed essential were included in a core sleep diary, and those deemed optional were retained for an expanded diary. Essential elements of the sleep diary included metrics to assess nightly SOL, WASO, total sleep time, total time spent in bed, sleep efficiency (i.e., the percent of the time asleep out of amount of time spent in bed), and sleep quality or satisfaction, which reflects a subjective global appraisal of each night's sleep.

Three versions of sleep diaries were created. The core Consensus Sleep Diary (CSD) contained 9 items considered by the workgroup to represent the most critical parameters. The questions ask about: (1) the time of getting into bed; (2) the time at which the individual attempted to fall asleep; (3) SOL; (4) number of awakenings; (5) duration of awakenings; (6) time of final awakening; (7) final rise time; (8) perceived sleep quality (rated via Likert scale); and (9) an additional space for open-ended comments from the respondent. As previously agreed upon, the core CSD was formatted so that 1 week of nightly sleep data could be recorded on a single diary page. The CSD instructions included general information, such as what to do if the respondent missed recording on a particular day, and item-specific instructions to enhance likelihood of correct item interpretation. For example, the instructions for item #6 tell the respondent to record

the time of the final awakening in the morning. The additional instructions indicate that all items are to be completed in the morning within 1 hour of getting out of bed.

The expanded CSD for morning included a number of optional items that could be completed in the morning upon arising. These include additional items about early (premature) morning awakenings, estimated total sleep time, Likert scale rating of the refreshing quality of sleep, napping/dozing, and alcohol, caffeine, and medication use. The instructions for the additional questions also stipulate that the diary should be completed in the morning.

Finally, the expanded CSD for evening included the same items as the morning version, but with instructions for morning and evening completion. The morning and evening items are grouped separately. The instructions stipulated that items about daytime activity such as caffeine, alcohol, and medication use or napping which appeared on 1 side of the diary are to be completed at night before going to bed, while the remaining items which appeared on the other side and query about the previous night's sleep are to be completed the next morning [Carney et al, 2012].

Sleep diaries have been used extensively in narcolepsy trials. A survey of 35 interventional studies in narcolepsy since 1994 suggests that approximately 46% employed a sleep diary as a primary or secondary outcome measure. For example, a 4-week, double-blind, randomized, placebo-controlled trial evaluated time to response with sodium oxybate for the treatment of EDS and cataplexy in patients with narcolepsy. There were 102 patients who received sodium oxybate and 34 who received placebo. Clinical response information included the number of cataplexy attacks recorded by patients in a daily diary. Cataplexy responder was defined as a patient with≥ 50% reduction from baseline in weekly cataplexy attacks. Results showed an approximately 50% reduction from baseline in weekly cataplexy attacks was the median change after 2 weeks of treatment with sodium oxybate [Bogan et al, 2015].

The sleep diary from Harvard Medical School – Division of Sleep Medicine will be used in this study to evaluate nightly sleep parameters throughout the duration of the study as indicated in the Schedule of Assessments (Table 1).

Sleep diaries will be distributed to eligible patients during the screening window and patients will start to record their sleep evaluations in it immediately. Diary entries will be reviewed at baseline and all subsequent visits.

7.2.2.3.5 Columbia Suicide Severity Scale

The CSSRS is a rating scale addressing suicide ideation and behavior. Questions assess ideation from a “wish to be dead” to “active suicidal ideation with specific plan and intent and behaviors”. Questions assessing behavior rate it from “actual attempt” to “completed suicide”. The trial will employ 2 distinct CSSRS forms: The Baseline-Screening version assesses lifetime prevalence of suicidal ideation and suicidal behavior, and the Since Last Visit form assesses ideation and behavior that have emerged since the last study visit.

The CSSRS has been shown to demonstrate good convergent and divergent validity with other multi-informant suicidal ideation and behavior scales and had high sensitivity and specificity for

suicidal behavior classifications compared with other behavior scales and an independent suicide evaluation board. Both the ideation and behavior subscales have been shown to be sensitive to change over time [Posner et al, 2011].

7.3 End of Study

A patient will have fulfilled the requirements for study completion when the patient has completed all study visits including the Day 21 safety follow-up visit.

The end of study is defined as the last patient's last visit.

8 SELECTION OF STUDY POPULATION

Section 7.1 provides information regarding the number of patients planned to be randomized.

8.1 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, 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 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/m^2.
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 patients 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 patient 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

(due to reasons including bilateral blocked fallopian tubes, bilateral oophorectomy, androgen insensitivity syndrome, and Müllerian agenesis).

- "Of childbearing potential" and practicing a highly effective method of birth control is defined as a patient following regulations consistent with the use of birth control methods for patients 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. Nonexhaustive 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 patient), or male partner is using condoms with spermicide; practicing true abstinence (the preferred and usual lifestyle of the patient). 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).

8.2 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 hours, 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 Appendix 3 for caffeine dosage definitions).
4. Nicotine dependence that has an effect on sleep (e.g., a patient 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 Appendix 2.
6. Current diagnosis of or past treatment for syndromes known to cause sleep disruption or any other cause of daytime sleepiness. If the Investigator confirms that any of the following syndromes are not clinically significant to the extent that it is causing sleep disturbance, this patient 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. Patients 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 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 patient'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. Patients 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 patient's lifetime, according to DSM-5 criteria. Patients with severe or uncontrolled depression that, in the judgment of the Investigator, makes the patient 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:
    - Patients who answer "Yes" on the CSSRS Suicidal Ideation Item 4 (active suicidal ideation with some intent to act, without specific plan) and whose most recent episode meeting criteria for this CSSRS Item 4 occurred within the last 6 months; or
    - Patients who answer "Yes" on the CSSRS Suicidal Ideation Item 5 (active suicidal ideation with specific plan and intent) and whose most recent episode meeting criteria for this CSSRS Item 5 occurred within the last 6 months; or
    - Patients who answer "Yes" on any of the 5 CSSRS 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 CSSRS Suicidal Behavior Items occurred within the last 2 years; or
    - Patients 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 patient to stop taking any wake promoting agent for more than 4 weeks. The patient's occupation (e.g., requirement for driving) may need to be considered.

8.3 Rescreening

Individuals who sign the ICF to participate in the study but who do not subsequently meet all the requirements as outlined in the inclusion and exclusion criteria and therefore do not enroll (screen failures) may be rescreened on a case-by-case basis after approval of the Sponsor.

8.4 Study Withdrawal, Removal, and Replacement of Patients

If a patient discontinues study treatment and is withdrawn from the study for any reason, the study site must immediately notify the medical monitor. The date and the reason for study discontinuation must be recorded on the electronic case report form (eCRF). Patients who complete or discontinue early from the study will be asked to return to the study site within 7 days of the last administration of study drug to complete the safety follow-up assessments as indicated in the Schedule of Assessments (Table 1).

Patients who want to discontinue early from the study (i.e., at the next visit), or who make a decision to withdraw during a scheduled visit, and who remain on study drug should complete

the rating scale/assessments indicated for that visit (Visit 2 or Visit 3) as well as the safety follow-up assessments according to the Schedule of Assessments (Table 1).

In the event that a patient discontinues prematurely from the study because of a TEAE or serious TEAE, the TEAE or serious TEAE will be followed until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the Investigator to no longer be clinically significant.

Once a patient is withdrawn from the study, the patient may not re-enter the study. Care of the patient will return to their usual doctor.

A patient may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- Unacceptable toxicity or AE.
- Clinically significant abnormal lab values:
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 8x upper limit of normal (ULN);
    - ALT or AST ≥ 3x ULN and total bilirubin ≥ 2x ULN at the same visit;
    - ALT or AST ≥ 3x ULN with the appearance of symptoms indicating hepatitis (e.g., worsening fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia).
- QT syndrome, Fridericia's formula corrected QT (QTcF) interval ≥ 470 ms (for male subjects) or ≥ 480 ms (for female subjects), or torsades de pointes. Abnormal results for ECGs should be confirmed with repeat ECG recordings to ensure reproducibility of the abnormality before withdrawing the subject from the study.
- A positive urinary drug screen at any visit.
- Patient withdrawal of consent: at any time, a patient's participation in the study may be terminated at his/her request or on the basis of the Investigator's clinical judgment. The reason for patient withdrawal will be noted on the eCRF.
- Intercurrent illness: a condition, injury, or disease unrelated to the primary diagnosis that became apparent during treatment and necessitated the patient's termination from the study.
- General or specific changes in the patient's condition that renders him/her ineligible for further treatment according to the inclusion/exclusion criteria.
- Patient fails to adhere to the protocol requirements (e.g., drug noncompliance, failure to return for defined number of visits).
- Lost to follow-up: the patient stopped coming for visits, and study personnel were unable to contact the patient.

- Pregnancy, as indicated in Section 12.7.6.

Additionally, the Sponsor may stop the study at any time for safety, regulatory, legal, or other reasons aligned with Good Clinical Practice (GCP). This study may be terminated at the discretion of the Sponsor or any regulatory agency. An Investigator may elect to discontinue or stop the study at his or her study site for any reason, including safety or low enrollment.

9 TREATMENTS

9.1 Details of Study Treatments

The study treatments to be used in this study are:

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

All study treatment supplies to be used in this study will be provided by the Sponsor.

Study treatment is provided in high density polyethylene (HDPE) bottles containing 10 tablets. Each bottle will contain the patient identification number, the name and address of the Sponsor, and any other information required by local regulations. Study treatment supplies should be stored in accordance with United States Pharmacopeia (USP) Controlled Room Temperature (20–25°C [68–77°F] with excursions permitted between 15 and 30°C [59–86°F]). Further information is provided in the Pharmacy Manual.

9.2 Dosage Schedule

Patients 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. Patients will be dosed for 14 days.

If a patient forgets to take their morning dose and remembers before 1:00 PM, then they should take it as soon as they remember. If a patient 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 patient has missed more than 1 dose, then they should only take the most recent forgotten dose.

9.3 Measures to Minimize Bias: Study Treatment Assignment and Blinding

9.3.1 Method of Study Treatment Assignment

Patients will be randomized to the 3 study treatments in a 1:1:1 ratio. This randomization will be stratified by at least 30% each based on whether they have narcolepsy with or without cataplexy (Na-1 or Na-2), respectively.

Patients will be randomized using an interactive response technology (IRT). The randomization number generated should be entered into the eCRF. Further details will be provided in the Pharmacy Manual.

9.3.2 Blinding

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 patient 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 patient.

Each patient 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 patient's study treatment that patient will be discontinued from the study unless there are ethical reasons for that patient 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 patient because of AEs or concerns for the patient's safety or wellbeing, the Investigator may break the randomization code for the patient 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.

9.4 Dosage Modification

No dose modification is permitted during this study.

9.5 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 patient 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 patients.

At each visit after initiation of treatment, study site personnel will record compliance of the patient with the patient's assigned regimen. Patients will be instructed to bring their diaries and unused/partially used/empty bottles back for inspection at each study visit. Patients 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.

Investigators will maintain records that adequately document that the patients 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.

9.6 Prior and Concomitant Therapy

9.6.1 Prior and Concomitant Medications

Restricted prior therapies are provided in Appendix 2. All medications and other treatments taken by the patient during the study, including those treatments initiated before the start of the study, must be recorded on the eCRF.

Medications taken by or administered to the patient for the time period before Screening will be recorded in the eCRF. After the baseline visit, medication to treat minor treatment-emergent illness(es) is generally permitted; however, the following therapies are expressly prohibited throughout the study:

- Adjunctive pharmacotherapy directed against EDS (including but not limited to methylphenidate, dextroamphetamine, methamphetamine, modafinil, and armodafinil)
- Adjunctive pharmacotherapy directed against cataplexy (including but not limited to venlafaxine, fluoxetine, and gamma hydroxybutyrate)
- Clomipramine
- Protriptyline
- Pitolisant

Any medication or therapy that is taken by or administered to the patient during the course of the study must be recorded in the eCRF. The entry must include the name, dose, regimen, route, indication, and dates of use.

After written informed consent is obtained from the patient, those patients who are taking the following medications must have the **minimum** washout periods specified below and not take the medications for the duration of the study:

- 14 days before randomization for agents targeting cataplexy
- 7 days before randomization for agents targeting EDS

10 STUDY PROCEDURES

Table 1 outlines the timing of procedures and assessments to be performed throughout the study. Section 12.5 specifies laboratory assessment samples to be obtained. See Sections 11, 12, and 13 for additional details regarding efficacy assessments, safety assessments and PK sampling, respectively.

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	
CSSRS[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; CSSRS, 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 patient 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 patient throughout the study. Vital signs may be collected prior to the PSG and the first MWT.

[c] Electrocardiograms should be obtained after the patient 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) postdose on Days 7 and 14.

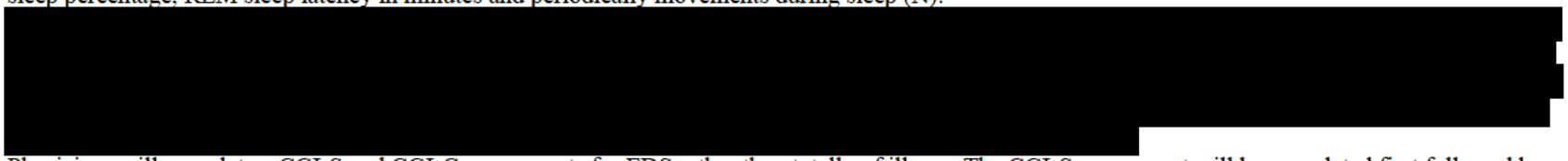
[d] Laboratory assessments are listed in Table 2.

[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 postdosing 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] 

[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 patient at each visit.

[k] ESS, PGI-C, CSSRS 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 CSSRS 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 patient 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 patient from Screening through Visit 3. The patient 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 patient 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.

10.1 Informed Consent

Before performing any study-related procedures, the Investigator (or designee) will obtain written informed consent from the patient.

10.2 Study Procedures

Assessments and their timing are to be performed as outlined in the Schedule of Assessments (Table 1). Section 12.5 specifies laboratory assessment samples to be obtained.

Efficacy assessments are described in Section 11 and include MWT, CGI-S, ESS, CGI-C, PGI-C, nocturnal overnight PSG, and sleep diary.

Safety assessments are described in Section 12 and include vital signs, physical examinations, ECGs, laboratory assessments, CSSRS, AEs, and AESIs.

The PK assessments are described in Section 13.

The Investigator may, at his/her discretion, arrange for a patient to have an unscheduled assessment, especially in the case of AEs that require follow-up or are considered by the Investigator to be possibly related to the use of study drug. The unscheduled visit page in the eCRF must be completed.

Study discontinuation procedures are described in Section 8.4. Follow-up of AEs and SAEs leading to study discontinuation are described in Section 8.4.

10.2.1 Assessment Order

During Visits 1 to 3, assessments should be performed in the following order, as applicable (not all procedures are required at all visits):

- Admit the night before the visit
- Inclusion/exclusion criteria (Visit 1 only)
- Collect IP (Visits 2 and 3 only)
- Concomitant medication check
- Adverse event check
- Urine collection for urine drugs screen (Visits 1, 2, and 3) and pregnancy test (Visits 1, 2, 3, and Safety Follow-up visits)
- Serum pregnancy test (Visit 1 only)
- Nocturnal overnight PSG
- Physical examination (Visits 1 and 3 only)
- Urine collection for urinalysis (Visits 1 and 3 only)
- Baseline ECG (Visit 1 only)

- Vital signs
- CGI-S
- CGI-C (Visits 2 and 3 only)
- Blood collection for safety (Visits 1 and 3 only) and PK (Visits 1, 2, and 3)
- Dosing (as soon as the patient wakes up; Visits 2 and 3 only)
- ESS
- PGI-C
- CSSRS
- MWT 1 (approximately 2 hours after awakening)
- Postdose ECG (approximately 3 hours postdose; Visits 2 and 3 only)
- PK (approximately 3 hours postdose; Visits 2 and 3 only)
- MWT 2 (2 hours post MWT 1)
- MWT 3 (2 hours post MWT 2)
- MWT 4 (2 hours post MWT 3)
- Randomization (Visit 1 only)
- Dispense IP (Visits 1 and 2 only)
- Dispense diary
- Discharge

11 EFFICACY ASSESSMENTS

The Schedule of Assessments (Table 1) outlines the efficacy assessments to be performed throughout the study and their timing.

11.1 Maintenance of Wakefulness Test

The [redacted] MWT will be utilized within this study and will be performed following a nocturnal overnight PSG at the times outlined in the Schedule of Assessments (Table 1). The MWT will begin at approximately 2 hours after awakening (4 total MWT sessions will be performed at 2-hour intervals). Patients will be required to recline in a quiet, dimly lit bedroom and instructed to remain awake for as long as possible. The MWT trial 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 REM sleep.

11.2 Clinical Global Impression of Severity

The CGI-S will be used to rate the severity of the patient's illness related to EDS symptoms, on a 7-point scale, which includes the following gradations: 1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill. These ratings should be based on the clinician's experience of patients suffering from the same condition. The ratings should be completed by the same physician for each patient throughout the study in order to maintain consistency.

11.3 Epworth Sleepiness Scale

The ESS consists of 8 questions in which the patient will be asked "How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?"

- Sitting and reading
- Watching television
- Sitting, inactive in a public place (e.g., a theatre or a meeting)
- As a passenger in a car for an hour without a break
- Lying down to rest in the afternoon when circumstances permit
- Sitting and talking to someone
- Sitting quietly after a lunch without alcohol
- In a car, while stopped for a few minutes in traffic

Patients will be asked to respond to each question with a score of 0–3 where:

- 0 = would never doze
- 1 = slight chance of dozing

- 2 = moderate chance of dozing
- 3 = high chance of dozing

The ESS will be completed by the patients themselves.

11.4 Clinical Global Impression of Change

The CGI-C is used by the physician to compare change in the patient's clinical condition at each visit after initiation of treatment to an established baseline taken prior to study treatment.

The CGI-C is based on a 7-point scale, where at each time point the physician will rate the change from baseline using the following query: "Compared to the patient's condition at admission to the project [prior to medication initiation], this patient's condition is: 1 = very much improved since the initiation of treatment; 2 = much improved; 3 = minimally improved; 4 = no change from baseline (the initiation of treatment); 5 = minimally worse; 6 = much worse; 7 = very much worse since the initiation of treatment." Within this study, the CGI-C assessment will be based on change observed from baseline related to EDS rather than on the totality of the disease.

The ratings should be completed by the same physician for each patient throughout the study in order to maintain consistency.

11.5 Patient Global Impression of Change

The PGI-C is used by the patient to compare change in their clinical condition at each visit after initiation of treatment to an established baseline taken prior to study treatment.

The PGI-C is based on a 7-point scale, where at each time point the patient will rate the change from baseline using the following query: "Since the start of the study, my overall status is: 1 = very much better; 2 = much better; 3 = a little better; 4 = no change; 5 = a little worse; 6 = much worse; 7 = very much worse." Within this study, the PGI-C assessment will be based on change observed from baseline related to EDS rather than on the totality of the disease.

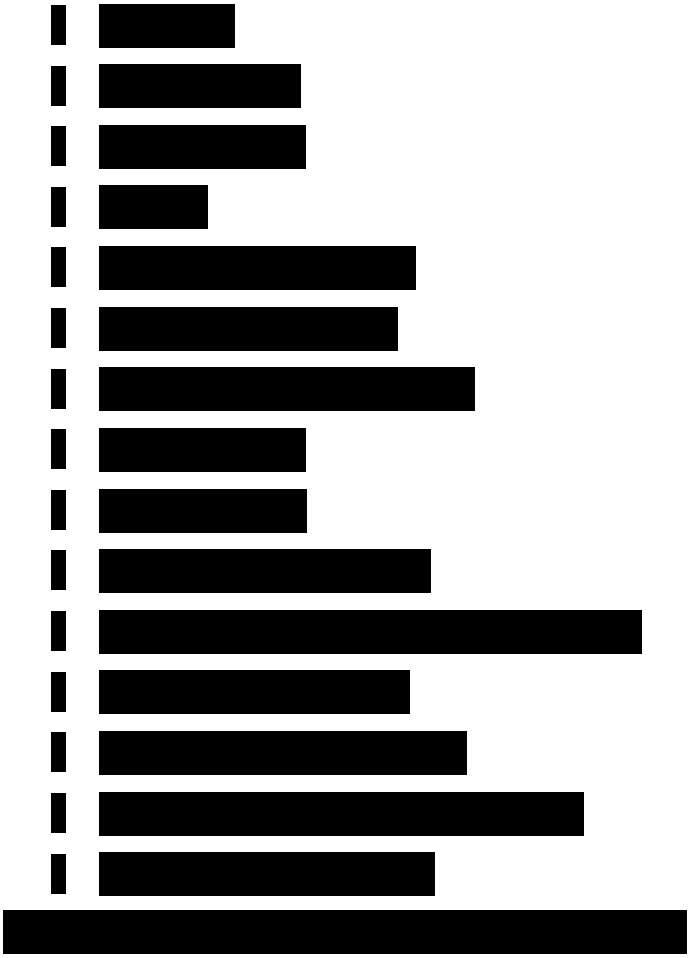
The patient will be asked to address the totality of experience on study medication, without attempts to demarcate between excessive daytime somnolence and cataplexy.

11.6 Nocturnal Overnight Polysomnography

The nocturnal overnight PSG will be completed at the times outlined in the Schedule of Assessments (Table 1). 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, WASO 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).

11.7 Sleep Diary

The sleep diary uses the following headers in a table that patients should complete daily, in relation to the onset, duration, and quality of sleep:



The diary will be completed electronically using a handheld eDiary.

12 SAFETY ASSESSMENTS

Safety assessments (vital signs, physical examinations, ECG recording, AEs, AESIs, CSSRS, and clinical laboratory results [routine hematology and biochemistry]) are to be performed at protocol-specified visits, as specified in the Schedule of Assessments (Table 1).

12.1 Medical History and Disease History

Medical history will be recorded at Screening. Investigators should document the occurrence, signs, and symptoms of the patient's pre-existing conditions, including all prior significant illnesses. Additional pre-existing conditions present at the time when informed consent is given and up to the time of first dosing are to be regarded as concomitant. Medical history will include alcohol consumption, smoking, substance abuse, and psychiatric history.

A detailed medical history will be taken in relation to the patient's narcolepsy (including cataplexy, if applicable). This will include date of diagnosis, diagnostic tests undertaken and symptoms experienced.

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 12.7. All changes not present at baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

Additionally, demographic data will be collected for all patients and will include date of birth, sex, and ethnicity.

12.2 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 (Table 1). All vital signs will be measured after the patient 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 sign measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range blood pressure, respiratory rate, or heart rate measurements will be repeated at the Investigator's discretion. Any confirmed, clinically significant vital sign measurements must be recorded as AEs.

12.3 Physical Examination

A complete physical examination (head, eyes, ears, nose and throat; heart; lungs; abdomen; skin; cervical and axillary lymph nodes; and neurological and musculoskeletal systems) will be performed at the visits indicated in the Schedule of Assessments (Table 1). Physical examinations will be performed by a physician or licensed practitioner.

12.4 Electrocardiograms

A 12-lead, resting ECG will be obtained at the visits indicated in the Schedule of Assessments (Table 1). The following parameters will be measured at a minimum: heart rate, PR, QRS, QT and Fridericia's correction of QT intervals. The same ECG machines should be used for each patient throughout the study.

At Screening, the Investigator will examine the ECG traces for signs of cardiac disease that could exclude the patient from the study. An assessment of normal or abnormal will be recorded; if the ECG is considered abnormal, the abnormality will be documented on the eCRF.

Electrocardiograms will be repeated if clinically significant abnormalities are observed or artifacts are present. A central cardiac laboratory will be used in this study.

12.5 Laboratory Assessments

Laboratory assessment samples (Table 2) are to be obtained at designated visits as detailed in the Schedule of Assessments (Table 1).

Table 2. Laboratory Assessments

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 urine 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.
Blood and urine samples will be analyzed at a central laboratory facility. Urine samples will be performed and analyzed by dipstick at the study site; a microscopic analysis will be performed if the results of dipstick indicate abnormalities to be further investigated. All laboratory reports must be reviewed, signed, and dated by the Investigator. A legible copy of all reports must be filed with both the patient's eCRF and medical record (source document) for that visit. Any laboratory test result considered by the Investigator to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention). Clinically significant abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilize, or are no longer clinically significant.

Further information on sample collection, processing and shipping can be found in the Laboratory Manual.

12.6 Columbia Suicide Severity Rating Scale

Two versions of the CSSRS 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 patient from enrollment in the study.

At each subsequent visit, the follow-up CSSRS is used (Since Last Visit form) to assess suicidal ideation and behavior since the last visit.

The CSSRS should be administered by a healthcare professional trained in its use.

12.7 Adverse Events

12.7.1 Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges after the patient signs the ICF or, if present at Screening, worsens after signing the ICF, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study) present at Screening will be documented in the medical history eCRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE eCRF during the rest of the study. Clinically significant laboratory abnormalities should also be recorded as AEs. Surgical procedures that were planned before the patient enrolled in the study are not considered AEs if the conditions were known before study inclusion; the medical condition should be reported in the patient's medical history.

Patients will be instructed to report AEs at each study visit. All AEs are to be followed up until resolution or a stable clinical endpoint is reached.

Each AE is to be documented on the eCRF with reference to date of onset, duration, frequency, severity, relationship to study drug, action taken with study drug, treatment of event, and outcome. Furthermore, each AE is to be classified as being serious or nonserious. Changes in AEs and resolution dates are to be documented on the eCRF.

For the purposes of this study, the period of observation for collection of AEs extends from the time the patient gives informed consent until the follow-up visit. Follow-up of the AE, even after the date of therapy discontinuation, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the Investigator.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

The severity of AEs will be graded according to Table 3.

Specific guidelines for classifying AEs by intensity and relationship to study drug are given in Table 3 and Table 4.

Table 3. Classification of Adverse Events by Intensity

MILD: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
MODERATE: An event that is sufficiently discomforting to interfere with normal everyday activities.
SEVERE: An event that prevents normal everyday activities.

Table 4. Classification of Adverse Events by Relationship to Study Drug

UNRELATED: This category applies to those AEs that are clearly and incontrovertibly because of extraneous causes (disease, environment, etc).
UNLIKELY: This category applies to those AEs that are judged to be unrelated to the test drug but for which no extraneous cause may be found. An AE may be considered unlikely to be related to study drug if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the test drug (2) it could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient (3) it does not follow a known pattern of response to the test drug or (4) it does not reappear or worsen when the drug is readministered.
POSSIBLY: This category applies to those AEs for which a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient or (3) it follows a known pattern of response to the test drug.
PROBABLY: This category applies to those AEs that the Investigator feels with a high degree of certainty are related to the test drug. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug (2) it could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the drug yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the test drug.
DEFINITELY: This category applies to those AEs that the Investigator feels are incontrovertibly related to test drug. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug(2) it could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient (3) it disappears or decreases on cessation or reduction in dose and recurs with reexposure to drug (if rechallenge occurs); and (4) it follows a known pattern of response to the test drug.

Abbreviation: AE, adverse event.

12.7.2 Adverse Events of Special Interest

An AESI (serious or nonserious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor could be appropriate. Such an event might require further investigation in order to characterize and understand it.

For the purposes of this study, the following AEs are classed as AESIs:

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

Such AESI should be recorded in the eCRF and reported to the medical monitor via email.

12.7.3 Serious Adverse Events

An SAE is any untoward medical occurrence, in the view of either the Investigator or Sponsor, that:

- Results in death
- Is life-threatening

- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to jeopardize the patient and/or require medical or surgical intervention to prevent one of the outcomes defining an SAE. Serious AEs are critically important for the identification of significant safety problems; therefore, it is important to take into account both the Investigator's and the Sponsor's assessment. If either the Sponsor or the Investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

12.7.4 Serious Adverse Event Reporting

An SAE occurring from the time informed consent is obtained, during the study, or within 14 days of stopping the treatment must be reported to the [redacted] Safety and Pharmacovigilance group and will be communicated to the Sponsor. Any such SAE because of any cause, whether or not related to the study drug, must be reported within 24 hours of occurrence or when the Investigator becomes aware of the event. Notification can be made using the dedicated fax line or email for the [redacted] pharmacovigilance group:

[redacted]

If the Investigator contacts the [redacted] pharmacovigilance group by telephone, then a written report must follow within 24 hours and is to include a full description of the event and sequelae in the format detailed in the SAE reporting form.

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed up by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. Serious AE reports must be made whether or not the Investigator considers the event to be related to the investigational drug.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The Investigator must report all additional follow-up evaluations to the [redacted] Safety and Pharmacovigilance group within 24 hours of becoming aware of the additional information or as soon as is practicable. All SAEs will be followed up until the Investigator and Sponsor agree the event is satisfactorily resolved.

Any SAE that is not resolved by the end of the study or upon discontinuation of the patient's participation in the study is to be followed up until it either resolves, stabilizes, returns to baseline values (if a baseline value is available), or is shown to not be attributable to the study drug or procedures.

12.7.5 Suspected Unexpected Serious Adverse Reactions

Any AEs that meet all of the following criteria will be classified as suspected unexpected serious adverse reactions (SUSARs) and reported to the appropriate regulatory authorities in accordance with applicable regulatory requirements for expedited reporting:

- Serious
- Unexpected (i.e., the event is not consistent with the safety information in the Investigators Brochure)
- There is at least a reasonable possibility that there is a causal relationship between the event and the study treatment

The Investigator will assess whether an event is causally related to study treatment. The Sponsor ([redacted]) will consider the Investigator's assessment and determine whether the event meets the criteria for being reportable as a 7-day or 15-day safety report. SUSARs that are fatal or life-threatening SUSARs must be reported to the regulatory authorities and the institutional review boards (IRBs; where required) within 7 days after the Sponsor ([redacted]) has first knowledge of them, with a follow-up report submitted within a further 8 calendar days. Other SUSARs must be reported to the relevant regulatory authorities and the IRBs within 15 calendar days after the Sponsor ([redacted]) first has knowledge of them.

The Sponsor ([redacted]) is responsible for reporting SUSARs and any other events required to be reported in an expedited manner to the regulatory authorities and for informing Investigators of reportable events, in compliance with applicable regulatory requirements within specific timeframes. Investigators will notify the relevant IRBs of reportable events within the applicable timeframes.

12.7.6 Pregnancy

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 patients or female partners of male patients will be reported until the patient completes or withdraws from the study. The pregnancy will be reported immediately by faxing/emailing a completed pregnancy report to the Sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the Investigator will follow-up with the patient/patient partner until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days after completion of the pregnancy. The Investigator should notify the Sponsor (or designee) of the pregnancy outcome by submitting a follow-up pregnancy report. If the outcome of the pregnancy involved spontaneous or

therapeutic abortion (any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly, the Investigator will report the event by faxing/emailing a completed pregnancy report form to the Sponsor (or designee) within 24 hours of knowledge of the event.

Upon discontinuation from the study, only those procedures that would not expose the patient to undue risk will be performed. The Investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a patient/patient partner is subsequently found to be pregnant after inclusion of the patient in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the Sponsor after delivery.

12.7.7 Overdose

The Investigator must immediately (within 24 hours) notify the Sponsor medical monitor, by email, of any occurrence of overdose with study drug. An overdose is classed as the patient taking more than 1 tablet in a calendar day.

13 PHARMACOKINETICS

13.1 Pharmacokinetic Sampling

13.1.1 Blood Samples

Blood samples for PK analysis of SUVN-G3031 levels will be collected at the time points indicated in the Schedule of Assessments (Table 1). The actual date and time of each blood sample collection will be recorded.

Details of PK blood sample collection, processing, storage, and shipping procedures are provided in a separate Laboratory Manual.

13.2 Pharmacokinetic Analytical Methodology

The concentration of study drug will be determined from the plasma samples using a validated analytical method. Details of the method validation and sample analysis will be included with the final clinical study report.

14 STATISTICAL ANALYSIS

A SAP will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a complement to the protocol and supersedes it in case of differences.

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 will be provided. Summary statistics will be presented by treatment group. For continuous variables, data will be summarized with the number of patients (n), mean, SD, standard error of mean, median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and proportion of patients for each category by treatment group.

An unblinded interim analysis is planned when approximately 50% of patients have completed 14 days of treatment (Visit 3 completed). This interim analysis is for the purpose of sample size re-estimation, and futility will not be examined. Interim analysis will occur under the supervision of an independently charted DMC. See Section 7.1.4.

14.1 Determination of Sample Size

This study plans to randomize 114 patients, using 1:1:1 treatment allocation (stratified by at least 30% each by reported cataplexy patient history, Na-1 or Na-2 respectively), 38 to each treatment group. Using an SD of 5.0, N = 38 randomized patients 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.

14.2 Analysis Populations

Intent-to-Treat (ITT) Population

The ITT population will include all patients who were randomized, received at least one dose of study drug, and had baseline and at least one post-baseline primary efficacy assessment.

Safety Population

The safety population will include all randomized patients 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.

Per Protocol (PP) Population

The PP population will be a subset of ITT consisting of those patients 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 patient being excluded from the PP set. Before database lock, potential patient exclusions from PP set will be reviewed by the Sponsor and documented in a patient evaluability document.

Pharmacokinetic (PK) Population

The PK population will include all patients who receive at least 1 dose of study treatment with sufficient postdose plasma concentration data. This population will be used for PK analysis.

14.3 Efficacy Analysis

All efficacy analyses will be performed using the ITT population.

14.3.1 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in the mean total ESS score at Day 14. A successful study requires demonstration of statistically significant differences between the combined SUVN-G3031 doses (2 mg and 4 mg) group and the placebo group at endpoint for the ESS.

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 endpoint will be analyzed using a mixed model repeated measures (MMRM) analysis that includes the mean total ESS score from baseline to 7 days through to 14 days. This method is the preferred approach to longitudinal analysis because it utilizes observed data efficiently.

The model will include randomized treatment, visit and treatment-by-visit interaction as explanatory variables, stratification factor for cataplexy patient history (presence or absence) and baseline total ESS score as covariates. The participant effect will be assumed to be random, and an unstructured covariance structure will be assumed for within participant variation. The main comparison will be a contrast between treatment groups at 14 days. Least square mean changes will be estimated for SUVN-G3031 and placebo.

This analysis will be repeated for the ITT and PP populations.

Various sensitivity analyses will be performed using an analysis of covariance (ANCOVA) and multiple imputation pattern mixture model to handle missing data. Estimands specification and sensitivity analyses details will be included in the SAP.

14.3.2 Analysis of Secondary Efficacy Endpoints

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

To control the Type I error rate, the testing of secondary endpoints will be controlled using hierarchical testing methods. Thus, only if the primary endpoint is statistically significant, will the first listed secondary endpoint be tested. Likewise, the second listed secondary endpoint will only be tested if the first secondary endpoint is also statistically significant.

The secondary endpoints will be analyzed analogous to the analysis of the primary efficacy endpoint, i.e., an MMRM using the ITT population with the same factors, except the baseline value for the respective variable will be used instead of baseline total ESS score.

14.3.3 Analysis of Exploratory Endpoints

Continuous exploratory endpoints (listed below) will be analyzed in a similar fashion as the primary endpoint, i.e., an MMRM using the ITT population with the same factors, except the baseline value for the respective variable will be used instead of baseline total ESS score.

- 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)

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.

- The proportion of patients reporting CGI-C scores of 1 or 2 at Day 14 (EDS)
- The proportion of patients reporting CGI-S scores related to EDS of 1 or 2 at Day 7 and Day 14

- Proportion of patients 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
- Additional exploratory endpoints may be included in the SAP

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

Exploratory measures will also include the evaluation of associated features of narcolepsy through a sleep diary and measures collected as part of the nocturnal overnight PSG assessments at Day 7 and Day 14 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).

14.4 Safety Analysis

14.4.1 Adverse Events

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 patient 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 patient, along with information regarding onset, duration, relationship and severity to study drug, action taken with study drug, treatment of event, and outcome.

14.4.2 Laboratory Evaluations

Descriptive statistics will be performed for those laboratory parameters on a continuous scale for the raw scores and change from baseline at each visit. 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.

14.4.3 Vital Signs

Actual and change from baseline values in vital signs (body temperature, respiration rate, heart rate, and systolic and diastolic blood pressure) and body weight will be summarized for each scheduled visit. The corresponding listing will be provided.

14.4.4 Electrocardiogram

Change from baseline in the 12-Lead ECG results will be calculated and summarized along with the actual results for each scheduled visit. ECG data will also be listed.

14.4.5 Prior and Concomitant Medications

All nonstudy medications will be classified using the dynamic version of the World Health Organization Drug Dictionary (WHODD). Coding includes the Anatomical Therapeutic Chemical (ATC) classification levels and preferred term.

All medications administered and stopped prior to first dose of study drug are considered as prior medications. Any medications taken before the first dose and continued after the first dose or medications taken on or after the first dose of study drug are classified as concomitant medications. Concomitant medications will be summarized by the ATC levels and preferred term. All nonstudy medications will be listed.

14.4.6 Physical Examination

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

14.4.7 Columbia Suicide Severity Rating Scale

Columbia Suicide Severity Rating Scale data will be listed for all patients.

14.4.8 Patient Disposition

All patients who discontinued from treatment will be listed and the reasons for discontinuation will be tabulated.

14.4.9 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics. Demographics and informed consent data will be listed for all randomized patients.

14.5 Pharmacokinetic Analysis

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

14.6 Interim Analysis

Because of uncertainty in the underlying assumption supporting the power calculation, an unblinded interim analysis is planned when approximately 50% of patients have completed 14 days of treatment (Visit 3 completed) in order to increase the sample size if this deemed necessary and thus to increase the likelihood for a positive study.

The unblinded interim analysis is for the purpose of sample size re-estimation, and futility will not be examined. Sample size re-estimation will be performed using conditional power calculations. In case of sample size increase the weighted Cui, Hung, Wang test-statistic will be used for the combination of the data prior to the interim analysis and after interim analysis. [redacted]

The sample size re-estimation will permit a maximum of 57 additional patients (19 per treatment arm) to be randomized, and it will not permit a reduction in the initial sample size of 114 total patients.

Unblinded interim analysis will be performed in a firewall-protected project folder by an independent unblinded DMC statistician. Unblinded results will remain confidential. Access to unblinded interim results and documentation will be limited to the DMC and unblinded DMC statistician.

14.7 Data Monitoring Committee

Unblinded interim analysis will occur under the supervision of an independently chartered DMC whose charter, composition, and methods of analysis and review will be presented separately prior to study initiation. [redacted] The DMC's specific duties as well as statistical monitoring guidelines and procedures will be fully described in a DMC charter.

15 STUDY MANAGEMENT

15.1 Approval and Consent

15.1.1 Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant regulations, set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the United States Code of Federal Regulations (CFR), in compliance with International Council for Harmonisation (ICH) and GCP guidelines and according to the appropriate regulatory requirements in the countries where the study will be conducted.

15.1.2 Institutional Review Board

Conduct of the study must be approved by an appropriately constituted IRB. Approval is required for the study protocol, protocol amendments (if applicable), Investigator's Brochure, ICFs, recruitment material and patient information sheets and other patient-facing material.

15.1.3 Informed Consent

For each study patient written informed consent will be obtained before any protocol-related activities. As part of this procedure, the Principal Investigator (PI) or designee must explain orally and in writing the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. The patient should be informed that he/she may withdraw from the study at any time, and the patient will receive all information that is required by local regulations and guidelines for ICH. The PI will provide the Sponsor or its representative with a copy of the IRB-approved ICF before the start of the study.

15.2 Data Handling

Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained. See also Section 15.3.

Clinical data will be entered by site personnel on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Sponsor must only include coded identifiers such that directly identifying personal information is not transmitted. The primary method of data transmittal is via the secure, internet-based electronic data capture (EDC) system maintained by [redacted] the EDC system is available to only authorized users via the study's internet web site, where a user unique assigned username and password are required for access.

Any changes made to data after collection will be made through the use of the EDC system. Electronic CRFs will be considered complete when all missing and/or incorrect data have been resolved.

15.3 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The Investigator will provide direct access to source documents and/or source data in the facilitation of trial-related monitoring, audits, review by IRBs, and regulatory inspections.

The Investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained if necessary.

15.4 Record Retention

Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study, at least 2 years after the drug being studied has received its last approval for sale, or at least 2 years after the drug development has stopped, and in accordance with the applicable local privacy laws, whichever is the longer time period.

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation).The Investigator shall ensure that study patient authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

15.5 Monitoring

The study will be monitored according to the monitoring plan to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

Monitoring visits, on-site and remote and contacts will be made at appropriate times during the study. The PI will assure he/she and adequate site personnel are available throughout the study to collaborate with clinical monitors. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each patient.

The Investigator will make available to the clinical monitor all source documents and medical records necessary to review protocol adherence and eCRFs. In addition, the Investigator will work closely with the clinical monitor and, as needed, provide them appropriate evidence that the

study is being conducted in accordance with the protocol, applicable regulations, and GCP guidelines.

15.6 Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the Sponsor lies with the Investigator generating the data.

The Sponsor will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating procedures, GCP and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

15.7 Protocol Amendment and Protocol Deviation

15.7.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on the safety of patient or the conduct of the study will be classed as administrative amendments and will be submitted to the IRB for information only. The Sponsor will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate regulatory authorities and the IRBs for approval and will not be implemented at sites until such approvals are received other than in the case of an urgent safety measure.

15.7.2 Protocol Deviations

Should a protocol deviation occur, the Sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Reporting of protocol deviations to the IRB and in accordance with applicable regulatory authority mandates is an Investigator responsibility.

15.8 Ethical Considerations

This study will be conducted in accordance with this protocol, the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR; Annex 1, D, 17 (a); and in compliance with GCP guidelines.

Institutional Review Boards will review and approve this protocol and the ICF. All patients are required to give written informed consent before participation in the study.

15.9 Financing and Insurance

Before the study commences, the Sponsor (or its designee) and the Investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the Investigator (or the institution signatory) and the Sponsor (or its designee).

The Investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide no-exclusion insurance coverage for the clinical study as required by national regulations.

15.10 Publication Policy/Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by Investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, Investigators will be required to assign all such inventions either to their institution or directly to the Sponsor or its designee, as will be set forth in the clinical study agreement.

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17 APPENDICES

Appendix 1 describes the contraception guidelines applicable for this study.

Appendix 2 describes prohibited and restricted medications in this study.

Appendix 3 describes caffeine dosages of common drinks.

Appendix 1. Contraception Guidelines

Women of childbearing potential (WOCBP) and men whose sexual partners are WOCBP must use at least 2 highly effective methods of contraception during the study and for 30 days after the last dose of study treatment.

A woman is considered to be a WOCBP (fertile) after menarche and until becoming postmenopausal, unless she is permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Highly effective methods of contraception are those which have a failure rate of <1% (when implemented consistently and correctly) and include:

- Combined (containing estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (administration may be oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (administration may be oral, injectable, or implantable)
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal ligation or occlusion
- Vasectomy (provided that the male has a medical assessment of surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk in relation to the duration of the clinical trial, in line with the preferred and usual lifestyle of the patient)

All patients will be strongly advised that they (or the female partners of male patients) should not become pregnant while on study treatment or for 30 days after the last dose. A female patient will be advised that she must report immediately to the study site for pregnancy testing and appropriate management in the event that she may be pregnant.

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Appendix 2. Prohibited or Restricted Medications

Restriction Rationale	Restriction	Medication Examples
As required anxiolytics may cause erratic variation/addiction patterns which confound study assessments.	Investigator has discretion to limit enrollment, on a case-by case basis. This must be approved by the Medical Monitor and a rationale given for its use.	Primarily benzodiazepines
Sleep aids or stimulants that affect efficacy assessment	Washout completed 7 days prior to randomization	Methylphenidate, dextroamphetamine, methamphetamine, modafinil and armodafinil, pseudoephedrine, amphetamines, pemoline, trazodone, hypnotics, benzodiazepines, barbiturates, opioids, Isocarboxazid, phenelzine, selegiline, rasagiline, tranylcypromine, bupropion
Marijuana/CBD/cannabinoids can affect sleep, mood, behavior	Use of medically prescribed cannabinoids without euphoric or soporific effects may be allowed by the Medical Monitor but must be avoided 48 h prior to assessments. Other substances are not permitted.	Marijuana/CBD/cannabinoids
Adjunctive pharmacotherapy directed against cataplexy confounds study treatment	Washout completed 14 days before randomization	Including but not limited to selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, anticonvulsant agents, sodium oxybate, pitolisant
Medications with subtle sedating effects may be permitted with PI discretion	Principal Investigator has discretion to limit enrollment on a case-by-case basis to those with mild conditions, with stable use (≥ 3 months), not likely to require treatment changes during the trial	Beta blockers are allowed to be continued, provided they are used at a stable dose

Appendix 3. Caffeine Dosages for Common Drinks

Brewed Green Tea – Please use the same content for Brewed Black Tea

- Short (8 oz, 237 ml) 25 mg
- Tall (12 oz, 355 ml) 55 mg
- Grande (16 oz, 473 ml) 80 mg
- Venti (20 oz, 591 ml) 110 mg

Brewed Coffee

- Short (8 oz, 237 ml) 175 mg
- Tall (12 oz, 355 ml) 260 mg
- Grande (16 oz, 473 ml) 330 mg
- Venti (20 oz, 591 ml) 410 mg

Espresso (and espresso drinks such as lattes, cappuccinos, etc)

- Espresso (single shot) 75 mg
- Double espresso 150 mg

Energy Drinks

- Red Bull™ 80 mg
- Monster™ 160 mg
- Rockstar™ 160 mg
- Full Throttle™ 144 mg
- No Fear™ 174 mg
- Amp™ 75 mg
- Tab Energy™ 95 mg
- Jolt Cola™ 280 mg
- NOS™ 250 mg
- VitaminWater™ Energy Citrus 50 mg

Classic Sodas

- Coca cola™ 35 mg
- Pepsi cola™ 38 mg
- Dr. Pepper™ 41 mg
- Mountain Dew™ 54 mg

5-hour Energy Drinks

- 5-hour Energy® 200 mg
- Extra strength 5-hour Energy® 230 mg

References

Caffeine contents of tea, coffee, and espresso drinks are based on data from Starbucks: https://globalassets.starbucks.com/assets/01D7B4F4783F4793A5113FAF415BA8D6.pdf

Caffeine contents of energy drinks are based on Table 1 from:
Reissig CJ, Strain EC, Griffiths RR. Caffeinated energy drinks--a growing problem. *Drug Alcohol Depend.* 2009;99(1-3):1-10.

Caffeine contents of 5-hour Energy products are based on data from the manufacturer: http://5hourenergy.com/facts/ingredients/. Accessed April 19, 2019.