CLINICAL STUDY PROTOCOL

A Randomized, Double-Blind, Single-Dose, 4-Way Crossover Study to Assess the Efficacy and Safety of SM-1 (50-mg Diphenhydramine, 5-mg Delayed-Release Zolpidem, and 0.5-mg Delayed-Release Lorazepam) versus 2 Comparators (50-mg Diphenhydramine and 5-mg Delayed-Release Zolpidem; 50-mg Diphenhydramine and 0.5-mg Delayed-Release Lorazepam) and Placebo in a 5-Hour Phase Advance Model of Transient Insomnia

SM-A-05

Sponsor: Sequential Medicine, Ltd
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Version of Protocol: Protocol 1.0, Amendment 1

Date of Protocol: 12 December 2017

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice.

Protocol Approval – Sponsor Signatory

Study Title A Randomized, Double-Blind, Single-Dose, 4-Way Crossover Study to Assess the Efficacy and Safety of SM-1 (50-mg Diphenhydramine, 5-mg Delayed-Release Zolpidem, and 0.5-mg Delayed-Release Lorazepam) versus 2 Comparators (50-mg Diphenhydramine and 5-mg Delayed-Release Zolpidem; 50-mg Diphenhydramine and 0.5-mg Delayed-Release Lorazepam) and Placebo in a 5-Hour Phase Advance Model of Transient Insomnia

Protocol Number SM-A-05

Protocol Date 12 December 2017

Protocol accepted and approved by:

Sponsor

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Representative

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Signature

29 DEC, 2017
Date

Protocol Approval – Coordinating Investigator

Study Title A Randomized, Double-Blind, Single-Dose, 4-Way Crossover Study to Assess the Efficacy and Safety of SM-1 (50-mg Diphenhydramine, 5-mg Delayed-Release Zolpidem, and 0.5-mg Delayed-Release Lorazepam) versus 2 Comparators (50-mg Diphenhydramine and 5-mg Delayed-Release Zolpidem; 50-mg Diphenhydramine and 0.5-mg Delayed-Release Lorazepam), and Placebo in a 5-Hour Phase Advance Model of Transient Insomnia

Protocol Number SM-A-05

Protocol Date 12 December 2017

Protocol accepted and approved by:

Coordinating Investigator

Thomas Roth, PhD
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Thomas Roth — JAN. 24, 2018

Signature **Date**

Protocol Approval – Lead Statistician

Study Title A Randomized, Double-Blind, Single-Dose, 4-Way Crossover Study to Assess the Efficacy and Safety of SM-1 (50-mg Diphenhydramine, 5-mg Delayed-Release Zolpidem, and 0.5-mg Delayed-Release Lorazepam) versus 2 Comparators (50-mg Diphenhydramine and 5-mg Delayed-Release Zolpidem; 50-mg Diphenhydramine and 0.5-mg Delayed-Release Lorazepam) and Placebo in a 5-Hour Phase Advance Model of Transient Insomnia

Protocol Number SM-A-05

Protocol Date 12 December 2017

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Signature Date

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Randomized, Double-Blind, Single-Dose, 4-Way Crossover Study to Assess the Efficacy and Safety of SM-1 (50-mg Diphenhydramine, 5-mg Delayed-Release Zolpidem, and 0.5-mg Delayed-Release Lorazepam) versus 2 Comparators (50-mg Diphenhydramine and 5-mg Delayed-Release Zolpidem; 50-mg Diphenhydramine and 0.5-mg Delayed-Release Lorazepam) and Placebo in a 5-Hour Phase Advance Model of Transient Insomnia" and the current Investigator's Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 1.0, Amendment 1, dated 12 December 2017, the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with Sequential Medicine Ltd or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to subjects. I agree to administer study treatment only to subjects under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Sequential Medicine Ltd.

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

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Protocol Synopsis

Protocol Number:	SM-A-05
Title:	A Randomized, Double-Blind, Single-Dose, 4-Way Crossover Study to Assess the Efficacy and Safety of SM-1 (50-mg Diphenhydramine, 5-mg Delayed-Release Zolpidem, and 0.5-mg Delayed-Release Lorazepam) versus 2 Comparators (50-mg Diphenhydramine and 5-mg Delayed-Release Zolpidem; 50-mg Diphenhydramine and 0.5-mg Delayed-Release Lorazepam) and Placebo in a 5-Hour Phase Advance Model of Transient Insomnia
Sponsor:	Sequential Medicine, Ltd 6F, No.135 Sec 3 Minsheng East Road Taipei, 10546 Taiwan, Republic of China
Study Phase:	3
Study Sites:	2 study centers in the US
Indication:	Transient insomnia
Rationale:	The current study will serve to confirm the efficacy, safety, and tolerability of SM-1 in subjects with a history of transient insomnia. In addition, the inclusion of the additional drug combination arms will serve to generate data to assess the contribution of zolpidem and lorazepam to the overall efficacy of the investigational product.
Objectives:	The primary objective of the study is to assess efficacy of SM-1 versus placebo and 2 additional combination products comprised of 2 of the 3 components of SM-1 (diphenhydramine plus zolpidem and diphenhydramine plus lorazepam) as measured by polysomnography (PSG)-defined total sleep time (TST). The secondary objectives of this study are: • To assess activity of SM-1 versus placebo and the two 2-drug combination products on additional PSG measures of sleep induction • To assess subject reported efficacy measures from the Post-Sleep Questionnaire (PSQ) • To assess the activity of the two 2-drug combination products versus placebo on PSG-defined TST and additional PSG measures of sleep induction The safety objective of this study is to assess safety of SM-1 in terms of adverse events (AEs) and morning measures of alertness

(Karolinska Sleepiness Scale [KSS] and Digit Symbol Substitution Test [DSST]).

Other objectives include the assessment of the effect of SM-1 and the two 2-drug combination products on sleep stage distribution.

Subject Population: The study will enroll male and female subjects 18 years of age or older in good general health who routinely spend between 6.5 and 9 hours in bed per night and report at least 1 prior episode of transient insomnia defined by all of the following criteria:

- Difficulty falling asleep or staying asleep
- Next day impairment or distress associated with the disturbed sleep
- Frequency of 1 to 7 nights per week
- Duration of less than 1 month or more than 1 month of intermittent episodes

Subjects should have no clinically significant medical, psychiatric, or sleep disorders.

Study Design: Potential subjects will be evaluated during a screening period (Visit 1). Subjects who satisfy all eligibility criteria will be issued a paper sleep diary and instructed to record the time they go to bed with the intention of sleeping and the time they get up for a minimum of 7 days during the screening period, with at least 5 entries completed over the 7 days (≥70% compliance). Information recorded in the diary will be communicated to study personnel no later than 24 hours prior to check-in for the first day of the first treatment period (Visit 2) to allow the calculation of each subject's median habitual bedtime.

At Visit 2, subjects will check-in at the study center approximately 7 hours earlier than their median habitual bedtime, as calculated from their diary data. Once eligibility has been reconfirmed, subjects will be randomly assigned to 1 of 4 treatment sequences as shown in the following table:

Randomized Treatment Sequences

	Treatment Period 1 Visit 2	**Treatment Period 2 Visit 3**	**Treatment Period 3 Visit 4**	**Treatment Period 4 Visit 5**
Sequence 1	SM-1	D+Z	D+L	Placebo
Sequence 2	D+Z	D+L	Placebo	SM-1
Sequence 3	D+L	Placebo	SM-1	D+Z
Sequence 4	Placebo	SM-1	D+Z	D+L

SM-1 = 50-mg diphenhydramine, 5-mg delayed-release zolpidem, and 0.5-mg delayed-release lorazepam; D+Z = 50-mg diphenhydramine and 5-mg delayed-release zolpidem; D+L = 50-mg diphenhydramine and 0.5-mg delayed-release lorazepam; placebo = identical in appearance to SM-1, D+Z, and D+L and has the same excipients, but no diphenhydramine, zolpidem, lorazepam, or delated-release coating materials.

Subjects will go to bed ("lights out") 5 hours ± 30 minutes before their median habitual bedtime. Prior to lights out, subjects will undergo a baseline DSST assessment, eat a light snack, have PSG electrodes applied, and the machine will be calibrated. Subjects will be administered their assigned treatment by study personnel 30 minutes prior to lights out. At the assigned lights out time the subject will go to bed, PSG biocalibration will be performed, and PSG recording will begin. The recording will continue for 8 hours. At the completion of the 8-hour PSG recording period, subjects will complete morning assessments (PSQ, KSS, and DSST) and will undergo a predischarge evaluation, consisting of tandem gait, the Romberg test, and an assessment of vital signs and AEs. Upon discharge, subjects will undergo an interdose washout interval of no less than 5 days and will be asked to complete a daily washout interval diary during this time. The schedule of procedures for Visits 3, 4, and 5 will be the same as for Visit 2 except that subjects will be given the next treatment in their randomization sequence and lights out will occur at the time established at Visit 2, ± 15 minutes.

Within 7 days after completion of Treatment Period 4 (Visit 5), but at least 72 hours after administration of the final dose, study personnel will contact the subject for a follow-up safety phone call. Outcomes of any AEs will be discussed and recorded. If indicated, a visit to the study center for safety assessments will be scheduled.

Estimated Study Duration:	Subjects will be evaluated during a screening period lasting at least 8 and no more than 21 days, followed by 4 inpatient PSG and treatment periods lasting approximately 11 to 12 hours from check-in to discharge. Between each treatment period, subjects will undergo an interdose washout interval of no less than 5 days. Subjects will then be contacted by telephone for a safety follow-up within 7 days but at least 72 hours after their last dose of study drug. From screening to the safety follow-up phone call, assuming a 7-day washout interval between each treatment period, subjects will participate in the study for approximately 8 weeks.
Efficacy Assessments:	Polysomnography data will be the primary source for efficacy endpoints, including TST, WASO, LPS, NAW, and TST by quarters of the night. Each night of PSG for each treatment period (Visits 2, 3, 4, and 5) will consist of an 8-hour (960 30-second epochs) assessment during which electroencephalographic, electrooculographic, electrocardiographic, and submental electromyographic activity will be recorded according to methods consistent with the standards of the American Academy of Sleep Medicine. Subject-reported efficacy measures will be assessed from data collected from the PSQ, which includes subject self-reporting of time to sleep onset, NAW, wake time during the night, TST, and sleep quality. The PSQ data will be used to determine subjective TST (sTST) and subjective sleep onset latency (sSOL). Subjects will also be required to complete a daily diary during each interdose washout interval.
Safety Assessments:	Safety and tolerability will be assessed in terms of the incidence, severity and relationship to treatment of AEs, and by morning measures of alertness (KSS and DSST). In addition, safety assessments will include alcohol screening, urine pregnancy testing for women of childbearing potential, vital sign measurements, and predischarge evaluations.
Study Drug, Dosage, and Route of Administration:	The SM-1 study drug contains 50-mg diphenhydramine, 5-mg delayed-release zolpidem, and 0.5-mg delayed-release lorazepam as active ingredients. The 2-drug combination D+Z study drug contains 50-mg diphenhydramine and 5-mg delayed-release zolpidem as active ingredients. The 2-drug combination D+L study drug contains 50-mg diphenhydramine and 0.5-mg delayed-release lorazepam as active ingredients.

The SM-1, D+Z, and D+L capsules are all Size 0 white capsules and contain the inactive excipients PROSOLV® SMCC HD 90, starch 1500, and magnesium stearate. Delayed-release coating materials include Eudragit L100-55, Eudragit L100, and Eudragit S100.

The placebo is identical in appearance to SM-1, D+Z, and D+L, and has the same excipients, but no diphenhydramine, zolpidem, lorazepam, or delayed-release coating materials.

For each treatment period (Visits 2, 3, 4, and 5), 30 minutes prior to each subject's lights out time (5 hours ± 30 minutes prior to the subject's median habitual bedtime), a single dose of study drug will be administered according to the subject's treatment sequence randomization. All doses of study drug will be administered orally by study personnel with 250 mL of water. An oral cavity check will be performed to assure compliance with treatment.

Sample Size: A minimum of 68 blinded subjects will be able to ensure 80% power to detect treatment difference in TST between SM-1 and all 3 controls (D+Z, D+L, and placebo) at a 2-sided 0.05 significance level. Approximately 84 subjects will be randomly assigned to receive study drug. A blinded interim analysis will be performed after approximately 50% of blinded subjects have completed the study to allow for an option to increase the sample size to preserve power if the observed SD of the primary efficacy endpoint is different than was estimated for the a priori sample size calculation.

Statistical Methods: Statistical analysis will be performed using SAS software Version 9.2 or later. Continuous variables will be summarized using the mean, SD, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Data will be provided in by-subject data listings.

All statistical tests will be 2-sided and performed using a 5% significance level, leading to 95% 2-sided CIs. The overall study wide type I error rate (alpha) will be 0.05.

The analysis of the primary efficacy endpoint will be conducted using an analysis of variance (ANOVA) method with the TST as the response variable and treatment, sequence, center, and period as the fixed effects. The primary comparison will be SM-1 with placebo, followed by SM-1 with D+Z, and SM-1 with D+L.

Analyses will be performed to evaluate effect of sex and age on TST using the same ANOVA model with addition of sex and age

(greater than median vs less than median) as fixed factors.

The data collected from PSG recordings and PSQ responses will be used to analyze the secondary efficacy endpoints for the comparisons of SM-1 versus placebo on WASO, LPS, NAW, sTST sSOL, and TST by quarters of the night; SM-1 versus both D+Z and D+L on WASO, LPS, NAW, sTST, sSOL, and TST by quarters of the night; and both D+Z and D+L versus placebo on TST, WASO, LPS, NAW, sTST, sSOL, and TST by quarters of the night. These analyses will be performed using the same ANOVA model as for the primary efficacy endpoint. Endpoints that are not normally distributed will be log-transformed first.

Adverse events will be summarized by using count summaries. Adverse events will be listed for each subject and summarized by system organ class and preferred term assigned to the event by the Medical Dictionary for Regulatory Activities.

The KSS and DSST data will be analyzed using the same statistical methods as the primary efficacy endpoint analysis.

Vital sign measurements will be summarized and listed. Physical examination findings, alcohol breath test results, and urine pregnancy test results will be provided in by-subject data listings.

Sleep stage will be summarized by the duration (in minutes) and percentage of each sleep stage. The latency to rapid eye movement (REM) will be summarized. The duration and percentage of each sleep stage (N1, N2, N3) and the latency to REM will be analyzed using the same statistical methods as for the primary endpoint analysis.

Disposition, demographics, medical history, sleep history, and concomitant medications will be summarized and listed.

Date of Protocol: 12 December 2017

List of Abbreviations

Abbreviation	Definition
AE	adverse event
ANOVA	analysis of variance
BMI	body mass index
CFR	Code of Federal Regulations
D+L	50-mg diphenhydramine plus 0.5-mg delayed-release lorazepam
D+Z	50-mg diphenhydramine and 5-mg delayed-release zolpidem
DSST	Digit Symbol Substitution Test
eCRF	electronic case report form
EDC	electronic data capture
ESS	Epworth Sleepiness Scale
FAS	full analysis set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board
KSS	Karolinska Sleepiness Scale
LPS	latency to persistent sleep
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified full analysis set
NAW	number of awakenings
OSA	obstructive sleep apnea
OTC	over the counter
PPD	Pharmaceutical Product Development, LLC
PPS	per-protocol set
PSG	polysomnography, polysomnographic
PSQ	Post-Sleep Questionnaire
REM	rapid eye movement
SAE	serious adverse event
SM-1	50-mg diphenhydramine, 5-mg delayed-release zolpidem, and 0.5-mg delayed-release lorazepam

Abbreviation	Definition
sSOL	subjective sleep onset latency
sTST	subjective total sleep time
TST	total sleep time
WASO	wakefulness after sleep onset

1 Introduction

Sequential Medicine Ltd (sponsor) is currently developing a product intended for the short-term treatment of individuals with transient insomnia. The product candidate, code-named SM-1, is a controlled-release combination of established medications intended to both induce and maintain sleep while avoiding impairment of next-day functioning. The dose of each drug in the SM-1 formulation is the lowest dose that has been shown to have sleep-promoting properties.

The formulation provides 50-mg immediate-release diphenhydramine, a histamine (H_1) receptor antagonist working on the wake side of the sleep/wake system, a 5-mg delayed-release dose of zolpidem, a drug which works on the sleep side of the sleep/wake system, and a low dose (0.5 mg) of delayed-release lorazepam with the intent of inducing and maintaining sleep without residual effects. This combination and staging is a unique approach to addressing the problem of transient insomnia, where most current treatments for difficulty sleeping tend to provide sleep onset relief, but inadequate benefit of duration or maintenance of sleep in the absence of morning impairment. If successful, SM-1 will be a unique and important therapeutic option for the treatment of transient insomnia.

The investigational product SM-1 was studied in a pharmacokinetic/pharmacodynamic study in normal healthy volunteers in a daytime sedation study. By both objective and subjective criteria, SM-1 displayed the desired activity profile with onset of sedative effects 0.5 to 1 hour following dose administration and offset generally 8 hours following dose administration, for a duration of action of 7 to 7.5 hours. The product was well-tolerated with minimal side effects.

A Phase 2 clinical study of SM-1 was conducted in the target patient population, 39 subjects who had a history of transient insomnia. During the clinical study, sleep disturbance was induced using a 5-hour phase advance model with 8 hours of polysomnographic (PSG) recording for the primary efficacy endpoint of total sleep time (TST). The efficacy of SM-1 was compared both with placebo and to a drug combination product comprised of 2 of the 3 components of SM-1 (5-mg delayed-release zolpidem plus 0.5-mg delayed-release lorazepam) in a double-blind, single-dose, 3-way crossover study.

The study's primary endpoint was the comparison of TST between SM-1 and placebo. Administration of SM-1 resulted in a significantly greater TST than placebo ($P<0.001$) as

well as the 2-drug combination (P=0.014). Administration of SM-1 reduced wakefulness after sleep onset (WASO) significantly compared with placebo (P<0.001). On waking, there were no residual drug effects as indicated by Karolinska Sleepiness Scale (KSS), Digit Symbol Substitution Test (DSST), or predischarge neurological examination results. The single doses of SM-1 were safe and well-tolerated in the study population that included male and female subjects who had reported occasional difficulty falling asleep of staying asleep but who were not experiencing such difficulties at the time of the study.

The current study will serve to confirm the efficacy, safety, and tolerability of SM-1 in subjects with a history of transient insomnia. In addition, the inclusion of additional drug combination arms will serve to generate data to assess the contribution of zolpidem and lorazepam to the overall efficacy of the investigational product.

2 Study Objectives

2.1 Primary Objectives

The primary objectives of this study are:

- To assess efficacy of SM-1 versus placebo as measured by PSG-defined TST
- To assess efficacy of SM-1 versus 2 additional combination products comprised of 2 of the 3 components of SM-1 (diphenhydramine plus zolpidem and diphenhydramine plus lorazepam) as measured by PSG-defined TST

2.2 Secondary Objectives

The secondary objectives of this study are:

- To assess activity of SM-1 versus placebo and the two 2-drug combination products on additional PSG measures of sleep induction and maintenance
- To assess subject-reported efficacy measures from the Post-Sleep Questionnaire (PSQ)
- To assess the activity of the two 2-drug combination products versus placebo on PSG-defined TST, and additional PSG measures of sleep induction and maintenance

2.3 Safety Objective

The safety objective of this study is to assess safety of SM-1 in terms of adverse events (AEs) and morning measures of alertness (KSS and DSST).

2.4 Other Objectives

Other objectives include the assessment of the effect of SM-1 and the two 2-drug combination products on sleep stage distribution.

3 Investigational Plan

3.1 Study Design

This is a randomized, double-blind, single dose, 4-way crossover study to assess the efficacy and safety of SM-1 compared with placebo and two 2-drug combination products in subjects who report previous transient insomnia. Sleep disturbance will be induced using a 5-hour phase advance model with 8 hours (960 30-second epochs) of PSG recording as the primary efficacy assay. The study consists of the following periods: screening, treatment and PSG periods, and a follow-up safety phone call.

Screening Period

Potential subjects will be evaluated during a screening period lasting at least 8 and no more than 21 days before the first day of the first treatment period. After signed written informed consent is obtained, screening visit (Visit 1) procedures will be performed as specified in the schedule of events (Table 6-1). Subjects who satisfy all eligibility criteria will be issued a pretreatment paper diary and instructed to record the time they go to bed with the intention of sleeping and the time they get up for a minimum of 7 nights, with at least 5 entries completed over the 7 nights. Information recorded in the diary will be communicated to study personnel no later than 24 hours before check-in for the first day of the first treatment period (Visit 2) to allow the calculation of each subject's median habitual bedtime. Before Visit 2, subjects will be contacted by study personnel and told the time and date to present for their first overnight visit. Subjects will be advised to eat lunch before check-in due to the long fasting intervals required by the study schedule.

Treatment and Polysomnography Periods

At Visit 2, subjects will check-in at the study center approximately 7 hours earlier than their median habitual bedtime, as calculated from their diary data and will return their paper diary to study personnel for review. Visit 2 procedures will be performed as specified in the schedule of events (Table 6-1) and according to the timing of sleep study events relative to each subject's habitual bedtime (Table 6-2). Each treatment and PSG period visit will last approximately 11 to 12 hours. Once eligibility has been reconfirmed, subjects will be randomly assigned to 1 of 4 treatment sequences as shown in Table 3-1.

Table 3-1 Randomized Treatment Sequences

	Treatment Period 1 Visit 2	Treatment Period 2 Visit 3	Treatment Period 3 Visit 4	Treatment Period 4 Visit 5
Sequence 1	SM-1	D+Z	D+L	Placebo
Sequence 2	D+Z	D+L	Placebo	SM-1
Sequence 3	D+L	Placebo	SM-1	D+Z
Sequence 4	Placebo	SM-1	D+Z	D+L

SM-1 = 50-mg diphenhydramine, 5-mg delayed-release zolpidem, and 0.5-mg delayed-release lorazepam; D+Z = 50-mg diphenhydramine and 5-mg delayed-release zolpidem; D+L = 50-mg diphenhydramine and 0.5-mg delayed-release lorazepam; placebo = identical in appearance to SM-1, D+Z, and D+L and has the same excipients, but no diphenhydramine, zolpidem, lorazepam, or delated-release coating materials

Subjects will go to bed ("lights out") 5 hours ± 30 minutes before their median habitual bedtime. Approximately 90 minutes before lights out, baseline DSST measurements will be obtained and subjects will be provided a light, low-fat snack (e.g., fruit and crackers). Approximately 60 minutes before lights out, PSG electrodes will be applied to the subject and the machine will be calibrated. Subjects will be administered their assigned treatment by study personnel 30 minutes before lights out and an oral cavity check will be performed to assure compliance with treatment. At the assigned lights out time subject will go to bed, PSG biocalibration will be performed, and PSG recording will begin. The recording will continue for 8 hours.

At the completion of the 8-hour PSG recording period, subjects will be awakened and allowed a bathroom visit. Approximately 30 minutes after the end of PSG recording, subjects will complete the PSQ, KSS, and DSST and will be served a standard breakfast. Before leaving the study center, subjects will undergo a brief discharge evaluation consisting of tandem gait, the Romberg test, and an assessment of vital signs and AEs. Subjects will remain at the study center until they are able to pass the evaluation. Upon discharge, subjects will be told the time and date to return for the next overnight visit, dispensed a daily washout interval diary and instructed to maintain their normal sleep patterns.

Following a washout interval of no less than 5 days, subjects will return to the study center at the assigned time and date and will return their paper diary to study personnel for review. The schedule of procedures for Visits 3, 4, and 5 will be the same as for Visit 2 except that subjects will be given the next treatment in their randomization sequence (Table 3-1) and

lights out will occur at the time established at Visit 2, ± 15 minutes. Subjects will be dispensed a new daily washout interval diary at Visits 3, and 4.

Follow-Up Safety Phone Call

Within 7 days after completion of Treatment Period 4 (Visit 5), but at least 72 hours after administration of the final dose, study personnel will contact the subject for a follow-up safety phone call. Outcomes of any AEs will be discussed and recorded. If indicated, a visit to the study center for safety assessments will be scheduled.

From screening to the follow-up safety phone call, assuming a 7-day washout interval between each treatment period, subjects will participate in the study for approximately 8 weeks.

3.1.1 Rationale of Study Design

A Phase 2 clinical study of SM-1 was previously conducted using a 5-hour phase advance model in subjects who had a history of transient insomnia. The efficacy of SM-1 was compared with both placebo and a drug combination product comprised of 2 of the 3 components of SM-1 (5-mg delayed-release zolpidem plus 0.5-mg delayed-release lorazepam) in a 3-way crossover design, with 8 hours of PSG recording for the primary efficacy endpoint of TST. The current study will serve to confirm the efficacy, safety, and tolerability of SM-1 and will generate data for the additional drug combination arms of 50-mg diphenhydramine plus 5-mg delayed-release zolpidem and 50-mg diphenhydramine plus 0.5-mg delayed-release lorazepam. These additional drug combination arms will serve to generate data to assess the contribution of zolpidem and lorazepam to the overall efficacy of the investigational product.

The crossover design enables subjects to serve as their respective controls, thereby increasing the efficiency of the study design with respect to the number of subjects that need to be treated in order to demonstrate efficacy. The phase advance model is an established approach to the assessment of the efficacy of agents being developed to improve sleep. Polysomnography offers objective assessment of sleep wake function, enabling a thorough understanding of the effect of SM-1 and its components on several aspects of sleep. The assessment of next-day effects on morning performance serves to establish the safety of SM-1 and to understand possible impacts on ability to conduct normal daily activities.

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 128 subjects will be screened, and 84 subjects will be randomly assigned to receive study drug at 2 study centers in the United States. Subjects will be assigned to study drug only if they meet all of the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed.

4.1.1 Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. Is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements.
2. Is 18 years of age or older at screening.
3. Reports at least 1 prior episode of transient insomnia meeting all of the following criteria:
    - Difficulty falling asleep or staying asleep
    - Next day impairment or distress associated with the disturbed sleep
    - Frequency of 1 to 7 nights per week
    - Duration of less than 1 month or more than 1 month of intermittent episodes
4. Routinely spends between 6.5 and 9 hours in bed each night with bed time varying no more than 2 hours over a week, as confirmed by data from a paper diary completed for a minimum of 7 days during the screening period, with at least 5 entries completed over the 7 days (≥70% compliance).
5. Has a body mass index (BMI) between 19 and 32 kg/m^2, inclusive at screening.
6. In the opinion of the investigator, is in good general health as determined by a thorough medical, sleep, and psychiatric history review, brief physical examination including vital sign measurements, and an assessment of screening laboratory test results.

7. Female subjects of childbearing potential must be using an acceptable method of contraception during the study and for the 30 days following the last dose of study drug and must have a negative urine pregnancy test at every study visit. Acceptable methods of contraception include oral, intrauterine, transdermal, and injectable contraceptives or double barrier methods (e.g., condom plus spermicidal gel or foam). Subjects who have been using oral contraceptives for less than 30 days before screening must agree to use an additional method of contraception from screening until they have been taking oral contraceptives for 30 days. Female subjects of non-childbearing potential are not required to use contraception if they have been surgically sterilized (tubal ligation, hysterectomy, or bilateral oophorectomy) or are postmenopausal as defined by the cessation of menses for a period of at least 2 years before screening.
8. Male subjects must use an acceptable method of contraception during the study and for the 30 days following the last dose of study drug. Acceptable methods of contraception include:
    a. Vasectomy with evidence of a sperm-negative ejaculate 3 months after vasectomy
    b. Condom and a female partner who meets one of the following conditions:
        i. Uses oral, intrauterine, transdermal, and injectable contraceptives
        ii. Uses a spermicidal foam/gel/film/cream/suppository
        iii. Uses a diaphragm or cervical/vault cap
    c. A female partner who is surgically sterile or postmenopausal
9. Is willing and able to be confined to the study center for 1 night in each of 4 treatment periods as required by the protocol.
10. Refrains from the use of alcohol within 24 hours of check-in on Visits 2, 3, 4, and 5.
11. Refrains from napping, defined as any sleep episode occurring outside of the subject's main sleep episode of on days of check-in for Visits 2, 3, 4, and 5.
12. Has an Epworth Sleepiness Scale (ESS) score ≤8 at screening.

4.1.2 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Females who are pregnant, breast-feeding, or planning a pregnancy during the study period.
2. Clinically significant medical disorder or currently unstable medical condition that, in the opinion of the investigator, would confound the results of the study.
3. An abnormal laboratory value at screening that is judged to be clinically significant as determined by the investigator.
4. History or current evidence of severe hepatic impairment.
5. Clinically significant psychiatric illness, or the history or presence of a major psychiatric illness in the past year.
6. Any clinically significant abnormal finding on physical examination, as determined by the investigator.
7. Lifetime history of seizure disorder (other than childhood febrile seizures) or serious head injury.
8. History of chronic insomnia or other sleep disorders, such as sleep apnea, narcolepsy, parasomnia, restless leg syndrome, or circadian rhythm disorder.
9. Air travel across more than 2 time zones, an expected change in sleep schedule, or involvement in night work or shift work within 1 month before screening or during the study period.
10. Reports a recent history of napping of more than once per week.
11. History of alcohol or substance use disorder within the year before screening, or current evidence of alcohol or substance use disorder as defined by the Diagnostic and Statistical Manual of the American Psychiatric Association, 5th Edition.
12. Self-report of a usual consumption of more than 14 units of alcohol per week. One unit of alcohol is equivalent to 12 ounces of beer, 4 ounces of wine, or 1 ounce of liquor.
13. Regular consumption of greater than 500 mg of caffeine per day.
14. History of routinely smoking during sleep period.

15. Discontinuation of smoking or participation in a smoking cessation program within 30 days of screening or plans to discontinue smoking during the study.
16. A positive urine drug screen at screening.
17. Positive alcohol breathalyzer test at any visit.
18. History of allergy or known sensitivity, hypersensitivity, or adverse reaction to diphenhydramine, zolpidem, or lorazepam or other drugs of the same pharmaceutical classes.
19. Use of any medication which affects sleep-wake function within 5 half-lives or 2 weeks, whichever is longer, before screening until study completion. This includes prescription, over-the-counter (OTC), and herbal (e.g., valerian root, melatonin) medications.
20. Use of any investigational drug within 30 days or 5 half-lives, whichever is longer, before screening.
21. Planned surgery (inpatient or outpatient) during the study period.
22. Is an employee or family member of the investigator or study center personnel.

4.2 Withdrawal of Subjects From the Study

The duration of the study is defined for each subject as the date signed written informed consent is provided through the follow-up safety phone call within 7 days after the last dose of study drug.

4.2.1 Reasons for Withdrawal/Discontinuation

Subjects may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study center. Every effort should be made to keep subjects in the study. The reasons for subjects not completing the study will be recorded. A subject may be withdrawn from the study for any of the following reasons:

1. Failure to continue to meet the protocol inclusion or exclusion criteria.
2. Noncompliance with the protocol or uncooperativeness.
3. In the investigator’s opinion, continuation in the study would be detrimental to the subject’s well-being.

4. Symptoms or an intercurrent illness not consistent with the protocol requirements or that justifies withdrawal.
5. Subject is lost to follow-up.
6. Other (e.g., pregnancy, development of contraindications of use of study drug).
7. The subject withdraws consent or the investigator or sponsor decides to discontinue the subject's participation in the study.

The investigator will also withdraw a subject if Sequential Medicine, Ltd terminates the study. Upon occurrence of a serious or intolerable AE, the investigator will confer with the medical monitor. If a subject is discontinued because of an AE, the event will be followed until it is resolved. Any subject may withdraw his or her consent at any time.

4.2.2 Handling of Withdrawals

Subjects are free to withdraw from the study or from receiving study drug at any time upon request. Subject participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

Subjects who discontinue study drug or active participation in the study will no longer receive study drug. When a subject withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the electronic case report form (eCRF).

Whenever possible, all subjects who discontinue study drug or withdraw from the study prematurely will be contacted within 24 hours of the final dose of study drug for a follow-up safety phone call (Visit 6). The outcomes of any AEs will be discussed and recorded. If indicated, a visit to the study center for safety assessments will be scheduled. Nonserious AEs that are ongoing at the subject's last study visit or follow-up safety phone call must be followed until resolution or for 30 days after the subject's last study drug dose, whichever comes first.

Subjects who are unable to be reached for the follow-up safety phone call will continue to be contacted by the study center in an attempt to have them comply with the protocol (2 documented telephone calls followed by 1 registered letter).

It is vital to obtain follow-up data on any subject withdrawn because of an AE or serious AE (SAE). In every case, efforts must be made to undertake protocol-specified, safety follow-up procedures. All data collected from all subjects, including early withdrawals and early discontinuations of treatment, will be used in the reporting and analysis of the study.

4.2.3 Replacements

Subject who discontinue study drug or withdraw from the study prematurely will not be replaced.

5 Study Treatments

5.1 Method of Assigning Subjects to Treatment Groups

Subjects will be randomly assigned equally to 1 of 4 treatment sequences, as presented in Table 3-1.

The Pharmaceutical Product Development, LLC (PPD) biostatistics department will generate the randomization schedules and randomization will be performed manually. Subjects will be assigned kit numbers in sequential order within each site. Within each assigned kit, 4 bottles will be labeled with the study visit (Visit 2, 3, 4, and 5) at which the study drug inside the bottle is to be administered per the subject's randomization sequence. The randomization schedule will also use an appropriate block size, which will not be revealed. No stratification will be used in this study.

5.2 Treatments Administered

For each treatment period (Visits 2, 3, 4, and 5), 30 minutes before each subject's lights out time (5 hours ± 30 minutes before the subject's median habitual bedtime), a single dose of study drug will be administered according to the subject's treatment sequence randomization. All doses of study drug will be administered orally by study personnel with 250 mL of water. An oral cavity check will be performed to assure compliance with treatment.

5.3 Identity of Investigational Product

The SM-1 study drug contains 50-mg diphenhydramine, 5-mg delayed-release zolpidem, and 0.5-mg delayed-release lorazepam as active ingredients.

The 2-drug combination D+Z study drug contains 50-mg diphenhydramine and 5-mg delayed-release zolpidem as active ingredients.

The 2-drug combination D+L study drug contains 50-mg diphenhydramine and 0.5-mg delayed-release lorazepam as active ingredients.

The SM-1, D+Z, and D+L capsules are all Size 0 white capsules and contain the inactive excipients PROSOLV® SMCC HD 90, starch 1500, and magnesium stearate. Delayed-release coating materials include Eudragit L100-55, Eudragit L100, and Eudragit S100.

The placebo is identical in appearance to SM-1, D+Z, and D+L, and has the same excipients, but no diphenhydramine, zolpidem, lorazepam, or delayed-release coating materials.

5.4 Management of Clinical Supplies

5.4.1 Study Drug Packaging and Storage

Study drug for each individual subject will be supplied in a single kit of 4 bottles. Each bottle contains a single dose of SM-1, D+Z, D+L, or placebo. Bottles will be labeled for the visit at which the dose of study drug should be administered (e.g., Visit 2, 3, 4, or 5) according to the subject's randomization sequence. All packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

At the study center, study drug must be stored in a secure area (e.g., a double-locked cabinet), protected from moisture, and kept at a controlled room temperature 15°C to 25°C (59°F to 77°F).

Further details on study drug packaging, labelling, storage, and administration instructions are provided in the Pharmacy Manual.

5.4.2 Study Drug Accountability

The investigator will maintain accurate records of receipt of all test articles, including dates of receipt. In addition, accurate records will be kept regarding when and how much test article is dispensed and used by each subject in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled and retained or destroyed according to applicable regulations.

5.4.3 Other Supplies

Urine dipsticks for urine pregnancy testing and on-site drug screening, an alcohol breathalyzer, and a tape measure to complete part of the STOP-Bang questionnaire will be provided to study centers.

5.5 Blinding

The study will be performed in a double-blind manner, with the subjects, investigator, and study center staff being blinded to the identity of study drug. All study drug will be supplied in identical packaging and will be identical in color, smell, taste, and appearance to enable double-blind conditions.

5.5.1 Breaking the Blind

A subject's treatment assignment will not be broken until the end of the study unless medical treatment of the subject depends on knowing the study drug the subject received. In the event that the blind needs to be broken because of a medical emergency, the investigator/subinvestigator may instruct the unblinded study personnel to reveal an individual subject's treatment allocation. A sealed copy of each subject's randomization scheme will be retained at the study center and treatment assignment will be unblinded by an individual delegated the responsibility for unblinding treatment assignment. Before unblinding a subject's treatment assignment, the investigator/subinvestigator should make every effort to contact the medical monitor to discuss the medical emergency and the reason for revealing the actual treatment received by that subject. If a subject's treatment is unblinded, the sponsor must be notified immediately. Reasons for treatment unblinding must be clearly explained and justified in the subject's eCRF. The date on which the blind was broken together with the identity of the person responsible for breaking the blind must also be documented. Please refer to the supplemental instructions in the Unblinded Process Document.

5.6 Treatment Compliance

Doses of study drug will be administered by study personnel and an oral cavity check will be performed to assure compliance with treatment.

5.7 Prior and Concomitant Therapy

The use of concomitant medications during this study is discouraged, unless required to treat AEs. The use of other concomitant medications should be approved by the investigator and sponsor (or designee) before subjects enroll in the study.

Any prior therapy within the 30 days before screening or concomitant therapy taken by a subject during the course of the study will be documented, along with the reason for its use.

Use of all concomitant medications will be recorded in the subject's eCRF. Concomitant medications will include all prescription drugs, OTC medications, herbal products, vitamins, minerals, and nutritional supplements. The minimum requirement is that medication name and the dates of administration are to be recorded. Any changes in concomitant medications will also be recorded in the subject's eCRF.

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the eCRF.

5.7.1 Prohibited Medications and Therapies

For the duration of the study, starting with signature of the informed consent, consumption or use of the following medications and therapies is prohibited:

- Any medication which affects sleep-wake function. This includes prescription, OTC, and herbal (e.g., valerian root, melatonin) medications.
- Illicit drugs or drugs prescribed for any individual except the subject
- Marijuana, marijuana oil, or extracts of marijuana containing cannabinoids
- Any investigational drug

In general, subjects are prohibited from using any prescription or OTC medications or alternative medicinal products (e.g., homeopathic preparations and herbal or dietary supplements) that may affect the outcome of the study. Use of vitamins, acetaminophen, or hormonal contraceptives during the study is permitted.

5.7.2 Restrictions

A subject's consumption of alcohol during the study is not to exceed 14 units of alcohol per week: 1 unit of alcohol is equivalent to 12 ounces of beer, 4 ounces of wine or 1 ounce of liquor. Subjects are not to consume greater the 500 mg of caffeine per day. Subjects are not to smoke during their sleep period. Furthermore, subjects should not discontinue smoking or participate in a smoking cessation program within 30 days of screening, or plan to discontinue smoking during the study.

On check-in days for PSG recording (Day 1 of each treatment and PSG period), subjects will be instructed to maintain their normal daily activities and not do anything unusual or engage in excessively strenuous activity. Subjects will be advised to eat lunch before check-in due to the long fasting intervals required by the study schedule. Subjects are to refrain from the use of alcohol and from napping, defined as any sleep episode occurring outside of the subject's main sleep episode of the day. To the extent possible, subjects are to avoid consuming any caffeinated beverage or caffeinated food (e.g., chocolate) for 5 hours before administration of study drug. Study drug will be administered with 250 mL of water and no additional water will be allowed until completion of all post-PSG activities.

6 Study Assessments and Procedures

Before performing any study procedures, each potential subject will sign an informed consent form (ICF). Subjects will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the subject. The investigator will also sign the ICF.

6.1 Study Visits

The schedule of events by study visit for this study is presented in Table 6-1. The timing of study procedures upon check-in to the study center during Treatment Periods 1, 2, 3, and 4 is presented in Table 6-2. Detailed instructions for the conduct of study assessments and procedures will be described in the study manual.

Table 6-1 Schedule of Events

	Screening[a]	Treatment and Polysomnography Periods[b]				Follow-Up Safety Phone Call[b]
		Period 1	Period 2	Period 3	Period 4	
Study Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Study Day	Day –21 to Day–8	Day 1	Day 8	Day 15	Day 22	3-7 days postdose
Assessments						
Informed consent	X					
Demographics	X					
Medical/psychiatric/medication history	X					
Sleep history[c]	X					
Epworth Sleepiness Scale	X					
Brief physical examination[d]	X					
Vital sign measurements[e]	X	X	X	X	X	
Urine pregnancy test (females of childbearing potential)	X	X	X	X	X	
Urine drug screen	X					
Alcohol breath test	X	X	X	X	X	
Clinical laboratory assessments[f]	X					
Inclusion/exclusion criteria	X	X				
Paper sleep diary issued[g]	X	X	X	X		
Diary return and review		X	X	X	X	
Study center check-in for overnight visit[h]		X	X	X	X	
Adverse events	X	X	X	X	X	X[i]
Concomitant medications	X	X	X	X	X	
Randomization[j]		X				
Treatment administration		X	X	X	X	

	Screening[a]	Treatment and Polysomnography Periods[b]				Follow-Up Safety Phone Call[b]
		Period 1	Period 2	Period 3	Period 4	
Study Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Study Day	Day –21 to Day–8	Day 1	Day 8	Day 15	Day 22	3-7 days postdose
Assessments						
Polysomnography		X	X	X	X	
Post-Sleep Questionnaire		X	X	X	X	
Karolinska Sleepiness Scale		X	X	X	X	
Digit Symbol Substitution Test training	X					
Digit Symbol Substitution Test		X	X	X	X	
Predischarge evaluation[k]		X	X	X	X	

[a] Potential subjects will be evaluated during a screening period lasting at least 8 and no more than 21 days before the first day of the first treatment period.

[b] Example study days are shown for a 1-week washout interval. Washout intervals must be no less than 5 days. Actual study days for Treatment Periods 2, 3, and 4 and the follow-up safety phone call will depend on the length of interdose washout intervals.

[c] Sleep history will be assessed using the STOP-Bang questionnaire, which includes 4 subjective items (STOP: snoring, tiredness, observed apnea, and high blood pressure) and 4 demographics items (Bang: body mass index, age, neck circumference, and gender).

[d] A brief physical examination will include evaluation of height (meters); body weight (kg); appearance; skin; head and neck; eyes, ears, nose, and throat; chest and lungs; heart; abdomen; and extremities. Each subject's height and weight measured at screening will be used to calculate their body mass index.

[e] Vital sign measurements will include pulse, blood pressure, and respiration rate. All vital signs will be measured after the subject has been supine for 5 minutes. On polysomnography recording days, vital signs will be measured at check-in approximately 7 hours earlier than each subject's median habitual bedtime and again before discharge from the study center.

[f] Clinical laboratory assessments will include hematology, chemistry, electrolytes, liver function tests, and renal function parameters.

[g] Subjects are to record the time they go to bed with the intention of sleeping and the time they get up in a pretreatment paper diary for a minimum of 7 days during the screening period, with at least 5 entries completed over the 7 days (≥70% compliance). Information recorded in the diary will be communicated to study personnel no later than 24 hours before check-in at Visit 2 to allow the calculation of each subject's median habitual bedtime. Subjects will return their paper diary to study personnel at each visit during the treatment and PSG period. Upon discharge from the study center at Visits 2, 3, and 4, subjects will be dispensed a new daily washout interval diary to record the time they went bed with the intention of sleeping and the time they got up. Subjects will be instructed to maintain their normal sleep patterns.

[h] Before Visit 2, subjects will be contacted by study personnel and told the time and date to present for their first overnight visit. Table 6-2 describes the timing of study procedures upon check in to the study center. Upon discharge from the study center at Visits 2, 3, and 4, subjects will be told the time and date to return for the next overnight visit.

i Subjects will be contacted by phone for a safety follow-up within the 7 days after completion of Treatment Period 4 (Visit 5) but at least 72 hours after administration of the final dose of study drug. Subjects who discontinue study drug or withdraw from the study prematurely will be contacted within 24 hours of the final dose of study drug. Outcomes of any adverse events will be discussed and recorded. If indicated, a visit to the study center for safety assessments will be scheduled.

j Once eligibility has been reconfirmed at Visit 2, subjects will be randomly assigned to 1 of 4 treatment sequences. Subjects will be crossed-over to their next treatment at each visit based on their treatment sequence randomization.

[k] Before leaving the study center at Visits 2, 3, 4, and 5, subjects will undergo a brief discharge evaluation consisting of tandem gait and the Romberg test.

Table 6-2 Sleep Study Events by Day for Treatment Periods 1, 2, 3, and 4

Treatment Period Day	Time Relative to Habitual Bedtime	Time Relative to Lights Out/Waking	Procedure[a]
Day 1	Approximately 7 hours before	Approximately 120 minutes before lights out	• Subjects report to the study center • Alcohol breathalyzer administered • Urine pregnancy testing performed for females of childbearing potential • Return and review diary • Pretreatment assessment of adverse events • Update concomitant medications and therapies • Vital signs measured
	Approximately 6.5 hours before	Approximately 90 minutes before lights out	• Baseline Digit Symbol Substitution Test measurement obtained • Subjects provided a light, low-fat snack (e.g., fruit and crackers)
	Approximately 6 hours before	Approximately 60 minutes before lights out	• PSG electrodes applied to the subject and machine calibrated
	5.5 hours before	30 minutes before lights out	• Subjects administered dose of study drug • Oral cavity check performed administered
	Period 1: 5 hours ± 30 minutes before Period 2, 3, and 4: Same as Period 1 ± 15 minutes before	Lights out	• Subjects go to bed • PSG biocalibration • Begin PSG recording
Day 2	—	Waking (8 hours after lights out)	• End PSG recording • Subjects awakened and allowed a bathroom visit
	—	30 minutes after waking (8.5 hours after lights out)	• Subjects complete the morning assessments in the following order: 1. Post-Sleep Questionnaire 2. Karolinska Sleepiness Scale 3. Digit Symbol Substitution Test • Subjects served a standard breakfast • Before leaving the study center, subjects undergo a predischarge evaluation consisting of tandem gait and the Romberg test, as well as an assessment of vital signs and adverse events to determine whether they may be safely discharged from the study center. • Subjects who pass this evaluation will be discharged from the study center. Failure will be considered an adverse event, and subjects will remain at the study center until able to pass.

Abbreviation: PSG, polysomnography

[a] Procedures must be conducted in the order they appear in the bulleted list.

6.2 Screening Assessments

Screening assessments will include medical history and other information, sleep history, vital sign measurements, physical examination, ESS, drug and alcohol screen, laboratory assessments and urine pregnancy test for females of childbearing potential.

6.2.1 Medical History and Other Information

Medical history information will be collected at screening and should include (but not be limited to) demographic information, current and past medical conditions, current and past medications, and current and past psychiatric conditions. This information must be documented in the subject's study chart before random assignment of study drug and also recorded in on the appropriate eCRF pages. In addition to conventional medical and psychiatric history, information pertaining the subject's average alcohol and caffeine consumption and average tobacco usage should be recorded in the eCRF.

6.2.2 Sleep History

Subject sleep history will be assessed by the investigator at screening to confirm subject eligibility for the study. In addition, the STOP-Bang questionnaire will be completed for each subject (STOP-Bang, 2012). The questionnaire, a simple, self-reportable paper screening tool, consists of 8 dichotomous (yes/no) items related to the clinical features of obstructive sleep apnea (OSA). It includes 4 subjective items (STOP: snoring, tiredness, observed apnea, and high blood pressure) and 4 demographics items (Bang: BMI, age, neck circumference, and gender). The total score ranges from 0 to 8 and subjects can be classified for OSA risk based on their respective scores. Subjects with a STOP-Bang score of 0 to 2 can be classified as low risk for moderate to severe OSA whereas those with a score of 5 to 8 can be classified as high risk for moderate to severe OSA. In subjects whose STOP-Bang scores are in the midrange (3 or 4), further criteria are required for classification. An example of the STOP-Bang questionnaire is presented in Appendix 12.1.

6.2.3 Vital Sign Measurements

Vital sign measurements will include pulse, blood pressure, and respiration rate. All vital signs will be measured after the subject has been supine for 5 minutes.

6.2.4 Physical Examination

A brief physical examination will be performed at screening and should include evaluation of height (meters); body weight (kg); appearance; skin; head and neck; eyes, ears, nose, and throat; chest and lungs; heart; abdomen; and extremities. All physical examination findings must be documented in the subject's study chart and also recorded in the eCRF.

The subject's height and weight measured at screening will be used to calculate BMI used for the STOP-Bang questionnaire and to ensure that the subject meets the BMI entry criterion.

6.2.5 Epworth Sleepiness Scale

The ESS, completed by each subject at the screening visit, is a self-administered paper questionnaire consisting of 8 questions (Johns, 1990; Johns, 1991; Johns, 1992; Johns, 2000). It provides a measure of a person's general level of daytime sleepiness, or their average sleep propensity in daily life. Subjects rate, on a 4-point scale (0 – 3), their usual chances of dozing off or falling asleep in 8 different situations or activities that most people engage in as part of their daily lives. The total ESS score is the sum of 8 item scores and can range between 0 and 24. The higher the score, the higher the person's level of daytime sleepiness. Eligible subjects must have an ESS score ≤8 at screening. An example of the ESS is presented in Appendix 12.2.

6.2.6 Drug and Alcohol Screen

Each subject's urine will be screened on-site by dipstick. In addition, the subject will undergo an alcohol breath test. Any subject who tests positive for any drug or alcohol at screening will be excluded from participating in the study.

6.2.7 Laboratory Assessments

Clinical laboratory assessments performed on samples of blood collected at screening will include hematology, chemistry, electrolytes, liver function tests, and renal function parameters.

6.2.8 Urine Pregnancy Test

A urine pregnancy test will be performed at screening for female subjects who are of childbearing potential. If the urine pregnancy test at screening is positive, the subject will not be eligible to participate in the study.

6.2.9 Pretreatment Sleep Diary

At the screening visit, subjects who satisfy all eligibility criteria will be issued a pretreatment paper diary and instructed to record the time they went bed with the intention of sleeping and the time they got up for a minimum of 7 days during the screening period, with at least 5 entries completed over the 7 days (≥70% compliance). Information recorded in the diary will be communicated to study personnel no later than 24 hours before check-in for Visit 2 to allow the calculation of each subject's median habitual bedtime.

6.3 Efficacy Assessments

Polysomnography data will be the primary source for efficacy endpoints, including TST, WASO, latency to persistent sleep (LPS), number of awakenings (NAW), and TST by quarter of the night. Subject-reported efficacy measures will be assessed from data collected from the PSQ, which includes subject self-reporting of time to sleep onset, NAW, wake time during the night, TST, and sleep quality. The PSQ data will be used to determine subjective TST (sTST) and subjective sleep onset latency (sSOL). Subjects will also be required to complete a daily diary during each interdose washout interval.

6.3.1 Polysomnography

Each night of PSG for each treatment period (Visits 2, 3, 4, and 5) will consist of an 8-hour (960 30-second epochs) assessment during which electroencephalographic, electrooculographic, electrocardiographic, and submental electromyographic activity will be recorded according to methods consistent with the standards of the American Academy of Sleep Medicine.

Polysomnography recordings will begin at bed time (lights out) 5 hours ± 30 minutes before the subject's median habitual bedtime calculated from each subject's diary data at screening. Approximately 60 minutes before lights out, PSG electrodes will be applied to the subject and the machine will be calibrated. At the assigned lights out time, PSG biocalibration will

be performed. Once the PSG recordings begin, they will continue for 8 hours. Subjects will be required to remain in bed for the duration of the PSG recording period, except for interruptions to use the bathroom.

All PSG recordings will be scored blind by a central site:

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New York, NY 10019 USA

Polysomnography recordings will provide all the data for the efficacy measures previously listed as well as the percentage and number of minutes of sleep stages NI, N2, N3, rapid eye movement (REM), and latency to REM sleep onset that will be used to assess sleep stage distribution for other analyses.

6.3.2 Post-Sleep Questionnaire

The PSQ includes subject self-reporting of time to sleep onset, NAW, wake time during the night, TST, and sleep quality. An example of the questions included in the PSQ is presented in Appendix 12.3.

6.3.3 Washout Interval Sleep Diary

Subjects will return their paper diary to study personnel at each visit during the treatment and PSG period. Upon discharge from the study center at Visits 2, 3, and 4, subjects will be dispensed a new daily washout interval diary to record the time they went bed with the intention of sleeping and the time they got up. Subjects will be instructed to maintain their normal sleep patterns. Washout intervals must be no less than 5 days.

6.4 Safety Assessments

Safety and tolerability will be assessed in terms of the incidence, severity and relationship to treatment of AEs, and by morning measures of alertness (KSS and DSST). In addition, safety assessments will include alcohol screening, urine pregnancy testing for women of childbearing potential, vital sign measurements, and predischarge evaluations.

6.4.1 Adverse Events

6.4.1.1 Definitions of Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

An AE is defined as any untoward medical occurrence in a subject enrolled into this study regardless of its causal relationship to study drug.

A treatment-emergent AE is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

An SAE is defined as any event that results in death, is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

6.4.1.2 Eliciting and Documenting Adverse Events

Adverse events will be assessed starting from the time the subject provides signed written informed consent and must be followed until resolution or for 30 days after the subject's last study drug dose, whichever comes first.

At every study visit, subjects will be asked a nonleading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (e.g., prescription and OTC medications, nutritional supplements, herbal remedies).

6.4.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes drug treatment, dose, event term, time of onset, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, any required treatment or evaluations, and outcome. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not change should not be reported as an AE; however, if it changes in severity, frequency, or intensity at any time during the study, it should be recorded as an AE.

Any AE that meets SAE criteria (Section 6.4.1.1) must be entered into the electronic data capture (EDC) system immediately (i.e., within 1 business day) after the study center personnel first learn about the event. Once the qualifying SAE data are entered, PPD Pharmacovigilance will be notified by an email alert, which will contain high-level safety information. Additional safety information will be obtained from the EDC system via applicable eCRF pages. If the EDC system is not available, the study center should send a completed manual paper SAE report form to PPD Pharmacovigilance by fax:

- **Safety Fax Line: 1-888-488-9697**

When the EDC system is again available, the study center must enter all applicable information into the EDC system. All supporting source information concerning the SAE (e.g., hospital records) should be provided by fax or email.

If there is a question concerning an SAE, the study center needs guidance regarding reporting of an SAE, the study center is returning a call from a PPD safety specialist, or the study center urgently needs to report an SAE or make PPD Pharmacovigilance aware of an SAE, the Safety Hotline should be used:

- **Safety Hotline: 1-888-483-7729**

If a study center makes an initial report of an SAE via the Safety Hotline, the study center must subsequently enter all applicable information into the EDC system immediately thereafter.

All SAEs must be reported starting from the time that signed written informed consent for study participation is provided. If the investigator becomes aware of an SAE within 30 days after the subject's last dose of study drug, the SAE must be reported. Serious AEs must be followed until the event resolves, the event or sequelae stabilize, or it is unlikely that additional information can be obtained after demonstration of due diligence with follow-up efforts (i.e., the subject or health care practitioner is unable to provide additional information, or the subject is lost to follow up). Serious AEs that occur more than 30 days after the last dose of study drug need not be reported unless the investigator considers them related to study drug.

6.4.1.4 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the subject's daily activities. The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

Mild:	These events require minimal or no treatment and do not interfere with the subject's daily activities.
Moderate:	These events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with normal functioning.
Severe:	These events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.4.1.5 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the

study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the study drug in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated: This relationship suggests that there is no association between the study drug and the reported event.

Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE, i.e., the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug, but could also have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely. The event disappears or decreases on cessation or reduction of the dose of study drug.

Definite: This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study drug is re-administered.

6.4.1.6 Follow-Up of Subjects Reporting Adverse Events

Adverse events assessed as nonserious will be reported through the 7 days following the subject's last dose of study drug (the follow-up safety phone call) or until the last study visit, whichever is later. Outcomes of any ongoing AEs will be discussed and recorded during the follow-up safety phone call and, if indicated, a visit to the study center for safety assessments will be scheduled. Nonserious AEs that are ongoing at the subject's last study visit or follow-up safety phone call must be followed until resolution or for 30 days after the subject's last study drug dose, whichever comes first.

6.4.2 Alcohol Screen

Upon check-in to the study center at Visits 2, 3, 4, and 5, subjects subject will undergo an alcohol breath test. Any subject who tests positive for alcohol will not be administered study drug.

6.4.3 Urine Pregnancy Test

Upon check-in to the study center at Visits 2, 3, 4, and 5, a urine pregnancy test will be performed for female subjects who are of childbearing potential. If a urine pregnancy test performed after assignment of study drug is positive, it should be confirmed by a serum pregnancy test. If a female subject is pregnant, she must be discontinued from the study.

6.4.4 Karolinska Sleepiness Scale

The KSS, completed on paper by each subject after waking at Visits 2 through 5, is a self-report instrument on which subjects rate their sleepiness on a 9-point, verbally anchored scale (Akerstedt T and Gillberg M 1990; Akerstedt T et al 2014). Categories and scores range from “extremely alert” (score = 1), “alert” (score = 3), “neither alert nor sleepy” (score = 5), “sleepy-but no difficulty remaining awake” (score = 7), and “extremely sleepy/fighting sleep” (score = 9). The steps in between have a scale value but no verbal label. An example of the KSS is presented in Appendix 12.4.

6.4.5 Digit Symbol Substitution Test

The DSST is a measure of attention, perceptual speed, motor speed, visual scanning, and memory. The DSST consists of 9 digit-symbol pairs, followed by a list (rows) of digits. Under each digit is an open field where the subject is asked to write down on paper the corresponding symbol as quickly as possible. The key outcome parameter for the DSST is the number of correct responses in 90 seconds. An example of the DSST is presented in Appendix 12.5.

During the screening visit, subjects will be trained on how to complete the DSST until they are considered proficient. Subjects will then complete the DSST approximately 90 minutes before lights out in each treatment period (Visits 2, 3, 4, and 5) to provide a baseline assessment. The DSST will be repeated approximately 30 minutes after waking in each treatment period.

6.4.6 Vital Sign Measurements

Vital signs will be measured at check-in and before discharge from the study center at Visits 2, 3, 4, and 5. Details of the vital sign measurements are presented in Section 6.2.3.

6.4.7 Predischarge Evaluation

Before leaving the study center at Visits 2, 3, 4, and 5, subjects will undergo a predischarge evaluation consisting of tandem gait and the Romberg test to assess whether they may be safely discharged from the study center. Subjects who pass this evaluation will be discharged from the study center. Failure will be considered an AE, and subjects will remain at the study center until they are able to pass.

6.5 Pregnancy

Pregnancy is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported to PPD Pharmacovigilance within 2 weeks of learning of its occurrence, using the EDC system (Section 6.4.1.3). The pregnancy must be followed-up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the subject was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study, and considered by the investigator as possibly related to the study drug, must be promptly reported to PPD.

6.6 Laboratory Analyses

Clinically significant safety assessments and laboratory analyses that are associated with the underlying condition, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

Laboratory analyses are reportable as AEs or SAEs if they are actionable, but not solely based on an abnormal result.

6.7 Sample Collections

Instructions for sample collection, handling, and shipping will be presented in a separate study manual that will be provided to study center as a separate document.

7 Statistical and Analytical Plan

All personnel involved with the analysis of the study will remain blinded until database lock. A comprehensive statistical analysis plan will be prepared before unblinding. Any subsequent amendments will be documented, with final amendments completed before unblinding of the data.

7.1 Primary Efficacy Endpoints

The primary efficacy endpoint for this study is TST on an 8-hour PSG comparing SM-1 versus placebo, SM-1 versus D+Z, and SM-1 versus D+L.

7.2 Secondary Efficacy Endpoints

The comparison of SM-1 versus placebo, SM-1 versus D+Z, and SM-1 versus D+L for data collected from PSG recordings and PSQ responses will be performed on WASO, LPS, NAW, sTST, sSOL, and TST by quarters of the night. The comparison of D+Z versus placebo and D+L versus placebo for data collected from PSG recordings and PSQ responses will be performed on TST, WASO, LPS, NAW, sTST, sSOL, and TST by quarters of the night.

7.3 Safety and Other Endpoints

Safety endpoints include:

- Incidence, severity, and relationship to treatment of AEs
- Karolinska Sleepiness Scale
- Digit Symbol Substitution Test

Other endpoints include percentage and number of minutes of sleep stages NI, N2, N3, and REM, and latency to REM sleep onset.

7.4 Sample Size Calculations

Sample size is estimated based on the following assumptions:

1. The difference in TST between SM-1 and placebo is 120 minutes,

2. The difference in TST between SM-1 and each of the two 2-drug combination products is 44 minutes,

3. The standard deviation of TST (defined as the square root of the within mean square error from a repeated measures analysis of variance [ANOVA]) is 88 minutes.

A minimum of 68 blinded subjects will be able to ensure 80% power to detect treatment difference between SM-1 and all 3 controls (D+Z, D+L, and placebo) at a 2-sided 0.05 significance level. Approximately 84 subjects will be randomly assigned to receive study drug.

A blinded interim analysis will be performed after approximately 50% of blinded subjects have completed the study to allow for an option to increase the sample size (see Section 7.7.5).

7.5 Analysis Sets

The following analysis sets will be used in the statistical analyses:

Full analysis set (FAS): The FAS will consist of all subjects who were randomly assigned to receive double-blind study drug and have taken any study drug during the prescribed treatment period. All analyses using the FAS will group subjects according to randomized treatment.

Modified FAS (mFAS): The mFAS will consist of all subjects included in the FAS, grouped according to randomized treatment. The mFAS will exclude any subjects from the FAS that may have become unblinded during the study.

Per-protocol set (PPS): The PPS will consist of all FAS subjects who fulfill all eligibility criteria, have taken all 4 doses of study drug, have not taken any prohibited medication, and have no significant protocol deviations. All analyses using the PPS will group subjects according to actual treatment received.

Safety set: The safety set will consist of all subjects who received any study drug. All analyses using the safety set will group subjects according to actual treatment received.

The mFAS will be used for the primary efficacy analyses. The FAS and PPS will be used for sensitivity analyses of the primary efficacy endpoint. The mFAS and FAS will be used for the secondary efficacy analyses and other analyses. The safety set will be used for the safety analyses.

7.6 Description of Subgroups to be Analyzed

Subgroup analysis of the primary efficacy endpoint will be performed by sex (male vs female) and age (greater than median vs less than median).

7.7 Statistical Analysis Methodology

Statistical analysis will be performed using SAS software Version 9.2 or later. Continuous variables will be summarized using the mean, SD, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Data will be provided in by-subject data listings.

Details of the statistical analyses, methods, and data conventions are described in the statistical analysis plan.

All statistical tests will be 2-sided and performed using a 5% significance level, leading to 95% 2-sided CIs. The overall study wide type I error rate (alpha) will be 0.05.

7.7.1 Analysis of Primary Efficacy Endpoint

The analysis of the primary efficacy endpoint will be conducted using an ANOVA method with the TST as the response variable and treatment, sequence, center, and period as the fixed effects. The primary comparison will be SM-1 with placebo, followed by SM-1 with D+Z and SM-1 with D+L.

Analyses will be performed to evaluate effect of sex and age on TST using the same ANOVA model with addition of sex and age (greater than median vs less than median) as fixed factors.

7.7.2 Analysis of Secondary Efficacy Endpoint

The data collected from PSG recordings and PSQ responses will be used for the comparisons of SM-1 versus placebo on WASO, LPS, NAW, sTST sSOL, and TST by quarters of the

night; SM-1 versus both D+Z and D+L on WASO, LPS, NAW, sTST, sSOL, and TST by quarters of the night; and both D+Z and D+L versus placebo on TST, WASO, LPS, NAW, sTST, sSOL, and TST by quarters of the night. These analyses will be performed using the same ANOVA model as for the primary efficacy endpoint. Endpoints that are not normally distributed will be log-transformed first.

7.7.3 Safety Analyses

Adverse events will be summarized by using count summaries. Adverse events will be listed for each subject and summarized by system organ class and preferred term assigned to the event by MedDRA.

The KSS and DSST data will be analyzed using the same statistical methods used for the primary efficacy endpoint analysis.

Vital sign measurements will be summarized and listed. Physical examination findings, alcohol breath test results, and urine pregnancy test results will be provided in by-subject data listings.

7.7.4 Other Analyses

Sleep stage will be summarized by the duration (in minutes) and percentage of each sleep stage. The latency to REM will be summarized. The duration and percentage of each sleep stage (NI, N2, N3) and the latency to REM will be analyzed using the same statistical methods as for the primary endpoint analysis.

Disposition, demographics, medical history, sleep history, and concomitant medications will be summarized and listed.

7.7.5 Interim Analyses

To address the uncertainty about the estimate of the SD of the primary efficacy endpoint, the pooled SD will be monitored by a blinded interim analysis performed after approximately 50% of blinded subjects have completed the study to allow for an option to increase the sample size to preserve power if the observed SD is different than was estimated for the a priori sample size calculation.

7.8 Data Quality Assurance

Standard operating procedures are available for all activities relevant to the quality of this study. Designated personnel will be responsible for implementing and maintaining quality assurance and quality control systems to ensure that the study is conducted and that data are generated, documented, and reported in compliance with the study protocol, Good Clinical Practice (GCP), and Good Laboratory Practice requirements as well as applicable regulatory requirements and local laws, rules, and regulations relating to the conduct of the clinical study.

An authorized quality assurance auditor will audit the study data and procedures at periodic intervals as indicated. Regulatory authorities, the institutional review board (IRB), and a sponsor-authorized auditor may request access to all study documentation for an on-site inspection or audit. The investigator must notify Sequential Medicine, Ltd of any regulatory authority inspections and forward copies of the inspection report to Sequential Medicine, Ltd.

Electronic data systems will be designed and used in accordance with applicable aspects of 21 Code of Federal Regulations (CFR) Part 11, International Council for Harmonisation (ICH) Guidelines, GCP, local laws and legislation, and the Health Insurance Portability and Accountability Act.

7.8.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports, questionnaire results, or paper diaries.

Electronic CRFs will be supplied by PPD for recording of all study data as specified by this protocol. Study center personnel will enter subject data into Medidata Rave (the eCRF program). The analysis data sets will be a combination of these data and data from other sources (e.g., data from laboratory reports).

Clinical data management will be performed in accordance with applicable standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and

inconsistencies in the data. Adverse events will be coded using MedDRA and concomitant medication terms will be coded using the World Health Organization Drug Dictionary.

After database lock, each study center will receive a CDROM containing all their site-specific eCRF data as entered into Medidata Rave for the study, including full discrepancy and audit history. Additionally, a CDROM copy of all the study center's data from the study will be created and sent to the sponsor for storage. PPD will maintain a duplicate CDROM copy for their records. In all cases, subject initials will not be collected or transmitted to the sponsor.

8 Ethics

8.1 Independent Ethics Committee or Institutional Review Board

Federal regulations and the ICH guidelines require that approval be obtained from an IRB before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with ICH harmonised tripartite guideline E6(R2): Good Clinical Practice will be maintained by the study center and will be available for review by the sponsor or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB. The investigator must promptly supply the sponsor or its designee, the IRB, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

8.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

8.3 Subject Information and Consent

A signed written informed consent in compliance with US Title 21 CFR Part 50 shall be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. An informed consent template may be provided by the sponsor to study centers. If any institution-specific modifications to study-related procedures are proposed or made by the study center, the consent should be reviewed by the sponsor or its designee or both before IRB submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB for review and approval before the

start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing the ICF.

The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the subject.

9 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

9.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject, except as necessary for monitoring and auditing by the sponsor, its designee, the US Food and Drug Administration (FDA), or the IRB.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor PPD is financially responsible for further treatment of the subject's disease.

9.3 Investigator Documentation

Before beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB approval
- Original investigator-signed investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae (CV) for the investigator and each subinvestigator listed on Form FDA 1572
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject, and
- Laboratory certifications and normal ranges for any local laboratories used by the study center, in accordance with 42 CFR 493

9.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical registers before enrollment of subjects begins.

9.5 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

9.6 Adverse Events and Study Report Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the time line and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study center IRB as appropriate.

9.7 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

9.8 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

9.9 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

10Study Management

10.1 Monitoring

10.1.1 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study center at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

10.1.2 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (e.g., FDA) access to all study records.

The investigator should promptly notify the sponsor and PPD of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

10.2 Management of Protocol Amendments and Deviations

10.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator’s IRB for approval before subjects can be enrolled into an amended protocol.

10.2.2 Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study subjects without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the subject or investigator that results in a significant, additional risk to the subject. Significant deviations can include nonadherence to inclusion or exclusion criteria, enrollment of the subject without prior sponsor approval, or nonadherence to FDA regulations or ICH GCP guidelines, and will lead to the subject being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB should be notified of all protocol deviations in a timely manner.

10.3 Study Termination

Although Sequential Medicine, Ltd has every intention of completing the study, Sequential Medicine, Ltd reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last subject completes the last visit (includes the follow-up safety phone call).

10.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the clinical study

reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, the sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate. The study results will be posted on publicly available clinical trial registers.

11Reference List

Akerstedt T and Gillberg M. Subjective and objective sleepiness in the active individual. Int J Neurosci. 1990;52(1-2):29-37.

Akerstedt T, Anund A, Axelsson J, et al. Subjective sleepiness is a sensitive indicator of insufficient sleep and impaired waking function. J Sleep Res. 2014;23(3):240-52.

Johns MW. Epworth Sleepiness Scale (ESS) [Internet]. Lyon, France: Mapi Research Trust; 1990. [updated 1997; cited 30 November 2017]. Available from: https://eprovide.mapi-trust.org/instruments/epworth-sleepiness-scale.

Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540-5.

Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. Sleep. 1992;15(4):376-81.

Johns MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the Epworth sleepiness scale: failure of the MSLT as a gold standard. J Sleep Res. 2000;9(1):5-11.

The official STOP-Bang website [Internet]. Toronto, Canada: Toronto Western Hospital, University Health Network, University of Toronto; 2012. STOP-Bang Questionnaire; 2012 [cited 30 November 2017]; [about 2 screens]. Available from: http://www.stopbang.ca/osa/screening.php.

12Appendices

12.1 Appendix 1: STOP-Bang Questionnaire

Yes ○ No ○	**S**noring? Do you **Snore Loudly** (loud enough to be heard through closed doors or your bed-partner elbows you for snoring at night)?
Yes ○ No ○	**T**ired? Do you often feel **Tired, Fatigued, or Sleepy** during the daytime (such as falling asleep during driving)?
Yes ○ No ○	**O**bserved? Has anyone **Observed** you **Stop Breathing** or **Choking/Gasping** during your sleep?
Yes ○ No ○	**P**ressure? Do you have or are being treated for **High Blood Pressure**?
Yes ○ No ○	**B**ody Mass Index more than 35 kg/m^2?
Yes ○ No ○	**A**ge older than 50 year old?
Yes ○ No ○	**N**eck size large? (Measured around Adams apple) For male, is your shirt collar 17 inches/43 cm or larger? For female, is your shirt collar 16 inches/41 cm or larger?
Yes ○ No ○	**G**ender = Male?

Modified from Chung F et al. Anesthesiology 2008; 108:812-21, Chung F et al Br J Anaesth 2012; 108:768–75, Chung F et al J Clin Sleep Med Sept 2014
"With permission from University Health Network, www.stopbang.ca"

12.2 Appendix 2: Epworth Sleepiness Scale

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (yrs): _____ Your gender (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired?

This refers to your usual way of life recently.

Even if you haven't done some of these things recently, try to figure out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = **no chance** of dozing
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each item as best as you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	___
Watching TV	___
Sitting inactive in a public place (e.g., a theater 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 or bus, while stopped for a few minutes in traffic	___

THANK YOU FOR YOUR COOPERATION

12.3 Appendix 3: Post-Sleep Questionnaire

Post-Sleep Questionnaire (PSQ)

How long did it take you to fall asleep?

How many times did you wake up during the night?

How much time in total did you spend awake during those times?

How much time in total did you sleep last night?

How would you describe the quality of your sleep last night?

1=Poor
2=Fair
3=Good
4=Excellent

12.4 Appendix 4: Karolinska Sleepiness Scale

KAROLINSKA SLEEPINESS SCALE

Time □□:□□
(24-hour clock)

Please, indicate your sleepiness during the 5 minutes before this rating by putting an "X" by the appropriate description

- □ 1= extremely alert
- □ 2=
- □ 3= alert
- □ 4=
- □ 5= neither alert nor sleepy
- □ 6=
- □ 7= sleepy- but no difficulty remaining awake
- □ 8=
- □ 9= extremely sleepy/fighting sleep

If used electronically, please make sure that the wording of the scale is presented at each rating for easy reference

References

Original study: Åkerstedt, T. and Gillberg, M. Subjective and objective sleepiness in the active individual. ***International Journal of Neuroscience***, 1990, 52: 29-37.

Recent review: Akerstedt, T., Anund, A., Axelsson, J. and Kecklund, G. Subjective sleepiness is a sensitive indicator of insufficient sleep and impaired waking function. ***Journal of Sleep Research***, 2014, 23: 240-52.

12.5 Appendix 5: Digit Symbol Substitution Test

INSTRUCTIONS FOR DIGIT SYMBOL SUBSTITUTION TEST (DSST)

ADMINISTRATION:

Please fill in patient's identification, baseline, allocation number, and date and time.

A smooth drawing surface must be provided. If the table has a rough surface, the Digit Symbol work-sheet should be placed over a piece of cardboard.

Hand the subject a pencil without an eraser. (Have a spare pencil ready, in case the subject breaks one during the test.) Place the worksheet in front of the subject, point to the Key above the test items, and say *(italics)*:

Notice that each symbol in this key (motion across key at top of page) ***has a number that goes with it. In the blank spaces below each number, write the symbol that goes with the number. Complete the practice items up to the dark line, then stop.***

If the subject makes an error on a practice item, correct the error immediately and review the use of the Key. Continue to help (if necessary) until the ten practice items have been filled in correctly. Do not proceed with the test until the subject clearly understands the task.

During the practice exercise, look to see if a left-handed subject blocks or partially blocks the Key when filling in the marks. If this occurs, fold a separate DSST worksheet in half, exposing the Key, and place it next to the subject's worksheet on the subject's right-hand side so that the Key is aligned with the one blocked by the subject's hand. Have the subject use the separate Key to complete the practice items and to take the actual test.

After the practice items are completed, the subject is given 90 seconds to complete as many items as possible. Verbal instructions are as follows *(italics)*:

Now you will be given 90 seconds to see how many of these you can complete. Remember to not skip any spaces and work from left to right (motion with pencil or finger across the form).

Ready...Begin!

If the subject omits an item or starts to do only one type (e.g. only '1's) say ***'Do them in order. Don't skip any'.***

Give no further assistance except (if necessary) to remind the subject to continue until instructed to stop, or to turn over the page

At the end of 90 seconds, say: ***"Stop."***

Timing must be precise on this test.

Sequential Protocol Number : SM-A-05	Subject Number _____	Subject initial: ___ ___ ___	☐ Practice ☐ Post dose	Study Day _____ Study Visit _____ Time ____ : ____

Digital Symbol Substitution Test (DSST) Worksheet

Test must be completed in 90 seconds

INSTRUCTIONS: Always work from left to right and do not skip any boxes!

1	2	3	4	5	6	7	8	9
–	⊥	⊃	∠	∪	○	∧	X	=

10 PRACTICE

2	1	3	7	2	4	8	1	5	4	2	1	3	2	1	4	2	3	5	2	3	1	4	6	3

1	5	4	2	7	6	3	5	7	2	8	5	4	6	3	7	2	8	1	9	5	8	4	7	3

6	2	5	1	9	2	8	3	7	4	6	5	9	4	8	3	7	2	6	1	5	4	6	3	7

9	2	8	1	7	9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6

1	8	2	6	3	9	5	4	3	6	9	1	7	4	5	8	3	1	9	4	1	7	3	4	5

2	8	3	7	9	1	2	8	5	4	6	5	8	1	4	7	6	3	1	7	9	3	4	2	5

3	8	7	5	6	4	2	6	8	4	1	9	7	3	4	5	2	3	4	6	7	1	3	9	4

TOTAL CORRECT: ☐ ***(Maximum Score: 165 points)***

TOTAL INCORRECT: ☐