Official Protocol Title:	A Phase III Randomized, Placebo-Controlled Clinical Trial to Study the Safety and Efficacy of Suvorexant (MK-4305) for the Treatment of Insomnia in Subjects with Alzheimer's Disease
NCT number:	NCT02750306
Document Date:	02-Jun-2017

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TITLE:

A Phase III Randomized, Placebo-Controlled Clinical Trial to Study the Safety and Efficacy of Suvorexant (MK-4305) for the Treatment of Insomnia in Subjects with Alzheimer's Disease

IND NUMBER: US 101,874
EudraCT NUMBER: 2015-003154-40

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
Multiple, including 1.0, 5.1.2, 5.1.3, 5.4, 5.5, and others as detailed below.	Multiple, including Trial Summary, Subject Inclusion Criteria, Subject Exclusion Criteria, Stratification, Concomitant Medications Allowed, and others as detailed below.	Multiple changes detailed in table below.	To facilitate recruitment and modify barriers to enrollment via modifying Exclusion Criterion #33, increased flexibility for trial partners, site logistics, and generalizability of the population to reflect older adults with insomnia and Alzheimer's disease.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
1.0	Trial Summary	Expected trial duration increased to 24 months.	Recruitment is taking longer than originally anticipated.
2.1	Trial Design	Added sentence describing circumstances for increasing suvorexant dose from 10 mg to 20 mg nightly.	Clarification to Section 2.1
4.2.2.2.	Starting Dose for This Trial	Added language on dose timing.	Clarification
5.1.2	Subject Inclusion Criteria, #4	Clarified language on insomnia diagnosis.	Clarification

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.1.2 and 7.1.5	Subject Inclusion Criteria, #10	Added bullet point and language regarding trial partner (TP) qualifications.	To exclude TPs with dementia, and to remove requirement for TPs to attend PSG visits.
5.1.3	Subject Exclusion Criteria, #1	Added language regarding subject living quarters.	To clarify that subjects residing in assisted living facilities may be eligible.
5.1.3	Subject Exclusion Criteria, #16	Added language that recently controlled or treated medical conditions may be considered for re-screening.	To allow trial re-screen for subjects who left for medical reasons and are stabilized, as appropriate.
5.1.3, 7.1.3.3.1, and 12.4	Subject Exclusion Criteria, #19, Laboratory Procedures/Assessments, Table 5, and Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types	Added language regarding Vitamin B12 and folic acid deficiency Clarified that subjects may be eligible once B12, folate, or thyroid abnormalities are treated. Methylmalonic acid and homocysteine tests added to "Other" column. Blood volumes added for supplemental laboratory tests (methylmalonic acid and homocysteine)	To allow for supplementary methylmalonic acid and homocysteine serum testing to identify subjects who have true B12 or folate deficiency rather than only low B12 or folate levels.
5.1.3	Subject Exclusion Criteria, #28	Added language on subject participation in other trials	Clarification that subjects participating in observational studies without an intervention may be eligible.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.1.3, 6.0, and 7.1.5.1.2	Subject Exclusion Criteria, #33 Trial Flow Chart, footnote dd, and Visit 2 Screening PSG and Visit 3 Baseline PSG	Age categories deleted, upper threshold for Apnea Hypopnea Index (AHI) score and number of periodic leg movements with arousal /hour (PLMA) increased to 30. Added language to allow subjects who screen failed due to exclusion criterion #33 to be re-screened if eligible based on the amended criteria.	AHI severity increases with age and AD severity. Increasing the AHI threshold will facilitate enrollment and evaluate the safety and efficacy of suvorexant in subjects with AHI of 26 to 30, which is a substantial proportion of subjects with AD and insomnia. Subgroup analysis based on AHI has been added to evaluate potential treatment effect for subjects with higher versus lower AHI values.
5.4	Stratification	Revised to state that approximately 30% of randomized subjects will be in the moderate AD stratum (MMSE score 12 to 20 at screening)	To allow some flexibility for moderate AD stratum.
5.5	Concomitant Medications Allowed	Table 3: revised to specify that quetiapine is allowed if used to treat neuropsychiatric behavior issues and not used to treat insomnia	To allow for the use of quetiapine to treat neuropsychiatric symptoms.
6.0	Trial Flow Chart, footnote e	Added language to note that screening visit window applies to several situations.	Clarification

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
6.0 and 7.1.5.2	Trial Flow Chart, footnote w, and Treatment Period – Visits 4 through 6	Time to collect PK samples expanded to 11 hour post-dose.	Assist with site logistics
6.0 and 7.1.5.2	Trial Flow Chart, footnote cc, and Treatment Period – Visits 4 through 6	Timing and location for V6 assessments specified	Clarification as provided in a Protocol Clarification Letter (PCL dated 4-August-2016)
7.1.1.5.1	Prior Medications	Changed following sentence as shown (new text underlined): "These earlier discussions will allow subjects to discuss discontinuation of prohibited medications with their primary care physician <u>once consented</u> ~~prior to Visit 2~~."	Clarification
7.1.1.8	Trial Compliance (Medication)	Clarifications to computation for medication compliance and the applicable period for assessing Events of Clinical Interest (ECI) of potential study medication misuse.	Clarification
7.1.2.2.10	Columbia Suicide Severity Rating Scale (C-SSRS)	Clarifications to instances of suicidal ideation or suicidal behavior that should be reported as Events of Clinical Interest (ECI).	Clarification to align with ECI guidance for events of suicidal ideation and behavior for the trial.
7.1.5.1.1	Visit 1 Screening	Added language regarding positive urine drug screen (UDS) at Visit 1.	Clarification

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
8.10	Subgroup Analyses	AHI categories added as a subgroup analysis	To evaluate the treatment effect, and possible differences, for the two AHI categories (<15, 15 to 30).
Global	Multiple sections	Global minor spelling, punctuation, grammar, style and wording changes	

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	Safety and Efficacy of suvorexant (MK-4305) for the treatment of insomnia in AD subjects
Trial Phase	Phase 3
Clinical Indication	Treatment of insomnia
Trial Type	Interventional
Type of control	Placebo
Route of administration	Oral
Trial Blinding	Double-blind
Treatment Groups	1) Placebo 2) Suvorexant 10 mg (dose may be increased to suvorexant 20 mg)
Number of trial subjects	Approximately 260 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 24 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial for approximately 9 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening/run-in period of approximately 3 weeks, each subject will receive assigned treatment for approximately 4 weeks. After the end of the 4-week treatment period, each subject will receive a follow-up phone contact at approximately 14 days post-treatment to assess for post-treatment adverse events (AEs).
Randomization Ratio	1:1

A list of abbreviations used in this document can be found in Appendix 12.5.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a randomized, placebo-controlled, parallel-group, multi-site, double-blind trial of suvorexant (MK-4305) for the treatment of insomnia in subjects with Alzheimer's disease (AD). This trial will be conducted in conformance with Good Clinical Practices.

The overall study is composed of a 3-week screening period (including a 2-week single-blind placebo run-in), a 4-week double-blind treatment period, and a 14-day post-treatment telephone contact (occurring after the subject's last dose of trial medication). In total, there

will be 6 clinic visits, 3 of which will be overnight polysomnography (PSG) visits (2 in the screening period and 1 at the end of the double-blind treatment period).

To qualify for randomization, subjects are required to meet diagnostic criteria for both AD and insomnia and have a qualified trial partner, in addition to other trial entry criteria. After the subject has been randomized to suvorexant 10 mg or matching placebo, subjects will take 1 tablet nightly. After 2 weeks of double-blind treatment, the subject's dose may be escalated from suvorexant 10 mg (or matching placebo) to suvorexant 20 mg (or matching placebo) if Clinical Global Impression - Severity, for Insomnia (CGI-S) $\geq$3 and acceptable subject tolerability based on investigator assessment.

An electronic diary (e-diary) to record sleep data (entered by the trial partner) and an activity/sleep watch (eg, watch-like device worn by the subject) will be used in this trial.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is depicted in Figure 1.

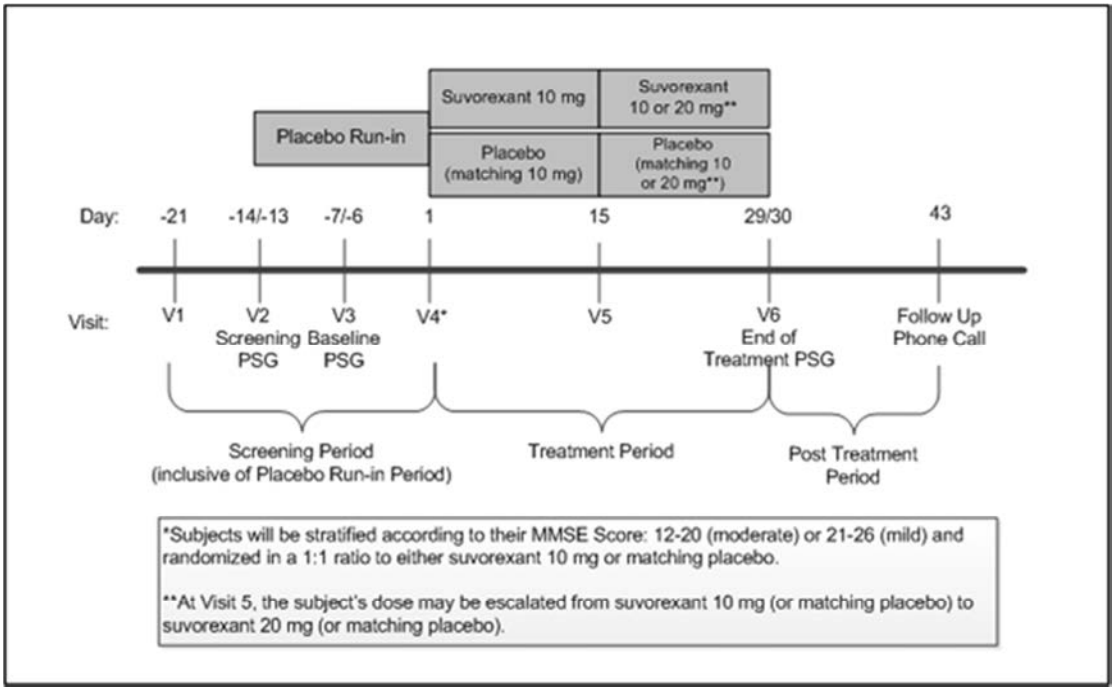


Figure 1 Trial Design Diagram

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

Objectives:

(1) To evaluate the efficacy of suvorexant compared with placebo in improving insomnia, as measured by change from baseline in PSG-derived total sleep time (TST), at Week 4.

(2) To evaluate the safety and tolerability of suvorexant for up to 4 weeks of treatment.

Hypothesis:

(1) Suvorexant is superior to placebo in improving insomnia as measured by change from baseline in PSG-derived TST, at Week 4.

3.2 Secondary Objective(s) & Hypothesis(es)

Objective:

(1) To evaluate the efficacy of suvorexant compared with placebo in improving insomnia as measured by change from baseline in PSG-derived wakefulness after persistent sleep onset (WASO), at Week 4.

Hypothesis:

(1) Suvorexant is superior to placebo in improving insomnia as measured by change from baseline in PSG-derived WASO, at Week 4.

3.3 Exploratory Objectives

Objectives:

(1) To evaluate other PSG parameters (eg, sleep efficiency [SE], latency to onset of persistent sleep [LPS]), and treatment response based on achieving a pre-specified clinically meaningful improvement in TST.

(2) To characterize sleep/wake activity using an activity/sleep watch.

(3) To evaluate the subject's sleep as reported by the trial partner and by subjective clinical assessment.

(4) To evaluate the subject's cognition and neuropsychiatric behavior.

(5) To evaluate the trial partner's sleep and levels of distress associated with the subject's sleep behaviors.

(6) To explore the relationship between Apolipoprotein E4 (APOE4) genotype status and AD diagnosis and their association with insomnia and/or clinical data collected in this study.

(7) To explore the relationship between genetic variation and response to the treatment(s) administered. Variation across the human genome will be analyzed for association with clinical data collected in this study.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB) and/or approved labeling for detailed background information on MK-4305.

4.1.1 Pharmaceutical and Therapeutic Background

Sleep disturbance and insomnia are common in AD, affecting up to 45% of individuals [1]. Patients and caregivers report symptoms attributable to nighttime sleep fragmentation and nighttime awakenings, early morning awakenings, increased time to fall asleep, decreased deep sleep, and increased daytime napping due to insufficient nighttime sleep [2]. Broader consequences of insomnia in AD span a wide range of potential morbidity, including physical disability, respiratory symptoms, hypertension, cardiac insufficiency, and decreased immune function [2]. Furthermore, insomnia can be associated with accentuation of depression and poor cognitive and psychological functioning [2]. Together, over time these physical and mental impairments can significantly impair capacity for daily self-care, leading to an increased need for and cost of healthcare. Additionally, nighttime awakenings and associated wandering can endanger AD patients and cause significant stress for family members and caregivers, often culminating in nursing home placement [2].

The underlying causes for insomnia in AD are not fully understood, but are likely heterogeneous in origin. In terms of neuroanatomical hypotheses, sleep disturbances in AD have been postulated to result from progressive deterioration and decrease in the number of neurons in the suprachiasmatic nucleus, with resultant fluctuations in neurohormones critical for the homeostatic maintenance of circadian rhythm [3]. Other findings suggest a role for neurodegenerative loss of hypothalamic hypocretin/orexin neurons, contributing to disturbed sleep-wake patterns [4]. Progression of AD itself may also cause dysregulation of the orexin system, leading to increased orexinergic output and promotion of inappropriate nighttime wakefulness in AD patients.

Important intersections between sleep, cognition, amyloid beta (Aβ), and orexin signaling exist. For instance, it is well established that sleep is essential for sleep-dependent learning and memory consolidation [5]. Sleep has been shown to promote increased Aβ clearance [6]. In a clinical study of cognitively intact, pre-symptomatic individuals deemed at-risk for AD, lower sleep quality was correlated with increasing amyloid deposition, as assessed by cerebrospinal fluid (CSF) Aβ42 levels, suggesting a potential linkage between sleep and

development of AD [7]. More recently, cognitive decline, tau and Aβ levels were shown to correlate with sleep disturbance and increased CSF orexin levels in AD patients, but not in age-matched cognitively intact controls [8]. These clinical findings are intriguing, particularly in light of a report that showed sleep-deprivation-related increases in Aβ levels and plaque formation in rodents were reduced by modulation of orexin signaling, using both genetic and pharmacological (via orexin receptor antagonist – [ORA]) approaches [9].

Options for effective pharmacological treatment of insomnia in AD are limited. Evidence for efficacy in randomized controlled trials of melatonin and the melatonin receptor agonist, ramelteon, has been inconsistent. For example, melatonin failed to achieve primary endpoints in 3 of 4 randomized controlled trials, as did ramelteon in its only trial in AD patients. Additionally, melatonin was observed to have a deleterious effect on mood in one of the studies [10],[11],[12],[13]. Second-generation antipsychotics have shown some improvement in insomnia, likely due to their sedating effects, but these medications are primarily used to target other neuropsychiatric and behavioral concerns associated with AD. Importantly, however, these agents also carry risk for significant adverse effects, including increased risk of metabolic abnormalities and sudden death [14]. Two sedating antidepressants, mirtazapine and trazodone, were also found to have inconsistent efficacy in 2 non-randomized studies [15],[16]. Furthermore, trazodone is associated with significant side effects, including daytime somnolence, orthostatic hypotension, dizziness, and priapism [17],[18],[19] and tolerance appears to develop in non-depressed subjects [20].

Potential for worsening of cognitive impairment is a concern encountered in treating sleep problems in AD subjects. In one study of medications commonly prescribed to AD subjects, it was found that the rate of deterioration was faster in those taking antipsychotic drugs and those taking sedatives than those not taking any of these drugs (OR 2.74 [95% CI 1.17, 6.41] and 2.77 [1.14, 6.73], respectively) [21]. Additionally, benzodiazepines and other sedatives, especially in combination with antipsychotic medications, have been observed to increase the rate of cognitive and functional decline in AD patients and falls in the elderly [22], [23]. The potential for next-day, negative cognitive effects in the elderly is cited in the zolpidem label. Collectively these data, along with the limited and inconsistent evidence of efficacy and safety in the randomized controlled trial setting, support that informed and effective treatment of insomnia in AD remains a significant challenge.

Suvorexant is a first-in-class ORA that enables sleep to occur via selective antagonism of the orexin receptors OX1R and OX2R. Suvorexant has previously been demonstrated to be efficacious and generally well-tolerated for the treatment of elderly and non-elderly adults with insomnia (references noted in Section 4.2.2). Suvorexant is currently approved and marketed for the treatment of insomnia in 2 countries: the United States and Japan. Via its novel ORA mechanism of action, suvorexant offers a potentially differentiating alternative treatment relative to currently available sleep agents. Moreover, its unique profile may overcome limitations of existing agents to address important unmet medical need in this growing patient population.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Transient and selective night-time antagonism of the orexin pathway may help stabilize and improve sleep-wake patterns in AD patients, by dampening orexin-mediated inappropriate wakefulness during the sleep cycle. Trials to evaluate sleep in Alzheimer's patients have typically focused on subjective endpoints. Although actigraphy has been used as a surrogate to provide objective sleep estimates, only a few appropriately powered polysomnography studies have been published to objectively characterize sleep in AD patients with insomnia. While the peer-reviewed literature characterizing insomnia in AD is growing, interpretation of this information is difficult given lack of uniformity in the diagnostic criteria used to identify patients across the various studies. In one published PSG trial of mild to moderate AD patients (N=35), the mean total sleep time at baseline was ~5 hours (298 minutes) indicating that global sleep deficits are substantial in this population [24].

In prior Phase 3 trials [25], suvorexant 20 mg (in non-elderly) and 15 mg (in elderly) improved total sleep time (TST) and sleep maintenance throughout the entire night (particularly during the 2nd and 3rd thirds of the night when wake-after-sleep-onset (WASO) is most prominent), with significant improvements compared to placebo in PSG-assessed TST of 44.8 minutes on Night 1 and 34.7 minutes at Month 1, as well as significant placebo-subtracted reductions in PSG-assessed WASO by 34.6 minutes on Night 1 and 25.4 minutes at Month 1 in the pooled efficacy data. Significant improvements versus placebo in TST of 48.4 minutes on Night 1 and 32.7 minutes at Month 1, as well as significant reductions versus placebo in WASO by 39.3 minutes on Night 1 and 26.9 minutes at Month 1 were observed in elderly subjects.

Given the demonstrated effectiveness of suvorexant, and the lack of available proven treatments for insomnia in AD, this study aims to examine the safety and efficacy of suvorexant to improve sleep in individuals with AD. The core treatment period in this parallel group, placebo-controlled study will assess suvorexant effects over a duration of 4 weeks, consistent with the primary 4 week efficacy assessment in the Phase 3 pivotal trials.

4.2.2 Rationale for Dose Selection/Regimen

The clinical safety and efficacy of the 10 and 20 mg doses of suvorexant for this study are supported by data from 4 Phase 2/3 insomnia studies: a Phase 2b insomnia trial evaluated suvorexant doses of 10 mg up to 80 mg [26]; two Phase 3 insomnia trials evaluated doses of 15 mg and 30 mg (in elderly) and 20 mg and 40 mg (in non-elderly) [25]; and a Phase 3 insomnia trial evaluated suvorexant 30 mg (in elderly) and 40 mg (in non-elderly) over one year [27]. Given overlapping PK and efficacy/safety profiles of the 15 mg and 20 mg doses in Phase 3, only the 20 mg dose will be included as an additional dose option in this study.

The dose titration regimen for the current study is consistent with the dosing and administration specified in the U.S. label. Subjects will initiate double-blind treatment with either 10 mg dose of suvorexant or placebo; then at Visit 5, the dose may be increased to

20 mg at the discretion of the investigator based on the subject's response to trial medication. The decision to increase the dose will based on insufficient efficacy (based on a Clinical Global Impressions of Insomnia Severity assessment [CGI-S]) and acceptable tolerability, as reported by the subject and/or trial partner. Additional guidance regarding the investigator's decision to dose escalate at Visit 5 is provided in Section 5.2.1.2.

4.2.2.1 Rationale for the Use of Placebo

Because insufficient Class I evidence exists to support the efficacy and safety of any available potential active comparator sleep medication for use in AD patients (see Section 4.1.1), this study will be placebo controlled. Placebo groups are commonly used in insomnia trials and are required for approval of insomnia medications. Similarities in drop-out rates observed across treatment groups in placebo-controlled trials in insomnia are supportive of the concept that subjects randomized to placebo in these trials are not exposed to harm, nor is the condition of insomnia sufficiently debilitating to require provision of rescue medication. In addition, given the subjective nature of several key clinical endpoints, inclusion of a placebo group in this trial will be important in demonstrating the safety, tolerability, and efficacy of suvorexant in AD patients. Inclusion of a placebo control group also provides an anchor between the new data collected in this study and the precedent observed in prior placebo-controlled insomnia clinical trials and will facilitate comparison of adverse event rates on suvorexant to rates on placebo.

4.2.2.2 Starting Dose for This Trial

The starting dose of suvorexant in this trial is 10 mg (1 tablet) per day, taken nightly.

4.2.2.3 Maximum Dose/Exposure for This Trial

Based on investigator assessment of the CGI-S score and subject tolerability at Visit 5 (see Section 5.2.1.2 for more details), the dose of suvorexant may be increased to a maximum dose of 20 mg per day, taken nightly. Therefore, the maximum exposure in this trial will be 10 mg for approximately 14 days, followed by 10 or 20 mg for approximately 14 additional days.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Until recently, validated instruments to measure sleep disturbances in AD patients were limited and so a variety of subjective report instruments have been used in the past. Studies to characterize sleep disturbances in AD have revealed that 50-82.3% of caregivers report patient awakenings during the night and 36-63% of caregivers report patients waking up too early [28], [29]. A quarter of caregivers reported that subjects took more than 30 minutes to fall asleep [29]. Another study reported that approximately 40% of a subject's time in bed is spent awake. Furthermore, the mean percent awake time in bed and mean number of nighttime awakenings increased with severity of AD [30].

Given the uncertain accuracy of subjective caregiver assessment of sleep in subjects with AD, polysomnography (PSG), the gold standard objective assessment of sleep has been selected for this study. A prior PSG study characterizing sleep in AD subjects with nocturnal agitation, found that mean total sleep time (TST) was 338.3 minutes, mean sleep latency to first epoch of sleep was 43.2 minutes, mean total wake time was 151.6 minutes, and mean sleep efficiency was 66.6% [31]. Among the numerous potential sleep assessments PSG provides, TST has been selected as the primary endpoint measure for this study, in part because TST reflects the most comprehensive global sleep assessment. Additionally, the standardized effect size (ie, difference between treatment groups divided by the standard deviation [SD]), is higher for TST than for any other PSG endpoint, indicating good endpoint stability, and thus allows for the smallest number of subjects to demonstrate a treatment difference between groups. The robust suvorexant treatment response observed in Phase 3 studies, as assessed by PSG (see Section 4.2.1), further supports the selection of TST as the primary efficacy endpoint measure in this study. Lastly, in light of suvorexant's demonstrated ability to help patients with insomnia stay asleep throughout the night, the measure of PSG-derived wake after persistent sleep onset (WASO), the gold standard objective assessment for sleep maintenance, will be a key secondary endpoint.

In addition to these and other objective PSG-derived sleep measurements, subjective sleep assessments and data from an activity/sleep watch will also be collected and evaluated as exploratory measures in this study.

4.2.3.2 Safety Endpoints

The safety and tolerability of suvorexant will be continuously assessed throughout the trial via Adverse Event reporting, and vital signs will be assessed at every trial visit. In addition, safety laboratory evaluations will be drawn, electrocardiograms (ECGs) will be conducted, and physical and neurological examinations will be performed during the trial. The Columbia-Suicide Severity Rating Scale (C-SSRS) will be conducted at every visit to prospectively assess for the emergence of suicidal ideation and behavior.

Protocol-specific ECIs (see Section 7.2.3.2) will be monitored as well. A supplemental document will be provided that contains a list of specific terms and guidance for additional information to be collected and reported. Additionally, pre-specified ECIs will be reviewed by an external clinical adjudication committee (CAC) (see Section 7.3.2).

4.2.3.3 Exploratory Endpoints

Measures of cognition and neuropsychiatric behavior are diminished in patients with AD; therefore, assessments to evaluate these features will be collected and evaluated as exploratory measures in this trial. Other exploratory measures will include subjective sleep measures (collected via e-diary), objective measures of sleep-wake (measured by an activity/sleep watch), and assessment of titration. The list of exploratory endpoints will be detailed in the supplemental Statistical Analysis Plan (sSAP).

4.2.3.4 Pharmacokinetic Endpoints

Plasma samples will be collected for evaluation of pharmacokinetic (PK) properties of MK-4305, and may be used to characterize the plasma concentration of MK-4305. Additionally, this data may be compared to that reported historically or used in population pharmacokinetic (PK) and/or pharmacodynamic (PD) model development and analysis. Plasma samples will be collected at specific visits as indicated in the Trial Flow Chart (Section 6.0).

The final decision as to which plasma samples will be assayed will be made by the Sponsor's Department of Pharmacokinetics, Pharmacodynamics, and Drug Metabolism (PPDM) and the Clinical Monitor.

Information regarding the collection and shipping of plasma samples will be provided in the administrative binder.

4.2.3.5 Pharmacodynamic Endpoints

Aside from efficacy and safety endpoints, there are no specific pharmacodynamics endpoints that will be collected in the current trial.

4.2.3.6 Planned Exploratory Biomarker Research

Planned Genetic Analysis

Understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

In addition to studying variation across the human genome, APOE4 will specifically be investigated since the presence of the APOE4 genotype predicts an increased chance of developing AD. Evolving literature additionally suggests the potential for association between AD and insomnia, thereby implicating the APOE4 genotype. The relationship, if any, between the APOE4 genotype and response to symptomatic treatment of insomnia in AD has not been established. For these reasons, the potential relationship of APOE4 genotype to insomnia and response to treatment in AD subjects may be analyzed as an exploratory objective.

4.2.3.7 Future Biomedical Research

The Sponsor may conduct Future Biomedical Research on DNA specimens collected for future biomedical research during this clinical trial.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from

appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Appendix 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Appendix 12.3.

4.3 Benefit/Risk

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male and female subjects aged 50 to 90 years (inclusive) with insomnia and Alzheimer's disease will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

Visit 1: Screening Inclusion

1. Be between 50 to 90 years of age (inclusive) on the day of signing informed consent.

2. Meet the criteria for a diagnosis of probable Alzheimer's disease based on either a) the National Institute on Aging – Alzheimer's Association (NIA-AA) criteria (Appendix 12.9), or b) the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, (DSM-5) criteria for AD (Appendix 12.8). (Note: information on documentation to support diagnosis of AD can be found in Section 7.1.5.1.1.)

3. Have a Mini Mental State Examination (MMSE) score ≥12 and ≤26 at Screening.

4. Have sleep complaints that meet DSM-5 criteria for the diagnosis of insomnia (eg, difficulty initiating or maintaining sleep, and/or early morning awakenings with inability to return to sleep for at least 3 nights per week for ≥the past 3 months prior

to Visit 1, despite adequate opportunity for sleep) based on the investigator's judgment and by the subject's sleep history, as assessed by the sleep items on the Insomnia Diagnostic Interview and Sleep History assessments. (Note: information on documentation to support diagnosis of insomnia can be found in Section 7.1.5.1.1.)

5. Be willing to stay overnight at a sleep laboratory and stay in bed for at least 8 hours for PSG testing.

6. Have a regular bedtime between 8 PM (20:00) and 1 AM (01:00) and is willing to maintain it for the duration of the trial.

7. Be able and willing to wear an activity/sleep watch on the wrist throughout the day and night. Additional details are provided in Section 7.1.2.2.16.

8. Each subject (or legal representative) must sign the informed consent form, **in accordance with local requirements**, after the scope and nature of the investigation have been explained to them, and before Screening assessments. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

9. Based on the investigator's judgment (with legal representative input, as applicable), the subject should:

    - Be able to speak, read, and understand the language of the trial staff and the informed consent form;

    - Possess the ability to respond verbally to questions, follow instructions, and complete study assessments;

    - Be able to adhere to dose and visit schedules.

10. Have a reliable and competent trial partner (eg, spouse, family member, or other caregiver) who meets the following requirements and trial obligations (see Section 7.1.5.1 for source documentation information):

    - Signs their own informed consent, after the trial has been explained to them, and before Screening assessments.

    - Is not diagnosed with dementia.

    - Resides with the subject overnight (see Section 7.1.5 for more details) and has a close relationship with the subject (defined as daily face-to-face contact, at least 15 waking hours a week for at least 3 months prior to Visit 1).

    - Accompanies the subject to and from trial visits and willing to stay overnight at the sleep laboratory, if needed, for the 3 PSG visits (See Section 7.1.5 for

more details regarding flexibility for alternate caregivers to accompany the subject on clinic visits and overnight PSG visits).

- Assumes responsibility for trial medication procedures (eg, witnessing and/or helping to administer trial medication, assessing compliance), for completion of the sleep e-diary each morning, and oversight of the activity/sleep watch worn throughout the trial.

- Answers questions regarding the trial partner's sleep quality and trial partner's distress related to the subject's behaviors.

11. Have results of clinical laboratory tests (complete blood count [CBC], blood chemistries, thyroid function tests, and urinalysis) within normal limits or clinically acceptable to the investigator at Screening.

12. Have results of a physical examination (PE), including neurological exam, vital signs, and ECG (Bazett's correction) within normal limits (based on the population under study, ie Alzheimer's disease and insomnia) or clinically acceptable based on investigator judgment at Screening.

13. If female, not be of childbearing potential as indicated by one of the following:

    - Has reached natural menopause, defined as ≥ 45 years of age with <u>either:</u>

      i. ≥12 months of spontaneous amenorrhea

      <u>or</u>

      ii. ≥6 months of spontaneous amenorrhea with serum follicle stimulating hormone (FSH) levels >40 IU/L as determined by the central laboratory

    - Has had a hysterectomy;

    - Has had bilateral tubal ligation; or

    - Has had a bilateral oophorectomy (with or without a hysterectomy) and greater than 6 weeks have passed since the surgery

14. Be willing to provide a blood sample for APOE genotyping.

<u>Visit 2: Screening PSG Inclusion</u>

Note: Continue to fulfill relevant Inclusion Criteria at Visit 1.

15. Have a TST ≤6.5 hours as determined by the Visit 2 Screening PSG confirmed by the central PSG rating vendor.

Visit 3: Baseline PSG Inclusion

Note: Continue to fulfill relevant Inclusion Criteria at Visit 1.

16. Have a mean TST <6 hours on the combined Screening (Visit 2) and Baseline (Visit 3) PSGs, where neither night is >6.5 hours as confirmed by the central PSG rating vendor.

Visit 4: Randomization Inclusion

Note: Continue to fulfill relevant Inclusion Criteria at Visit 1.

17. Have a trial partner who is ≥70% compliant with completing the e-diary during the Run-in Period (eg, the last 10 available days of e-diary data from Visit 4).

18. Have ≥75% trial medication compliance rate for trial medication taken from Visit 2 to Visit 4. This should be assessed with a standard pill count (ie, number of pills taken divided by (/) number of nights from Visit 2 (inclusive) to the day prior to Visit 4).

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Resides in a nursing home (or similar institutional facility). Note: assisted-living facilities are not excluded if full-time nursing care is not required.

2. Has a Modified Hachinski Ischemia Scale (MHIS) Score >4 at Screening (ie, evidence of vascular dementia).

3. Has a known history of recent (or past) stroke that in the investigator's opinion confounds the diagnosis of either AD or insomnia.

4. Has evidence of a clinically relevant neurological disorder other than the disease being studied (ie, probable AD) at Screening, including but not limited to: vascular dementia, parkinsonism, frontotemporal dementia, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, progressive supranuclear palsy, neurosyphilis, dementia with Lewy bodies, other types of dementia, mental retardation, hypoxic cerebral damage, cognitive impairment due to other disorders, or history of head trauma with loss of consciousness that either led to persistent cognitive deficits or in the opinion of the investigator confounds the diagnosis of either AD or insomnia.

5. Has a history of seizures or epilepsy within the last 5 years before Screening.

6. Has a history or diagnosis of any of the following conditions, in the opinion of the investigator:

    - Narcolepsy
    - Cataplexy (familial or idiopathic)
    - Circadian Rhythm Sleep Disorder
    - Parasomnia including nightmare disorder, sleep terror disorder, sleepwalking disorder
    - REM behavior disorder
    - Significant degree of sleep-related Breathing Disorder (ie, AHI >30, and/or use of Continuous Positive Airway Pressure (CPAP) or Bilevel Positive Airway Pressure (BIPAP))
    - Periodic Limb Movement Disorder
    - Restless Legs Syndrome
    - Primary Hypersomnia
    - Excessive Daytime Sleepiness (EDS) characterized by uncharacteristic chronic and persistent sleepiness throughout the day

7. Has a clinically significant movement disorder, such as akinesia, that would affect the activity/sleep watch differentiation of sleep and wakefulness.

8. In the opinion of the investigator, has difficulty sleeping primarily due to a confounding medical condition. Note: "Medical Conditions" may include chronic pain syndromes, chronic migraine, cardiac disease, nocturia (>3 times/night), asthma, gastroesophageal reflux disease (GERD), or hot flashes.

9. Has evidence of a current episode of major depression based on investigator's judgment. A score of 5 or more on the 15-item Geriatric Depression Scale (GDS) requires an assessment by an appropriate health care professional (a psychiatrist or other trained mental health professional, such as a licensed psychologist, social worker or mental health nurse practitioner or comparable professional qualification in countries outside the United States) to evaluate for the presence of major depression. Subjects with a score of 5 or more who are not diagnosed with major depression following such an assessment may be included in the trial. Major depression in remission is not exclusionary.

10. Has any of the following based on clinician interview and DSM-5 criteria:

    - Lifetime history of bipolar disorder, a primary psychotic disorder, or posttraumatic stress disorder; or,

    - A psychiatric condition requiring treatment with a prohibited medication; or,

    - Other psychiatric condition that, in the investigator's opinion, would interfere with the subject's ability to participate in the study.

11. Is at imminent risk of self-harm, based on clinical interview and responses on the Columbia-Suicide Severity Rating Scale (C-SSRS), or of harm to others in the opinion of the investigator. Subjects must be excluded if they report suicidal ideation with intent, with or without a plan or method (eg, positive responses to items 4 or 5 in assessment of suicidal ideation on the C-SSRS) in the *past 2 months* or suicidal behavior in the *past 6 months*.

12. Has a history of alcoholism or drug dependency/abuse within the last 5 years of Screening.

13. Has a recent history (within the 6 months prior to Screening) of regular consumption (3 or more days per week) of either:

    - More than 2 alcoholic beverages per day or alcohol consumption within 3 hours prior to bedtime

    - More than >600 mg caffeine a day (eg, 4 standard 8-ounce cups of brewed coffee, See Appendix 12.7 for a list of caffeinated products) or consumes caffeine after 4pm (16:00)

14. Consumes the equivalent of >15 cigarettes a day and the investigator confirms that the subject's insomnia is in part the result of tobacco consumption (eg, subjects unable to refrain from smoking during the night, subjects who interrupt sleep to smoke or use tobacco products, or subjects who require a cigarette within 30 minutes of waking in the morning).

15. Has a history of excessive daytime napping (defined as more than 3 hours a day for more than 3 days of the week based on trial partner estimates, on average for the past 4 weeks).

16. Has a recent or ongoing, uncontrolled, clinically significant medical condition or major surgery where participation in the trial would pose a significant medical risk to the subject within 3 months of Screening, such as:

    - Conditions including but not limited to diabetes, hypertension, Human Immunodeficiency Virus (HIV) or other relevant infections, thyroid or endocrine disease, Chronic Obstructive Pulmonary Disease (COPD), delirium, congestive heart failure, angina, cardiac or gastrointestinal disease, or renal disease requiring dialysis.

      Note: Controlled co-morbid conditions (including diabetes, hypertension, heart disease, etc.) are not exclusionary if stable within 3 months of the Screening Visit. All concomitant medications, supplements, or other substances must be kept as stable as medically possible during the trial. Urinary tract infections at Screening are not exclusionary if adequately treated (as documented by repeat urinalysis) prior to Visit 2.

- Major surgery including not limited to abdominal, thoracic, cardiac or orthopedic surgery, or any procedure requiring general anesthesia

Subjects with recently controlled or treated medical conditions may be considered for re-screening on a case-by-case basis after consultation with the Sponsor.

17. Has confirmed abnormal pre-randomization laboratory values per the guidance below or other clinically significant, unexplained laboratory abnormality in the opinion of the investigator:

    - Alanine transaminase (SGPT or ALT) ≥3 x the upper limit of normal (≥3 x ULN)
    - Aspartate transaminase (SGOT or AST) ≥3 x ULN
    - Total bilirubin ≥1.5 x ULN

    Should a liver function test (LFT) be abnormal (ALT/AST >ULN but <3x ULN, T-BIL >ULN but <1.5x ULN) at Screening but not meet the specified criteria, the investigator should attempt to characterize at entry the reason(s) for the elevation (eg, alcohol abuse, metabolic syndrome with fatty liver, etc.). Subjects with suspected Gilbert's Syndrome who have isolated T-BILI ≥1.5x ULN may enter the trial upon genetic confirmation (eg, uridine diphosphate glucuronosyltransferase 1A1 [UGT1A] assessment).

    See Appendix 12.12 for an algorithm for assessing out-of-range laboratory values.

18. Has an estimated creatinine clearance of less than 30 mL/min:

    - For Males: Creatinine Clearance = $\frac{(140 - \text{Age[yr]}) \times \text{Weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72}$

    - For Females: Creatinine Clearance = $\frac{0.85 \times (140 - \text{Age[yr]}) \times \text{Weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72}$

19. Has one of the following:

    - Vitamin B12 or folate deficiency at Visit 1 that is confirmed by serum homocysteine or methylmalonic acid levels (supplemental testing as needed for abnormal B12 and folate at Visit 1), as determined by central laboratory normal values;

    - Clinically significant untreated B12 or folate deficiency 1 month prior to Visit 1;

    - Abnormal thyroid function tests at Visit 1, as determined by central laboratory normal values, or clinically significant untreated thyroid disease 1 month prior to Visit 1.

Note: Subjects are eligible for re-screening, after consultation with the Sponsor, once B12 deficiency, folate deficiency, or thyroid disease treatment has been stable for at least 1 month.

20. Has a history of hepatitis or liver disease that, in the opinion of the investigator, has been active within the 6 months prior to Visit 1.

21. Has a positive Visit 1 urine drug screen (eg, positive for benzodiazepines, cannabinoids, cocaine, etc.). Note: The screen may be repeated at investigator's discretion and as warranted by medical history and concomitant medications. A repeat drug screen must be negative prior to randomization.

22. Has a known allergy or hypersensitivity to suvorexant or to any of the formulation components (refer to Investigator' Brochure [Section 3.4] for the pharmaceutical formulation).

23. Has a history of hypersensitivity or idiosyncratic reaction to more than 3 chemical classes of drugs, including prescriptions and over-the-counter medications.

24. Has donated blood products or has had phlebotomy of >300 mL within 8 weeks of signing informed consent, or intends to donate or receive blood products during participation in the study.

25. Has a history of malignancy occurring within the 5 years immediately before Screening, except for a subject who has been adequately treated for:

    - Basal cell or squamous cell skin cancer;
    - In situ cervical cancer;
    - Localized prostate carcinoma;
    - Who has undergone potentially curative therapy with no evidence of recurrence for ≥3 year post-therapy, and who is deemed at low risk for recurrence by her/his treating physician.

26. Is pregnant, is attempting to become pregnant, or is nursing children.

27. Has a Body Mass Index (BMI) >40 kg/m^2. BMI is calculated by taking the subject's weight in kg and dividing by the subject's height in meters, squared (see Appendix 12.6).

28. Is currently participating or has participated in a study with an investigational compound or device within 30 days of signing informed consent. Note: participation in observational studies without an intervention may be allowed after consultation with the Sponsor.

29. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

30. Is taking, or plans to take, one or more of the following medications (non-inclusive), shown in Table 1 within the specified washout period prior to Visit 2 (unless specified by a note below) and throughout the course of the trial (a detailed list of the prohibited medications is provided in Section 5.5).

Table 1 Prohibited Medications that Require a Washout Period Prior to Visit 2 (Non-inclusive List).

Prohibited Medications, Supplements, and Other Substances	Washout Period prior to Visit 2*
Investigational compounds	4 weeks or 5 $t_{½}$ lives
Moderate or Strong CYP3A4 Inhibitors eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, refinavir, ritonavir, saquinavir, telithromycin, and voriconazole	2 weeks or 5 $t_{½}$ lives
Strong CYP3A4 Inducers eg, barbiturates, carbamazepine, efavirenz, modafinil, nevirapine, phenytoin, pioglitazone, primidone, rifabutin, rifampin, rifapentin, St. John's Wort (hypericum), and systemic glucocorticoids **Exception:** inhaled corticosteroids are permitted)	2 weeks or 5 $t_{½}$ lives
Antihistamines (sedating) eg, chlorpheniramine, clemastine, cyproheptadine, diphenhydramine, hydroxyzine, thiothixene, trifluoperazine	2 weeks
Hypnotics eg, acetaminophen and diphenhydramine (Tylenol™ PM), diphenhydramine (Nytol™), doxylamine (Unisom™), eszopiclone, zaleplon, zolpidem, zopiclone	2 weeks or 5 $t_{½}$ lives for intermittent use: defined as use of <4 times/week 4 weeks or 5 t½ lives for chronic use: defined as use of ≥4 times/week
Anxiolytics (benzodiazepines, non-benzodiazepines) eg, chlordiazepoxide, clonazepam, diazepam, flurazepam, lorazepam, meprobamate, triazolam,	2 weeks or 5 $t_{½}$ lives for intermittent use: defined as use of <4 times/week 4 weeks or 5 t½ lives for chronic use: defined as use of ≥4 times/week
Anticonvulsants and Mood Stabilizers eg, carbamazepine, lamotrigine, levetiracetam, lithium, phenytoin, valproic acid **Exception:** Use of gabapentin or pregabalin for neuropathic pain is acceptable.	4 weeks or 5 t½ lives
Anti-Parkinsonian eg, amantadine, bromocriptine, I-deprenyl/selegiline, L-dopamine, pergolide, pramipexole, ropinirole	4 weeks or 5 t½ lives
Other CNS depressants eg, MAOI, trazodone, or tricyclic antidepressants used for sleep complaints are excluded.	2 weeks
Stimulants / Diet Pills eg, amphetamine, atomoxetine, methylphenidate, modafinil,	2 weeks
Supplements with possible psychotropic effects eg, kava-kava, melatonin, S-Adenosyl methionine [SAMe], St. John's Wort, tryptophan, and valerian	2 weeks
* Interval notes minimum washout period. Washout should occur for 5 half-lives or the minimum specified period (2 or 4 weeks), whichever is longer to systemically eliminate the compound.	

Visit 2: Screening PSG Exclusion:

Note: Meets any relevant Visit 1 Exclusion criteria. Additionally, meets any of the following Exclusion criteria based upon Visit 2 tests/results:

31. Has a positive urine drug screen test, as confirmed by central laboratory vendor at Visit 2. Note: See details in Section 7.1.3.1.2.

32. Has a positive alcohol breath test as analyzed by a breathalyzer machine at Visit 2. Note: The test may be repeated at investigator's discretion (eg, recent use of mouthwash) and as warranted by medical history. A repeat test must be negative prior to the PSG. Note: See details in Section 7.1.3.1.3.

33. Has an underlying pathology of sleep, identified and confirmed by the central PSG rating vendor, during the Visit 2 Screening PSG as follows:

    - An Apnea Hypopnea Index of >30;
    - >30 periodic leg movements associated with an arousal per hour of sleep (PLMAs);
    - Evidence of an exclusionary sleep disorder as detailed in Exclusion Criteria 6 (eg, REM behavior disorder, parasomnia, etc.).

    Note: Subjects who initially screen failed based on this exclusion criterion (AHI and/or PLMA) may be considered for re-screening. If the Visit 2 Screening PSG would be eligible based on the amended criteria (ie, AHI $\leq$30 and PLMA $\leq$30 as confirmed by Central PSG vendor), subjects may be re-screened after consultation with the Sponsor. Details regarding the schedule of re-screening assessments will be provided in a Sponsor Communication Form.

Visit 3: Baseline PSG Exclusion:

Note: Meets any relevant Visit 1 Exclusion criteria. Additionally, meets any of the following Exclusion criteria based upon Visit 3 tests/results.

34. PSG reveals evidence of any exclusionary sleep disorder(s) as listed in Exclusion Criteria 6 (eg, REM behavior disorder, parasomnia, etc.) at Visit 3.

35. Has a positive urine drug screen at Visit 3. See Note in Exclusion 31.

36. Has a positive alcohol breath test at Visit 3. See Note in Exclusion 32.

Visit 4: Randomization Exclusion:

Note: Meets any relevant Visit 1 Exclusion criteria.

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in Table 2.

Table 2 Trial Treatments

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Single-Blind Placebo Run-in Period					
Placebo (to match suvorexant 10 mg)	0 mg tablet	1 tablet every night	Oral	Nightly for 2 weeks	Placebo
Double-Blind Treatment Period					
Suvorexant 10 mg	10 mg tablet	1 tablet every night	Oral	Nightly for 4 weeks	Investigational
Placebo (to match suvorexant 10 mg)	0 mg tablet	1 tablet every night	Oral	Nightly for 4 weeks	Placebo
***Options for dose escalation (per investigator's discretion) – beginning at Visit** 5					
Suvorexant 20 mg*	20 mg tablet	1 tablet every night	Oral	Nightly for 2 weeks	Investigational
Placebo (to match suvorexant 20 mg) *	0 mg tablet	1 tablet every night	Oral	Nightly for 2 weeks	Placebo
*At Visit 5, the dose of suvorexant may be increased to 20 mg (or matching placebo). See Section 5.2.1.2.					

The first dose of trial medication for the single-blind placebo Run-in Period will begin the night of Visit 2; dosing will continue until the subject returns for randomization at Visit 4.

The first dose of trial medication for the randomized double-blind Treatment Period will begin the night of Visit 4. Subjects will remain on the specified trial medication that they are randomized to (suvorexant or matching placebo) throughout the trial, with their last dose on the night of Visit 6. At Visit 5, the investigator may increase the subject's trial medication dose for the remaining 2 weeks. Please see Section 5.2.1.2 for more information.

To maintain blinding with respect to the treatment period (ie, Run-in, Treatment), subjects will not be informed when transitioning between the treatment periods.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.1.2 Dose Modification/Titration

At Visit 5, the dose of trial medication may be increased from 1 tablet of 10 mg suvorexant (or 10 mg matching placebo) to 1 tablet of 20 mg suvorexant (or 20 mg matching placebo). The decision to increase the dose will be made by the investigator, and is to be based on the following 2 criteria: 1) CGI-S score ≥3, and 2) acceptable tolerability. This dose adjustment will be performed in a double-blind manner, with maintenance of the original treatment assignment (eg, subjects assigned to placebo treatment will continue to receive placebo to match the 20 mg suvorexant dose). The modified dose will be taken for the remainder of the trial, barring emergence of tolerability issues.

If the subject (or trial partner on behalf of the subject) reports a tolerability issue after the dose titration step at Visit 5, the site investigator will determine the subject's treatment plan and next steps (ie, continue current 20 mg dose of suvorexant, down-titrate to the original 10 mg dose of suvorexant, or discontinue trial medication). A clinic visit may be required for further evaluation.

All trial medication assignments/adjustments will be completed using the IVRS/IWRS system.

5.2.2 Timing of Dose Administration

For at-home dosing, subjects are to be instructed (and reminded) to take their trial medication within 30 minutes prior to bedtime. The trial partner is responsible for providing and witnessing daily dosing of trial medication to the subject, and may assist in administration of trial medication if needed. During PSG visits in the sleep lab, trial medication will be administered within 30 minutes before bedtime (Lights Off), and dosing will be witnessed by study personnel.

Each morning, the trial partner will record the dosing time from the previous night, in the e-diary, along with the responses to other e-diary questions.

If a subject happens to miss their evening dose, they should resume taking their medication the following night. The subject should not take an additional dose (ie, the morning following the missed dose) to 'make up' the missed dose. Missed doses should be reported to the site.

It is important that subjects have taken trial medication for at least 3 days prior to a PSG visit (with the exception of Visit 2); therefore, in the event trial medication is interrupted on nights leading up to the end-of-treatment PSG visit (ie, Visit 6), the visit should be rescheduled.

5.2.3 Trial Blinding/Masking

A double-blind/masking technique will be used. All doses of suvorexant and their respective matching placebo for the 4-week double-blind Treatment Period will be packaged identically so that blind/masking is maintained. The subject, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects are unaware of the group assignments.

Additionally, a single-blind/masking technique will be used for the Run-in Period. See Section 7.1.4.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

5.3 Randomization

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects will be assigned randomly in a 1:1 ratio to either suvorexant or placebo.

5.4 Stratification

Treatment allocation/randomization will be stratified by the IVRS/IWRS system according to the following factors:

- Alzheimer's disease severity category, mild versus moderate, as defined by MMSE score ranges at Visit 1 Screening: 12 to 20 (moderate), 21 to 26 (mild). Approximately 30% of the randomized subjects will be assigned to the moderate AD stratum.

5.5 Concomitant Medications/Vaccinations (Allowed)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy requires the mutual agreement of the investigator, the Sponsor and the subject.

Table 3 displays the list of concomitant medications that are allowed during the trial. While the list is not inclusive of all medications within a given category, the investigator should use his/her medical judgment when a subject presents with a medication not on the list that falls within a relevant category. When medically possible, the dose of a concomitant medication should be kept stable throughout the entire trial.

It is strongly encouraged, but not required, that the dose of allowed medications, supplements, and other substances for chronic conditions be stable for at least one month

prior to screening and remain stable during the trial. This is particularly important for medications that can impact cognition (eg, pregabalin and gabapentin). Exception: acetylcholinesterase inhibitors and memantine are allowed during the trial, but the dose must be stable for at least one month prior to Visit 1, and should not be changed during the trial unless medically necessary to ensure subject safety.

If necessary, the medications, supplements, and other substances in Table 3 can be initiated during the trial if medically indicated. Note that the use of any concomitant medication must relate to the documented medical history, prophylaxis, or an adverse event of the subject.

In the event that a subject requires an extended washout period (ie, greater than 2 weeks) for a prohibited medication(s) or other therapy, an abbreviated Visit 1 may be performed (see Section 7.1.5.1.1). After the subject has completed the proper washout based on , the subject will return to complete the remaining Visit 1 procedures/assessments. Once the subject has fully completed Visit 1 and eligibility has been confirmed, the subject may proceed to Visit 2 per protocol.

Concomitant medications should be collected during the post-treatment follow-up phone call in the event an AE is reported.

Table 3 Allowed Medications, Supplements, and Other Substances (non-inclusive list)

Medication Category	Examples*/ Notes (*specific medications listed are examples of class compounds and are not limited to those listed)
AD medications	eg, donepezil, galantamine, memantine, rivastigmine **Note:** Subject must be on a stable dose for at least 1 month prior to Screening Visit.
Antidepressants	eg, SSRI and SNRI medications, including bupropion, citalopram, escitalopram, fluoxetine, mirtazapine, paroxetine, sertraline, venlafaxine
Antihistamines: Non-sedating	**Note:** Non-sedating antihistamines are not to be taken more than twice a week. **Note:** Montelukast sodium (SINGULAIR™) and inhaled corticosteroids may be used more than twice weekly as needed for allergic symptoms
Antipsychotics	eg, aripiprazole, asenapine, olanzapine, risperidone, ziprasidone **Note:** quetiapine is allowed if used on an as needed basis for daytime control of neuropsychiatric symptoms, but quetiapine is prohibited if used for sleep. Subjects should avoid taking quetiapine for at least 3 hours before going to bed throughout the duration of the study, and refrain from using quetiapine, for at least 24 hours before, and during, PSG visits.

Medication Category	Examples*/ Notes (*specific medications listed are examples of class compounds and are not limited to those listed)
Centrally acting analgesics	eg, codeine, hydromorphone, morphine, oxycodone, propoxyphene, and its variations, & combination products that contain a narcotic. May be taken as needed for pain relief (with the documented approval of the Merck clinical monitor), but use may not exceed 3 consecutive days or >4 days per any week. **Note:** Use of narcotics for pain relief should be avoided if there are effective alternative therapies such as non-steroidal anti-inflammatory agents. Sponsor must be notified of any use exceeding 3 consecutive days or >4 days per any week.
Muscle relaxants (centrally acting with psychotropic effects)	eg, methocarbamol **Note:** Use of centrally acting muscle relaxants should be avoided if there are effective alternative therapies such as non-steroidal anti-inflammatory agents. Sponsor must be notified of any use exceeding 3 consecutive days or >4 days per any week.
Over-the-Counter (OTC), combination products containing caffeine for pain relief	eg, acetaminophen, aspirin, and caffeine (EXCEDRIN™), and aspirin and caffeine (ANACIN™) **Note:** 2 tablets are equivalent to a caffeinated beverage and should be counted as such toward the maximum 600 mg caffeine per day (eg, 4 standard 8-ounce cups of brewed coffee). As with any caffeinated beverages, patients should be advised to refrain from using these medications after 4 PM. These medications should not be taken on days/nights when PSGs are conducted.
Pseudoephedrine	**Note:** May only be used before 2 PM, and no more than twice a week. Dosage is limited to 30 mg of active ingredient in each tablet. Extended release formulations are prohibited. These medications should not be taken on days/nights when PSGs are conducted.

Suvorexant is a substrate of CYP3A4 and should not be co-administrated with strong to moderate CYP3A4 inhibitors (see). Suvorexant is a weak inhibitor of CYP3A and the intestinal P-glycoprotein (P-gp) transporter following consecutive, multiple-dose administration. For most drugs metabolized by CYP3A4, suvorexant is not expected to increase plasma levels of other medications to a clinically significant degree. Concomitant administration of suvorexant with digoxin slightly increased digoxin levels due to inhibition of intestinal P-gp. Subjects may continue on digoxin with digoxin level monitoring during the study, consistent with general clinical practice. No clinically significant pharmacokinetic interactions were observed following co-administration of suvorexant with warfarin. The investigator should use his/her clinical judgment to determine if any concomitant medications (not specifically prohibited) should be discontinued, or alternatively, if careful clinical monitoring is sufficient.

5.6 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

5.7 Diet/Activity/Other Considerations

The following are recommendations/guidance for subjects; monitoring is not required.

5.7.1 Diet

Subjects should maintain their usual diet throughout the duration of the trial.

5.7.2 Use of Alcohol, Caffeine, and Tobacco

The site should advise subjects/trial partner that alcohol should NOT be consumed in combination with suvorexant because of potential additive effects.

The site should advise subjects to limit their alcohol intake as follows:

- Do NOT consume alcohol in combination with suvorexant
- Limit consumption to no more than 2 drinks a day and avoid alcohol at least 3 hours before going to bed throughout the duration of the study.
    - One drink is defined as a 12-ounce bottle/can of beer (~14 grams alcohol) or a 4-ounce glass of wine (~12 grams alcohol) or 1 ounce of liquor (80 proof or 40 % alcohol, ~ 9 grams alcohol).
- Refrain from consuming any alcohol for at least 24 hours prior to and during PSG visits.

Note that subjects will be asked to take an alcohol breath test at PSG visits; if a subject tests positive on the alcohol breath test, that visit should be rescheduled as soon as possible. See Section 7.1.3.1.3 for more details.

The site should advise subjects to limit their caffeine consumption as follows:

- Limit their daily caffeine consumption to ≤600 mg caffeine, and avoid caffeine after 4 PM (16:00) throughout the duration of the trial. (See Appendix 12.7 for additional guidance on caffeine products and content.)
- Refrain from consuming any caffeine after 1 PM (13:00) on the day of PSG visits. In addition, caffeinated products should not be consumed until after completion of all morning procedures at the PSG visit.

The site should advise subjects to limit their tobacco use as follows:

- Refrain from the equivalent of >15 cigarettes a day during the trial, and
- Refrain from smoking during the night, interrupting their sleep to smoke, or smoking within 30 minutes of waking in the morning

The day before a PSG visit, it is recommended that sites call the subject/trial partner to remind them of alcohol and caffeine limitations. It is also recommended that the site staff inquire about alcohol, caffeine, and tobacco consumption when a subject/trial partner returns for a visit, and record any information regarding this consumption in the subject's source documentation.

5.7.3 Activity

Subjects should not drive, operate hazardous machinery, or do other dangerous activities, after taking trial medication, until they feel fully awake.

Subjects who are provided non-trial treatments, such as day-care, may continue these throughout the trial. The frequency should not change unless medically indicated.

During the study, every effort should be made by the subject to maintain a habit of going to bed at their regular bedtime. The regular bedtime for subjects should be between 8:00 PM (20:00) and 1:00 AM (01:00). "Bedtime" is defined as the time when the subject intends/attempts to fall asleep for the night (eg, lying down or reclining with eyes closed with intention of getting a full night of sleep). The subject should sleep in a conducive environment (ie, a darkened room, a relatively quiet room, a room free from distractions).

Throughout the study, and in particular on the nights just prior to a PSG visit, trial partners should ensure that subjects have adequate opportunity for sleep (ie, at no time during the trial should the time allotted for sleep be shortened). If for some reason, the subject's opportunity for sleep the night prior to a PSG visit is inadequate or disrupted due to extenuating circumstances (eg, traveling, illness), then it is recommended that the subject's PSG visit be rescheduled in a timely manner, preferably within 1-3 days of the originally scheduled visit.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

Table 4 provides reasons why a subject must be discontinued from treatment but may continue to be monitored in the trial, as well as reasons why a subject must be discontinued from treatment and the trial.

Table 4 Discontinuation Scenarios

Reason for Discontinuation Scenario	Action
The subject or legal representative (such as a parent or legal guardian) withdraws consent.	Discontinuation from Treatment and Trial
The subject's treatment assignment has been unblinded by the investigator, Merck subsidiary or through the emergency unblinding call center.	Discontinuation from Treatment, but Continue in Trial
The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk through continued participation in the trial or does not allow the subject to adhere to the requirements of the protocol.	Discontinuation from Treatment and Trial
The subject's trial partner is no longer willing (withdraws consent) or able to participate in the trial or is not compliant with trial-related procedures, and a suitable replacement trial partner cannot be identified within a reasonable period of time.	Discontinuation from Treatment and Trial
The subject is no longer able to participate in the trial or is not compliant with trial-related procedures.	Discontinuation from Treatment and Trial
The subject has an elevated ALT, AST, or T-BIL meeting any one of the following criteria: • ALT or AST ≥8x ULN; • ALT or AST ≥5x ULN for more than 2 weeks; • ALT or AST ≥3x ULN and T-BIL ≥2x ULN at the same visit; • ALT or AST ≥3x ULN with the appearance of symptoms indicating hepatitis (eg, worsening fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia). Note: The Sponsor or its delegate should be immediately contacted when a subject is discontinued from trial medication or trial medication is interrupted because of an AE or a laboratory safety test abnormality.	Discontinuation from Treatment, but Continue in Trial
The subject takes a prohibited medication during the trial.	This deviation should be documented, and the Sponsor should be consulted regarding the management of the subject.
Subjects who report suicidal ideation with intent, with or without a place or method (ie, a positive response to items 4 or 5 in the assessment of suicidal ideation on the C-SSRS) or suicidal behavior may meet discontinuation criteria.	Please refer to Section 7.1.2.2.11, 7.2.3.2 and the ECI guidance document for details.

Discontinuation from treatment is "permanent." Once a subject is discontinued, he/she shall not be allowed to restart treatment.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

There are no pre-specified criteria for terminating the trial early.

6.0 TRIAL FLOW CHART

	Screening Period					Treatment Period				Discontinuation	Post-Treatment
		Placebo Run-in									
Visit Number/Title:	1 Screening[a, b]	2 Screening PSG		3 Baseline PSG		4 Rand[c]	5 End of Week 2	6 End of Week[cc] 4 - PSG		Discon	Follow-up TC[d]
Scheduled Week/Day	Day -21	Day -14/-13		Day-7/-6		Day 1	Day 15	Day 29/30			14 days Post-dose
Scheduling Window by Days:	+28[e]	-3/+3[f]		-3/+4		-3/+3	-3/+5	-3/+5			+2
Administrative Procedures		PM[g]	AM	PM [g]	AM			PM[g]	AM		
Informed Consent – Subject	X										
Informed Consent – Trial partner	X										
Informed Consent – Future Biomedical Research (FBR)	X										
Inclusion/Exclusion Criteria	X	X	X	X	X	X[h]					
Subject Identification Card	X										
Medical History	X										
Prior Medication Review	X										
Concomitant Medication Review	X	X		X		X	X	X		X	X
Monitor Trial Medication Compliance				X		X	X	X		X	
Call/Log-in to IVRS/IWRS	X	X				X	X[i]		X	X	
Dispense Trial Medication to Subject/Trial partner		X[j]				X	X[i]				
Site Witnessed Trial Medication Dose prior to PSG		X		X				X			
E-diary Training	X										
E-diary monitoring[k]	X----------								-X	X	
Activity/Sleep Watch Training		X									
Activity/Sleep Watch monitoring[l]		X----------							-X		
Clinical Procedures/Assessments		PM	AM	PM	AM			PM	AM		
AD Diagnosis: NIA-AA or DSM-5 criteria [m]	X										
Mini-Mental State Examination (MMSE) [n]	X					X		X		X	
Modified Hachinski Ischemia Score (MHIS)	X										
Insomnia Diagnosis: DSM-5 criteria [m]	X										
Insomnia Diagnosis: Insomnia Diagnostic Interview (IDI) [m]	X										
Insomnia Diagnosis: Sleep History (SHX) [m]	X										
15-item Geriatric Depression Scale (GDS)	X										
Neuropsychiatric Inventory (NPI)						X		X		X	
Clinical Global Impression – Severity (CGI-S), for insomnia						X	X		X	X	
Columbia-Suicide Severity Rating Scale (C-SSRS) - *Screening*	X										
Columbia-Suicide Severity Rating Scale (C-SSRS) - *Since Last Visit*			X		X	X	X		X	X	X[o]

		Screening Period					Treatment Period				Discontinuation	Post-Treatment
			Placebo Run-in									
Visit Number/Title:		1 Screening[a, b]	2 Screening PSG		3 Baseline PSG		4 Rand[c]	5 End of Week 2	6 End of Week 4 - PSG[cc]		Discon	Follow-up TC[d]
Scheduled Week/Day		Day -21	Day -14/-13		Day-7/-6		Day 1	Day 15	Day 29/30			14 days Post-dose
Scheduling Window by Days:		+28[e]	-3/+3[f]		-3/+4		-3/+3	-3/+5	-3/+5			+2
Digit Symbol (DS) [p]						X				X	X	
Polysomnography (PSG)			X		X				X			
Neurological Examination (NE)		X							X		X	
Physical Examination (PE)		X							X		X	
12-Lead Electrocardiogram (ECG)		X								X	X	
Vital Signs		X	X	X	X	X	X	X	X	X	X	
Height [q]		X										
Weight [q]		X								X	X	
Daily morning e-diary	Morning sleep questions [r] (trial partner- assessed)	X----------X									X	
	Sleep Quality Rating (SQR) [s] (trial partner-assessed)	X----------X									X	
	Sleep Disorders Inventory (SDI) [t] (trial partner-assessed)						X----completed weekly----X				X	
Activity/Sleep Watch (wrist worn continuously)			X----------X								X	
Single-item Sleep Quality Scale - Caregiver (SSQC) (trial partner-endpoint) [u]							X	X		X	X	
Modified Cataplexy Questionnaire (MCQ) [v]		X----------X										
Adverse Experience Monitoring		X----------X										
Laboratory Procedures/Assessments			PM	AM	PM	AM			PM	AM		
Pharmacokinetic (PK) Sampling							X			X [w]	X [x]	
Hematology		X								X	X	
Urinalysis		X								X	X	
Chemistry		X								X	X	
Serum Follicle-stimulating Hormone (FSH) Blood Samples [y]		X										
Urine Drug Screen [z]		X	X		X				X			
Alcohol Breath Test [aa]			X		X				X			
Blood for Genetic Analysis [bb]							X					

a) Assessments may be conducted over the course of more than 1 day to decrease subject/trial partner burden. See Section 7.1.5 for details.
b) Subjects with screening values/findings outside ranges described in the protocol may, at the discretion of the investigator, be re-screened. Only 1 re-screen per subject will be allowed and they should retain their same screening number. See Section 7.1.1.6 and 7.1.5.1 for more information..

c) Assessments taken prior to randomized dosing at this visit reflect placebo run-in treatment and will serve as baseline values for analysis purposes.
d) Subjects will be contacted by telephone 14 days after their last dose of trial medication, regardless of when the Discontinuation visit is performed. This is to assess for any AEs as well as review concomitant medications that may have been initiated due to an AE.
e) The +28 day visit window prior to Visit 2, is provided to accommodate up to a 4-week washout period for prohibited medications, resolve/stabilize any conditions or treatments, provide flexible scheduling, and repeat of study procedures, if needed..
f) The minimum interval of time between Visits 2, 3, and 4 should be 4 days in order to allow for confirmation of PSG results from the central PSG reading center.
g) Measurements that are performed in the PM, with the exception of the PSG, will be conducted prior to trial medication. This applies to all PSG visits.
h) Final eligibility should be confirmed prior to randomization.
i) At Visit 5, if the subject has adequate tolerability and residual insomnia (defined as CGI-S ≥3), as assessed by the investigator, dose escalation to 20 mg suvorexant for the subject will occur. If tolerability issues by the subject occur after Visit 5, new medication may be dispensed via IVRS/IWRS when the subject returns for follow-up.
j) If the PSG center is separate from the trial site, the PSG center should make arrangements with the trial site to obtain the subjects trial medication that will be administered the night of Visit 2 PSG. Trial medication should not be dispensed earlier than the actual PSG visit day.
k) E-diary monitoring should begin after completion of Visit 1.
l) Activity/Sleep watch monitoring should begin after the completion of Visit 2.
m) Source documentation to support the diagnosis of AD and insomnia should be available in the subject's source documents.
n) The subject's MMSE score will be inputted into IVRS/IWRS during the Visit 2 IVRS transaction to stratify the subject.
o) C-SSRS may be done over the telephone during the post-treatment visit.
p) Please refer to the Manual of Assessments (MOA) regarding visit specific versions to use.
q) Body Mass Index (Appendix 12.6) will be calculated only at Visit 1 from weight and height. Please refer to Appendix 12.6 for calculation of BMI.
r) The trial partner will complete a morning e-diary daily at home, preferably within an hour of the subject awakening for the day. See Section 7.1.2.2.15 for more details.
s) The SQR will be completed daily by the trial partner in the e-diary following completion of the morning sleep questions.
t) The SDI will be completed weekly by the trial partner in the e-diary following completion of the morning sleep questions. This will be initiated at Visit 4.
u) The Single-item Sleep Quality Scale – Caregiver is completed by the trial partner and is a self-assessment of the trial partner's sleep.
v) MCQ will be completed for any report of an AE of cataplexy, events suggestive of cataplexy, or falls/ataxia/worsening of balance (to rule out cataplexy).
w) The PK sample taken at this visit should be drawn between 8.5 hours to 11 hours post-dosing on the AM portions of this visit.
x) A PK sample should only be taken if the subject discontinued the trial due to an AE. The trial partner should also be asked about AE(s) that the subject experienced.
y) A blood sample for determining serum FSH should be collected only if serum FSH levels are required to determine childbearing potential as defined in Section 5.1.2.
z) At Visit 1, urine drug screen test should be sent into central lab vendor for eligibility confirmation. At visits thereafter, subjects will undergo an on-site drug test. If a subject has a positive urine drug test, a sample must be sent to the central laboratory for confirmation and the PSG should be rescheduled.
aa) Subjects should have a negative alcohol breath test on the PSG visit nights. If positive, the test may be repeated per investigator discretion; however the subject must have a negative result prior to the PSG
bb) This sample will be drawn for APOE4 genotyping and for planned analysis of the association between genetic variants in DNA and drug response. Data analysis will be limited to APOE4 genotyping if the IRB/IEC does not approve of, or if there is a documented law or regulation prohibiting, the planned analysis of the association between DNA variations and drug response. Leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. This sample should be drawn at V4; however, in the event this is not possible, it can be drawn at a subsequent post-randomization visit.
cc) Visit 6 PSG and associated assessments (eg, alcohol breath test, UDS, witnessed dose of trial medication, DS, PK sampling) are to be conducted at the PSG center; DS and PK samples are to be completed in the morning, after completion of the PSG. Safety and ancillary assessments (eg, ECG, labs, vital signs, physical exam, neurology exam, CGI-S, NPI, or C-SSRS, etc) may be completed as noted in the Trial Flow Chart or either on the day of the PSG PM Visit (Target Day 29) or PSG AM Visit (Target Day 30) .
dd) Subjects who initially screen failed based on exclusion criterion #33 (AHI and/or PLMA) on the Screening PSG may be considered for re-screening. If the Visit 2 Screening PSG would be eligible based on the amended criteria (ie, AHI ≤30 and PLMA ≤30 as confirmed by Central PSG vendor), subjects may be re-screened after consultation with the Sponsor. Details regarding the schedule of re-screening assessments will be provided in a Sponsor Communication Form.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. Documented consent from each subject's trial partner (referred to as trial partner consent) will also be obtained by the investigator or qualified designee.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion. Trial partner consent will similarly be documented by the trial partner's dated signature on a consent form and the dated signature of the person conducting the consent discussion.

A copy of the respective signed and dated consent forms (subject and trial partner consents) should be given to the subject and trial partner before participation in the trial.

The initial subject and trial partner informed consent forms, any subsequent revised written informed consent forms and any written information provided to the subject/trial partner must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative and the subject's trial partner should be informed in a timely manner if new information becomes available that may be relevant to the subject's/trial partner's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form(s) or addendum to the original consent form(s) that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature, or by the trial partner's dated signature.

Specifics about a trial and the trial population will be added to the consent form template(s) at the protocol level.

Informed consent(s) will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed at Visits 1, 2, 3, and 4 by the investigator or qualified designee to ensure that the subject (and trial partner) qualifies for the trial.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 30 days before starting the trial. If the subject has used medications to treat their insomnia within the last 12 months prior to Screening (Visit 1) these should also be recorded.

Prohibited medications will be discontinued in accordance with the schedule stated in . In the event that a subject requires an extended washout period (ie, greater than 2 weeks) for a prohibited medication(s) or other therapy, an abbreviated Visit 1 may be performed (see

Section 7.1.5.1.1). After a subject has completed the specified washout, he/she will return to complete the remaining Visit 1 procedures. Once the subject completes the Visit 1 procedures, he/she may proceed to Visit 2 if Visit 1 entry criteria are satisfied.

For sites who pre-screen subjects (eg, telephone calls prior to Visit 1), it is suggested that they review the subject's medication list for any prohibited medications and discuss the washout requirements with the subject and trial partner. These earlier discussions will allow subjects to discuss discontinuation of prohibited medications with their primary care physician once consented.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication(s), if any, taken by the subject during the trial. Any changes to medication(s) (ie, dose, frequency), including background AD therapy, should also be recorded. If the subject reports taking any prohibited medications during the study, this should be recorded as a study deviation. Concomitant medications should preferably not be changed during the course of study, without first consulting the investigator, except in cases of medical emergencies or other obvious exceptions. Please see Section 5.5 for more details.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment/randomization number.

7.1.1.8 Trial Compliance (Medication)

The trial partner is responsible for the following aspects of trial medication administration:

- Storing and dispensing the trial medication to the subject at home;

- Witnessing the subject taking trial medication at bedtime (and aiding in dosing as needed);
- Recording the subject's dosing time in the morning e-diary each day;
- Returning trial medication/blister packs to the clinic at each study visit;
- Assisting the site staff in providing any information regarding missed doses or overdoses of the trial medication.

During PSG visits, administration of trial medication will be witnessed by the investigator and/or trial staff.

It is important that subjects have taken trial medication for at least 3 days prior to a PSG visit (with the exception of Visit 2); therefore, in the event trial medication is interrupted on nights leading up to the end-of-treatment PSG visit (ie Visit 6), the visit should be rescheduled. The site should monitor trial medication compliance by the e-diary reports provided by the central e-diary vendor.

Accounting of trial medication will be conducted as specified in the Trial Flow Chart. The trial medication will be returned to the clinic at each study visit (beginning at Visit 3).

For assessment of compliance with trial medication at Visit 4 (see criterion in Section 5.1.2), the number of pills taken will be divided by (/) the number of nights from Visit 2 (inclusive) to the day prior to Visit 4. After Visit 4, trial medication compliance will be monitored and determined at each visit by subject/trial partner interview, pill count, and e-diary data. In the event that there is a discrepancy, please consult the data entry guidelines (DEGs) for specific information.

Instances of trial medication non-compliance (missed doses or overdose) should be documented as follows:

- Less medication was taken than prescribed: Instances where a subject failed to take trial medication as prescribed and missed a dose(s) should be documented. The subject and trial partner will be counseled by the study staff regarding the importance of study drug compliance.

- More medication was taken than prescribed: Instances where a subject/trial partner reports taking more medication than prescribed could be considered an AE of "*overdose*." These AEs will be reported as Events of Clinical Interest (ECI) or as Serious Adverse Events (SAE); see Section 7.2.1 for details regarding reporting of overdoses.

Monitoring for Potential Trial Medication Misuse:

To monitor for potential trial medication misuse, the site will document certain discrepancies, based on predefined criteria, where less trial medication during the 4-week double-blind treatment period is returned than expected based on the study interval and what the

subject/trial partner reports was taken. In such cases, the site will assess if the discrepancy meets the predefined criteria for an ECI of "potential trial medication misuse," based on a discrepancy of missing trial medication of more than 1 pill per week (eg, more than 2 pills over a 2 week period). Refer to see Section 7.2.3.2 for standard reporting procedure of ECIs.

Interruptions from the protocol specified treatment for 3 or more consecutive days require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

7.1.1.9 Interactive Voice Response System/Integrated Web Response System

The investigator or designee will call/log into IVRS/IWRS as specified in the Trial Flow Chart. Upon confirmation of a subject's eligibility at Visit 4, the investigator or designee will call IVRS or log into IWRS to randomize the subject. Subjects who do not meet eligibility criteria at Visit 4 will be screen-failed in IVRS/IWRS. For all randomized subjects, the investigator or designee will continue to call/log into IVRS/IWRS as per the Trial Flow Chart. For completed or discontinued subjects, the investigator or designee will make the final call/web action into IVRS/IWRS at their last trial visit. For additional information, please refer to Section 5.3.

7.1.1.10 Trial Medication Dispensing

At the visits specified in the Trial Flow Chart, the site will dispense trial medication using the IVRS/IWRS system. The site will provide the trial medication to the trial partner as well as inform the trial partner and subject of the dosing instructions.

Subjects will receive a blister pack to adequately cover the time period between each visit, according to the Trial Flow Chart. Subject/trial partner should be reminded that trial medication should remain in the blister pack provided; it should not be removed and put into another container (ie, pill box).

Specific for Visit 2: If the PSG site is separate from the clinical site, arrangements should be between both sites to obtain the subject's trial medication for the Visit 2 PSG. See footnote i in Trial Flow Chart.

7.1.1.11 E-diary and Activity/Sleep Watch Training and Monitoring

Please refer to Sections 7.1.2.2.15 for e-diary and 7.1.2.2.16 for activity/sleep watch for details.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Physical Assessments/Examinations

7.1.2.1.1 Physical Examination/Neurological Examination (PE/Neuro Exam)

A complete physical examination (PE), including a neurological exam, will be performed by a primary investigator or sub-investigator (M.D., D.O., Nurse Practitioners (N.P.) or Physician's Assistant (P.A.) in areas where N.P.s and P.A.s are licensed to perform a PE). This examination will also be performed in the event of early discontinuation. The following body systems should be included in these exams:

- Head, Eyes, Ear, Nose, and Throat
- Neck
- Cardiovascular system
- Respiratory system
- Abdomen
- Skin
- Extremities
- Neurological system (see Appendix 12.11)
- Musculoskeletal system

Examination of the breast, rectum, and urogenital system are at the investigator's discretion (ie, clinically indicated). If a physical or neurological abnormality is noted post-treatment, the investigator will indicate whether or not the result is clinically significant and if it constitutes an adverse event.

7.1.2.1.2 Lead Electrocardiogram

A 12-lead electrocardiogram will be performed according to the instructions in a separate ECG Instruction Manual by the central ECG vendor.

7.1.2.1.3 Vital Signs

Body Temperature: Body temperature will be measured with an oral or tympanic thermometer. The same method (eg, oral or tympanic, ºF/ºC) should be used for all measurements for each individual subject and should be the same for all subjects throughout the trial.

Heart Rate (HR), Blood Pressure (BP) and Respiratory Rate (RR): Subjects should be resting in a **semi-recumbent position for at least 10 minutes** prior to having vital sign measurements obtained. The **same position** should be used for all measurements for each individual subject and should be the same for all subjects throughout the trial. The correct size of the blood pressure cuff and the correct positioning on the subject's arm is essential to increase the accuracy of blood pressure measurements. The same method (eg, manual or

automated) should be used for all measurements for each individual subject and should be the same for all subjects throughout the study.

7.1.2.1.4 Body Height/Weight

Height (cm/in) and body weight (kg/lbs) will be collected and recorded. Measurements should be recorded to the nearest centimeter/inch and kilogram/pound. Body weight data will be collected without shoes and with heavy clothing (such as coats) removed. Body weight should be performed on the same scale for the same individual throughout the study.

7.1.2.2 Clinical and Neurobehavioral Assessments

The role of trial raters and administrators is to elicit optimal effort from participating subjects, while adhering to standardized administration and scoring procedures, to maximize data quality and integrity. Recommended minimum education and experience standards will be determined for each neurobehavioral and clinical assessment. Education and experience credentials of potential raters will be compared to these criteria to pre-qualify raters for trial participation. Following credentials review, pre-qualified raters will undergo training (and certification if applicable) prior to trial initiation. After the start of the trial, similar procedures will be implemented for initiating any new raters. Details regarding the rater qualifications, training, and other specifications will be specified in the Manual of Assessments (MOA). In order to qualify for the trial, all potential raters must be evaluated and approved by the Sponsor. Whenever possible, the same rater should conduct the same assessment(s) throughout the trial for a given subject and trial partner.

The MOA will also provide guidance on the order that clinical assessments should be conducted and provides estimated times for completion of the assessments.

7.1.2.2.1 The National Institute on Aging – Alzheimer's Association (NIA-AA)

The NIA-AA criteria for AD may be used to confirm the diagnosis of the subject's AD. These criteria can be found in Appendix 12.9.

7.1.2.2.2 The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)

The DSM-5 criteria for AD may be used to confirm the subject's AD diagnosis.

The DSM-5 criteria for insomnia will be used to confirm the subject's insomnia diagnosis. These criteria can be found in Appendix 12.10.

7.1.2.2.3 Mini-Mental State Examination (MMSE)

The paper version of the MMSE [11] a brief cognitive screening measure, will be administered to the subject and scored by a qualified, trained rater as described in the MOA. Raters should make every effort to elicit subjects' best effort to help ensure data validity (eg,

a subject is not too tired to complete the assessment). Additional detailed information concerning administration and scoring may also be provided in the MOA.

7.1.2.2.4 Modified Hachinski Ischemia Scale (MHIS)

The MHIS [22] a tool to identify the possibility of a vascular etiology for the subject's dementia, will be completed by a subject and trial partner interview and scored in paper form by a qualified, trained rater, as described in the MOA. Additional detailed information concerning administration and scoring may also be provided in the MOA.

7.1.2.2.5 Insomnia Diagnostic Interview (IDI)

The Insomnia Diagnostic Interview is an assessment tool which incorporates the DSM-5 Insomnia criteria into an interview format to aid in confirmation of the insomnia diagnosis and to rule out other possible causes for sleep difficulty (eg, other sleep related disorders, comorbid conditions, concomitant medications). This assessment will be completed in paper form by a qualified trained rater, by a subject and trial partner interview, as described in the MOA.

7.1.2.2.6 Sleep History (SHX)

The Sleep History assessment collects information regarding number of nights per week of problematic sleep, hour of usual bedtime, total time asleep and time to fall asleep during the past 3 months. It also collects information regarding the subject's napping habits as well as what medications the subject may have taken over the past year to treat their insomnia. This assessment will be completed in paper form by a qualified trained rater, by a subject and trial partner interview, as described in the MOA.

7.1.2.2.7 Geriatric Depression Scale (GDS)

The 15-item GDS [21] is a paper, interview-based depression screening tool; it will be completed and scored by a qualified trained rater, via subject/trial partner interview, as described in the MOA. Additional detailed information concerning administration and scoring may also be provided in the MOA.

7.1.2.2.8 Neuropsychiatric Inventory (NPI)

The NPI [20] is an interview-based tool that has been widely used in clinical trials to assess behavior in AD and other dementias. The NPI is organized into 12 behavioral domains including: Hallucinations, Delusions, Agitation/aggression, Dysphoria/depression, Anxiety, Irritability, Disinhibition, Euphoria, Apathy, Aberrant motor behavior, Sleep and night-time behavior change, Appetite and eating change. The Sleep and night-time behavior change questions will be assessed via the e-diary in this trial. The assessment captures frequency and severity of symptoms within these domains as well distress to the trial partner. The NPI (paper version) will be completed by an interview with the trial partner and scored by a qualified trained rater, as described in the MOA. Additional detailed information concerning administration, scoring and recording may also be provided in the MOA.

7.1.2.2.9 Clinical Global Impressions – Severity, for Insomnia (CGI-S)

The CGI-S scale is a psychometrically validated instrument widely used in psychopharmacologic research to provide a global assessment of illness severity (CGI-S) [32]. In this trial, the CGI-S is intended to measure the severity of the subject's insomnia. When administering the CGI-S, the rater should use his/her total clinical experience with this subject population to judge how ill the subject is at the time of the rating; this scale will be completed in paper form, and will be scored by a qualified trained rater, as described in the MOA.

7.1.2.2.10 Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidal ideation and behavior will be prospectively assessed during this study using the Columbia Suicide Severity Rating Scale (C-SSRS). The C-SSRS should be administered by trained raters at specified time points, as indicated in the Trial Flow Chart, as well as at unscheduled visits as clinically indicated. Site staff should review the contents of the C-SSRS for completeness. Note that the C-SSRS assessment is not considered complete until all available sources of information have been considered (eg, trial partner input may be necessary).

If the C-SSRS is administered by someone other than the Investigator, consider providing the completed C-SSRS to the Investigator for review, prior to their assessment of the subject, and to further inform their evaluation.

The C-SSRS is not explicit about whether the subject specifically has ideation at the time of screening. If a subject reports a prior history of ideation/behavior, the assessor should also inquire and document if this is also present at the time of the screening visit.

Subjects who at any time during this trial report suicidal ideation or behavior that is considered to be an adverse event, either between visits or during visit interviews, must be assessed by the Investigator. Subjects who report suicidal ideation with intent, with or without a plan or method (ie, a positive response to items 4 or 5 in the assessment of suicidal ideation on the C-SSRS) or suicidal behavior must be evaluated that day by a psychiatrist or other trained mental health professional who is a licensed psychologist, social worker or mental health nurse practitioner (or comparable professional qualification in countries outside the United States). Only subjects whose suicidal ideation is passive, who expressly deny any intent to act, and who, after evaluation, are not judged to be at serious risk for self-harm during the course of the trial may continue in the study; others must be discontinued from trial participation and receive appropriate clinical follow-up care to ensure their safety. In addition, any reports of 1) suicidal behavior; 2) suicidal ideation with intent, with or without a plan or method; or 3) suicidal ideation considered to be a clinically significant change, including all cases of suicidal ideation that are treatment- emergent (ie, start or worsen after trial medication is initiated) must be recorded as an Event of Clinical Interest (See Section 7.2.3.2). Sites should designate which health care professionals are to be responsible for acute care on-site and to specify referral center(s) to be used for further evaluation.

The C-SSRS will be completed in paper form, and will be scored by the qualified trained rater, via a subject (and trial partner if necessary) interview, as described in the MOA. Additional detailed information concerning administration and scoring may also be provided in the MOA.

7.1.2.2.11 Digit Symbol (DS)

The DS evaluates coordination and attention processes, and has been used extensively in the development of hypnotics [33],[34]. The DS should be administered to the subject preferably within 1 hour of getting out of bed on the morning after completion of the overnight PSG. The DS will be administered in paper form, and will be scored by qualified trained rater as described in the MOA. Additional detailed information concerning administration and scoring may also be provided in the MOA.

7.1.2.2.12 Single-Item Sleep Quality Scale-Caregiver (SSQC)

A single-item, self-rated, global sleep quality assessment called the Single-Item Sleep Quality Scale (SSQC, caregiver version) will be administered in paper form to the trial partner to assess their overall sleep quality over a 7-day recall period. The trial partner is asked to consider core components of sleep quality such as: how many hours of sleep they had, how easily they fell asleep, how often they woke up during the night, how often they woke up earlier than they had to in the morning, and how refreshing their sleep was. The SSQC will be administered to and completed by the subject's trial partner and documented by the qualified trained designee as described in the MOA. Additional detailed information concerning the administration and scoring may also be provided in the MOA.

7.1.2.2.13 Modified Cataplexy Questionnaire (MCQ)

The Modified Cataplexy Questionnaire (MCQ) is a modified version of Part V of the Stanford Center for Narcolepsy Sleep Inventory (SCNSI), a 51-item questionnaire developed and validated for the assessment of cataplexy [35]. The MCQ is to be used to assess a single episode of a subject's spontaneously-reported cataplexy-like behavior. The MCQ is completed by the subject (with trial partner assistance if needed) and will be assessed by the investigator or other qualified rater in conjunction with ECI reporting of the event, and as part of the ECI assessment of falls/ataxia/worsening of balance in order to rule out cataplexy. Additional information concerning the administration of the MCQ may also be provided in the MOA.

All reports of cataplexy, cataplexy-like events, and falls/ataxia/worsening of balance must be recorded as ECIs. The MCQ, administered in conjunction with documentation of these events, will be provided to the clinical adjudication committee. Please refer to Section 7.2.3.2 for additional information.

7.1.2.2.14 Polysomnography (PSG)

7.1.2.2.14.1 PSG Definitions and Scoring

A polysomnogram consists of an electroencephalogram (EEG) for registration of brain activity during sleep, an electro-oculogram (EOG) for registration of the eye movements during sleep, and an electromyogram (EMG) for recording chin muscle activity during sleep. Sleep stage scoring will be performed in 30-second epochs according to the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events [36]. The data will be captured electronically, in order to permit subsequent spectral analysis. PSG data will be scored by a centralized PSG reading center. Screening and baseline PSG results will initially be reviewed by qualified site scorers, prior to sending to the centralized PSG reading center for confirmation of subject eligibility.

7.1.2.2.14.2 PSG Measurements

Efficacy measures used in this study will be completed as indicated below.

a. PSG Recording and Evaluation Procedures

   The central PSG vendor for the trial will provide a standard operating procedure (SOP) detailing how screening and other PSG sessions will be conducted. The SOP will address what types of recordings will be made (eg, the EEG electrode montages, EMG electrodes, cardiac electrodes, plethysmography (strain gauges) to assess respiratory effort) or other recordings to be specified in the SOP. Thus, the definitive set of recordings to be conducted during a PSG screening session will be specified in the SOP, and the SOP will detail which of the recordings will be used on subsequent PSG recording nights.

b. Bedtime and Timing of PSG (Lights-Off and Lights-On)

   The time of bedtime in the lab should approximate the subject's bedtime at home (median habitual bedtime), where "bedtime" is defined as the time when the subject intends/attempts to fall asleep, eg, lying down or reclining with eyes closed. The environment should be conducive for sleep (ie, a darkened room, a relatively quiet room, a room free from distractions).

   The Lights-Off time for Visit 2 Screening PSG is defined as approximately ±10 minutes of the subject's reported median habitual bedtime based on approximately 4 or more days of e-diary data accumulated up to Visit 2-PSG. The Lights-Off time for Visit 3 Baseline PSG is defined as approximately ±10 minutes of the subject's reported median habitual bedtime based on the last 14 available days of e-diary data leading up to Visit 3. The median habitual bedtime for both Visits 2 and 3 will be calculated by the e-diary and displayed via the vendor e-diary reports.

   The Lights-Off time at Visit 6 will be based on the subject's habitual sleep time determined at Visit 3.

The entire PSG recording period from Lights-Off to Lights-On will be 8 hours. Immediately prior to the Lights-Off time, the subject gets into bed, room lights are turned off (ie, the room is dark), and the technician exits the room. The Lights-Off time marks the initiation of the PSG recording period. Lights-Off time must be indicated on the technician's log.

For the timing of electrode calibrations and other PSG activities, refer to the central vendor PSG SOP.

7.1.2.2.14.3 Alcohol Breathalyzer

An alcohol breath test will be performed as specified in the Trial Flow Chart. Subjects should have a negative alcohol breath test on the PSG visit nights. If a subject has a positive alcohol breath test, the test may be repeated at the investigator's discretion and the repeat test must be negative prior to conducting the PSG recording session. If the repeat test continues to be positive, the investigator should determine if the subject should be excluded (Visits 2, 3) or discontinued (Visit 6) from the trial or the PSG visit should be rescheduled. If the decision is to reschedule the PSG, this PSG should take place no sooner than 24 hours and no later than 48 hours. A breathalyzer will be provided to each site by the Sponsor.

7.1.2.2.15 Electronic Diary (e-diary)

Sites will be trained on the proper use of the e-diary by an external e-diary vendor. Sites will use the training e-diary and supplemental training materials provided by the vendor to train the trial partners on how to operate the e-diary and complete the e-diary entries, including the expectation that the trial partner report the subject's actual times to the best of their ability.

E-diary compliance will be monitored throughout the study by compliance reports that the site will review from the e-diary vendor (viewed via e-diary vendor web portal). They are expected to monitor subject data for the e-diary frequently throughout the trial. Sites should re-train trial partners who are not compliant with e-diary completion. Rigorous monitoring is especially important during the screening period (Visit 1 up to Visit 4), to ascertain problems with non-compliance as early as possible and to ensure that trial partners experiencing difficulties are re-trained, as appropriate, prior to subject's randomization at Visit 4, where a specific e-diary compliance inclusion is assessed (see Inclusion Criteria).

Trial partners will complete the Morning Diary questions via the e-diary every morning starting the morning after Visit 1 through the morning of Visit 6 (the end of the Week 4 treatment period). The questions should be completed each morning. Trial partners should be instructed to bring the e-diary to the clinic at each visit. In some instances, when the subject/trial partner returns to the site for a visit, the site staff may need to download/upload data off of the e-diary to the vendor's web portal.

In addition to the morning diary, the trial partner will complete The Sleep Quality Rating and The Sleep Disorders Inventory for Dementia within the e-diary; specifics on these questionnaires are noted below.

7.1.2.2.15.1 Morning Sleep Diary

The morning sleep diary consists of a set of questions assessing the subject's previous night's sleep, the time they wake up in the morning, napping, and administration of trial medication. These questions will be completed each morning within the e-diary by the subject's trial partner, beginning with the morning after completion of Visit 1. The trial partner will be instructed to answer the e-diary questions to the best of their ability. Additional details will be provided in supplemental documents provided by the e-diary vendor.

7.1.2.2.15.2 Sleep Quality Rating (SQR)

The SQR is a single-item questionnaire [28] consisting of 5 responses, that assesses the subject's quality of sleep from the night before. It will be completed by the subject's trial partner daily each morning in the e-diary.

7.1.2.2.15.3 Sleep Disorders Inventory for Dementia (SDI)

The SDI is a 7-item questionnaire that captures the frequency, severity, and trial partner distress of 7 sleep-disturbed behaviors during a period prior to its administration [34]. The SDI is based on an expansion of the sleep disturbance question in the NPI. The subject's trial partner will complete the SDI weekly in the e-diary, initiating at Visit 4.

7.1.2.2.16 Activity/Sleep Watch

The activity/sleep watch will be used to monitor the subject's daytime and nighttime activity (eg, walking, sitting, napping, sleeping). This device is a wrist-worn device, mimicking a watch that someone might wear, and will be given to the subject after the completion of Visit 2 PSG (assuming the subject remains eligible to continue). Subjects are expected to keep this device on at all times during the trial if possible (except when charging), and they should wear it to each of the clinic visits. Subjects should also wear the device during PSG assessments. The device is waterproof and may be worn during showering/bathing. In instances where the subject needs to take the watch off, the watch should be put back on as soon as possible to limit missing data.

Sites will be trained on the proper operation and use of the activity/sleep watch, and trained site staff will then train the subject/trial partner. Training documentation and any supplemental documentation to assist the site and subject/trial partner on the use of this device will be provided by the activity/sleep watch vendor.

The staff will be responsible for monitoring the activity/sleep watch data via a dedicated web portal, frequently, using monitoring reports. In some instances, when the subject/trial partner returns to the site for a visit, the site staff may need to download/upload data off of the activity/sleep watch to the web portal.

The details of the activity/sleep watch data scoring and variables will be part of a supplemental document.

7.1.2.2.17 Adverse Experience Monitoring

AE monitoring should be conducted throughout the entire trial. Please refer to Section 7.2 for additional information.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in Appendix 12.4.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry, Urinalysis, and Other)

7.1.3.1.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and other study specific tests are specified in Table 5.

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Alanine aminotransferase (ALT)	Appearance	Vitamin B12
Hemoglobin	Albumin	Bacteria	Folate
Platelet count	Alkaline phosphatase	Bilirubin	Follicle-stimulating Hormone (FSH) – female only, if applicable
RBC count	Aspartate aminotransferase (AST)	Blood	Thyroid-stimulating Hormone (TSH; with reflex free T4 and T3 if TSH abnormal)
WBC (total and differential)	Bicarbonate	Color	Urine Drug Screen
	Bilirubin, Total	Glucose	Methylmalonic acid if B12 or Folate abnormal
	Blood Urea Nitrogen (BUN)	Ketone	Homocysteine level if B12 or Folate abnormal
	Calcium	Leukocyte esterase	
	Chloride	Microscopic exam, if abnormal results are noted	
	Creatine Phosphokinase	Mucus	
	Creatinine	Nitrite	
	Creatinine Clearance Estimation	pH	
	Glucose	Protein	
	Lactate dehydrogenase	RBC count	
	Magnesium	Specific gravity	
	Phosphorus	WBC count	
	Potassium		
	Sodium		
	Uric Acid		
Laboratory safety tests do not require subjects to be in a fasting state.			

All laboratory samples will be collected as per the Trial Flow Chart and they will be analyzed by the central laboratory. Detailed instructions for specimen collection, packaging, and shipment will be provided in a Laboratory Manual by the Central Laboratory.

Subjects with screening laboratory values/findings outside ranges described in the protocol may, at the discretion of the investigator, have a repeat determination performed. If the repeat value satisfies the criterion, subjects may continue in the screening process. Only the specific out of range value/finding should be repeated (not the entire panel). See Appendix 12.12 for guidance on out of range laboratory values, and refer to a supplemental document for follow up requirements for evaluation of ALT and/or AST values elevated ≥3x ULN (Upper Limit of Normal).

7.1.3.1.2 Urine Drug Screen

A urine drug screen (UDS) will be performed as specified in Trial Flow Chart. The Visit 1 UDS must be sent to the central laboratory vendor for confirmation. The subject must have a negative UDS in order to move onto Visit 2.

For all other visits, an on-site urine drug screen will be performed at the site. If the test is positive, a confirmatory urine drug screen will be sent to the central laboratory for confirmation, and subject should be tentatively rescheduled until a confirmatory test is known. If the test is confirmed as positive, the Sponsor should be contacted to determine continued eligibility.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

The final decision as to which plasma samples collected will be assayed for evaluation of pharmacokinetics/pharmacodynamics will be made by the Sponsor's Departments of Pharmacokinetics, Pharmacodynamics, and Drug Metabolism (PPDM) and the Clinical Monitor, (eg, samples at lower doses may not be assayed if samples at higher doses reveal undetectable drug concentrations). If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

7.1.3.2.1 Blood Collection for Plasma MK-4305

Sample collection, storage and shipment instructions for plasma samples will be provided in a laboratory manual provided by the central laboratory.

7.1.3.3 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the laboratory manual provided by the central laboratory. See Appendix 12.3 for the Pharmacogenomics Informational Brochure.

7.1.3.4 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of Future Biomedical Research:

Leftover DNA for future research.

See Appendix 12.2 for the Collection and Management of Specimens for Future Biomedical Research.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit, as outlined in Section 6.0 Trial Flow Chart, should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject’s personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.1.4.2 Blinding/Unblinding

When the investigator or sub-investigator needs to identify the drug used by a subject and the dosage administered in case of emergency e.g., the occurrence of serious adverse experiences, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or sub-investigator the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the sponsor. The emergency unblinding call center will make a record promptly however, the investigator or sub-investigator must enter the intensity of the adverse experiences observed, their relation to study drug, the reason thereof, etc., in the medical chart etc., before unblinding is performed.

Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call

center is not available for a given site in this trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

7.1.4.3 Domiciling

Subjects and their trial partners will report to the clinical research unit (CRU)/PSG facility on the day of each PSG visit (Visits 2, 3, and 6) and remain in the unit until all procedures for that visit have been completed on the following day.

7.1.4.4 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

- PSG equipment – details can be found in supplemental documentation at the site/or corresponding PSG facility.
- Alcohol Breathalyzer – details can be found in supplemental documentation at the site, provided by the Sponsor.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

Trial Partner Trial Specifics (non-inclusive):

- For the trial partner to be eligible, they must be present in the same residence (awake or asleep) when the subject is sleeping at night.
- While at home, the subject/trial partner should maintain their current sleeping arrangements. The trial partner does not need to be awake during the night in order to complete the morning e-diary questions.

- Every effort should be made by the trial partner to accompany the subject to each visit. However, at the discretion of the investigator, exceptions are acceptable. In circumstances where the trial partner is unable to accompany the subject to a visit, the trial partner should discuss alternative arrangements with the site (eg, subject transportation, return of trial medication) and availability of the trial partner to complete trial assessments (eg, by phone) as soon as possible**.**

- Depending on the subject, willing to spend the night at the PSG facility (separate room), if needed to assist in accurately completing the morning e-diary questions. If the trial partner is unable to spend the night, the trial partner should discuss with the site alternative arrangements.

- Every effort should be made to maintain the same trial partner for the duration of the study. However, if the trial partner is unable to continue with the study requirements, the trial partner should discuss with the site whether a suitable replacement can be found. If a new trial partner is identified, the new trial partner will need to sign the trial partner informed consent.

7.1.5.1 Screening

Each visit should be performed as noted in the Trial Flow Chart. For visits that require additional explanations, please see those specific visits below.

7.1.5.1.1 Visit 1 Screening

At Visit 1, subjects who provide informed consent will undergo a series of diagnostic and safety assessments to determine if they are eligible for the trial. A designated trial partner must also consent to participate and will be asked to complete certain assessments throughout the trial. Subjects planning to undergo elective procedures during the study (known prior to trial start) should not proceed until such procedures have been completed.

Documentation requirements to support the subject's diagnoses of AD and insomnia, as well as trial partner eligibility (eg, inclusion 10) can be found in a supplemental source documentation guidance document.

If a site wishes to split the subject's Visit 1, they may do so for the following reasons:

- Visit 1 may be split to decrease the burden of the subject/trial partner due to the length of the visit.

- Visit 1 may be split in the event that a subject requires an extended washout period (ie, greater than 2 weeks) for prohibited medication(s) or other therapy, in accordance with ; this is to help avoid the necessity to repeat any prior Visit 1 procedures assessed at the initial Visit 1.

If the site chooses to split Visit 1 for either of the reasons noted above, the following is a recommendation of what procedures (non-inclusive) should be conducted at the initial portion of Visit 1:

- Obtain informed consent
- Review sleep and medical history
- Preliminary review of inclusion/exclusion criteria
- Review of prior and concomitant medications
- Assignment of subject baseline/screening number from the data entry system

The final portion of Visit 1 should be conducted preferably within 2 days of the initial portion of Visit 1, if splitting due to visit length. Subjects required to washout of a prohibited medication will return to complete the final Visit 1 procedures once the washout has been completed. Subjects with positive UDS due to prohibited medication(s) at Visit 1 must repeat the UDS and have a negative UDS to move on to Visit 2. Once a subject completes Visit 1 in its entirety, he/she may proceed to Visit 2 one week later. Guidelines for how to enter data into the data collector will be provided in the DEGs.

Subjects who meet the overall criteria at the completion of Visit 1 will return home and their trial partner will begin reporting observed sleep times in the e-diary the following morning.

A subject may be re-screened, but the Sponsor should be consulted prior to any re-screening. Re-screenings will be handled on a case-by-case basis. Only 1 re-screen is allowed per subject.

7.1.5.1.2 Visit 2 Screening PSG and Visit 3 Baseline PSG

Visit 2 Screening PSG:

Subjects/Trial Partners will return to the clinic for Visit 2, per the Trial Flow Chart, for an overnight Screening PSG. Subjects will be expected to have completed their washout of any prohibited medications, if applicable. Subjects/Trial partners will be instructed to arrive at the sleep lab approximately 2 hours prior to their median habitual bedtime (obtained by the site by viewing e-diary reports). Subjects/Trial partners should be advised to eat dinner prior to arrival at the sleep lab and subjects should be reminded to refrain from alcohol, caffeine, and smoking as recommended in Section 5.7.2.

The trial partner should bring the e-diary to the clinic and the site should review e-diary compliance and perform any re-training, if necessary. The site should also review applicable eligibility criteria prior to the PSG. For urine drug screen and alcohol breath test details, please see Sections 7.1.3.1.2 and 7.1.2.2.14.3, respectively.

After subjects have met initial Visit 2 eligibility, the site will call/log into IVRS/IWRS where they will be prompted to enter the subject's MMSE score obtained at Visit 1. This entry is critical for proper stratification. Please ensure no transcription errors occur within

IVRS/IWRS by reviewing the IVRS/IWRS output after the transaction has completed. If there is a transcription error, please contact the IVRS/IWRS vendor immediately to correct the score.

The site, via the IVRS/IWRS system, will then dispense single-blind placebo trial medication to the subject and the subject will be instructed to take their trial medication within 30 minutes of their bedtime (“Lights-Off”) prior to the start of the PSG recording; dosing will be witnessed by site staff personnel. (Note: if the PSG center is separate from the trial site, the PSG center should make arrangements with the trial site to obtain the subject’s trial medication. The "Lights-Off" time will be at approximately the subject’s median habitual bedtime. Subjects will spend the night in the sleep laboratory for an 8-hour PSG recording session (Screening PSG) to determine trial eligibility based on screening PSG variables and detection of other sleep and neurological disorders. Depending on subject’s need, the trial partner or alternate person (e.g., family, children), if possible, should also be willing to spend the night at the sleep lab in an effort to help acclimate the subject and to be able to answer the morning e-diary questions accurately the following morning. Alternate arrangements can be made in the event that a trial partner is unable to attend all study visits. The following morning, the subject will be awakened (or will be allowed to get out of bed if already awake) after 8 hours of PSG recording and will complete their normal morning routine, followed by assessments, such as the DS and PK sampling as indicated in the Trial Flow Chart. The subject should continue to wear the activity/sleep watch. The e-diary should be completed by the trial partner prior to leaving the clinic. It is recommended that caffeinated products not be consumed until after completion of all morning procedures.

The Screening PSG will be initially reviewed by a Sponsor-approved PSG scorer at a PSG certified site, to determine if the PSG entry criteria have been met. It is highly recommended that the site scores the PSG for eligibility criteria immediately following completion of the PSG recording; this will prevent ineligible subjects from leaving the clinic with trial medication, the e-diary, and the activity/sleep watch.

If after the initial review by the site, the subject has not met the criteria for Visit 2 Screening PSG, the subject should be excluded and the PSG recording should not be sent to the central PSG reading center. The e-diary should be returned to site personnel. (Note: if the subject’s PSG scores are borderline to the eligibility criteria, sites may send the PSG recording to the central PSG center for confirmation).

If the subject is deemed eligible after the site has reviewed the PSG, the site will forward the Screening PSG recording to the Central PSG Reader for confirmation. The trial partner will be given the single-blind placebo trial medication, for the subject, with instructions to dose within 30 minutes of bedtime; the trial partner will be instructed to witness the nightly dosing and to continue completing the morning e-diary daily. The subject will be given the activity/sleep watch to wear continuously throughout their trial participation and will begin wearing the watch at the completion of Visit 2, prior to leaving the clinic. The site will train the subject/trial partner on the activity/sleep watch at this visit. In rare instances where the activity/sleep watch is unavailable to be dispensed at Visit 2, the watch may be dispensed at a

later date, but a minimum of 3 days prior to Visit 3, to allow acclimation to the activity/sleep watch.

Subjects who meet the PSG screening criteria at the completion of Visit 2, as assessed by the Central PSG vendor, will continue in the placebo run-in period. Sites should monitor subject data for both the e-diary and the activity/sleep watch using respective vendor monitoring reports.

Confirmation of the qualifying Screening PSG variables and other sleep and neurological disorders from the central PSG vendor must be received by the site prior to conducting the Visit 3 Baseline PSG. If the subject has not met entry criteria and they were released home prior to notification, sites should advise the subject/trial partner to return to the clinic to return trial medication, e-diary, activity/sleep watch, and any other trial supplies.

Subjects who initially screen failed based on exclusion criterion #33 (AHI and/or PLMA) on the Screening PSG may be considered for re-screening. If the Visit 2 Screening PSG would be eligible based on the amended criteria (ie, AHI $\leq$30 and PLMA $\leq$30 as confirmed by Central PSG vendor), subjects may be re-screened after consultation with the Sponsor. Details regarding the schedule of re-screening assessments will be provided in a Sponsor Communication Form.

Visit 3 Baseline PSG:

If subjects continue to meet trial criteria, they and their trial partner will return to the clinic for Visit 3 Baseline PSG. This visit should be conducted in a similar manner as outlined above for Visit 2 Screening PSG (eg, subject/trial partner arrive per median habitual bedtime, site staff witness dose of trial medication, scoring of the subject's PSG prior to subject/trial partner leaving, trial partner completes e-diary, etc.). Subjects should also be wearing the activity/sleep watch. For those subjects who do not meet eligibility criteria, they should return trial medication, e-diary, activity/sleep watch and any other trial supplies. Subjects who meet the Visit 3 Baseline PSG criteria, as assessed by the Central PSG vendor, will continue the placebo run-in period until returning to the clinic for Visit 4 (randomization).

7.1.5.2 Treatment Period – Visits 4 through 6

Each visit should be performed as noted in the Trial Flow Chart. For visits that require additional explanations, please see those specific visits below.

Trial medication, the e-diary, and the activity/sleep watch should accompany the subject/trial partner at each visit for site review.

Visit 4:

Subjects will be assessed for final eligibility per Inclusion/Exclusion criteria as described in Section 5.1, including ensuring compliance with trial medication, e-diary, and activity/sleep watch. The subject may be randomized into the trial and will be assigned a randomization number (via IVRS/IWRS) only after ensuring that the subject meets all criteria. After final

eligibility has been determined, subjects will undergo assessments as noted in the Trial Flow Chart. Subjects/trial partners should not be informed of when they are transitioning into a different trial period (eg, treatment period).

Visit 5:

At Visit 5, assessments will be conducted as stated in the Trial Flow Chart. For details on dose escalation, please refer to Section 5.2.1.2.

Visit 6:

Subjects/Trial partners will return for their final in-clinic/overnight visit, Visit 6 End of Week 4 PSG. Subjects/Trial partners will be instructed to arrive at the sleep lab approximately 2 hours prior to their median habitual bedtime as calculated at Visit 3 Baseline PSG. Subjects/Trial partners should be advised to eat dinner prior to arrival at the sleep lab and subjects should be reminded to refrain from alcohol, caffeine, and nicotine as recommended in Section 5.7.2.

Subjects/Trial partners should be instructed to bring all trial supplies (eg, e-diary, activity/sleep watch, trial medication) to the site for final compliance and accountability. The subject should still be wearing the activity/sleep watch until completion of the PSG the following morning.

Visit 6 PSG and associated assessments are to be conducted at the PSG center the night of (ie, alcohol breath test, UDS, witnessed dose of trial medication) or the morning after (ie, DS and PK sampling) completion of the PSG. Safety and ancillary assessments (eg, ECG, labs, vital signs, physical exam, neurology exam, CGI-S, NPI, or C-SSRS, etc) may be completed as noted in the Trial Flow Chart either on the day of the PSG PM Visit (Target Day 29) or PSG AM Visit (Target Day 30) to provide flexibility for subjects and trial partners that need to travel between the primary research site and a PSG center or to assist site staff with scheduling.

For trial medication dosing, please refer to Section 5.2.1.2. For urine drug screen and alcohol breath test details, please see Sections 7.1.3.1.2 and 7.1.2.2.14.3 , respectively.

The PK sample taken at this visit should be drawn between 8.5 to 11 hours post-dosing of trial medication on the AM portion of the visit.

The PSG recording for this visit does not need to be scored by the site. The Visit 6 PSG recording will be forwarded directly to the Central PSG Reader for scoring.

7.1.5.3 Procedures for Subjects Who Discontinue Treatment But Continue in the Trial

Every attempt should be made to have subjects remain on trial medication and continue to follow all protocol procedures. Subjects who discontinue from trial medication, but choose to remain in the trial will follow the guidance below:

- For subjects who discontinue trial medication prior to Visit 5, but will continue in the trial, Visits 5 and 6 are to be completed as per the Trial Flow Chart (with the exception of no trial medication being dispensed).

- For subjects who discontinue trial medication after Visit 5, but will continue in the trial, Visit 6 is to be completed as per the Trial Flow Chart.

In the event subjects (now off trial medication) want to discontinue trial participation at a later time, the Discontinuation Visit should be performed per the Trial Flow Chart (eg, in a case where a subject continues trial medication prior to Visit 5 and completes Visit 5, but then after Visit 5 discontinues the trial, a Discontinuation visit will be performed).

Details on how data will be entered into the data collector for these subjects can be found in the DEGs.

7.1.5.4 Post-Treatment Follow-up

Sites will be required to perform a follow-up phone call 14 days after the last dose of trial medication (regardless of the date of the Discontinuation Visit, if applicable) to determine if any AEs have occurred since the post-trial clinic visit.

If a subject (or trial partner on behalf of the subject) reports suicidal ideation and/or behavior, then the C-SSRS must be conducted. Subjects who report suicidal ideation with intent, with or without a plan or method or suicidal behavior must be taken to the site that same day to be evaluated by a psychiatrist or other trained mental health professional who is a licensed psychologist, social worker or mental health nurse practitioner (or comparable professional qualification in countries outside the United States), as noted in Section 7.1.2.2.10.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 14 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

In this trial, an overdose is any dose higher than the specified dose to be administered nightly in a calendar day (accidental or intentional).

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 14 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a cancer;
- Is associated with an overdose.

Refer to Table 6 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor’s product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment

and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

Additional protocol specific ECIs for this trial include:

3. Suicidal ideation and/or behavior
4. Events associated with potential for abuse
5. Complex sleep-related behaviors
6. Hypnagogic or hypnopompic hallucinations
7. Somnolence resulting in dose reduction or discontinuation of trial medication
8. Sleep paralysis and sleep-onset paralysis (adjudicated)
9. Cataplexy (adjudicated)
10. Falls/ataxia/worsening of balance (adjudicated to rule out cataplexy)
11. Agitation – daytime or nighttime
12. Confusion or cognitive impairment - daytime or nighttime

Regarding items #11 and 12 above, agitation, confusion or cognitive impairment should be considered an ECI if in the investigator's opinion an acute worsening from baseline has occurred, or there is an unusual or atypical presentation of symptoms for a given subject.

A guidance document for the reporting of ECIs will be provided to sites to provide specific information relevant to the collection and reporting of these events.

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 6. The investigator's assessment of causality is required for each adverse event. Refer to Table 6 for instructions in evaluating adverse events.

Table 6 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor’s product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

7.3.2 Clinical Adjudication Committee

A Clinical Adjudication Committee (CAC) will evaluate the following events for the purposes of confirming them according to the criteria in Section 8.0 – Statistical Analysis Plan, as well as evaluating the presence of confounding factors.

ECIs pre-specified for adjudication are those that suggest potential intrusion of REM into either:

1) Wakefulness (ie, cataplexy or events suggestive of cataplexy) or,

2) Initiation of sleep (eg, sleep onset paralysis) or,

Falls/ataxia/worsening of balance will also be adjudicated to enhance data collection for these events, and to further evaluate whether an event might be due to cataplexy.

All personnel involved in the adjudication process will remain blinded to treatment allocation throughout the trial. Specific details regarding endpoint definitions can be found in the Adjudication Charter.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding/final database lock, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Separate analysis plans (ie, separate documents from the sSAP) will be developed to detail other planned analyses (ie, those specific to the analysis of PK data and pharmacogenomics analysis).

8.1 Statistical Analysis Plan Summary

All evaluations of suvorexant (with the exception of selected exploratory analyses) will be conducted without distinguishing the dose of suvorexant received (10 mg or 20 mg).

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Section 8.2 through 8.12.

Study Design Overview	A Phase III Randomized, Placebo-Controlled Clinical Trial to Study the Safety and Efficacy of Suvorexant (MK-4305) for the Treatment of Insomnia in Subjects with Alzheimer's Disease
Treatment Assignment	The study will be conducted as a double-blind study under in-house blinding procedures. Treatment .allocation/randomization will occur centrally using an interactive voice response system (IVRS). Subjects will be assigned randomly in a 1:1 ratio to either suvorexant or placebo. The randomization will be stratified according to MMSE score (mild: 21 to 26, moderate: 12 to 20) assessed at the screening visit. Randomization will be monitored to ensure that approximately 30% of randomized subjects are in the moderate AD stratum.
Analysis Populations	Efficacy: Full Analysis Set (FAS) The FAS population is defined as randomized subjects who had: 1) at least 1 post-randomization observation for the analysis endpoint subsequent to at least 1 dose of trial medication and, 2) baseline data for those analyses that require baseline data. The number of subjects included in the FAS population may vary across endpoints due to the degree of missing data for each endpoint. Safety: All Subjects as Treated (ASaT) The ASaT population includes all subjects who took at least 1 dose of randomized trial medication. Subjects will be analyzed according to the treatment actually received.
Primary Endpoint(s)	PSG-derived Total Sleep Time (TST) in minutes, at Week 4.
Key Secondary Endpoints	PSG-derived Wakefulness After Sleep Onset (WASO) in minutes, at Week 4.
Statistical Methods for Key Efficacy Analyses	The primary hypothesis will be evaluated by comparing suvorexant and placebo with respect to change from baseline in PSG-derived total sleep time (TST) in minutes, at Week 4. Analysis of covariance (ANCOVA) using a general linear model for change from baseline in TST at Week 4, with terms for baseline TST value, baseline severity category (MMSE score of 12 to 20, 21 to 26), age category (non-elderly, elderly), gender, region, and treatment, will be used to evaluate the primary hypothesis. The significance of the difference between suvorexant and placebo in least squares means for change from baseline in TST will be evaluated using an appropriate contrast of model parameters, and according to the multiplicity testing strategy described below.
Statistical Methods for Key Safety Analyses	Program specific pre-specified adverse events of clinical interest (ECIs) will be assessed as Tier 1 events in this study. Estimates of the difference between treatments in the percentage of subjects with these events, 95% confidence intervals, and p-values, will be computed for these Tier 1 events. Tier 2 events are those events for which treatment differences and 95% confidence intervals (but not p-values) will be provided. Tier 3 safety parameters are those for which only descriptive statistics for treatment differences will be provided. Tier 1, 2 and 3

	safety parameters are summarized in Table 8 of Section 8.6.2, Statistical Methods for Safety Analysis.
Interim Analyses	No interim analysis for efficacy or safety is planned for this study.
Multiplicity	Statistical significance for the primary and secondary efficacy hypotheses will be based on a fixed sequential multiplicity strategy to control the overall Type I error at the two-sided 5% significance level. If the comparison of the primary endpoint between treatments is significant at the 5% significance level, then the comparison of the secondary endpoint between treatments will be evaluated at the 5% level of significance.
Sample Size and Power	This study will randomize approximately 130 subjects into the suvorexant group and approximately 130 subjects into the placebo group, for a total of 260 randomized subjects in order to obtain 117 evaluable subjects per treatment group. **Power for the primary hypothesis** With approximately 130 subjects randomized per treatment group and assuming a standard deviation of 68 minutes for change from baseline in TST (based on insomnia subjects ≥65 years who had PSG in MK-4305 Protocols 028 and 029 pooled), a 2-sided α=0.05, and a dropout rate of 10% at Week 4 (approximately twice the drop-out rate observed for insomnia subjects ≥65 years who had PSG in MK-4305 Protocols 028 and 029 pooled), the study has approximately 92% power to detect a true difference of 30 minutes between treatment groups with respect to change from baseline in TST at Week 4 (standardized effect size (SES) = 0.44); it has approximately 80% power to detect a 25-minute difference (SES = 0.37).

8.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

The study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol violators have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for trial medication assignment. Randomization will be implemented by an interactive voice response system (IVRS).

8.3 Hypotheses

Objectives and hypotheses of the study are stated in Section 3.

8.4 Analysis Endpoints

Key efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints. Exploratory efficacy endpoints will be documented in the sSAP.

8.4.1 Efficacy and Ancillary Endpoints

Rationale for the key efficacy endpoints is given in Section 4.2.3.1 and an initial description of the efficacy measures is included in Section 7.1.2.2. In general, if a baseline value exists for a particular efficacy measure, then the change from baseline in that value will be evaluated. The primary efficacy evaluation period of this trial is the 1-month double-blind treatment period.

Primary Endpoint

The primary endpoint for this study is:

- total sleep time (TST) as measured in the sleep laboratory by PSG during an 8-hour recording period beginning at the subject's habitual bedtime, at Week 4 (minutes)

Secondary Endpoint

The secondary endpoint for this study is:

- wakefulness after persistent sleep onset (WASO) as measured in the sleep laboratory by PSG during an 8-hour recording period beginning at the subject's habitual bedtime, at Week 4 (minutes)

Exploratory Endpoints

The exploratory endpoints for this trial (eg other PSG parameters which further characterize the subject's sleep, treatment response based on achieving a clinically relevant predefined improvement in TST, sleep and activity parameters measured continuously during the trial by the activity/sleep watch, assessments of the subject's and trial partner's sleep, neuropsychiatric behavior inventory parameters and trial partner distress associated with the identified behaviors, high level assessments of the subject's mental state and performance, and trial medication titration history) will be detailed in the sSAP.

8.4.2 Safety Endpoints

An initial description of the safety measures is included in Sections 7.1.2.1, 7.1.2.2.10 and 7.1.3.

Safety and tolerability will be assessed by statistical and clinical review of the following data collected throughout the study: adverse experiences (AEs), laboratory values, ECGs, physical examinations, vital signs and treatment-emergent suicidality.

The Columbia-Suicide Severity Rating Scale (C-SSRS) will be used to systematically and prospectively ascertain and document the occurrence of suicidal events (ie, ideation and behavior). Responses on the C-SSRS are classified according to 11 pre-specified categories as described in Appendix 12.14.

The primary time period for safety analyses is the 1-month double-blind treatment period; safety summaries for the 14-day follow-up period (following the treatment period) will also be summarized.

Safety endpoints are classified into 3 tiers (see Statistical Methods for Key Safety Analyses in Section 8.1 for Tier definitions).

Tier 1 Safety Endpoints include the following program-specific pre-specified events of clinical interest (ECIs):

1. Suicidal ideation and/or behaviors
2. Events associated with potential for abuse
3. Complex sleep-related behaviors
4. Hypnagogic or hypnopompic hallucinations
5. Somnolence resulting in dose reduction or discontinuation of trial medication
6. Sleep paralysis and sleep-onset paralysis (adjudicated)
7. Cataplexy (adjudicated)
8. Falls/ataxia/worsening of balance (adjudicated to rule out cataplexy)
9. Agitation (daytime/nighttime)
10. Confusion or cognitive impairment (daytime/nighttime)

Tier 2 Safety Endpoints include (the proportion of subjects with):

1. Any AE
2. Any Serious AE
3. Any Drug-Related AE
4. Any Serious and Drug-Related AE
5. Discontinuation due to AE
6. Specific AEs, System Organ Class (SOC) AEs , and Predefined Limits of Change (PDLC) which have incidence of ≥4 subjects in 1 of the treatment groups

Tier 3 Safety Endpoints include:

1. Specific AEs, SOC AEs or PDLCs which have incidence <4 subjects in all of the treatment groups
2. Change from baseline results for labs, ECGs and vital signs

In addition to the pre-specified ECI of suicidal ideation and/or behaviors based on AE reporting, which will be analyzed as a Tier 1 safety endpoint as described above, suicidal ideation and/or behaviors as reported on the C-SSRS will also be considered as a Tier 1 safety endpoint, in the event an investigator may determine for a given subject that suicidal

ideation reported on the C-SSRS is not in fact an adverse event. An analysis of this additional Tier 1 safety endpoint, based on positive responses on the C-SSRS rather than on AEs, will also be performed. Three pre-specified categories which summarize information reported on the C-SSRS (suicidal ideation, suicidal behaviors, and non-suicidal self-injurious behavior) and 5 pre-specified subcategories related to suicidal ideation and 5 pre-specified subcategories related to suicidal behaviors, as outlined in Appendix 12.14, will be considered as either Tier 2 or Tier 3 events (depending on the number of subjects with events observed during the assessment period). Counts for these pre-specified categories and subcategories will be analyzed according the strategy outlined in Section 8.6.2, both with and without consideration of prior history of suicidal ideation and/or behaviors.

8.4.3 Derivations of Efficacy Endpoints

PSG Data

Sleep stage scoring of the PSG recordings will be performed for each 30-second epoch according to the 2007 American Academy of Sleep Medicine (AASM) scoring conventions by a central sleep scoring laboratory. Each 30-second epoch will be scored as wake, Stage N1, N2, N3 or R. For example, TST is defined as the sum of Stages N1+N2+N3+R (in minutes) and WASO is defined as the sum of all wake epochs beginning from persistent sleep (ie, the first epoch of 20 consecutive epochs of Stage N1, N2, N3 or R sleep) to lights on (in minutes). The primary and exploratory PSG endpoints for analysis will be derived by the central sleep scoring laboratory from this information according to pre-specified PSG endpoint definitions contained in a PSG endpoint definition document. The day range for PSG analysis endpoints is defined as follows: Week 4 (+/-7 days from the target Day 30).

8.4.4 Derivations of Safety Endpoints

Cataplexy and sleep-onset paralysis are defined as ECIs in this study which will be adjudicated by an independent, external CAC. Falls/ataxia/worsening of balance will also be evaluated as part of this adjudication process to rule out cataplexy. The adjudicated events will be evaluated as Tier 1 events as part of the tiered analysis strategy (see Section 8.6.2). Specific adverse experience terms relating to these ECIs will be identified and confirmed as part of the adjudication process prior to final study unblinding. Other Tier 1 events (eg, selected events associated with potential for abuse and complex sleep-related behaviors) that consist of multiple AE terms will be defined separately prior to unblinding.

Changes from baseline during the treatment period will be evaluated for laboratory, vital signs, and ECG data in accordance with predefined criteria noted Appendix 12.13.

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all randomized subjects who:

- Received at least 1 dose of trial medication,
- Have at least 1 post-randomization observation for the analysis endpoint subsequent to at least 1 dose of trial medication
- Have baseline data for those analyses that require baseline data

The number of subjects included in the FAS population may vary across endpoints due to the degree of missing data for each endpoint and the applicability of exclusion criteria to each endpoint (eg, need for baseline data only applies to those endpoints that are derived relative to baseline).

A supportive analysis using the Per-Protocol population will be performed for the primary and secondary efficacy endpoints. The Per-Protocol population excludes subjects due to important deviations from the protocol that may substantially affect the results of the primary and secondary efficacy endpoints. Potential violations that may be result in the exclusion of a subject from the Per-Protocol population will be defined and determined and documented in a separate memo prior to the unblinding of the database.

Subjects will be included in the treatment group to which they were randomized for the analysis of efficacy data using both the FAS and Per-Protocol populations. Details on the approach to handling missing data are provided in Section 8.6.1 Statistical Methods for Efficacy Analysis.

8.5.2 Safety Analysis Population

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least 1 dose of trial medication. Subjects will be included in the treatment group corresponding to the trial medication they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect trial medication for the entire treatment period will be included in the treatment group corresponding to the trial medication actually received.

At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of trial medication is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.6 Statistical Methods

Statistical testing and inference for efficacy analyses is described in Section 8.6.1 and in Section 8.6.2 for safety analyses. Efficacy results that will be considered to be statistically significant after consideration of the strategy for controlling the Type I error are described in Section 8.8, Multiplicity. Nominal p-values may be computed for other efficacy analyses as a measure of the strength of the evidence of a treatment effect for an endpoint rather than a formal test of hypothesis. Unless otherwise stated, all statistical tests will be conducted at the 5% level of significance (2-sided). All p-values will be displayed to 3 decimal places.

All evaluations of suvorexant (with the exception of selected exploratory analyses) will be conducted without distinguishing the dose of suvorexant received (ie, 10 mg or 20 mg).

8.6.1 Statistical Methods for Efficacy Analysis

An analysis of covariance (ANCOVA) using a general linear model for change from baseline in TST at Week 4 with terms for baseline value, baseline severity category (MMSE score of 12 to 20, 21 to 26), age category (non-elderly, elderly), gender, region, and treatment, will be used to evaluate the primary hypothesis. The significance of the difference between suvorexant and placebo in least squares means for TST will be evaluated using an appropriate contrast of model parameters. Sensitivity analyses using this ANCOVA model in conjunction with multiple imputation (MI) to estimate the missing data and measurements collected following discontinuation of trial medication (if available) will also be performed. Details regarding the sensitivity analyses will be provided in the sSAP. The same ANCOVA model will be used to evaluate change from baseline in WASO at Week 4 according to the multiplicity testing strategy as described in Section 8.8. Statistical methods for the analysis of exploratory endpoints will be detailed in the sSAP.

Table 7 summarizes key efficacy analyses.

Table 7 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Timepoint)	Statistical Method	Analysis Population	Missing Data Approach
Primary:			
TST – Change from baseline at Week 4	ANCOVA†	Full Analysis set	Primary: Observed data Sensitivity: Multiple Imputation (Tipping Point)
Secondary:			
WASO – Change from baseline at Week 4	ANCOVA†	Full Analysis set	Primary: Observed data Sensitivity: Multiple Imputation (Tipping Point)
†ANCOVA model with terms for baseline value, baseline severity category (MMSE score of 12 to 20, 21 to 26), age category (nonelderly, elderly), gender, region, and treatment. ANCOVA = Analysis of Covariance Observed data = data observed during Treatment Phase which does not include data collected following discontinuation of trial medication			

8.6.2 Statistical Methods for Safety Analysis

Safety and tolerability will be assessed by statistical and clinical review of the following data collected throughout the study: adverse experiences (AEs), laboratory values, ECGs, vital

signs, and treatment-emergent suicidality derived from the C-SSRS. Safety will be evaluated with doses combined; selected safety analyses will be performed for doses separately.

The analysis of safety results will follow a tiered approach (Table 8). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered as Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. P-values and/or 95% confidence intervals for between-treatment differences in the percentage of subjects with events will be computed using the Miettinen and Nurminen (unstratified) method according to the safety parameter tier as defined above.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory, vital signs, and ECG parameters that are not pre-specified as Tier 1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 subjects in any treatment group exhibit the event; all other adverse experiences and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.

Continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters that are not pre-specified as Tier 1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Program specific pre-specified adverse events of clinical interest (ECIs) including: suicidal ideation and/or behaviors, events associated with potential for abuse, complex sleep-related behaviors, hypnagogic or hypnopompic hallucinations, somnolence resulting in dose reduction or discontinuation of trial medication, sleep paralysis and sleep-onset paralysis (adjudicated), cataplexy (adjudicated), falls/ataxia/worsening of balance (adjudicated to rule out cataplexy), agitation (daytime/nighttime), and confusion or cognitive impairment (daytime/nighttime) are pre-specified as Tier 1 events. See Table 8 for a classification of safety endpoints as Tier 1, 2, or 3 and the corresponding analysis strategy for each endpoint.

Table 8 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint[†]	p-Value[§]	95% CI for Treatment Comparison[§]	Descriptive Statistics
Tier 1	Adverse Events during the four-week treatment period:			
	• Suicidal ideation and/or behaviors	X	X	X
	• Events associated with potential for abuse	X	X	X
	• Complex sleep-related behaviors	X	X	X
	• Hypnagogic or hypnopompic hallucinations			
	• Somnolence resulting in dose reduction or discontinuation of trial medication	X	X	X
	• Sleep paralysis and sleep-onset paralysis (adjudicated)	X	X	X
	• Cataplexy (adjudicated)	X	X	X
	• Falls/ataxia/worsening of balance (adjudicated to rule out cataplexy)	X	X	X
	• Agitation (daytime/nighttime)	X	X	X
	• Confusion or cognitive impairment (daytime/nighttime)	X	X	X
Tier 2	Any AE		X	X
	Any Serious AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Discontinuation due to AE		X	X
	Specific AEs, SOCs, or PDLCs (incidence ≥4 subjects in 1 of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs or PDLCs [‡] (incidence <4 subjects in all of the treatment groups)			X
	Change from Baseline Results (Labs, ECGs, Vital Signs)			X

[†] Adverse Event (AE) references refer to both Clinical and Laboratory AEs.
[‡] Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier-2 endpoints.
[§] P-value and CI for safety endpoints based upon Miettinen & Nurminen method
Note: SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.6.3.1 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed.

Demographic variables (eg, age, gender, race), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 Interim Analysis

No interim analyses for efficacy or safety are planned for this study because of the favorable efficacy and safety profiles observed for suvorexant in the Phase 3 program in insomnia subjects.

8.8 Multiplicity

While nominal p-values will be computed for all comparisons of suvorexant with placebo, statistical significance for comparison of the primary and secondary efficacy endpoints between treatments will be based on a fixed sequential multiplicity strategy to control the overall Type I error at the two-sided 5% significance level. If the comparison of the primary efficacy endpoint between treatments is significant at the 5% significance level, then comparison of the secondary endpoint between treatments will be evaluated at the 5% level of significance. More specifically, the difference between treatments in change from baseline in TST at Week 4 will be tested at the 5% level. If the difference at Week 4 is significant, then the difference between treatments in change from baseline in WASO at Week 4 will be tested at the 5% significance level. If the difference between treatments in TST at Week 4 is not significant, then the difference between treatments for WASO at Week 4 will not be evaluated for significance.

8.9 Sample Size and Power Calculations

Sample size

This study will randomize approximately 130 subjects into the suvorexant group and approximately 130 subjects into the placebo group, for a total of 260 randomized subjects in order to obtain 117 evaluable subjects per treatment group.

Power for the primary hypothesis

With approximately 130 subjects randomized per treatment group and assuming a standard deviation of 68 minutes for change from baseline in TST (based on insomnia subjects ≥65 years who had PSG in MK-4305 Protocols 028 and 029 pooled), a 2-sided α=0.05, and a dropout rate of 10% at Week 4 (approximately twice the drop-out rate observed for insomnia subjects ≥65 years who had PSG in MK-4305 Protocols 028 and 029 pooled), the study has approximately 92% power to detect a true difference of 30 minutes between treatment groups with respect to change from baseline in TST at Week 4 (standardized effect size (SES) = 0.44). The study has approximately 80% power to detect a 25-minute difference in change from baseline in TST between treatment groups (SES = 0.37).

There are few studies in the literature which provide descriptive statistics for PSG endpoints in insomnia subjects with AD. The sample sizes for these studies are small relative to the size

of the suvorexant Phase 3 studies, and estimates of the standard deviation of TST (but not for change from baseline in TST) were reported. The studies also did not restrict the recording period to 8 hours so variability estimates from these studies are likely to be higher than those for a study with a recording period restricted to 8 hours, as in this study. The standard deviation for TST varied considerably across these studies; some were smaller than the standard deviation for TST from Protocols 028 and 029, and others were larger. Since the number of insomnia subjects in the MK-4305 Phase 3 database is over 10-fold larger than the studies in the literature, and for the other reasons given, estimates of standard deviation for calculating the sample size and power for this study were based on elderly insomnia subjects who had PSG in MK-4305 Protocols 028 and 029.

The standard deviation of 68 minutes for change from baseline in TST was based on pooled data for the suvorexant low dose (15 mg for elderly and 20 mg for non-elderly) and placebo groups for the subset of elderly insomnia subjects (age ≥65) who had PSG in the MK-4305 Phase 3 trials (Protocol 028 and Protocol 029). This standard deviation is similar to, but slightly higher than, the standard deviation observed for elderly and nonelderly insomnia subjects combined (67 minutes) in these trials. The assumed true difference of 30 minutes in TST between suvorexant low dose and placebo for elderly insomnia subjects is slightly smaller (ie, more conservative) than the observed difference of 33 minutes for elderly and non-elderly insomnia subjects combined. These more conservative estimates based on the subset of elderly subjects are appropriate to use for sample size determination as a greater proportion of elderly than non-elderly subjects are expected to be enrolled in this trial. Note that a 30-minute increase in change from baseline in TST can be thought of as resulting from a reduction in LPS by approximately 10 minutes (SES ≈ 0.19) plus a reduction in WASO by approximately 20 minutes (SES ≈ 0.34) or, approximately, the sum of any reductions in LPS and WASO which add to 30 minutes (eg, a reduction in LPS by approximately 15 minutes (SES ≈ 0.29) plus a reduction in WASO by approximately 15 minutes (SES ≈ 0.26)).

Table 9 summarizes the power for the primary endpoint (TST at Week 4) assuming a variety of values for the standard deviation and true difference between treatment groups.

Table 9 Power (%) for Comparing the Primary Efficacy Endpoint (TST at Week 4) Between the Suvorexant and Placebo Treatment Groups with approximately 130 Subjects Randomized to Each Treatment Group

Underlying Standard Deviation of Change from Baseline (minutes)	**Underlying Difference of Mean Change from Baseline for Suvorexant minus Placebo (minutes)**		
	35	**30**	**25**
82	90%	80%	64%
71	96%	90%	77%
68	98%	92%	80%
65	98%	94%	83%
Note: The power is calculated based on 117 evaluable subjects per treatment group, a 2-sided α=0.05, and a dropout rate of 10% at Week 4.			

Power for the secondary hypothesis

With approximately 130 subjects per treatment group and assuming a standard deviation of 58 minutes for change from baseline in WASO, a 2-sided α=0.05, and a dropout rate of 10% at Week 4 (based on MK-4305 Protocols 028 and 029 insomnia subjects pooled), the study has approximately 91% power to detect a true difference of 25 minutes between treatment groups with respect to change from baseline in WASO at Week 4 (SES = 0.43). This is a slightly smaller difference than the difference of 27 minutes observed between low dose and placebo for elderly insomnia subjects (based on MK-4305 Protocols 028 and 029 subjects pooled), and the standard deviation is larger than the estimate of 54 minutes for the standard deviation for change from baseline observed at Week 4 for elderly plus nonelderly insomnia subjects for the 2 studies combined. The study has approximately 98% power to detect a 30-minute difference in change from baseline in WASO between treatment groups (SES = 0.52) and 75% power to detect a 20-minute difference in change from baseline in WASO between treatment groups (SES = 0.34).

Multiplicity-adjusted power

There is approximately 87% power to declare both treatment comparisons, change from baseline in TST at Week 4 for the primary hypothesis and change from baseline in WASO at Week 4 for the secondary hypothesis, as significant (computed from the marginal power for each hypothesis and a correlation of -0.77 between these endpoints at Month 1, estimated from the pooled data for subjects ≥65 years who had PSG in Protocols 028 and 029) (see Table 10).

Table 10 Power (%) for Comparing the Primary Endpoint (TST at Week 4) and the Secondary Endpoint (WASO at Week 4) Between Treatment Groups According to the Multiplicity Testing Strategy

Endpoint/Timepoint	Underlying Difference in Mean Change from Baseline for Suvorexant minus Placebo (minutes)	Marginal Power[†]	Multiplicity-adjusted Power: Both[‡]
Week 4 TST	30	92%	NA
Week 4 WASO	25	91%	87%

[†] Based upon a 5% (2-sided) t-test for each endpoint, and assuming N=130 subjects randomized per group, a dropout rate 10% at Week 4, and a standard deviation of 68 minutes for change from baseline in TST at Week 4 and a standard deviation of 58 minutes for change from baseline in WASO at Week 4.
[‡] "Both" refers to both endpoints declared to be significant according to the multiplicity strategy (see Section 8.8 Multiplicity). NA stands for 'not applicable'.

8.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary and

secondary efficacy endpoints will be estimated and plotted within each category of the following classification variables:

- Gender (female; male)
- Age group (<65; ≥65 years)
- Race (white; non-white)
- Region (North America; Europe, Other)
  - Note that if other countries are added to the study, they will be mapped to 1 of these regions and documented prior to unblinding.
- Severity of baseline insomnia for each endpoint (ie, TST, WASO) will be evaluated according to their corresponding baseline value categories: <baseline median; ≥baseline median)
- Severity of baseline MMSE category (mild=21 to 26, moderate=12 to 20)
- AHI (<15, ≥15 to ≤30)

If APOE is determined, it will be included as an additional classification variable.

The consistency of the treatment effect over levels of the classification variables listed above will be assessed by running the appropriate analysis model separately for each subgroup of the primary efficacy analysis population. Treatment effects and nominal 95% confidence intervals by category for the classification variables listed above will be reported as well as presented graphically. Formal statistical testing of these interactions will not be performed.

Key safety analyses (such as Tier 1 and 2 events as well as Tier 3 AEs) may be evaluated by age group (<65; ≥65 years) and/or MMSE category (moderate=12 to 20, mild=21 to 26).

8.11 Compliance (Medication Adherence)

In this study, as part of the routine recording of the amount of trial medication taken by each subject, the number of tablets remaining in study packaging will be counted, reviewed, and recorded at regular intervals. These results will be used to calculate subject compliance.

A day within the study will be considered an "On-Therapy" day if the subject takes the required number of tablets as noted in Section 5.2.

For a subject who is followed for the entire 1-month Treatment period, the "Number of Days Should be on Therapy" is the total number of days from randomization to the last scheduled day for treatment administration for that subject. For a subject who discontinued from the study permanently, the "Number of Days Should be on Therapy" is the total number of days from randomization to the date of the last dose of trial medication.

For each subject, percent compliance will then be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days Should be on Therapy}} \times 100.$$

Summary statistics will be provided on percent compliance by treatment group for all subjects randomized.

8.12 Extent of Exposure

The total number of days each subject took a particular total daily dose of trial medication will be identified and then summarized (as subject counts and percentages) within duration categories (eg, for the Treatment period: <1 week, ≥1 week but <2 weeks, ≥2 weeks but <3 weeks, ≥3 weeks but <4 weeks, and ≥4 weeks; where 1 week is defined as 7 days). Additionally, the mean number of days and range of days on study drug will also be provided.

Exposure will be evaluated for the entire study sample as well as by age group

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 11.

Table 11 Product Descriptions

Product Name & Potency	Dosage Form
MK-4305 10 mg[1]	1 Tablet
Placebo to match MK-4305 10 mg[1]	1 Tablet
MK-4305 20 mg[1,2]	1 Tablet
Placebo to match MK-4305 20 mg[1,2]	1 Tablet
[1]MK-4305 = SUVOREXANT [2]Subjects may be titrated to a higher dose of 20 mg at investigator discretion.	

All placebos were created by the Sponsor to match the active product.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Subjects will receive a single-blind 2 week blister card at Visit 2 and a double-blind 2 week blister card at Visits 4 and 5. No kitting is required.

9.3 Clinical Supplies Disclosure

The emergency unblinding call center will use the treatment/randomization schedule for the trial to unblind subjects and to unmask treatment identity. In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic treatment allocation/randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unmask treatment identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

Treatment identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded to treatment assignment. Subjects whose treatment assignment has been unblinded (by the investigator, Merck subsidiary, or through the emergency unblinding call center) must be discontinued from study drug.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

For trials using Controlled Substances, all Federal, State, Province, Country, etc. regulations must be adhered to in regard to the shipping, storage, handling and dispensing of controlled substances. Additionally, the investigator should have the appropriate controlled drug license(s) as mandated by Federal, State, Province, Country, etc. laws in which the trial is being conducted.

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IVRS/IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;

2. hospital or clinic address and telephone number;

3. curriculum vitae or other summary of qualifications and credentials; and

4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC member that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and

all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for

a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007, and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trials directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue

participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided

the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 LIST OF REFERENCES

[1] Singer C, Tractenberg RE, Kaye J, Schafer K, Gamst A, Grundman M, et al. A multicenter, placebo-controlled trial of melatonin for sleep disturbance in alzheimer's disease. Sleep 2003;26(7):893-901.

[2] Swearer JM, Drachman DA, O'Donnell BF, Mitchell AL. Troublesome and disruptive behaviors in dementia; Relationships to diagnosis and disease severity. JAGS 1988;36:784-90.

[3] Wu Y-H, Swaab DF. Disturbance and strategies for reactivation of the circadian rhythm system in aging and Alzheimer's disease. Sleel Medicine 2007;8:623-36.

[4] Fronczek R, van Geest S, Frölich M, Overeem S, Roelandse FWC, Lammers GJ, et al. Hypocretin (orexin) loss in Alzheimer's disease. Neurobiol Aging 2012;33:1642-50.

[5] Stickgold R, Walker MP. Sleep-dependent memory triage: evolving generalization through selective processing. Nat Neurosci. 2013 Feb;16(2):139-45.

[6] Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, et al. Sleep drives metabolite clearance from the adult brain. Science. 2013 Oct 18;342(6156):373-7.

[7] Ju YE, McLeland JS, Toedebusch CD, Xiong C, Fagan AM, Duntley SP, et al. Sleep quality and preclinical Alzheimer disease. JAMA Neurol. 2013 May;70(5):587-93.

[8] Liguori C, Romigi A, Nuccetelli M, Zannino S, Sancesario G, Martorana A, et al. Orexinergic system dysregulation, sleep impairment, and cognitive decline in Alzheimer disease. JAMA Neurol. 2014 Dec;71(12):1498-505.

[9] Kang JE, Lim MM, Bateman RJ, Lee JJ, Smyth LP, Cirrito JR, et al. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. Science. 2009 Nov 13;326(5955):1005-7.

[10] Serfaty M, Kennell-Webb S, Warner J, Blizard R, Raven P. Double blind randomised placebo controlled trial of low dose melatonin for sleep disorders in dementia. Int J Geriatr Psychiatry 2002;17:1120-7.

[11] Asayama K, Yamadera H, Ito T, Suzuki H, Kudo Y, Endo S. Double blind study of melatonin effects on the sleep-wake rhythm, cognitive and non-cognitive functions in Alzheimer type dementia. J Nippon Med Sch 2003;70(4):334-41.

[12] Gehrman PR, Connor DJ, Martin JL, Shochat T, Corey-Bloom J, Ancoli-Israel S. Melatonin fails to improve sleep or agitation in a double-blind randomized placebo-controlled trial of institutionalized patients with Alzheimer's disease. Am J Geriatr Psychiatry 2009;17(2):166-9.

[13] MRL Clinical Study Report (Synopsis), Multicenter Study: Takeda Global Research and Development Center, Inc. (TGRD); A randomized, double-blind, placebo-controlled study to assess the subjective response to treatment with ramelteon in adult subjects with chronic insomnia by utilizing an interactive voice response system (IVRS) for collecting diary data; Clinical Trial Synopsis 01-04-375-041, NCT#00672724 .

[14] Salami O, Lyketsos C, Rao V. Treatment of sleep disturbance in Alzheimer's dementia. Int J Geriatr Psychiatry 2013;26:771-82.

[15] Raji MA, Brady SR. Mirtazapine for treatment of depression and comorbidities in Alzheimer disease. Ann Pharmacother 2001;35:1024-7.

[16] López-Pousa S, Garre-Olmo J, Vilalta-Franch J, Turon-Estrada A, Pericot-Nierga I. Trazodone for Alzheimer's disease: A naturalistic follow-up study. Arch Gerontol Geriatr 2008;47:207-15.

[17] Neirenberg AA, Keck PE, Jr. Management of monoamine oxidase inhibitor-associated insomnia with trazodone. J Clin Psychopharmacol 1989;9(1):42-5.

[18] Thompson JW, Jr., Ware MR, Blashfield RK. Psychotropic medication and priapism: a comprehensive review. J Clin Psychiatry 1990;51(10):430-3.

[19] Walsh JK, Erman M, Erwin CW, Jamieson A, Mahowald M, Regestein Q, et al. Subjective hypnotic efficacy of trazodone and zolpidem in DSMIII-R primary insomnia. Hum Psychopharmacol 1998;13:191-8.

[20] Roehrs T, Roth T. Hypnotics: efficacy and adverse effects. In: Kryger MH, Roth T, Dement WC, Zorab R, Carroll C, Cannon AL, eds. Principles and practice of sleep medicine. 3rd ed. Philadelphia: W.B. Saunders Company, 2000:414-8.

[21] Ellul J, Archer N, Foy CML, Poppe M, Boothby H, Nicholas H, et al. The effects of commonly prescribed drugs in patients with Alzheimer's disease on the rate of deterioration. J Neurol Neurosurg Psychiatry 2007;78:233-9.

[22] Elmståhl S, Stenberg I, Annerstedt L, Ingvad B. Behavioral disturbances and pharmacological treatment of patients with dementia in family caregiving: A 2-year follow-up. Int Psychogeriatr 1998;10(3):239-52.

[23] Huang AR, Mallet L, Rochefort CM, Eguale T, Buckeridge DL, Tamblyn R. Medication-related falls in the elderly causative factors and preventive strategies. Drugs Aging 2012;29(5):359-76.

[24] Moraes WS, Poyares DR, Guilleminault C, Ramos LR, Bertolucci PH, Tufik S. The effect of donepezil on sleep and REM sleep EEG in patients with Alzheimer disease: a double-blind placebo-controlled study. Sleep. 2006 Feb;29(2):199-205.

[25] Herring WJ, Connor KM, Ivgy-May N, Snyder E, Liu K, Snavely DB, et al. Suvorexant in Patients with Insomnia: Results from Two 3-Month Randomized Controlled Clinical Trials. Biol Psychiatry. 2014 Oct 23. [Epub ahead of print].

[26] Herring WJ, Snyder E, Budd K, Hutzelmann J, Snavely D, Liu K, et al. Orexin receptor antagonism for treatment of insomnia. A randomized clinical trial of suvorexant. Neurology 2012;79:2265-74.

[27] Michelson D, Snyder E, Paradis E, Chengan-Liu M, Snavely DB, Hutzelmann J, et al. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2014 May;13(5):461-71.

[28] Tractenberg RE, Sinton CM, Kaye JA. Symptoms of sleep disturbance in persons with alzheimer's disease and normal elderly. J Sleep Res 2005;14:177-85.

[29] Vitiello MV, Bliwise DL, Prinz PN. Sleep in Alzheimer's disease and the sundown syndrome. Neurology 1992;42 [Suppl 6]:83-94.

[30] Rose KM, Beck C, Tsai P-F, Liem PH, Davila DG, Kleban M, et al. Sleep disturbances and nocturnal agitation behaviors in older adults with dementia. Sleep 2011;34(6):779-86.

[31] Alzheimer's Association. 2014 Alzheimer's disease facts and figures. Alzheimers Dement. 2014 Mar;10(2):e47-92.

[32] Guy W, editors. Clinical Global Impressions (CGI) Scale [Internet]. Washington (DC): American Psychiatric Association (APA); 2000. Available from: http://www.psywellness.com.sg/docs/CGI.pdf.

[33] Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

[34] Tractenberg RE, Sinton CM, Cummings JL, Thal LJ. The sleep disorders inventory: an instrument for studies of sleep disturbance in persons with alzheimer's disease. J Sleep Res 2003;12:331-7.

[35] Anic-Labat S, Guilleminault C, Kraemer HC, Meehan J, Arrigoni J, Mignot E. Validation of a cataplexy questionnaire in 983 sleep-disorders patients. Sleep 1999;22(1):77-87.

[36] Morgenthaler T, Alessi C, Friedman L, Owens J, Kapur V, Boehlecke B, et al. Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: An update for 2007. Sleep 2007;30(4):519-29.

12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.4 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed,

present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of patient consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses

will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com) and a form will be provided to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. Documentation will be sent to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject’s personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is

accomplished using network security policies and practices based on international standards (e.g., ISO17799) to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Subjects

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject health, limitations of predictive capability, and concerns regarding misinterpretation.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information. After the clinical trial has completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available through appropriate mechanisms (e.g., scientific publications and/or presentations). Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (ie, only leftover samples are being retained).

The Sponsor has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

12. Questions

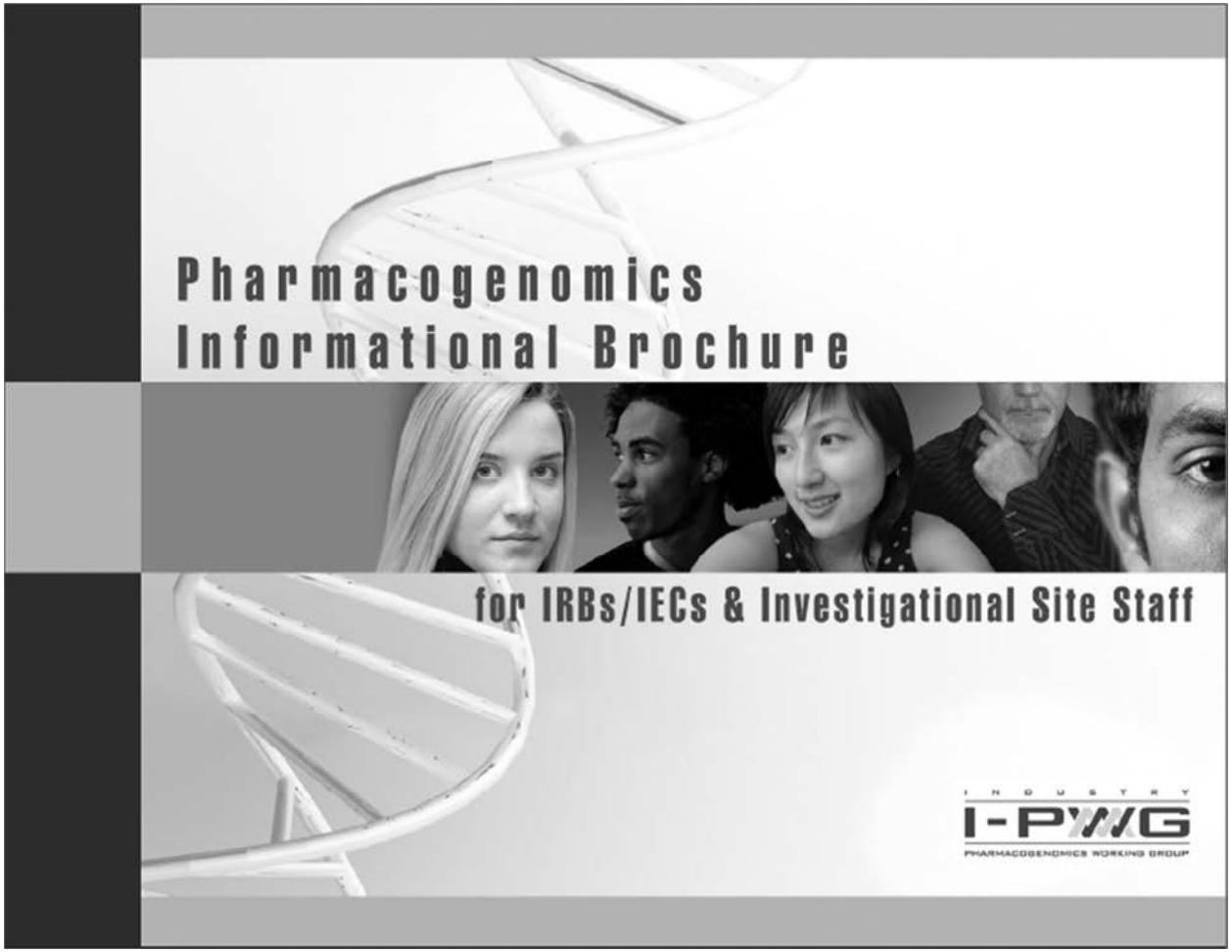
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker

2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

12.3 Pharmacogenetics Informational Brochure for IRBs/IECs & Investigational Site Staff



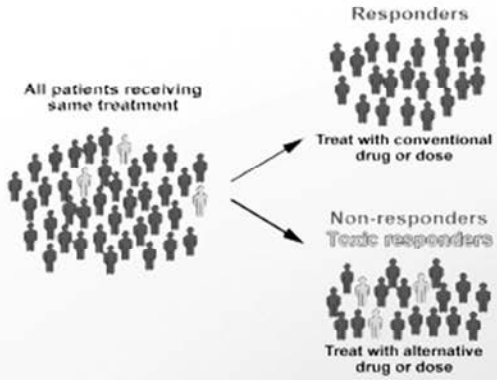
This Informational Brochure is intended for IRBs/IECs & Investigational Site Staff. The brochure was developed to address issues relevant to DNA collection and research in the context of pharmaceutical drug development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

What is DNA and What is Pharmacogenomics?

The cells of the body contain **deoxyribonucleic acid (DNA)**. DNA is inherited, and carries a code (in the form of **genes**), which determines physical appearance and other personal features. In a process called gene transcription, DNA is copied into a related molecule, ribonucleic acid (RNA), before ultimately being translated into proteins, which determine cellular function. Naturally-occurring variation in DNA is a major determinant of differences among people. This variation, referred to as **genetic polymorphism**, occurs both within genes and outside of genes throughout the entire **human genome**. This variation partly explains why some people develop certain diseases and others do not, why some people respond better than others to certain drugs, and why some people develop side effects while others do not.

Pharmacogenomics (PGx) is a branch of science that uses genetic/genomic information to better understand why people respond differently to drugs. The terms **pharmacogenomics** and **pharmacogenetics** are often used interchangeably, although pharmacogenetics generally refers to the study of DNA, while pharmacogenomics is a broader term encompassing the study of both DNA and RNA[1], and generally on a larger scale. Pharmacogenomic research is different from **genetic testing** done for the purpose of diagnosing a person with a certain disease or for risk for developing a certain disease (e.g., genetic testing for Huntington's Disease). PGx focuses on genetic variability that affects response to drugs. This primarily occurs through pathways related to drug metabolism, drug mechanism of action, disease etiology or subtype, and adverse events. PGx overlaps with **disease genetics** research since different disease subtypes can respond differently to drugs.

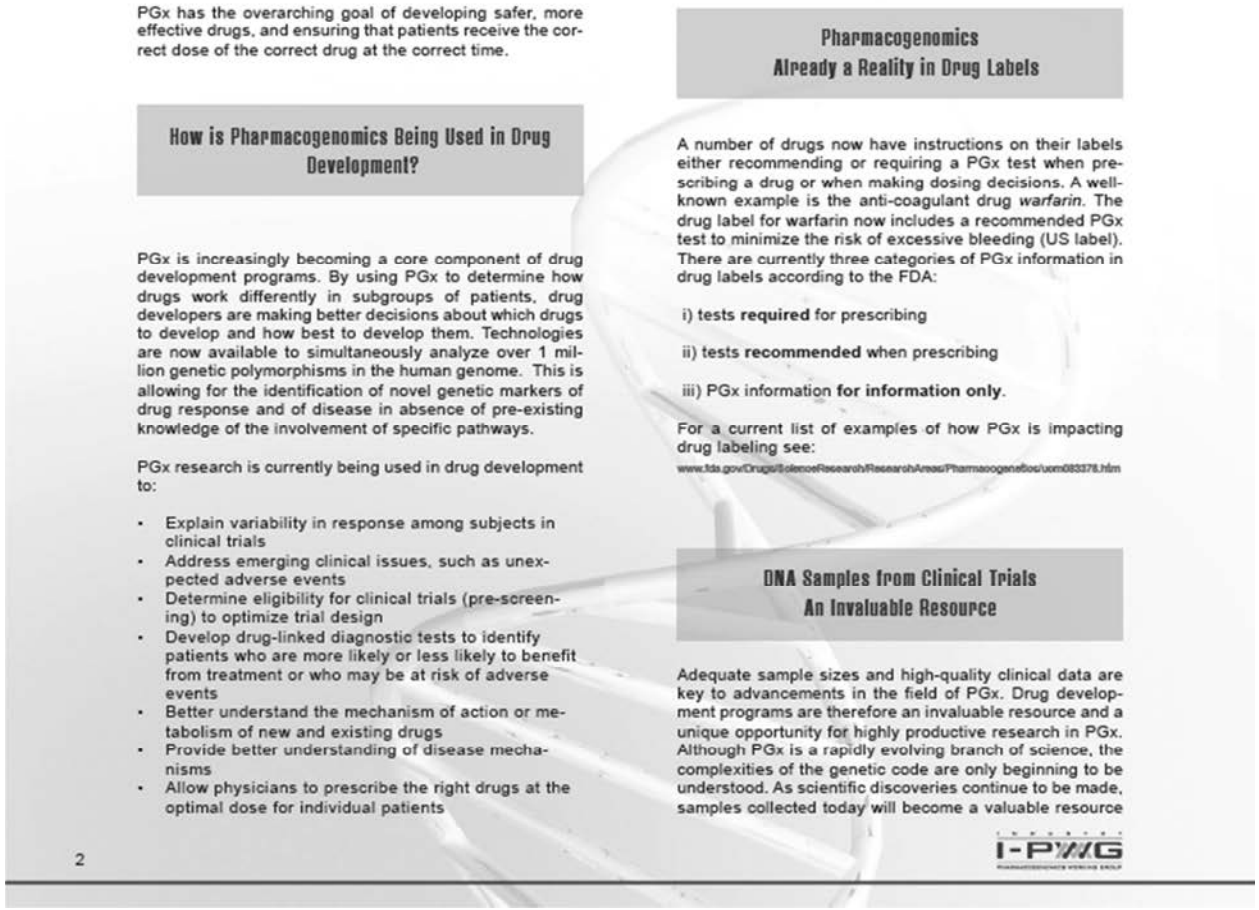


Why is Pharmacogenomics Important?

PGx is one approach to explore whether a drug will be useful or harmful in certain people. By identifying genetic polymorphisms that are associated with drug efficacy and safety, PGx is allowing for more individualized drug therapies based on the genetic makeup of patients. This is sometimes referred to as **personalized medicine**. By better understanding diseases at the molecular level, PGx is opening opportunities for the discovery of novel drugs.

I-PWG

1


PGx has the overarching goal of developing safer, more effective drugs, and ensuring that patients receive the correct dose of the correct drug at the correct time.
How is Pharmacogenomics Being Used in Drug Development?
PGx is increasingly becoming a core component of drug development programs. By using PGx to determine how drugs work differently in subgroups of patients, drug developers are making better decisions about which drugs to develop and how best to develop them. Technologies are now available to simultaneously analyze over 1 million genetic polymorphisms in the human genome. This is allowing for the identification of novel genetic markers of drug response and of disease in absence of pre-existing knowledge of the involvement of specific pathways.
PGx research is currently being used in drug development to:
• Explain variability in response among subjects in clinical trials
• Address emerging clinical issues, such as unexpected adverse events
• Determine eligibility for clinical trials (pre-screening) to optimize trial design
• Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of adverse events
• Better understand the mechanism of action or metabolism of new and existing drugs
• Provide better understanding of disease mechanisms
• Allow physicians to prescribe the right drugs at the optimal dose for individual patients
2
Pharmacogenomics Already a Reality in Drug Labels
A number of drugs now have instructions on their labels either recommending or requiring a PGx test when prescribing a drug or when making dosing decisions. A well-known example is the anti-coagulant drug warfarin. The drug label for warfarin now includes a recommended PGx test to minimize the risk of excessive bleeding (US label). There are currently three categories of PGx information in drug labels according to the FDA:
i) tests required for prescribing
ii) tests recommended when prescribing
iii) PGx information for information only.
For a current list of examples of how PGx is impacting drug labeling see:
DNA Samples from Clinical Trials An Invaluable Resource
Adequate sample sizes and high-quality clinical data are key to advancements in the field of PGx. Drug development programs are therefore an invaluable resource and a unique opportunity for highly productive research in PGx. Although PGx is a rapidly evolving branch of science, the complexities of the genetic code are only beginning to be understood. As scientific discoveries continue to be made, samples collected today will become a valuable resource
I-PWG

for future research. This may lead to the future development of new drugs that are better targeted to certain individuals and to disease subtypes.

For these reasons, it is vital to systematically collect DNA samples across all centers recruiting subjects into clinical trials that include a PGx component (where local regulations permit). Consent for storage of samples for future research should also be obtained if maximum benefit is to be derived from DNA samples donated by subjects. The scope of the research that may be performed both during the trial and in the future should be clearly defined in the informed consent form.

Informed Consent

Policies and regulations for legally effective informed consent vary on national, state, and local levels. There currently are no internationally recognized regulations that dictate the basic elements of informed consent for PGx research. The I-PWG has published an article on the elements of informed consent to be considered in PGx research studies[2]. These elements build upon existing basic elements of informed consent for clinical research on human subjects[3].

Return of Genomic Research Results to Study Subjects

Policies for the return of genomic results to study subjects vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of PGx research results to study subjects. These include i) the conditions under which genomic results were generated (i.e., research laboratory environment versus accredited diagnostic laboratory), ii) whether the results will have an impact on patient medical care, iii) whether genetic counseling is necessary, and iv) international, national, and local guidelines, policies, legislation, and regulations regarding subjects' rights to access data generated on them. These considerations are addressed in detail in Renegar et al. 2006[4].

Privacy, Confidentiality, and Patient Rights

An issue that is generally perceived to be of relevance to clinical genetic research is the risk associated with inadvertent or intentional disclosure and misuse of genetic data. Although coded specimens generally have been considered adequate to protect patient privacy in most clinical development, companies and other institutions involved in PGx research have historically applied a variety of additional safeguards that can be used alone, or in combination, to further minimize the potential risk of disclosure and misuse of genetic data. These include:

i) Sample Labeling

DNA samples and corresponding clinical data can be labeled in several ways to achieve different levels of patient privacy and confidentiality. Definitions of labeling methods are provided in the glossary and are described in greater detail in the ICH Guidance E15[1]. It is important to recognize that there is a trade-off between the level of patient privacy protection and the ability to perform actions related to withdrawal of consent, data return, clinical monitoring, subject follow-up, and addition of new data (see Table 1)[1]. The *Identified* and *Anonymous* labeling categories described in the table are generally not applicable to pharmaceutical clinical trials.

3

I-PWG

Table adapted from ICH Guidance E15

Sample Coding Category		Link Between Subject's Personal Identifiers and Genomic Biomarker Data	Traceability back to the Subject (Actions Possible, Including e.g., Sample Withdrawal or Return of Individual Genomic Results at Subject's Request	Ability to Perform Clinical Monitoring, Subject Follow-up, or Addition of New Data	Extent of Subject's Confidentiality and Privacy Protection
Identified		Yes (Direct) Allows for Subjects to be Identified	Yes	Yes	Similar to General Healthcare Confidentiality and Privacy
Coded	Single	Yes (Indirectly) Allows for Subjects to be Identified (via Single, Specific Coding Key)	Yes	Yes	Standard for Clinical Research
	Double	Yes (Very Indirectly) Allows for Subjects to be Identified (via the Two Specific Coding Keys)	Yes	Yes	Added Privacy and Confidentiality Protection over Single Code
Anonymized		No Does not Allow Subject to be Re-Identified as the Coding-Key(s) Have Been Deleted	No	No	Genomic Data and Samples no Longer Linked to Subject as Coding Key(s) have been Deleted
Anonymous		No – Identifiers Never Collected and Coding Keys Never Applied. Does not Allow for Subjects to be Identified	No	No	Genomic Data and Samples Never Linked to Subject

ii) Separation of Data and Restricted Access

- Maintaining PGx-related documentation separate from other medical records.
- Restricting access to data and samples by means of password-protected databases and locked sample storage facilities.

PGx studies in pharmaceutical development are generally conducted in research laboratories that are not accredited diagnostic laboratories. Therefore, PGx research data usually cannot be used to make clinically meaningful or reliable decisions about a subject's health or health risks. Furthermore, confidentiality protections described above serve to guard against inappropriate disclosure of these data. For these reasons, the potential risk to a subject's employment or health/life insurance is considered to be minimal. The measures taken to protect subjects against reasonably foreseeable risks should be addressed in the informed consent form[2].

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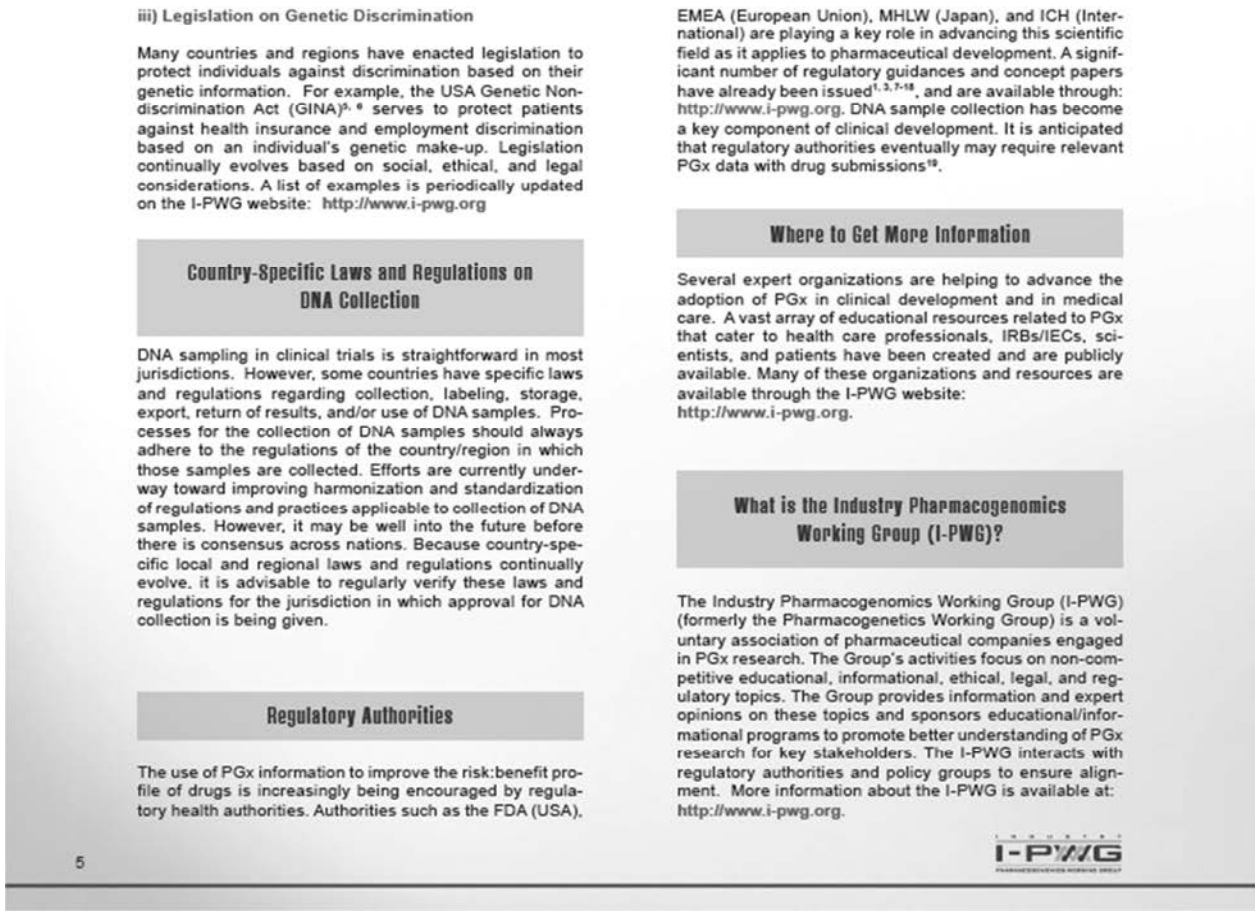
I-PWG



iii) Legislation on Genetic Discrimination

Many countries and regions have enacted legislation to protect individuals against discrimination based on their genetic information. For example, the USA Genetic Non-discrimination Act (GINA)[5, 6] serves to protect patients against health insurance and employment discrimination based on an individual's genetic make-up. Legislation continually evolves based on social, ethical, and legal considerations. A list of examples is periodically updated on the I-PWG website: http://www.i-pwg.org

Country-Specific Laws and Regulations on DNA Collection

DNA sampling in clinical trials is straightforward in most jurisdictions. However, some countries have specific laws and regulations regarding collection, labeling, storage, export, return of results, and/or use of DNA samples. Processes for the collection of DNA samples should always adhere to the regulations of the country/region in which those samples are collected. Efforts are currently underway toward improving harmonization and standardization of regulations and practices applicable to collection of DNA samples. However, it may be well into the future before there is consensus across nations. Because country-specific local and regional laws and regulations continually evolve, it is advisable to regularly verify these laws and regulations for the jurisdiction in which approval for DNA collection is being given.

Regulatory Authorities

The use of PGx information to improve the risk:benefit profile of drugs is increasingly being encouraged by regulatory health authorities. Authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development. A significant number of regulatory guidances and concept papers have already been issued[1, 3, 7-18], and are available through: http://www.i-pwg.org. DNA sample collection has become a key component of clinical development. It is anticipated that regulatory authorities eventually may require relevant PGx data with drug submissions[19].

Where to Get More Information

Several expert organizations are helping to advance the adoption of PGx in clinical development and in medical care. A vast array of educational resources related to PGx that cater to health care professionals, IRBs/IECs, scientists, and patients have been created and are publicly available. Many of these organizations and resources are available through the I-PWG website: http://www.i-pwg.org.

What is the Industry Pharmacogenomics Working Group (I-PWG)?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in PGx research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of PGx research for key stakeholders. The I-PWG interacts with regulatory authorities and policy groups to ensure alignment. More information about the I-PWG is available at: http://www.i-pwg.org.

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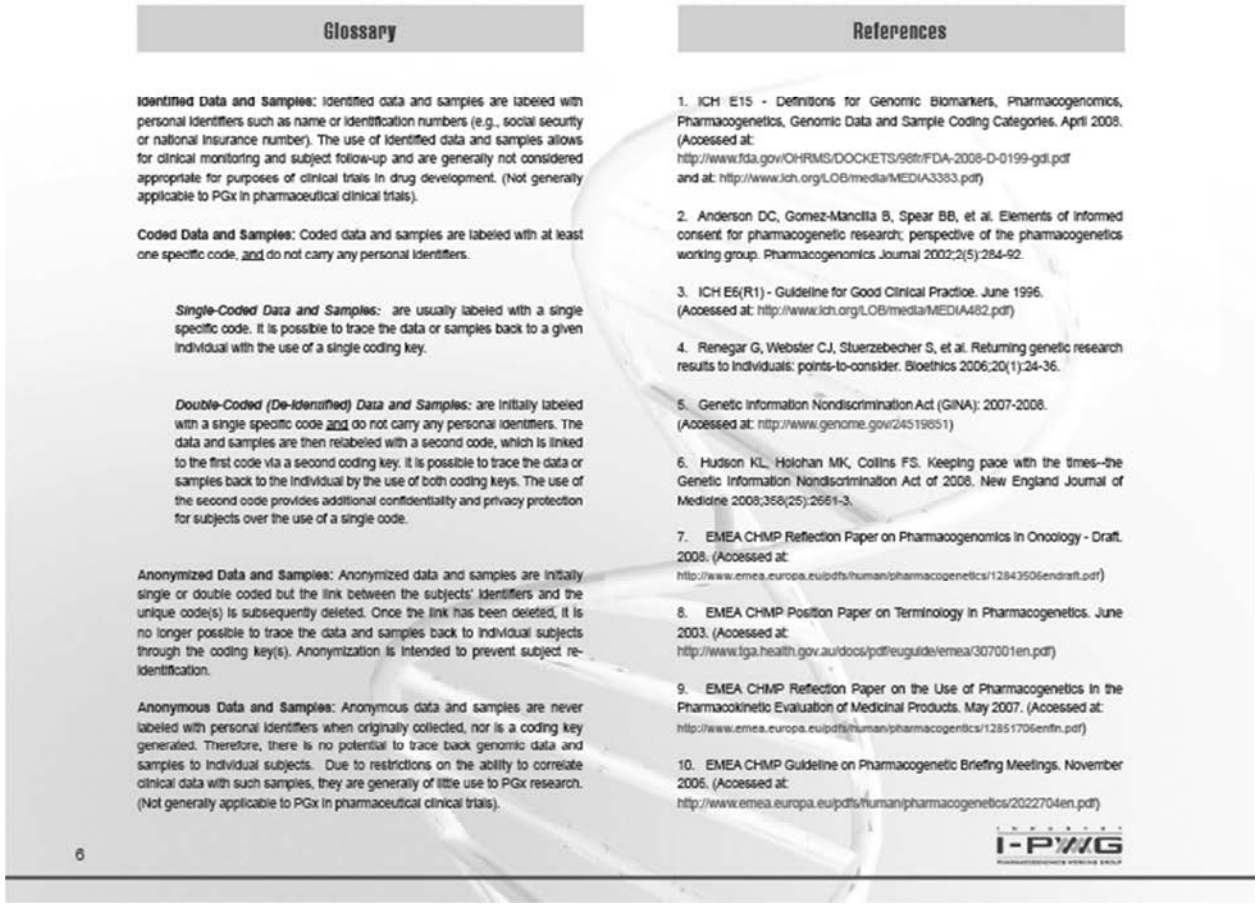

Glossary

Identified Data and Samples: Identified data and samples are labeled with personal identifiers such as name or identification numbers (e.g., social security or national insurance number). The use of identified data and samples allows for clinical monitoring and subject follow-up and are generally not considered appropriate for purposes of clinical trials in drug development. (Not generally applicable to PGx in pharmaceutical clinical trials).

Coded Data and Samples: Coded data and samples are labeled with at least one specific code, and do not carry any personal identifiers.

Single-Coded Data and Samples: are usually labeled with a single specific code. It is possible to trace the data or samples back to a given individual with the use of a single coding key.

Double-Coded (De-Identified) Data and Samples: are initially labeled with a single specific code and do not carry any personal identifiers. The data and samples are then relabeled with a second code, which is linked to the first code via a second coding key. It is possible to trace the data or samples back to the individual by the use of both coding keys. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code.

Anonymized Data and Samples: Anonymized data and samples are initially single or double coded but the link between the subjects' identifiers and the unique code(s) is subsequently deleted. Once the link has been deleted, it is no longer possible to trace the data and samples back to individual subjects through the coding key(s). Anonymization is intended to prevent subject re-identification.

Anonymous Data and Samples: Anonymous data and samples are never labeled with personal identifiers when originally collected, nor is a coding key generated. Therefore, there is no potential to trace back genomic data and samples to individual subjects. Due to restrictions on the ability to correlate clinical data with such samples, they are generally of little use to PGx research. (Not generally applicable to PGx in pharmaceutical clinical trials).

6

References

1. ICH E15 - Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. April 2008. (Accessed at: http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0199-gdl.pdf and at: http://www.ich.org/LOB/media/MEDIA3383.pdf)

2. Anderson DC, Gomez-Mancilla B, Spear BB, et al. Elements of informed consent for pharmacogenetic research: perspective of the pharmacogenetics working group. Pharmacogenomics Journal 2002;2(5):284-92.

3. ICH E6(R1) - Guideline for Good Clinical Practice. June 1996. (Accessed at: http://www.ich.org/LOB/media/MEDIA482.pdf)

4. Renegar G, Webster CJ, Stuerzebecher S, et al. Returning genetic research results to individuals: points-to-consider. Bioethics 2006;20(1):24-36.

5. Genetic Information Nondiscrimination Act (GINA): 2007-2008. (Accessed at: http://www.genome.gov/24519851)

6. Hudson KL, Holohan MK, Collins FS. Keeping pace with the times--the Genetic Information Nondiscrimination Act of 2008. New England Journal of Medicine 2008;358(25):2661-3.

7. EMEA CHMP Reflection Paper on Pharmacogenomics in Oncology - Draft. 2008. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/12843506endraft.pdf)

8. EMEA CHMP Position Paper on Terminology in Pharmacogenetics. June 2003. (Accessed at: http://www.tga.health.gov.au/docs/pdf/euguide/emea/307001en.pdf)

9. EMEA CHMP Reflection Paper on the Use of Pharmacogenetics in the Pharmacokinetic Evaluation of Medicinal Products. May 2007. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/12851706enfin.pdf)

10. EMEA CHMP Guideline on Pharmacogenetic Briefing Meetings. November 2006. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/2022704en.pdf)

I-PWG

11. EMEA CHMP Reflection Paper on Pharmacogenomic Samples, Testing, and Data Handling. November 2007. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/20191406en.pdf)

12. EMEA CHMP Reflection Paper on the Use of Genomics in Cardiovascular Clinical Intervention Trials. November 2007. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/27878906enfin.pdf)

13. EMEA CHMP Biomarkers Qualification: Guidance to Applicants. 2008. (Accessed at: http://www.emea.europa.eu/pdfs/human/biomarkers/7289408en.pdf)

14. EMEA CHMP Understanding Terminology Used in Pharmacogenetics July 2004. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/384204en.pdf)

15. FDA Companion Guidance - Pharmacogenomic Data Submissions - draft. August 2007. (Accessed at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079855.pdf)

16. FDA. FDA Guidance - Pharmacogenetic Tests and Genetic Tests for Heritable Markers. June 2007. (Accessed at: www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077862.htm)

17. FDA Guidance - Pharmacogenomic Data Submissions. March 2005. (Accessed at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126957.pdf)

18. EMEA FDA - Processing Joint FDA EMEA VGDSs within the framework of the Confidentiality Arrangement May 2006. (Accessed at : http://www.emea.europa.eu/pdfs/general/direct/pr/FDAEMEA.pdf)

19. Rittenhouse P. Framing DNA collection in the clinic. Bioentury, The Bernstein Report on BioBusiness March 2006:A13-5.

Created by the Industry Pharmacogenomics Working Group Education Task Force

7

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12.4 Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types

Trial Visit/Period:	Screening Visit 1/ Screening	Visit 4 Rand/ Treatment [a]	Visit 6 – End of Week 4/ Treatment	Discon
Blood Parameter	**Approximate Blood Volume (mL)**			
Hematology (~2 mL)	2 mL		2 mL	2 mL
Serum/Plasma Chemistry (~8.5 mL) Includes TSH, Vitamin B12 and Folate	8.5 mL		8.5 mL	8.5 mL
Serum Follicle-stimulating Hormone (FSH)[b] (~3.5 mL)	3.5 mL			
Methylmalonic acid and homocysteine[c]	3 mL			
Suvorexant PK (~4 mL)		4 mL	4 mL	4 mL[d]
Blood for Genetic Analysis		8.5 mL		
Expected Total (mL)	10.5-17 mL	12.5 mL	14.5 mL	10.5-14.5 mL

a) Lab values at randomization will be pre-treatment values since randomized trial medication does not initiate until the night of Day 1.

b) A blood sample for determining serum FSH should be collected only if serum FSH levels are required to determine childbearing potential as defined in Section 5.1.2.

c) A blood sample for serum methylmalonic acid and homocysteine should only be collected if B12 or folate levels are below the central laboratory's normal range

d) Only drawn if subject discontinues due to an AE.

12.5 List of Abbreviations and Definition of Terms

Abbreviation	Definition
AASM	American Academy of Sleep Medicine
Aβ	Amyloid Beta
AE	Adverse Experience
AD	Alzheimer's disease
AHI	Apnea Hypopnea Index
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
APOE4	Apolipoprotein E4
ASaT	All Subjects as Treated
AST	Aspartate Aminotransferase
βhCG	Beta-Human Chorionic Gonadotropin
BMI	Body Mass Index
BP	Blood Pressure
BIPAP	Bi-Level Positive Airway Pressure
CAC	Clinical Adjudication Committee
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impressions of Insomnia Severity
CI	Confidence Interval
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CRU	Clinical Research Unit
CSF	Cerebrospinal Fluid
CSM	Clinical Specimen Management
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Scale
CYP	Cytochrome P450
DEGs	Data Entry Guidelines
DNA	Deoxyribonucleic Acid
DS	Digit Symbol
DSM-5	Diagnostic and Statistical Manual of Mental Disorder, 5th Edition
ECG	Electrocardiogram
ECI	Events of Clinical Interest
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDS	Excessive Daytime Sleepiness
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electro-Oculogram
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
GERD	Gastroesophageal Reflux Disease
Hg	Mercury
HIV	Human Immunodeficiency Virus
HR	Heart Rate

Abbreviation	Definition
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDI	Insomnia Diagnostic Interview
IEC	Independent Ethics Review Committee
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
kg	Kilogram
lb	Pound
LFT	Liver Function Test
LPS	Latency to Onset of Persistent Sleep
MCQ	Modified Cataplexy Questionnaire
MHIS	Modified Hachinski Ischemia Scale
MI	Multiple Imputation
MMSE	Mini Mental State Examination
MOA	Manual of Assessments
MRL	Merck Research Laboratories
NAW	Number of Awakenings
NCS	Not Clinically Significant
NE	Neurological Examination
NIA-AA	National Institute on Aging – Alzheimer's Association
NOA	Number of Arousals
NPI	Neuropsychiatric Inventory
NREM	Non-REM
NTIB	Nighttime Time in Bed
NTST	Nighttime Total Sleep Time
ORA	Orexin Receptor Antagonist
OTC	Over-the-Counter *or (depending on context)* On-Treatment Completers
PD	Pharmacodynamic
PDLC	Pre-Defined Limit of Change.
PE	Physical Examination
PGx	Pharmacogenomics
PK	Pharmacokinetic
PLM	Periodic Limb Movement
PPDM	Pharmacokinetics, Pharmacodynamics, and Drug Metabolism
PSG	Polysomnography
REM	Rapid Eye Movement
RNA	Ribonucleic Acid
RR	Respiratory Rate
SAC	Scientific Advisory Committee
SAE	Serious Adverse Experience
SAP	Statistical Analysis Plan
SCNSI	Stanford Center for Narcolepsy Sleep Inventory
SD	Standard Deviation
SDI	Sleep Disorders Inventory
SE	Sleep Efficiency
SES	Standardized Effect Size
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SHX	Sleep History
SOC	System Organ Class

Abbreviation	Definition
SOL	Sleep Onset Latency
SOP	Standard Operating Procedure
SQR	Sleep Quality Rating
sSAP	Supplemental Statistical Analysis Plan
SSQC	Single-item Sleep Quality Scale - Caregiver
T-BILI	Total Bilirubin
TIB	Time in Bed
TST	Total Sleep Time
TTA	Total Time Awake
UDS	Urine Drug Screen
UGT1A	Uridine Diphosphate Glucuronosyltransferase 1A1 Assessment
ULN	Upper Limit of Normal
WASO	Wakefulness After Sleep Onset

12.6 Calculating Body Mass Index (BMI)

Formula and calculation for pounds and inches:

Calculate BMI by dividing weight in pounds (lbs) by height in inches (in) squared and multiplying by a conversion factor of 703.

Example: Weight = 150 lbs, Height = 5'5" (65")

Calculation: [150 ÷ (65)2] x 703 = 24.96

Formula and calculation for kilograms and meters (or centimeters):

Formula: weight (kg) / [height (m)]2

With the metric system, the formula for BMI is weight in kilograms divided by height in meters squared. Because height is commonly measured in centimeters, divide height in centimeters by 100 to obtain height in meters.

Example: Weight = 68 kg, Height = 165 cm (1.65 m)

Calculation: 68 ÷ (1.65)2 = 24.98

Source: www.cdc.gov

Body Mass Index Table

	Normal						Overweight					Obese										Extreme Obesity																
BMI	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	**42**	**43**	**44**	**45**	**46**	**47**	**48**	**49**	**50**	**51**	**52**	**53**	**54**
Height (inches)	**Body Weight (pounds)**																																			
58	91	96	100	105	110	115	119	124	129	134	138	143	148	153	158	162	167	172	177	181	186	191	196	201	205	210	215	220	224	229	234	239	244	248	253	258
59	94	99	104	109	114	119	124	128	133	138	143	148	153	158	163	168	173	178	183	188	193	198	203	208	212	217	222	227	232	237	242	247	252	257	262	267
60	97	102	107	112	118	123	128	133	138	143	148	153	158	163	168	174	179	184	189	194	199	204	209	215	220	225	230	235	240	245	250	255	261	266	271	276
61	100	106	111	116	122	127	132	137	143	148	153	158	164	169	174	180	185	190	195	201	206	211	217	222	227	232	238	243	248	254	259	264	269	275	280	285
62	104	109	115	120	126	131	136	142	147	153	158	164	169	175	180	186	191	196	202	207	213	218	224	229	235	240	246	251	256	262	267	273	278	284	289	295
63	107	113	118	124	130	135	141	146	152	158	163	169	175	180	186	191	197	203	208	214	220	225	231	237	242	248	254	259	265	270	278	282	287	293	299	304
64	110	116	122	128	134	140	145	151	157	163	169	174	180	186	192	197	204	209	215	221	227	232	238	244	250	256	262	267	273	279	285	291	296	302	308	314
65	114	120	126	132	138	144	150	156	162	168	174	180	186	192	198	204	210	216	222	228	234	240	246	252	258	264	270	276	282	288	294	300	306	312	318	324
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74	148	155	163	171	179	186	194	202	210	218	225	233	241	249	256	264	272	280	287	295	303	311	319	326	334	342	350	358	365	373	381	389	396	404	412	420
75	152	160	168	176	184	192	200	208	216	224	232	240	248	256	264	272	279	287	295	303	311	319	327	335	343	351	359	367	375	383	391	399	407	415	423	431
76	156	164	172	180	189	197	205	213	221	230	238	246	254	263	271	279	287	295	304	312	320	328	336	344	353	361	369	377	385	394	402	410	418	426	435	443

Source: Adapted from *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report.*

Source: www.nhlbi.nih.gov

12.7 List of Caffeine Products and Caffeine Content

This list is not inclusive; many products contain caffeine, including over-the-counter medications, weight loss products, mineral and herbal supplements, etc. Please check the labels of any concomitant therapies, supplements, etc. for caffeine content.

Product	Serving Size (in fluid ounces [oz] and milliliters [mL])	Caffeine (mg)
Coffee		
Brewed	8 oz. (237 mL)	95-200 mg
Brewed, decaffeinated	8 oz. (237 mL)	2-12 mg
Brewed, single-serve varieties	8 oz. (237 mL)	75-150 mg
Brewed, single-serve varieties, decaffeinated	8 oz. (237 mL)	2-4 mg
Espresso, restaurant-style	1 oz. (30 mL)	47-75 mg
Espresso, restaurant-style, decaffeinated	1 oz. (30 mL)	0-15 mg
Instant	8 oz. (237 mL)	27-173 mg
Instant, decaffeinated	8 oz. (237 mL)	2-12 mg
Specialty drink (latte or mocha)	8 oz. (237 mL)	63-175 mg
Tea		
Brewed tea		
Black tea	8 oz. (237 mL)	14-70 mg
Black tea, decaffeinated	8 oz. (237 mL)	0-12 mg
Green tea	8 oz. (237 mL)	24-45 mg
Iced tea		
Instant, prepared with water	8 oz. (237 mL)	11-47 mg
Ready-to-drink, bottled	8 oz. (237 mL)	5-40 mg
Soft Drinks		
A&W Root Beer	12 oz. (355 mL)	0 mg
Barq's Root Beer	12 oz. (355 mL)	16-18 mg
Coca-Cola	12 oz. (355 mL)	23-35 mg
Diet Coke	12 oz. (355 mL)	23-47 mg
Diet Pepsi	12 oz. (355 mL)	27-37 mg
Dr. Pepper, regular and diet	12 oz. (355 mL)	36-42 mg
Mountain Dew, regular and diet	12 oz. (355 mL)	42-55 mg
Mug Root Beer, regular and diet	12 oz. (355 mL)	0 mg
7UP	12 oz. (355 mL)	0 mg
Pepsi	12 oz. (355 mL)	32-39 mg
Sierra Mist, regular and diet	12 oz. (355 mL)	0 mg
Sprite, regular and diet	12 oz. (355 mL)	0 mg
Energy Drinks		
Amp, regular or sugar-free	8 oz. (237 mL)	71-74 mg
5-Hour Energy shot	2 oz. (60 mL)	200-207 mg
Full Throttle, regular or sugar-free	8 oz. (237 mL)	70-100 mg
Red Bull, regular or sugar-free	8.4 oz. (248mL)	75-80 mg
Rockstar, regular or sugar-free	8 oz. (237 mL)	79-80 mg
Other Products		
Chocolate chips, semisweet	1 cup (168 grams)	104 mg
Dark chocolate-coated coffee beans	28 pieces	336 mg
Energy mints	2 mints	95-200 mg

Source: www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/caffeine/art-20049372?pg=1

12.8 DSM-5 Criteria for Major or Mild Neurocognitive Disorder Due to Alzheimer's Disease

Diagnostic Criteria:

A. The criteria are met for major or mild neurocognitive disorder.

B. There is insidious onset and gradual progression of impairment in 1 or more cognitive domains (for major neurocognitive disorder, at least 2 domains must be impaired

C. Criteria are met for **probable Alzheimer's disease as follows:**

For major neurocognitive disorder:

Probable Alzheimer's disease is diagnosed if either of the following is present:

1. Evidence of a causative Alzheimer's disease genetic mutation from family history or genetic testing.
2. All 3 of the following are present:
   a. Clear evidence of decline in memory and learning and at least 1 other cognitive domain (based on detailed history or serial neuropsychological testing).
   b. Steadily progressive, gradual decline in cognition, without extended plateaus.
   c. No evidence of mixed etiology (ie, absence of other neurodegenerative or cerebrovascular disease, or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline).

For mild neurocognitive disorder:

Probable Alzheimer's disease is diagnosed if there is evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history.

D. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder.

Reference: American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013.

12.9 National Institute on Aging-Alzheimer's Association (NIA-AA) diagnostic guidelines for Alzheimer's disease

Recommendations for the diagnosis of dementia due to Alzheimer's disease:

Criteria for all-cause dementia: Core clinical criteria

The diagnosis of dementia is intended to encompass the spectrum of severity, ranging from the mildest to the most severe stages of dementia. The methodology for staging of dementia severity was beyond the charge of the workgroup. Dementia is diagnosed when there are cognitive or behavioral (neuropsychiatric) symptoms that:

1. Interfere with the ability to function at work or at usual activities; and
2. Represent a decline from previous levels of functioning and performing; and
3. Are not explained by delirium or major psychiatric disorder;
4. Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a "bedside" mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.
5. The cognitive or behavioral impairment involves a minimum of 2 of the following domains:
    a. Impaired ability to acquire and remember new information—symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.
    b. Impaired reasoning and handling of complex tasks, poor judgment—symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.
    c. Impaired visuospatial abilities—symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.
    d. Impaired language functions (speaking, reading, writing)—symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors.
    e. Changes in personality, behavior, or comportment—symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors.

Probable AD dementia: Core clinical criteria

Probable AD dementia is diagnosed when the patient:

1. Meets criteria for dementia described earlier in the text, and in addition, has the following characteristics:
   A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;
   B. Clear-cut history of worsening of cognition by report or observation; and
   C. The initial and most prominent cognitive deficits are evident on history and examination in 1 of the following categories.
      a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least 1 other cognitive domain, as defined earlier in the text.
      b. Nonamnestic presentations:
         - Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.
         - Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.
         - Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.
   D. The diagnosis of probable AD dementia should not be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of Dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

Note: All patients who met criteria for "probable AD" by the 1984 NINCDS–ADRDA criteria[1] would meet the current criteria for probable AD dementia mentioned in the present article.

Probable AD dementia with increased level of certainty

Probable AD dementia with documented decline

In persons who meet the core clinical criteria for probable AD dementia, documented cognitive decline increases the certainty that the condition represents an active, evolving pathologic process, but it does not specifically increase the certainty that the process is that of AD pathophysiology.

Probable AD dementia with documented decline is defined as follows: evidence of progressive cognitive decline on subsequent evaluations based on information from informants and cognitive testing in the context of either formal neuropsychological evaluation or standardized mental status examinations.

Probable AD dementia in a carrier of a causative AD genetic mutation

In persons who meet the core clinical criteria for probable AD dementia, evidence of a causative genetic mutation (in APP, PSEN1, or PSEN2), increases the certainty that the condition is caused by AD pathology. The workgroup noted that carriage of the ε4 allele of the apolipoprotein E gene was not sufficiently specific[2] to be considered in this category.

Source: http://www.alzheimersanddementia.com/article/S1552-5260(11)00101-4/fulltext#sec4

[1] The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia – The Journal of the Alzheimer's Association. May 2011. Vol.7, Issue 3, 263-269.

[2] Saunders, A.M., Shea, S., Mirra, S., Evans, D., Roses, A.D. et al. Utility of the apolipoprotein E genotype in the diagnosis of Alzheimer's Disease. Alzheimer's Disease Centers Consortium on Apolipoprotein E and Alzheimer's Disease. N. England J Med. 1998; 338: 506-511

12.10 DSM-5 Criteria for Insomnia Disorder

Diagnostic Criteria

A. predominant complaint of dissatisfaction with sleep quantity or quality, associated with 1 (or more) of the following symptoms:

   1. Difficulty initiating sleep.

   2. Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings.

   3. Early-morning awakening with inability to return to sleep.

B. The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning.

C. The sleep difficulty occurs at least 3 nights per week.

D. The sleep difficulty is present for at least 3 months.

E. The sleep difficulty occurs despite adequate opportunity for sleep.

F. The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder (eg, narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep-wake disorder, a parasomnia).

G. The insomnia is not attributable to the physiological effects of a substance (eg, a drug of abuse, a medication).

H. Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia.

Reference: American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013.

12.11 General Neurological Exam

The General Neurological Examination will be performed at the timepoint(s) specified in the protocol flow chart.

Note to the investigator: If at any time abnormalities are observed in the General Neurological Exam, the Investigator should do additional examinations as needed based on his or her medical judgment.

The **General Neurological Examination** includes all of the modules listed below, ***with the exception of Module 1,*** and is intended to be a general screening examination and sufficient for this study and subject population.

MODULE 2 – CRANIAL NERVE ASSESSMENT

A. II – Visual Fields and acuity

B. II, III – Pupil Size and Reactivity

C. III, IV, VI – Extraocular Movements (range of motion, smooth pursuit, saccades, nystagmus)

   1. Observe for nystagmus during eye movements, increased nystagmus at the end of gaze or other oculomotor changes (mild nystagmus at extremes of gaze is normal). Note direction of nystagmus

D. V – Facial Sensation, Jaw Strength

E. VII – Muscles of Facial Expression (wrinkle brow, squeeze eyes shut, smile)

F. VIII – Auditory Acuity (assessed using a bed-side screening test eg by rubbing fingers on each side of subject's head or by whispering numbers)

G. IX – Gag reflex

H. X – Swallow

I. XI – Shoulder shrug

J. Tongue Protrusion (midline)

Score: left and right (except for G, H, J)

Grade: **NORMAL or IMPAIRED and describe abnormality**

MODULE 3 - MOTOR SYSTEM

A. Muscle Tone

   1. Ask the volunteer to relax.
   2. Flex and extend the volunteer's elbows and knees (bilaterally).
   3. There is a small, continuous resistance to passive movement.

4. Observe for involuntary movements (eg, tremor, tics, fasciculations). Observe for resistance to passive movement; observe for decreased (flaccid) or increased (rigid/spastic) tone.

   Score: left and right

   Grade: **NORMAL, INCREASED or DECREASED**

B. Muscle Strength

1. Ask the subject to stand up from sitting without using hands

   Grade: ***NORMAL, IMPAIRED*** **and describe abnormality**

2. Test proximal limb strength by having the volunteer flex and extend the knees and elbows against your resistance.

   Test bilaterally, and compare 1 side to the other.

   Score: left and right

   Grade: 5/5: normal; 4/5: movement against resistance impaired; 3/5: movement against gravity but not against resistance; 2/5: visible movement but not against gravity; 1/5: visible contraction; 0/5: no visible activity

3. Test distal limb strength by having the volunteer conduct dorsiflexion and plantar flexion of the volunteer's feet; finger abduction and handgrip strength against your resistance.

   Test bilaterally, and compare 1 side to the other.

   Score: left and right

   Grade: 5/5: normal; 4/5: movement against resistance impaired; 3/5: movement against gravity but not against resistance; 2/5: visible movement but not against gravity; 1/5: visible contraction; 0/5: no visible activity

C. Pronator Drift

1. Ask the volunteer to hold both arms straight forward with, palms up and eyes closed for ~10-15 seconds as tolerated; watch for how well the arm position is maintained.

2. Instruct the volunteer to keep both arms still while you tap them briskly downward. The volunteer should normally be able to maintain extension and supination. Inability to maintain extension and supination (and drift into pronation) indicates an upper motor neuron deficit.

   Score: left and right

   Grade: **NORMAL or IMPAIRED and describe abnormality**

MODULE 4 - REFLEXES

A. Biceps

B. Knee

Note: *Other deep tendon reflexes may be tested at Investigator's discretion (eg elbow, wrist or Achilles tendon)*

Score: left and right

Grade: **NORMAL, INCREASED, DECREASED or ABSENT**

C. Babinski

Score: left and right

Grade: **NORMAL or ABNORMAL**

MODULE 5 - COORDINATION AND GAIT

A. Rapid, Rhythmic Alternating Movements

1. Testing each hand separately, ask the volunteer to tap the distal thumb with the tip of each finger, in sequence, as fast as possible.

   Score: left and right

   Grade: **NORMAL or IMPAIRED**

   Reminder: If the rapid alternate movements are disturbed, the subject will be asked to strike his hand on the thigh, raise the hand, turn it over and then strike the back of the hand down on the same place. (This test is impaired in cerebellar disease, extra pyramidal disease and upper MN weakness.)

B. Point-to-Point Movements

1. Ask the volunteer to touch your index finger and their nose alternately several times. Move your finger about as the volunteer performs this task.

   Score: left and right

   Grade: **NORMAL or IMPAIRED**

   Reminder: If the point-to-point testing is disturbed, the subject will be asked to place 1 heel on the opposite knee and then run it down the shin to the big toe. Repeat this for both sides. (Impaired tests indicate cerebellar disease.)

C. Romberg

1. Ask the volunteer to stand with both feet together and eyes closed for 20 to 30 seconds without support.

2. Be prepared to catch the volunteer if they are unstable.

Grade: **NORMAL or IMPAIRED**

D. Gait

1. Ask the volunteer to walk across the room, turn and come back (assess posture, balance, swinging of arms and movement of the legs).

Grade: **NORMAL or IMPAIRED and describe abnormality**

2. Ask the volunteer to walk heel-to-toe in a straight line (tandem gait).

Grade: **NORMAL or IMPAIRED and describe abnormality**

MODULE 6 - SENSORY

A. Light touch sense: cotton wisp on skin of forearms and legs, bilaterally.

B. Pin prick: safety pin touched lightly to skin of forearms and legs, bilaterally.

C. Temperature: warm or cool object touched to skin of forearms and legs, bilaterally.

D. Vibration: tuning fork vibration detection in hands, feet bilaterally.

E. Position sense: perception of thumb and toe movement, bilaterally.

F. Stereognosis: (identify common objects placed in hand, eg, coin, key).

Score: left and right

Grade: **NORMAL OR IMPAIRED and describe abnormality (for each A to F)**

12.12 Algorithm for Assessing Out-of-Range Laboratory Values

For all laboratory values obtained at screening visit evaluation:

A. If all protocol-specified laboratory values are normal, the subject may enter the study.

B. If a protocol specified laboratory value is outside of the parameter(s) outlined in the inclusion/exclusion criteria (including a repeat if performed), the subject will be excluded from the study

C. If ≥1 protocol-specified laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:

   1. The subject may be excluded from the study;

   2. The subject may be included in the study if the abnormal value(s) is not clinically significant (NCS) (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document);

   3. The subject may be included in the study if the abnormality is consistent with a pre-existing medical condition which is not excluded per protocol (eg, elevated eosinophil count in a subject with asthma or seasonal allergies)(this should be annotated on the laboratory report); or

   4. The abnormal test may be repeated (refer items a. and b. below for continuation of algorithm for repeated values).

      a. If the repeat test value is within the normal range, the subject may enter the study.

      b. If the repeat test value is still abnormal, the study investigator will evaluate the potential subject with a complete history and physical examination, looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the subject may enter the study.

D. If there is any clinical uncertainty regarding the significance of an abnormal value, the Subject will be excluded from the study.

12.13 Predefined Limits Of Change Criteria

Table 1

Predefined Limits of Change Criteria for Laboratory Data

Laboratory Test	Criteria† as a % of a Limit of Normal Range
Hematology	
Hematocrit (M)	≤94.9% LLN
Hematocrit (F)	≤94.1% LLN
Hemoglobin (M)	≤90.5% LLN
Hemoglobin (F)	≤81.9% LLN
WBC	≤64.2% LLN
	≥149.0% ULN
Neutrophils	≤37.0% LLN
Eosinophils	≥147.0% ULN
Platelets	≤57.7% LLN
	≥177.7%ULN
Hepatic Function	
Bilirubin	≥166.7% ULN
Alkaline Phosphatase	≥300% ULN
AST (SGOT)	≥300% ULN
ALT (SGPT)	≥300% ULN
Renal Function	
Creatinine	≥142.9% ULN
Clinical Chemistry	
Sodium	≤94.7% LLN
	≥105.4% ULN
Potassium	≤88.2% LLN
	≥111.1% ULN

† A laboratory value must represent a worsening from baseline (ie, be more abnormal in the direction of interest) to meet the definition.
LLN=Lower limit of normal.
ULN=Upper limit of normal.

Table 2

Predefined Limits of Change Criteria for Vital Signs, Weight, and Temperature

Measurement	Criteria
Systolic blood pressure	≥180 mm Hg and ≥20 mm Hg increase from baseline
	≤90 mm Hg and ≥20 mm Hg decrease from baseline
Diastolic blood pressure	≥105 mm Hg and ≥15 mm Hg increase from baseline
	≤50 mm Hg and ≥15 mm Hg decrease from baseline
Pulse	≥120 bpm and ≥15 bpm increase from baseline
	≤50 bpm and ≥15 bpm decrease from baseline
Orthostatic blood pressure	>20 mm Hg systolic sitting to standing after treatment (but not in baseline)
Weight	≥7 % increase from baseline
	≥7 % decrease from baseline
Temperature	≥101°F and ≥2°F increase from baseline (≥38.3°C and ≥1°C increase from baseline)

Table 3

Predefined Limits of Change Criteria for ECGs

Measurement	Criteria
QTc Interval[†]	Prolongation compared to baseline ≥30 to ≤60 msec
	Prolongation compared to baseline >60 msec
	Value ≥500 msec[‡]

[†] Correction based on Bazett's formula.
[‡] The QTc Interval value must also represent a worsening compared to baseline to meet the definition.

12.14 Mapping Between the 11 Categories of Suicidal Ideation and Behavior, the C-SSRS, and CDR for Programming Standard Tables

Table 1

Mapping Between the 11 Categories
of Suicidal Ideation and Behavior and the C-SSRS

Category	C-SSRS Question (from eCRF)[†]
Suicidal ideation	
Passive	1. Wish to be dead
Active - nonspecific (no method, intent, or plan)	2. Non-specific active suicidal thoughts
Active - method, but no intent or plan	3. Active suicidal ideation with any methods (not plan) without intent to act
Active - intent, with or without a method, but no plan	4. Active suicidal ideation with some intent to act, without specific plan
Active - method, intent and plan	5. Active suicidal ideation with specific plan and intent
Suicidal behavior	
Preparatory actions toward imminent suicidal behaviors	Preparatory acts or behavior
Aborted attempt	Aborted attempt
Interrupted attempt	Interrupted attempt
Suicide attempt	Actual attempt
Completed suicide	Completed suicide
Self-injurious behavior, no suicidal intent	Has subject engaged in non-suicidal self-injurious behavior?
[†]Data are "yes" or "no"	

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – Assessing and Recording Adverse Events. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	