Official Protocol Title:	A Phase 3 multicenter, randomized, placebo-controlled, double-blind clinical study to evaluate the efficacy and safety of MK-4305 (suvorexant) for reducing incidence of delirium in Japanese participants at high risk of delirium.
NCT number:	NCT04571944
Document Date:	25-Jul-2022

Title Page

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Protocol Title: A Phase 3 multicenter, randomized, placebo-controlled, double-blind clinical study to evaluate the efficacy and safety of MK-4305 (suvorexant) for reducing incidence of delirium in Japanese participants at high risk of delirium.

Protocol Number: 085-03

Compound Number: MK-4305

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	Not Applicable
EudraCT	Not Applicable

Approval Date: 25 July 2022

Sponsor Signatory

Typed Name:
Title:

Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name:
Title:

Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 3	25-JUL-2022	• Sponsor underwent an entity name change and update to the address.
Amendment 2	08-JUN-2021	• Acceptance of the enrollment of participants with acute disease who can be randomized within 24 hours after admission.
Amendment 1	11-AUG-2020	• Acceptance of elective surgery 2 days after admission • Addition of prohibited medications [hypnotics (prescription Chinese herbs)] • Addition of Modified Cataplexy Questionnaire (MCQ) • Setting of Clinical Adjudication Committee (CAC)
Original Protocol	28-MAY-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

Overall Rationale for the Amendments:

- Sponsor underwent an entity name change and update to the address.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page Section 2.2.1 Pharmaceutical and Therapeutic Background Section 10.1.1 Code of Conduct for Clinical Trials	Sponsor entity name and address change	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3 multicenter, randomized, placebo-controlled, double-blind clinical study to evaluate the efficacy and safety of MK-4305 (suvorexant) for reducing incidence of delirium in Japanese participants at high risk of delirium.

Short Title: Phase 3 placebo-controlled, double-blind study of MK-4305 (suvorexant) in Japanese participants at high risk of delirium (085 study)

Acronym: Not Applicable

Hypotheses, Objectives, and Endpoints:

In Japanese participants at high risk of delirium:

Objectives	Endpoints
Primary	
• Objective: To evaluate the efficacy of suvorexant compared with placebo on the proportion of participants with delirium as assessed by DSM-5 during the assessment period. • Hypothesis: Suvorexant reduces the proportion of participants with delirium compared with placebo as assessed by DSM-5.	• Delirium as assessed by DSM-5
• Objective: To evaluate the safety and tolerability of suvorexant compared with placebo.	• Adverse Events • Study medication discontinuations due to adverse events
Secondary	
• Objective: To evaluate the efficacy of suvorexant compared with placebo on the severity of delirium as assessed by DRS-R-98 (maximum of the daily total score) during the assessment period.	• Severity of delirium as assessed by DRS-R-98 (maximum of the daily total score)

Objectives	Endpoints
• Objective: To evaluate the efficacy of suvorexant compared with placebo on the proportion of participants with delirium as assessed by DRS-R-98 (any daily total score ≥14.5) during the assessment period.	• Delirium as assessed by DRS-R-98 (any daily total score ≥14.5)

Overall Design:

Study Phase	Phase 3
Primary Purpose	Prevention
Indication	Reducing incidence of delirium
Population	Japanese participants at high risk of delirium
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo
Study Blinding	Double-blind with in-house blinding
Blinding Roles	Participants or Subjects, Investigator, Monitor, Data Analyst, and Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 16 months from the time the first participant (and their legally acceptable representative as needed) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 200 participants will take study medications.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Adminis-tration</th><th>Regimen/ Intervention Period</th><th>Use</th></tr>
<tr><td>Suvorexant</td><td>MK-4305</td><td>15 mg</td><td>QD</td><td>Oral</td><td>One tablet QD before bedtime for 5 - 7 days</td><td>Experi-mental</td></tr>
<tr><td>Placebo</td><td>Placebo</td><td>0 mg</td><td>QD</td><td>Oral</td><td>One tablet QD before bedtime for 5 - 7 days</td><td>Placebo</td></tr>
<tr><td colspan="7">Abbreviations: QD=once daily</td></tr>
</table>
</td></tr>
<tr><td>Total Number of Intervention Groups/ Arms</td><td>2</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study for up to approximately 5 weeks from the time the participant provides documented informed consent through the final contact. After a screening period of up to 14 days, each participant will enter in the assessment period for up to 8 days. After the end of intervention each participant will be followed for 14 days.</td></tr>
</table>

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	Yes
Study governance considerations are outlined in Appendix 1.	

Study Accepts Healthy Volunteers: No

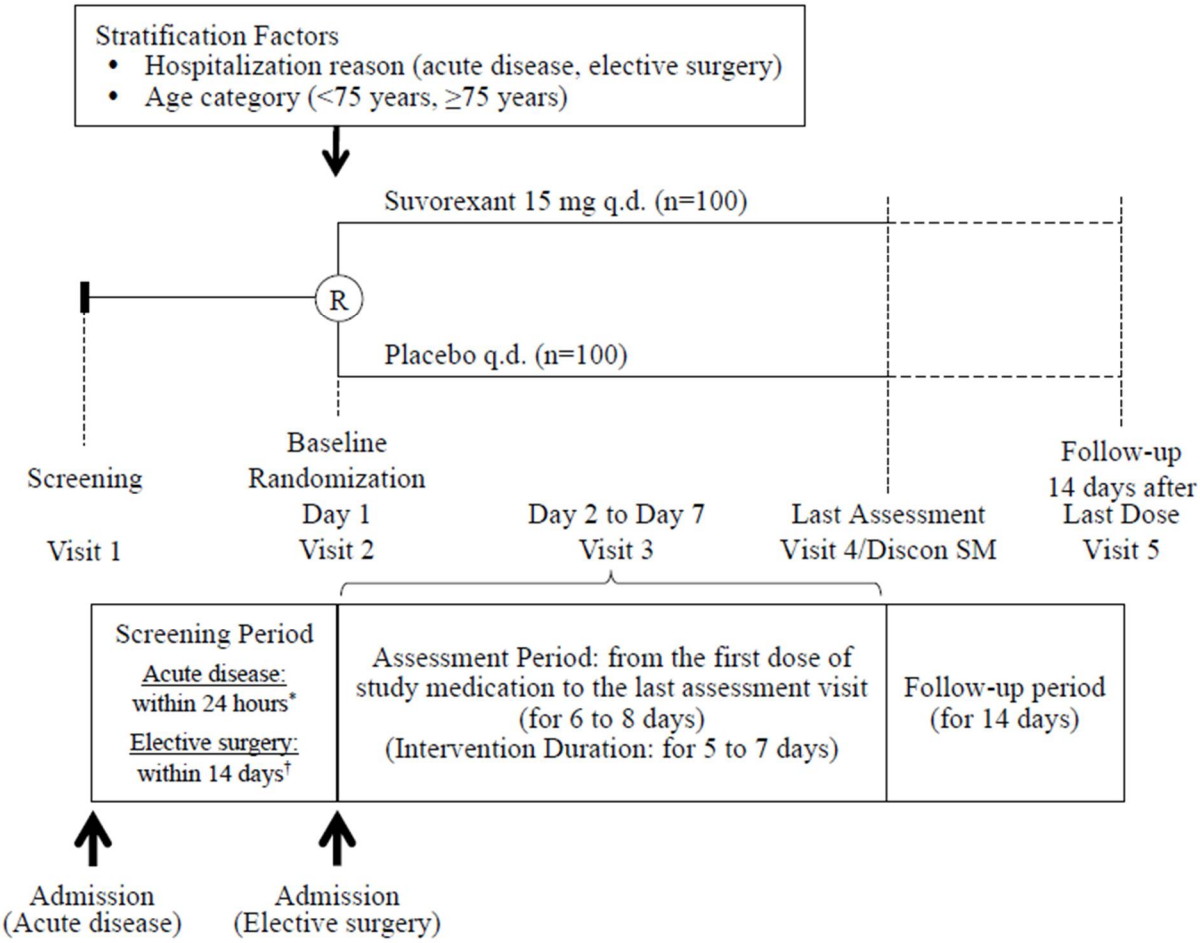
A list of abbreviations used in this document can be found in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1.

The last assessment visit is the next day after the last dose of study medication for the completed participants, OR the timing that the assessment is performed after decision of discontinuation of study medication for the discontinued participants. The assessment period is from the first dose of study medication to the last assessment visit.

Figure 1 Study Design



Discon SM= Discontinuation of study medication, R = Randomization

* For the participant hospitalized due to acute disease, the randomization is performed within 24 hours after admission.

† For the participant hospitalized due to elective surgery, the procedures of Visit 1 are performed within 14 days before admission.

1.3 Schedule of Activities

Study Period:	Screening Period		Assessment Period (From the first dose to last assessment visit)			Follow-up Period	Notes
Visit Title:	Screening	Baseline		Last Assessment		Follow-up	Screening Period: For the participant hospitalized due to acute disease, the randomization is performed within 24 hours after admission. For the participant hospitalized due to elective surgery, the procedures of Visit 1 are performed within 14 days before admission. When Visit 1 and Visit 2 are the same day, the overlapping procedures at both visits (e.g., checking the inclusion/exclusion criteria) should be performed only once. If the allowance range is not described, the visit does not have the allowance.
Visit Number:	1	2	3	4	Discontinuation of study medication	5	
Visit Timing (Allowance):	Acute disease: within 24 hours Elective surgery: within 14 days	Day 1 Before Randomization	After Randomization	Day 2 to Day 7	The next day after last dose		14 days post last dose (± 3 days)	
Administrative Procedures								
Informed Consent	X							Informed consent must be obtained before any study procedures (Informed consent may be obtained before 14 days prior to the first dose).
Inclusion/ Exclusion Criteria	X	X						
Participant Identification Card	X	X						At Visit 2, add Randomization Number in ID card and provide to the participant. ID card may be provided at the discharge.
Medical History (including history of delirium)	X	X						

Study Period:	Screening Period	Assessment Period (From the first dose to last assessment visit)					Follow-up Period	Notes
Visit Title:	Screening	Baseline			Last Assessment		Follow-up	Screening Period: For the participant hospitalized due to acute disease, the randomization is performed <u>within 24 hours after admission</u>. For the participant hospitalized due to elective surgery, the procedures of Visit 1 are performed <u>within 14 days before admission</u>. When Visit 1 and Visit 2 are the same day, the overlapping procedures at both visits (e.g., checking the inclusion/exclusion criteria) should be performed only once. If the allowance range is not described, the visit does not have the allowance.
Visit Number:	1	2		3	4	Discontinuation of study medication	5	
Visit Timing (Allowance):	<u>Acute disease:</u> within 24 hours <u>Elective surgery:</u> within 14 days	Day 1 Before Randomi-zation	After Randomi-zation	Day 2 to Day 7	The next day after last dose		14 days post last dose (± 3 days)	
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	
APACHE II (Only for acute disease)	X							Perform laboratory tests locally for assessment of APACHE II.
ECOG PS (Only for acute disease)	X							
NM Scale	X							
Non-pharmacological Therapies for Delirium		X ⟷ X				X		See Section 5.3.1.
Participant Registration	X	X	X					
Randomization		X						
Study Medication (MK-4305 or Placebo) Dispensing			X					

Study Period:	Screening Period	Assessment Period (From the first dose to last assessment visit)					Follow-up Period	Notes
Visit Title:	Screening	Baseline			Last Assessment		Follow-up	Screening Period: For the participant hospitalized due to acute disease, the randomization is performed <u>within 24 hours after admission</u>. For the participant hospitalized due to elective surgery, the procedures of Visit 1 are performed <u>within 14 days before admission</u>. When Visit 1 and Visit 2 are the same day, the overlapping procedures at both visits (e.g., checking the inclusion/exclusion criteria) should be performed only once. If the allowance range is not described, the visit does not have the allowance.
Visit Number:	1	2		3	4	Discontinuation of study medication	5	
Visit Timing (Allowance):	<u>Acute disease:</u> within 24 hours <u>Elective surgery:</u> within 14 days	Day 1 Before Randomi-zation	After Randomi-zation	Day 2 to Day 7	The next day after last dose		14 days post last dose (± 3 days)	
Study Medication (MK-4305 or Placebo) Administration and Compliance			X	X				Administer study medications for 5 - 7 days.
Hospitalization	X (Acute disease)	X (Elective surgery) ⟷ X				X		For the hospitalization period, see Section 5.1. When Visit 1 and Visit 2 are the same day, the participants will be hospitalized at Visit 1/Visit 2.
Surgery (Only for elective surgery)				X (Day 2 or Day 3)				For acute disease, the need for surgery, the timing of surgery and the operative method is not limited.

Study Period:	Screening Period			Assessment Period (From the first dose to last assessment visit)			Follow-up Period	Notes
Visit Title:	Screening	Baseline			Last Assessment		Follow-up	Screening Period: For the participant hospitalized due to acute disease, the randomization is performed <u>within 24 hours after admission</u>. For the participant hospitalized due to elective surgery, the procedures of Visit 1 are performed <u>within 14 days before admission</u>. When Visit 1 and Visit 2 are the same day, the overlapping procedures at both visits (e.g., checking the inclusion/exclusion criteria) should be performed only once. If the allowance range is not described, the visit does not have the allowance.
Visit Number:	1	2		3	4	Discontinuation of study medication	5	
Visit Timing (Allowance):	<u>Acute disease:</u> within 24 hours <u>Elective surgery:</u> within 14 days	Day 1 Before Randomi-zation	After Randomi-zation	Day 2 to Day 7	The next day after last dose		14 days post last dose (± 3 days)	
Efficacy Procedures								
DSM-5		X	X	X (every day)	X	X		Assess if the participant develops delirium after randomization and maximum of 3 hours prior to the first dose. If the assessment before randomization is performed within 3 hours before the first dose, the re-assessment after randomization is not needed. At Visit 3 and Visit 4, assess in the morning.
DRS-R-98		X		X (every day)	X	X	X	At Visit 3 and Visit 4, assess in the morning.
RCSQ		X		X (every day)	X	X		In the assessment period, assess in the morning.

Study Period:	Screening Period			Assessment Period (From the first dose to last assessment visit)			Follow-up Period	Notes
Visit Title:	Screening	Baseline			Last Assessment		Follow-up	Screening Period: For the participant hospitalized due to acute disease, the randomization is performed <u>within 24 hours after admission</u>. For the participant hospitalized due to elective surgery, the procedures of Visit 1 are performed <u>within 14 days before admission</u>. When Visit 1 and Visit 2 are the same day, the overlapping procedures at both visits (e.g., checking the inclusion/exclusion criteria) should be performed only once. If the allowance range is not described, the visit does not have the allowance.
Visit Number:	1	2		3	4	Discontinuation of study medication	5	
Visit Timing (Allowance):	<u>Acute disease:</u> within 24 hours <u>Elective surgery:</u> within 14 days	Day 1 Before Randomi-zation	After Randomi-zation	Day 2 to Day 7	The next day after last dose		14 days post last dose (± 3 days)	
Undesirable hospitalized patient outcomes (fall, accidental or intentional catheter/tube removal [i.e., bladder, intravenous], and body restraint)				X (every day)	X	X	X	In the follow-up period, collect undesirable hospitalized patient outcomes from hospitalized participant.
Safety Procedures								
Physical examination	X				X	X	X	
Vital Signs (blood pressures, pulse rate, and body temperature)		X		X (every day)	X	X		Utilize same procedure, and the same position/side and the same timing of procedure throughout the study as much as possible.
Hematology		X (Central)			X (Central)	X (Central)		

Study Period:	Screening Period	Assessment Period (From the first dose to last assessment visit)					Follow-up Period	Notes
Visit Title:	Screening	Baseline			Last Assessment		Follow-up	Screening Period: For the participant hospitalized due to acute disease, the randomization is performed <u>within 24 hours after admission</u>. For the participant hospitalized due to elective surgery, the procedures of Visit 1 are performed <u>within 14 days before admission</u>. When Visit 1 and Visit 2 are the same day, the overlapping procedures at both visits (e.g., checking the inclusion/exclusion criteria) should be performed only once. If the allowance range is not described, the visit does not have the allowance.
Visit Number:	1	2		3	4	Discontinuation of study medication	5	
Visit Timing (Allowance):	<u>Acute disease:</u> within 24 hours <u>Elective surgery:</u> within 14 days	Day 1 Before Randomi-zation	After Randomi-zation	Day 2 to Day 7	The next day after last dose		14 days post last dose (± 3 days)	
Chemistry		X (Central and Local)			X (Central)	X (Central)		Measure ALT, AST and total bilirubin locally for assessment of exclusion criteria at Visit 2. For the participants hospitalized due to acute disease, the local laboratory test results after the admission may be referred.
Urinalysis		X (Central)			X (Central)	X (Central)		
AE Review	X ← → X							Review AEs which occur <u>for 14 days</u> after the last dose at follow-up visit. If Visit 5 occurs less than 14 days after the last dose of study intervention, a subsequent follow-up telephone call should be made more than 14 days post the last dose of study intervention.

<table>
<tr><td>Study Period:</td><td colspan="2">Screening Period</td><td colspan="4">Assessment Period
(From the first dose to last assessment visit)</td><td>Follow-up Period</td><td>Notes</td></tr>
<tr><td>Visit Title:</td><td>Screening</td><td>Baseline</td><td colspan="3"></td><td>Last Assessment</td><td>Follow-up</td><td rowspan="3">Screening Period: For the participant hospitalized due to acute disease, the randomization is performed <u>within 24 hours after admission</u>. For the participant hospitalized due to elective surgery, the procedures of Visit 1 are performed <u>within 14 days before admission</u>.
When Visit 1 and Visit 2 are the same day, the overlapping procedures at both visits (e.g., checking the inclusion/exclusion criteria) should be performed only once.
If the allowance range is not described, the visit does not have the allowance.</td></tr>
<tr><td>Visit Number:</td><td>1</td><td colspan="3">2</td><td>3</td><td>4</td><td>Discontinuation of study medication</td><td>5</td></tr>
<tr><td>Visit Timing (Allowance):</td><td><u>Acute disease:</u>
within 24 hours
<u>Elective surgery:</u>
within 14 days</td><td colspan="2">Day 1
Before Randomi-zation</td><td>After Randomi-zation</td><td>Day 2 to Day 7</td><td>The next day after last dose</td><td></td><td>14 days post last dose
(± 3 days)</td></tr>
<tr><td>MCQ Review</td><td></td><td></td><td colspan="5">X ⟵ If receiving any report of an adverse event of cataplexy including cataplexy-like event or fall ⟶ X</td><td>Review MCQ completed by the participant, if receiving any report of an adverse event of cataplexy including cataplexy-like event or fall.</td></tr>
</table>

2 INTRODUCTION

Pathophysiology and Diagnosis of Delirium

Delirium is a disease state presenting with various psychiatric symptoms including cognitive dysfunction such as disorientation, hallucination delusion, fluctuation of the mood with the consciousness disorder (consciousness change) which develops acutely due to the change of the body condition and drug use.

There are three categorized factors for delirium: predisposing factor (which is vulnerability for delirium), precipitating factor (which triggers delirium), and facilitating factor (which induces delirium easily and aggravates and prolongs delirium), and delirium is developed with multiple combined factors. Patients who have multiple predisposing factors are at high risk of delirium. Because these predisposing factors are individual factors and unlikely to improve, they serve as "indicators of intervention" to determine whether hospitalized patients are at high risk. Precipitating factors include physical illness, drugs, surgery. Examination of disease treatment and stop and/or changes in drug regimen could be considered, if physical illness or drug is the precipitating factor. Predisposing factors include older age, cognitive dysfunction, severe physical illness, a history of head disease (e.g., cerebral infarction, cerebral hemorrhage, head trauma), a history of delirium, alcohol abuse, and before highly invasive surgery (e.g., long surgery procedure or surgery requiring general anesthesia). Facilitating factors include physical factors, mental factors, environmental changes, and sleep. Many of the facilitating factors are able to be intervened, and it is essential to reduce or eliminate the individual factors [Inoue S, et al. 2013].

The gold standard for delirium diagnosis is the criteria of the " DSM-5 (diagnostic and statistical manual of mental disorders 5th edition)" issued by the American Psychiatric Association. Delirium is classified into three subtypes; hyperactive characterized by agitation, restlessness, irritation, hallucinations, delusions; hypoactive with symptoms like dementia and depression such as listlessness, somnolence, and decreased spontaneity; and a mixed type that presents with both symptoms. In DSM-5, the identification of subtype is required during diagnostics [American Psychiatric Association. 2013].

Epidemiology of Delirium

The prevalence of delirium varies depending on the individuals' characteristics, setting of care, and sensitivity of the detection method, but is known to be highest among older individuals. The estimates of the incidence of delirium arising during hospitalization range from 6 to 56% in general hospital population [American Psychiatric Association. 2013]. In addition, among the elderly aged 65 years and older, the incidence rate has been reported as 10 to 42% of hospitalized patients, 17 to 61% of postoperative patients, and 80% of postoperative ICUs patients [Japanese Society of General Hospital Psychiatry. 2015].

2.1 Study Rationale

In Japan, the number of hospital beds per population is higher than in other countries [Maeda Y. 2009], and the rate of elderly hospitalized patients is increasing with the aging of the

population [Ministry of Health, Labour and Welfare. 2017]. Therefore, the number of elderly hospitalized patients at risk to develop delirium is increasing. Once a patient develops delirium, it not only disturbs continuation of treatment to the underlying disease and his/her recovery but can also lead to undesirable hospitalized patient outcomes such as accidental or intentional catheter/tube removal (i.e., bladder, intravenous) and fall. Identifying measures to reduce delirium is an important medical issue, since the number of medical staff treating these patients are limited in the clinical practice and their burden is greatly increased when patients develop delirium. Though it was previously considered that the occurrence of delirium was a transient disease state, it has been clarified that delirium affects not only the physical and medical economic prognoses, but also can result in sustained impairment of cognitive function, once it occurs [Davis DH et al. 2012] [Inouye SK, et al. 2014] [Kishi Y. 2016] [Salluh JI, et al. 2015] [Sano S, et al. 2013] [Sasaki Y, et al. 2014] [Witlox J, et al. 2010] [Yamaguchi T, et al. 2014] [Zhang Z, et al. 2013]. Therefore, the importance of preventing delirium development is now recognized in addition to the one of treatment of delirium in onset.

Sleep is one of facilitating factors of delirium, and improvement of sleep-awake cycle might contribute the prevention of delirium. Recently, interest in the preventive effect of suvorexant on delirium by improving sleep-wake cycle through orexin receptors has increased in Japan. Based on these circumstances, the Sponsor plans to conduct a phase III study to investigate the efficacy and safety of suvorexant in Japanese elderly participants who will be hospitalized for acute disease or elective surgery requiring general anesthesia, AND has cognitive impairment or a history of delirium (hereinafter referred to as “at high risk of delirium”).

2.2 Background

Refer to the IB/approved labeling for detailed background information on suvorexant.

2.2.1 Pharmaceutical and Therapeutic Background

The measures for delirium have non-pharmacological and pharmacological therapy as approaches and preventive and therapeutic interventions as objectives. Non-pharmacological therapies (e.g., encouraging cognitive function and orientation such as setting a calendar and/or a clock, treating physical factors including dehydration, constipation and pain, and countermeasure for sleeping such as controlling light and noise) have been recommended as preventive interventions but have limited efficacy. Regarding preventive pharmacological therapy, preventive interventions such as antipsychotics, cholinesterase inhibitors, melatonin, and melatonin receptor agonists have been studied in order to investigate drugs with fewer risks of side effects and effective for delirium prevention [Japanese Society of General Hospital Psychiatry. 2015]. However, no drugs have been approved for preventive intervention yet. As a pharmacological therapy for therapeutic intervention, tiapride was approved in Japan, but the target of patients eligible for treatment is limited to the delirium associated with sequelae of cerebral infarction, and there are no other drugs that can be used widely. Therefore, the antipsychotic drug is used in the clinical practice, though it is the off-label use. However, the use of antipsychotics poses a number of problems, including FDA alert that "both conventional and atypical antipsychotics are associated with an increased risk

of mortality in elderly patients treated for dementia-related psychosis", increasing the incidence of adverse events in the elderly in general, side effects such as oversedation and extrapyramidal disorders, the risk of sudden death, and contraindications for patients with diabetes mellitus.

Suvorexant (MK-4305) is a potent and reversible orexin receptor antagonist developed by Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD). In September 2014, suvorexant was approved for manufacturing and marketing in Japan as a new class of insomnia treatment that facilitates sleep by blocking strongly and selectively both orexin receptor 1 and orexin receptor 2, which are broadly expressed in cortical, thalamic and hypothalamic neuronal circuits involved in the regulation of wakefulness, and controlling orexin neurotransmission, which maintains a high physiological function of sleep and wakefulness. Since suvorexant is not chemically related to benzodiazepines, non-benzodiazepines, barbiturates or other drugs with hypnotic properties, nor does suvorexant possess the intrinsic myorelaxant or anxiolytic properties accompanying interaction with GABA type A receptors, it provides a new treatment option for insomnia.

The relationship between delirium and sleep disturbances has been studied for many years, but it is still uncertain. However, based on previous findings, many variable factors affecting the peripheral, systemic, and central nervous systems are risk factors for developing delirium, but sleep-disruption are more likely to interact with each other [Weinhouse GL, et al. 2009]. Actually, multiple clinical research studies have also shown an association between sleep disruption and delirium [Evans JL, et al. 2017] [Fadayomi AB, et al. 2018] [Leung JM, et al. 2015] [Meagher DJ, et al. 2007] [Trompeo AC, et al. 2011]. Thus, improvement of sleep-awake cycle might contribute the prevention of delirium. Recently, in Japan, several investigator-initiated prospective clinical trials [Azuma K, et al. 2018] [Hatta K, et al. 2017] and retrospective studies [Masuyama T, et al. 2018] [Tamura K, et al. 2019] have been conducted to evaluate the preventive effect of suvorexant on delirium. The investigator-initiated prospective randomized controlled trials [Azuma K, et al. 2018] [Hatta K, et al. 2017] demonstrated that suvorexant reduced the incidence of delirium compared with the placebo or the conventional treatment in patients admitted due to emergency, and all reports including retrospective studies consistently suggested the efficacy of suvorexant in reducing incidence of delirium.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from intervention during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

Because suvorexant has demonstrated efficacy and safety in treating disturbances of sleep initiation and maintenance in patients with insomnia, and disrupted sleep-wake cycle is a potential contributing factor to delirium, administration of suvorexant may reduce delirium incidence. The safety and tolerability of suvorexant has been previously demonstrated in Phase 3 clinical studies, post-marketing surveillance and in ongoing review of post-marketing data in patients with insomnia. In the clinical studies in patients with insomnia

including Japanese, the main adverse reactions of suvorexant were somnolence, headache, and fatigue.

Additional details regarding other specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In Japanese participants at high risk of delirium:

Objectives	Endpoints
Primary	
• Objective: To evaluate the efficacy of suvorexant compared with placebo on the proportion of participants with delirium as assessed by DSM-5 during the assessment period. • Hypothesis: Suvorexant reduces the proportion of participants with delirium compared with placebo as assessed by DSM-5.	• Delirium as assessed by DSM-5
• Objective: To evaluate the safety and tolerability of suvorexant compared with placebo.	• Adverse Events • Study medication discontinuations due to adverse events
Secondary	
• Objective: To evaluate the efficacy of suvorexant compared with placebo on the severity of delirium as assessed by DRS-R-98 (maximum of the daily total score) during the assessment period.	• Severity of delirium as assessed by DRS-R-98 (maximum of the daily total score)
• Objective: To evaluate the efficacy of suvorexant compared with placebo on the proportion of participants with delirium as assessed by DRS-R-98 (any daily total score ≥14.5) during the assessment period.	• Delirium as assessed by DRS-R-98 (any daily total score ≥14.5)

Objectives	Endpoints
Exploratory	
• Objective: To evaluate the efficacy of suvorexant compared with placebo on the sub-item score of DRS-R-98 related to sleep (sleep-wake cycle disturbance) during the assessment period.	• Sub-item score of DRS-R-98 related to sleep (sleep-wake cycle disturbance)
• Objective: To evaluate the efficacy of suvorexant compared with placebo on Richards-Campbell Sleep Questionnaire (RCSQ) score during the assessment period.	• RCSQ score
• Objective: To evaluate the efficacy of suvorexant compared with placebo on the proportion of participants with undesirable hospitalized patient outcomes (fall, accidental or intentional catheter/tube removal [i.e., bladder, intravenous], and body restraint) until the follow-up visit.	• Undesirable hospitalized patient outcomes (fall, accidental or intentional catheter/tube removal [i.e., bladder, intravenous], and body restraint) (composite and each event)
• Objective: To evaluate the impact of suvorexant compared with placebo on the use of antipsychotic medications (CP equivalent and proportion of individuals) until the follow-up visit	• Antipsychotic medications consumption
• Objective: To evaluate the efficacy of suvorexant compared with placebo on the sub-item scores of DRS-R-98 related to cognitive function (orientation, attention, short-term memory, long-term memory, and visuospatial ability) until the follow-up visit	• Sub-item scores of DRS-R-98 related to cognitive function (orientation, attention, short-term memory, long-term memory, and visuospatial ability)

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, parallel-group, multi-site, double-blind clinical study to evaluate the efficacy and safety of suvorexant for reducing incidence of delirium in Japanese participants at high risk of delirium.

This study consists of a screening period of up to 14 days (for acute disease, within 24 hours after admission; for elective surgery, within 14 days before admission), an assessment period of up to 8 days (from the first dose of study medication to the last assessment visit: for 6 to 8 days), and a follow-up period of 14 days.

The target population includes Japanese participants at high risk of delirium between the ages of 65 and 90 years, inclusive. Participants judged as eligible in the screening period will be randomized in a 1:1 ratio to receive either suvorexant or placebo at Visit 2, and they will take one tablet of study medication (suvorexant 15 mg tablet or matching placebo tablet) once daily (q.d.) orally before bedtime for 5-7 days in a double-blind manner. The participants who develop delirium after randomization but prior to the first dose of study medication will be withdrawn from the study without the study medication administration. The participants hospitalized due to elective surgery will receive surgery on the next day or 2 days after admission/the first dose of study medication and will take study medications for 4 days at least after surgery. For the participants who develop delirium during the assessment period, the study intervention is discontinued at this timing. The use of prohibited medications including antipsychotics for treatment of delirium is allowed in the opinion of the investigator after completion or following a decision of discontinuation of study medication administration. The follow-up visit 14 days after last dose of study intervention will be performed for all participants received study medication.

The target number of participants receiving study medication is approximately 200 participants. Intervention randomization will be stratified according to hospitalization reason (acute disease, elective surgery) and age category (<75 years, ≥75 years). If either the proportion of participants hospitalized due to acute disease or those hospitalized due to elective surgery exceeds approximately 60% of the total targeted sample size, the remaining participants will only be enrolled into the other stratum within this stratification factor.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

There are some guidelines related to delirium in Japan; "Clinical guidelines for delirium [Treatment guidelines for delirium, Second version]" issued by delirium guideline revision group of the Japan society of general hospital psychiatry, "Japanese clinical practice guidelines for the management of pain, agitation, and delirium in adults patients in the intensive care unit" issued by J-PAD guidelines preparation committee of the Japanese society of intensive care medicine, and "Delirium guidelines for patients with cancer 2019" issued by Japan psycho-oncology society and the Japanese association of supportive care in cancer, respectively. All guidelines mention that the gold standard for delirium diagnosis is the criteria of the “DSM-5 (diagnostic and statistical manual of mental disorders 5th edition)”

issued by the American Psychiatric Association. Based on the above, the primary efficacy endpoint of this study is the proportion of participants with delirium as assessed by DSM-5.

DRS-R-98 is a structured diagnostic scale for delirium assessment, with established reliability and validity, and already available in Japanese. While it may be difficult to diagnose the presence or absence of delirium based solely on scores, the DRS-98 covers the items necessary for delirium evaluation and is useful for the evaluation of delirium severity. Because of this, the secondary efficacy endpoints are the severity of delirium as assessed by DRS-R-98 (maximum of the daily total score) and the proportion of participants with delirium as assessed by DRS-R-98 (any daily total score ≥14.5) in this study.

The symptoms of delirium tend to fluctuate in severity during course of a day, and it is difficult to detect the fluctuation of the symptoms' severity based on only the condition which are observed at the time of the assessment. Therefore, DSM-5 and DRS-R-98 will be assessed not only on participants' symptoms at the time of assessment but also on the basis of symptoms observed from the previous assessment until the next assessment, so that all symptoms developing during the assessment period can be confirmed continuously without missing. The frequencies of assessments of DSM-5 and DRS-R-98 are once a day, so that the fluctuation of severity such as sleep-wake cycle can be assessed comprehensively based on medical records and information from a medical staff.

4.2.1.2 Safety Endpoints

The following endpoints will be collected to assess the safety of suvorexant. Pre-specified ECIs will be reviewed by an external CAC (see Section 10.1.4.1).

- Adverse events including ECIs (for ECIs, see Section 8.4.7.)
- Vital signs (blood pressures, pulse rate, and body temperature)
- Laboratory tests

4.2.2 Rationale for the Use of Placebo

The comparison between suvorexant group and a control group enables an exclusion of influences of the target population, changes over time, and other factors, and an objective characterization of reducing incidence of delirium of suvorexant. In addition, any measurements in the target population requires a control group to adequately characterize any potential positive/negative effects of suvorexant in the target population. Considering the importance of this study in adequately characterizing the efficacy and safety of suvorexant use in participants deemed at high risk for development of delirium, the control group is designed into the assessment period.

Additionally, because no approved medication is indicated for delirium prevention to use as active comparator, placebo is the best appropriate intervention for the control arm of this study.

4.3 Justification for Dose

4.3.1 Dose for This Study

Delirium and disrupted sleep have a close relationship, and improvement of sleep-awake cycle might contribute to the prevention of delirium. Thus, the dose which is established for efficacy for sleep (suvorexant 15 mg once daily, approved dose for elderly insomnia in Japan) is considered appropriate to investigate the potential for suvorexant to reduce incidence of delirium in elderly patients.

In a combined analysis of phase 3 studies conducted in patients with insomnia at the time of its development, the incidence of adverse events in elderly patients aged 65 years or older are comparable among 15 mg, 30 mg (unapproved dose) and placebo groups. In addition, and the incidences of serious adverse events, and adverse events leading to discontinuation were low, and no differences between treatment groups. These suggested that suvorexant 15 mg and 30 mg is generally safe and well tolerated in the doses studied. Furthermore, as for post-marketing surveillance for suvorexant, the efficacy and safety information of suvorexant was collected in patients with insomnia who were first treated with suvorexant in Japan, with a follow-up of up to 6 months after the initiation of treatment [Asai Y, et al. 2018]. The administration of suvorexant 15 mg q.d. to hospitalized elderly patients was well tolerated in clinical practices.

Additionally, the efficacy of suvorexant 15 mg in reducing incidence of delirium when administered to elderly patients has been consistently suggested in several investigator-initiated clinical trials, and was well tolerated [Azuma K, et al. 2018] [Hatta K, et al. 2017].

Based on the above, suvorexant 15 mg q.d. before bed time is for this study.

4.3.2 Rationale for Dose Interval and Study Design

The frequent onset timing of delirium is about 3 days after hospitalization in patients with acute disease [Azuma K, et al. 2018] [Hasegawa M. 1999] [Hatta K, et al. 2014] [Hatta K, et al. 2017] [Regal PJ. 2017] and about 3 days after surgery in patients with postoperative delirium [Booka E, et al. 2017] [Chaiwat O, et al. 2019] [Lee HJ, et al. 2011]. It is reported most cases of delirium occur within 7 days after admission or surgery. On the other hand, although timing and duration of hospitalization is defined based on the physical condition of each patient such as underlying disease and/or policy of each hospital, in recent years, length of stay at general hospital has become shorter in tendency. Considering those points, to evaluate the efficacy of suvorexant in reducing incidence of delirium during the period of the most frequent occurrence of delirium, the administration of study medication will be started from the day (for acute disease or elective surgery) or the next day (for acute disease only) of admission and treated 5 days at least according to the length of stay for each patient in this study. The study medication will be administered for preventive objective in this study, therefore, the administration duration should be limited. The maximum administration duration is set as up to 7 days considering the period of developing delirium.

For participants hospitalized due to elective surgery, if the period from hospitalization to elective surgery is longer, it may affect the evaluation because the administration period of the study medication after surgery becomes shorter. Therefore, in case of hospitalization for elective surgery, participants who schedule surgery on the next day or 2 days after hospital admission are eligible for this study, since such participants can have enough the administration period of the study medication after surgery.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant (and their legally acceptable representative as needed) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

Male/Female Japanese participants at high risk of delirium between the ages of 65 and 90 years, inclusive will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. Is hospitalized for any one of followings;

    (1) Acute disease: meets all following criteria;

        a) Is hospitalized due to any one of following diseases;

Infections	pneumonia, urinary tract infection, soft tissue infection, intra-abdominal infection, cerebral infection, bacteraemia, and sepsis
Cerebral disorders	cerebrovascular disorders (e.g., cerebral infarction, and cerebral haemorrhage)
Heart disorders	cardiac failure, and myocardial infarction
Respiratory diseases	respiratory failure
Injuries	fracture, traumatic injury, and thermal burn
Neoplasms	

AND

b) Meets any one of followings at Screening;

- Has severe disease state (APACHE II: 8 -30)
- Shows decreased daily living function (ECOG PS: 3 or 4)

(2) Elective surgery: meets all following criteria;

a) Requiring general anesthesia

AND

b) Scheduled on the next day or 2 days after admission/Day 1

2. Meets any one of followings;

- Has mild cognitive impairment or mild dementia
- Has a history of delirium in any prior hospitalization

Demographics

3. Is male or female, from 65 years to 90 years of age inclusive, at the time of signing the informed consent.

Informed Consent

4. Has provided documented informed consent/assent for the study (or legally acceptable representative in addition to the participant, as needed).

Other Criteria

5. Requires hospitalization of any one of following estimated period for acute disease or elective surgery.

(1) For acute disease;

- For the randomization/the first dose of study medication on the day of admission: for 6 days and 5 nights or longer
- For the randomization/the first dose of study medication on the next day after admission: for 7 days and 6 nights or longer

(2) For elective surgery;

- For elective surgery scheduled on the next day after admission/Day 1: for 6 days and 5 nights or longer

- For elective surgery scheduled 2 days after admission/Day 1: for 7 days and 6 nights or longer

6. Is able to take study medications orally during the assessment period.

7. Is confirmed that he/she has an ability to follow study procedures and complete the study by the investigator prior to randomization. (e.g., has vision and hearing abilities to perform the clinical study and can speak.)

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Has moderate or severe dementia.

2. Has whose APACHE II is 31 or more at Screening (Only for acute disease).

3. Has a history of epilepsy or Parkinson's disease.

4. Currently uses any of psychotropic agents, or has unstable mental condition including schizophrenia, other mental diseases, bipolar disorder and major depression.

5. Has a history of drug or alcohol abuse within 5 years before Screening, or consumes over 60 g per day of alcohol on average (e.g., 60 g alcohol is 3 *goes* of Japanese sake, 3 middle bottles of beer, or 5 glasses of wine), or has alcoholic disease such as alcoholic liver disease or gastritis alcoholic.

6. Has delirium as assessed by DSM-5 or DRS-R-98 (total score ≥14.5) during the screening period.

7. Is at imminent risk of self-harm or of harm to others in the opinion of the investigator. Participants must be excluded if they report suicidal ideation with intent, with or without a plan or method in the *past 2 months* or suicidal behavior in the *past 6 months*.

8. Has history of narcolepsy or cataplexy.

9. Has history of hypersensitivity to suvorexant.

10. Meets any contraindication or warning listed on package inserts of suvorexant and which are not contained in the exclusion criteria of this protocol.

Prior/Concomitant Therapy

11. Has used any of following medications within 2 weeks before Randomization.

    - Hypnotics (benzodiazepine receptor agonists, orexin receptor antagonists, melatonin receptor agonists, and/or prescription Chinese herbs)
    - Antipsychotics
    - Mood stabilizers
    - Antidepressants
    - Anxiolytics
    - Psychostimulants
    - Anticonvulsants
    - Tiapride

12. Is likely to require during time periods specified by this protocol the treatment with a prohibited medication specified in Section 6.5.1.

Prior/Concurrent Clinical Study Experience

13. Is currently participating in or has participated in an interventional clinical study with an investigational compound or device within 30 days before Screening.

14. Has previously participated AND been randomized in this study.

Diagnostic Assessments

15. Has any exclusionary local laboratory values as listed in the table below at Baseline.

Table 1 Local Laboratory Exclusion Criteria (at Baseline/Visit 2)

Parameter	Study Limit for Exclusion
ALT	3 or more times ULN
AST	3 or more times ULN
Total bilirubin	1.5 or more times ULN
Note: For the participants hospitalized due to acute disease, the local laboratory test results after admission may be referred.	

Other Exclusions

16. Is unable to participate in and complete the requirements of the trial in the investigator's or the Sponsor's judgment for other unlisted reasons.

    Example:

    - *Has mental condition which affects the study participation.*
    - *Is likely to increase the risk associated with study participation or study intervention or to interfere with the interpretation of study result.*

17. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

5.3.1 Non-pharmacological Therapy

From the day of Randomization to the end of the assessment period, the investigator and/or the site staff will confirm the need for the non-pharmacological therapy and take appropriate actions considering the individuals' conditions.

See the following table for the non-pharmacological therapy to be performed;

Table 2 Examples of Non-pharmacological Therapy

Items	Examples of Specific Action Items
Measures to orientation	Setting of a calendar and a clock, and/or conversation with the participant at care, treatment and medical examinations
Measures to physical factors (dehydration and pain)	The confirmation and measures to cause Dehydration: correction of dehydration, promotion of water intake Pain: adjustment of the body position, massage, cooling/heating, psychological support, administration of analgesic, etc.
Measures to inactivity	Promotion of early mobilization, daytime movement of range of motion (passive movement or rehabilitation by physiotherapist if active movement is difficult), avoiding body restraint as possible.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

If a participant discontinues the study due to delirium after randomization before the first dose of study medication, a replacement participant may be enrolled. The replacement participant will generally receive the same intervention as the participant being replaced. The replacement participant will be assigned a unique treatment/randomization number.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies study intervention(s) provided by the Sponsor will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 3.

Table 3 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Intervention period	Use	IMP/ NIMP	Sourcing
Suvorexant	Experimental	MK-4305	Drug	Tablet	15 mg	15 mg	Oral	One tablet QD before bedtime for 5 - 7 days	Experimental	IMP	Provided centrally by the Sponsor
Placebo	Placebo Comparator	Placebo	Drug	Tablet	0 mg	0 mg	Oral	One tablet QD before bedtime for 5 - 7 days	Placebo	IMP	Provided centrally by the Sponsor
The classification of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed.											

All supplies indicated in Table 3 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.12 for details regarding administration of the study intervention.

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study 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.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

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 study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to suvorexant and placebo, respectively.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

1. Hospitalization reason (acute disease, elective surgery)

   If either the proportion of participants hospitalized due to acute disease or those hospitalized due to elective surgery exceeds approximately 60% of the total targeted sample size, the remaining participants will only be enrolled into the other stratum within this stratification factor.

2. Age category (<75 years, ≥75 years)

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. MK-4305 and placebo will be packaged identically so that blind is maintained. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

See Section 8.1.14 for a description of the method of unblinding a participant during the study should such action be warranted.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified intervention plan for ≥2 days in total require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

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

The use of concomitant medications and medications that may cause delirium should be limited to a bare minimum to minimize the impact on efficacy and safety assessment.

6.5.1 Prohibited Therapy

From 2 weeks before Randomization to the end of the assessment period

- Hypnotics (including prescription Chinese herbs, and other than study medications)
- Antipsychotics
- Mood stabilizers
- Antidepressants
- Anxiolytics
- Psychostimulants
- Anticonvulsants
- Tiapride

From the day of Randomization to the end of the assessment period

- Strong CYP3A inhibitors

  Examples: Itraconazole, clarithromycin, ritonavir, nelfinavir, voriconazole, and posaconazole.

From 30 days before Screening to the end of the study

- Other investigational medications

The use of these prohibited medications including antipsychotics for treatment of delirium is allowed in the opinion of the investigator after completion or following a decision of discontinuation of study medications administration.

6.5.2 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

6.6 Dose Modification

No dose modifications are permitted in this study.

6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.14). The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 8.1.14 for a description of the method of unblinding a participant during the study should such action be warranted.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified intervention period will still continue to participate in the study as specified in Section 1.3 and Section 8.9.3.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.13 and Section 8.9.3.

A participant must be discontinued from study intervention but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Developing delirium as assessed by DSM-5

  After randomization, when the qualified rater judges that a participant developed delirium as assessed by DSM-5.
- Adverse events

  In the case that the investigator assesses that administration of the study medication should be discontinued due to the occurrence of adverse experiences.

- Protocol Violation

  It becomes inappropriate to continue study intervention as a result of a significant protocol deviation.

- Non-Compliance with Study Drug

  When a participant has not agreed with or followed the instructions related to the study medication, or a study intervention is not initiated on the day of Randomization.

- In addition, the investigator and/or the Sponsor judges that participant should discontinue the study medications for any other reason.

  Example: When a participant has either transferred to another hospital after the initiation of study medication and is no longer able to participate in the study.

The study procedures of assessment period after discontinuation from study intervention are not performed, since the objectives of this study is to investigate the efficacy of suvorexant on reduction in incidence of developing delirium.

Discontinuation from study intervention is “permanent.” Once a participant is discontinued from study intervention, they shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant’s legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, are outlined in Section 8.1.13. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant’s last

known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (and their legally acceptable representative as needed) prior to participating in this clinical study. If there are

changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant (and their legally acceptable representative as needed) must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (and his/her legally acceptable representative as needed) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant before participation in the study.

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

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

The investigator will review a medical history including a history of delirium in any prior hospitalization.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator will review prior medication use, and record prior medication taken by the participant within 30 days before Screening.

8.1.5.2 Concomitant Medications

The investigator will record medication, if any, taken by the participant during the study.

8.1.6 APACHE II

The investigator will assess APACHE II [Knaus WA, et al. 1985] for participants hospitalized due to acute disease and confirm the eligibility of the enrollment.

Procedures conducted after the admission as part of the participant's routine clinical management (e.g., the measurement of vital signs and laboratory tests) and obtained before signing of ICF may be utilized for the assessment of APACHE II.

8.1.7 ECOG PS

The investigator will assess ECOG PS [Oken MM, et al. 1982] for participants hospitalized due to acute disease and confirm the eligibility of the enrollment.

8.1.8 NM Scale

The investigator will assess the cognitive function using NM scale [Otsuka T, et al. 1991] for all participants and refer to the assessment at the enrollment (mild cognitive impairment or severity of dementia).

8.1.9 Non-pharmaceutical Therapy

According to Section 5.3.1, the non-pharmaceutical therapy to be performed (See Table 2) will be confirmed and it will be mentioned in the medical record. From the day of Randomization to the end of the assessment period, the investigator and/or the site staff will conduct the non-pharmaceutical therapy per the nursing plan.

The investigator will confirm whether non-pharmaceutical therapy had been conducted per the nursing plan and record it.

8.1.10 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

8.1.11 Assignment of Treatment/Randomization Number

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

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

8.1.12 Study Intervention Administration

Each participant will take the first dose before bedtime on the day of randomization.

If the rater judges a participant develop delirium after randomization and before the first dose, the participant must discontinue the study without taking study medication.

8.1.12.1 Timing of Dose Administration

From the day of randomization, each participant will take one tablet of study medication once daily orally before bedtime for 5 – 7 days in double-blind manner according to the individuals' hospitalization duration. On the day of the last assessment visit, the study medication should not be administered.

If the participant missed a dose of study medication, the missed dose of last night should not be administered and one tablet of study medication should be administered before the next bedtime. The study medication must not be taken upon awakening in the middle of the night, even if the participant failed to take study medication at bedtime that previous night. Two or more tablets of the study medication must not be taken a night.

If the participant is not able to take study medication due to his/her condition, the investigator should inform the Sponsor promptly and discuss the continuation of study medications administration of this participant with the Sponsor.

8.1.13 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the assessment period should be encouraged to complete the follow-up visit as outlined in the SoA and Section 8.9.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the last assessment visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.14 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study intervention, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention, but should complete the follow-up visit.

8.1.15 Hospitalization

The participants hospitalized due to acute disease will be randomized within 24 hours after admission to the clinical site.

The participants hospitalized due to elective surgery will be admitted to the clinical site on the day or 2 days before the surgery AND before randomization on the day of the first dose of study medication. If the scheduled date of the surgery is changed by any reasons after randomization, the investigator should contact the Sponsor promptly to discuss whether the participant should continue the study or not.

The participant will be hospitalized for 6 days and 5 nights from the day of the first dose of study medication or longer in cases of acute disease OR elective surgery scheduled on the next day after admission/Day 1, OR, for 7 days and 6 nights in cases of elective surgery scheduled 2 days after admission/Day 1. In the case that the hospitalization duration from the day of the first dose of the study medication is for over 7 days, the intervention duration will be for 7 days.

8.1.16 Calibration of Equipment

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

8.2 Efficacy Assessments

The raters of DSM-5 and DRS-R-98 must receive the training provided by the Sponsor and meet the qualification before rating of this study. The rater qualifications, training and applicable certification process are established in a separate document. The rater should assess according to the manuals as a separate document. To minimize variability, it is preferred that the same rater(s) perform the same evaluation(s) for each participant during the study.

8.2.1 DSM-5

During the assessment period, the qualified rater will review the medical record including the nursing record and question from the participant. The necessary information for the assessment will be collected from the family of the participant and/or the site staff as well, as needed. Based on this information, the rater will assess whether the participant had developed delirium or not as measured by DSM-5 since the last assessment once daily in morning at least, and will record it. DSM-5 assessment should be performed anytime if the rater finds symptoms of suspected delirium in the participant. Assessing DSM-5, the information for assessment of DRS-R-98 should be referred, in principle. If assessing that the participant develops delirium during the assessment period, the subtype and causes of delirium (using the etiology checklist [Trzepacz PT, et al. 2009]) will be assessed, they will be recorded.

If the rater assess that the participant developed delirium as measured by DSM-5, that should be entered in AE eCRF as well.

8.2.2 DRS-R-98

During the assessment period, the qualified rater will review the medical record including the nursing record and question from the participant. The necessary information for the assessment will be collected from the family of the participant and/or the site staff as well, as

needed. Based on this information, the rater will assess the condition of the participant since the last assessment using the items specified in DRS-R-98 once daily in morning at least. The scores will be recorded.

At the follow-up visit, the qualified rater will collect the necessary information from the interview of the participant (and his/her family or site staff(s), and/or the medical record, as needed), and assesses items specified in DRS-R-98. The scores will be recorded.

8.2.3 Richards Campbell Sleep Questionnaire (RCSQ) Score

During the assessment period, the participant will complete 5-item visual analog scale (VAS) about the last-night sleep in the sleep questionnaires once daily in the morning. The clinical coordinator measures the mark written by the participant with a ruler and enters it in millimeter (mm) unit in the eCRF.

8.2.4 Undesirable Hospitalized Patient Outcomes (Fall, Accidental or Intentional Catheter/Tube Removal, and Body Restraint)

The investigator will collect the information related to all events of falls, accidental or intentional catheter/tube removal (i.e., transfusional line, bladder catheter, drain), and body restraints which occur during hospitalization (including the follow-up period when the participant is hospitalized). When falls, accidental or intentional catheter/tube removal, and/or body restraints occur, the investigator will evaluate its relationship to delirium referring to the following criteria.

- Related to delirium: There is evidence of occurrence of delirium. The temporal sequence of the undesirable hospitalized patient outcome onset relative to the occurrence of delirium is reasonable. The undesirable hospitalized patient outcome is more likely explained by delirium than by another cause, e.g., an adverse event other than delirium, a patients' background and/or an environmental factor including use of a concomitant medication or a complication.

- Not related to delirium: Participant did not develop delirium OR temporal sequence of the undesirable hospitalized patient outcome onset relative to the occurrence of delirium is not reasonable OR the undesirable hospitalized patient outcome is more likely explained by another cause than delirium.

"Fall" should be entered in AE eCRF as ECIs as well.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A physical examination will be conducted by the investigator at Screening as per institutional standard evaluations, the last assessment visit and the follow-up visit.

8.3.2 Vital Signs

Blood pressures, pulse rate, and body temperature will be measured once daily from the day of Randomization to the last assessment visit. It is preferred that vital signs are utilized same procedure, same position/side and the same timing of procedure throughout the study.

Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

For the participants hospitalized due to acute disease, the measurements of heart rate and respiratory rate are necessary at Screening for assessment of APACHE II.

8.3.3 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.4 Modified Cataplexy Questionnaire (MCQ) Review

If the investigator receives a report that the participant had cataplexy including cataplexy-like event or fall after randomization, he/she will ask the participant to complete the MCQ (a modified version of Cataplexy Questionnaire [Anic-Labat S, et al. 1999]) and will review it.

If an event is fall, the investigator will review MCQ in order to rule out cataplexy. The administration of the MCQ is provided in a separate document.

All reports of cataplexy including cataplexy-like event and fall, which occurred after randomization, must be recorded as ECIs (See Section 8.4.7). The MCQ, administered in conjunction with documentation of these, will be provided to the CAC.

Falls which occur during hospitalization must be reported as Undesirable Hospitalized Patient Outcomes as well (See Section 8.2.4).

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the time of intervention randomization through 14 days after cessation of study intervention, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified in the previous paragraph must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 4.

Table 4 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential DILI - Require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Information in this section is not applicable since target population of this study is elderly participants.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

There are no disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs in this study. Note that delirium as measured by DSM-5 should be reported as an AE eCRF as well, if the investigator assesses that the participant developed delirium as measured by DSM-5.

8.4.7 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. 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 study site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

2. Complex sleep-related behaviors

3. Sleep paralysis (including sleep onset paralysis [adjudicated])

4. Hypnagogic or hypnopompic hallucinations

5. Somnolence resulting in discontinued intervention

6. Fall (adjudicated to rule out cataplexy)

7. Suicidal ideation, suicidal behaviors

8. Selected events associated with potential for abuse

9. Cataplexy (adjudicated)

CAC will adjudicate events, which occurred after randomization, of “cataplexy”, “sleep onset paralysis” and “fall” reported by the investigators (For the details, see Section 10.1.4.1).

8.5 Treatment of Overdose

In this study, an overdose is any dose higher than 15 mg per night (i.e., 1 tablet per night).

For the specific treatment for an overdose, see the IB/approved labeling.

Decisions regarding dose interruptions will be made by the investigator in consultation with the Sponsor based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Future Biomedical Research Sample Collection

Future biomedical research samples will not be collected in this study.

8.9 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.9.1 Screening Period (from Screening until First Dose of Study Medication)

8.9.1.1 Screening/Visit 1

After the documented informed consent from the participant, the investigator will review whether he/she meet the inclusion and does not meet exclusion criteria.

Note: For participants hospitalized due to acute disease, APACHE II and ECOG PS will be assessed.

Note: For participants hospitalized due to elective surgery, the operative method (i.e., surgery requiring general anesthesia) will be confirmed.

After completing the above, the participants will be registered.

In case Visit 1 and Visit 2 occur on the same day, the overlapping procedures at both visits (e.g., reviewing the inclusion/exclusion criteria) specified in SoA should be performed only once.

In case Visit 1 and Visit 2 occur on different days, the procedures of Visit 1 and the randomization should be performed within 24 hours after admission for participants hospitalized due to acute disease, and the procedures of Visit 1 should be performed within 14 days before admission for participants hospitalized due to elective surgery.

8.9.1.2 Baseline/Visit 2 (until Randomization)

The qualified rater will assess DSM-5 and DRS-R-98 on the day of randomization. The participant will complete RCSQ.

After reviewing whether the participant meets the inclusion and does not meet exclusion criteria based on the above assessments, the eligible participant will be registered and randomized. In addition, the participant will receive appropriate non-pharmacotherapy based on his/her condition (See Section 5.3.1).

The received randomization number will be entered in the participant identification card. The study medication will be prescribed to the participant according to the Component ID. The investigator will instruct the participant to take one tablet of study medication once daily orally before bedtime from the day.

8.9.1.3 Visit 2 (from Randomization until First Dose of Study Medication)

Within 3 hours before the first dose of study medication, the qualified rater will assess DSM-5 again to confirm whether the participant does not develop delirium after randomization. If the assessment before randomization is performed within 3 hours before the first dose of study medication, the re-assessment after randomization is not needed.

If the participant has symptom suspected delirium after the rater assessed before the first dose of study medication, the rater will reassess DSM-5 based on the information to confirm whether the participant does not develop delirium. If the rater judges the participant develops delirium as assessed by DRM-5 or if the rater cannot deny that the participant develops delirium as assessed by DRM-5, the participant must be discontinued from the study without administering study medication.

After the rater assessed before the first dose of study medication, in the case that the participant did not have symptom suspected delirium or in the case that the rater assessed the participant had not developed delirium even if he/she had symptom suspected delirium, the study medication will be administered to him/her.

The investigator or the clinical research coordinator will enter whether the participant had initiated to take the study medication or not to IRT.

8.9.2 Assessment Period (from First Dose of Study Medication until Last Assessment Visit)

The qualified rater will assess the efficacy once daily in the morning at least from the day after the first dose of study medication. The participant will complete RCSQ once daily in the morning.

At the last visit, the procedures specified in SoA will be performed in addition to the above.

The clinical coordinator should make sure that the participant has the participant identification card when he/she is discharged.

8.9.3 Follow-up Period

8.9.3.1 Follow-up Visit

Participants will be required to return to the clinical site 14±3 days after the last dose of study intervention for the follow-up visit. If the follow-up visit occurs less than 14 days after the last dose of study intervention, a subsequent follow-up telephone call should be made more than 14 days post the last dose of study intervention to determine if any AEs have occurred since the follow-up visit.

In the event any serious drug-related adverse event occurred later than 14 days after the last dose of study intervention, it will be subjected to the follow-up evaluation.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to the database lock, changes are made to the primary hypothesis, or the statistical methods related to the hypothesis, 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 the 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.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2-9.12.

Study Design Overview	A Phase 3 multicenter, randomized, placebo-controlled, double-blind clinical study to evaluate the efficacy and safety of MK-4305 (suvorexant) for reducing incidence of delirium in Japanese participants at high risk of delirium.
Treatment Assignment	Participants will be randomized to suvorexant or placebo in a 1:1 ratio, stratified by hospitalization reason (acute disease, elective surgery) and age category (<75 years, ≥75 years).
Analysis Populations	Efficacy: Full Analysis Set (FAS) Safety: All Participants as Treated (APaT)
Primary Endpoint(s)	Proportion of participants with delirium during the assessment period as assessed by DSM-5
Statistical Methods for Key Efficacy Analyses	The treatment difference in the proportion of participants with delirium during the assessment period as assessed by DSM-5, along with the corresponding 95% confidence interval (CI) and the p-value based on the Miettinen and Nurminen method [Miettinen O, et al. 1985], will be provided. The analysis will be stratified by hospitalization reason (acute disease, elective surgery) and age category (<75 years, ≥75 years). The Cochran-Mantel-Haenszel weight will be used to obtain stratum-adjusted proportion difference.

Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. p-Values for treatment comparison (Tier 1), and treatment differences along with 95% CIs (Tiers 1 and 2), will be calculated based on the unstratified Miettinen and Nurminen method for the proportion of participants with respective events.
Interim Analyses	There are no planned interim analyses for this study.
Multiplicity	No multiplicity adjustment is planned as the study has a single primary hypothesis that will be addressed with a single comparison of two treatments using one endpoint.
Sample Size and Power	A total of 200 participants will be randomized to suvorexant or placebo in a 1:1 ratio. The study will have a power of 90 (80) % with a two-sided significance level of 0.05 to detect a difference between treatments if the true proportion of participants with delirium in the suvorexant group is 11.6 (13.7) % compared to 30% in the placebo group. If there are occurrences of delirium after randomization but prior to the first dose of study medication, then the number of randomized participants will be increased to account for such participants.

9.2 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.

This 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 deviations have been identified, and data have been declared final and complete. The randomized allocation schedule(s) for study treatment assignment will be generated by a clinical schedule manager who is otherwise not involved in the study. Randomization will be implemented using IRT (or equivalent).

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

Key efficacy and safety endpoints are listed below. The baseline value is defined as the last available measurement prior to the first dose of study medication.

9.4.1 Efficacy Endpoints

The primary efficacy endpoint is the proportion of participants with delirium during the assessment period as assessed by DSM-5.

The secondary efficacy endpoints are:

1. Severity of delirium during the assessment period as assessed by DRS-R-98, defined as the maximum (i.e., worst) of total score among those obtained daily during the assessment period.

2. Proportion of participants with delirium during the assessment period assessed by DRS-R-98, defined as the proportion of participants with the maximum total score of 14.5 or greater during the assessment period.

9.4.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events, laboratory values and vital signs. The a priori safety events of interest are as follows: complex sleep-related behaviors, sleep paralysis (including sleep onset paralysis [adjudicated]), hypnagogic or hypnopompic hallucinations, somnolence resulting in discontinued intervention, falls (adjudicated to rule out cataplexy), suicidal ideation and/or behaviors, selected events associated with potential for abuse, cataplexy (adjudicated). Those events which consist of multiple AE terms (e.g., complex sleep-related behaviors, selected events associated with potential for abuse) will be defined separately prior to unblinding.

9.5 Analysis Populations

9.5.1 Efficacy Analysis population

The FAS population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all randomized participants who have at least one assessment of delirium by DSM-5 following administration of at least one dose of study medication. Occurrences of delirium after randomization but prior to the first dose of study medication will thus be excluded from the analysis.

A supportive analysis using the Per-Protocol (PP) population may be performed for the primary efficacy endpoint if there is a substantial number of protocol violators (>10% of FAS) that will be excluded from the PP population. The PP population excludes participants due to major deviations from the protocol that may substantially affect the results of the primary efficacy endpoint. Potential deviations that may result in the exclusion of a participant from the PP population include:

- Significant violation to the inclusion/exclusion criteria that may affect the results of the primary efficacy endpoint
- Missing assessment of delirium by DSM-5 at any time during the assessment period
- Treatment duration of less than 5 days, with the exception of discontinuation due to delirium as assessed by DSM-5
- Missed dose(s) of study treatment at any time during the trial
- Use of prohibited concomitant medications

The final determination on major protocol deviations, and thereby the composition of the PP population, will be made prior to the unblinding of the database and will be documented in a separate memo.

Participants will be included in the treatment group to which they are randomized for the analysis of efficacy data.

9.5.2 Safety Analysis Population

Safety analyses will be conducted in the APaT population, which consists of all randomized participants who received at least one dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. For most participants this will be the treatment group to which they are randomized. Participants who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of the respective safety parameters. To assess change from baseline, a baseline measurement is also required.

9.6 Statistical Methods

Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (2-sided) level.

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods for supportive analyses and those related to exploratory objectives will be described in the sSAP.

Primary endpoint

The treatment difference in the proportion of participants with delirium during the assessment period as assessed by DSM-5, along with the corresponding 95% CI and the p-value based on the Miettinen and Nurminen method, will be provided. The analysis will be stratified by hospitalization reason (acute disease, elective surgery) and age category (<75 years, ≥75 years). The Cochran-Mantel-Haenszel weight will be used to obtain stratum-adjusted proportion difference.

Missing assessments will be considered not having delirium. A supportive analysis using survival analytic methods will be conducted to assess the robustness of the conclusion from the primary analysis to the assumption about the missing assessment of delirium. Details will be described in the sSAP.

Secondary endpoints

The proportion of participants with delirium during the assessment period as assessed by DRS-R-98 will be analyzed in the same manner as the primary endpoint. The severity of delirium during the assessment period as assessed by DRS-R-98 will be compared between treatments using an aligned rank test [Mehrotra DV, et al. 2010], taking into consideration the potential non-normality of the data. Within each stratum, the data from individual

participants will be pooled across treatments and transformed by subtracting the Hodges-Lehmann estimate. The transformed values from all strata will then be analyzed for treatment comparison using the unstratified Wilcoxon rank-sum test.

Missing responses for the individual items of DRS-R-98 will be scored as the midpoint of the smallest and the largest possible scores (e.g., as 1.5 for those items rated as 0, 1, 2 or 3), which is consistent with the approach employed in the validation of DRS-R-98 [Trzepacz PT, et al. 2001]. If the assessment is entirely missing on a particular day, the score will be considered missing on that day.

Table 5 summarizes key efficacy analyses.

Table 5 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Hypothesis			
Proportion of participants with delirium during the assessment period as assessed by DSM-5	Stratified Miettinen and Nurminen†	FAS	Missing data due to missed assessments will be considered not having delirium
Secondary Objective #1			
Severity of delirium during the assessment period as assessed by DRS-R-98	Aligned rank test	FAS	Missing responses for the individual items of DRS-R-98 will be scored as the midpoint of the smallest and the largest possible scores. If the assessment is entirely missing on a particular day, the score will be considered missing on that day.
Secondary Objective #2			
Proportion of participants with delirium during the assessment period as assessed by DRS-R-98, defined as the proportion of participants with the maximum total score of 14.5 or greater during the assessment period	Stratified Miettinen and Nurminen†	FAS	Missing responses for the individual items of DRS-R-98 will be scored as the midpoint of the smallest and the largest possible scores. If the assessment is entirely missing on a particular day, the score will be considered missing on that day.
† Miettinen and Nurminen method stratified by hospitalization reason (acute disease, elective surgery) and age category (<75 years, ≥75 years). The Cochran-Mantel-Haenszel weight will be used to obtain stratum-adjusted proportion difference.			

9.6.2 Statistical Methods for Safety Analyses

The analysis of safety results will follow a tiered approach (Table 6). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as system organ class terms) and events that meet predefined limits of change (PDLCs) in laboratory and vital sign parameters are either pre-specified as “Tier 1” endpoints, or will be classified as belonging to "Tier 2" or "Tier 3" based on the number of participants with events.

Tier 1 events

Safety parameters or AEs of special interest that are identified a priori (see Section 9.4.2) constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% CIs to be provided for between-treatment differences in the proportion of participants with events; these analyses will be performed using the unstratified Miettinen and Nurminen method.

Tier 2 events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events (also via the unstratified Miettinen and Nurminen method).

Membership in Tier 2 requires that at least 4 participants in any treatment group exhibit the event. The threshold of at least 4 events was chosen because the 95% CI 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 for Tier 2 events may be provided without adjustment for multiplicity, the CIs 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 events and safety parameters that meet predefined limits of change.

In addition to individual events that occur in 4 or more participants in any treatment group, the broad AE categories consisting of the proportion of participants with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, and discontinuation of study medication due to an AE will be considered Tier 2 endpoints.

Tier 3 events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Continuous safety measures

For continuous measures such as changes from baseline in laboratory and vital sign parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Table 6 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Difference	Descriptive Statistics
Tier 1	Complex sleep-related behaviors	X	X	X
	Sleep paralysis (including sleep onset paralysis [adjudicated])			
	Hypnagogic or hypnopompic hallucinations			
	Somnolence resulting in discontinued intervention			
	Falls (adjudicated to rule out cataplexy)			
	Suicidal ideation and/or behaviors			
	Selected events associated with potential for abuse			
	Cataplexy (adjudicated)			
Tier 2	Any AE[†]		X	X
	Any drug-related AE			
	Any serious AE			
	Any drug-related serious AE			
	Discontinuation of study medication due to AE			
	Specific AEs, SOCs, or PDLCs (incidence ≥4 participants in at least one of the treatment groups)			
Tier 3	Specific AEs, SOCs or PDLCs[‡] (incidence <4 participants in all of the treatment groups)			X
	Change from Baseline Results (Labs, Vital Signs)			

[†] Indicates broad AE category of the number of participants reporting any adverse event
[‡] Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier 2 endpoints

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The comparability of the treatment groups for each relevant demographic and baseline 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 participants screened and randomized, and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

There are no planned interim analyses for this study.

9.8 Multiplicity

No multiplicity adjustment is planned as the study has a single primary hypothesis that will be addressed with a single comparison of two treatments using one endpoint.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Efficacy Analyses

A total of 200 participants will be randomized to suvorexant or placebo in a 1:1 ratio. The study will have a power of 90% with a two-sided significance level of 0.05 to detect a difference between treatments if the true proportion of participants with delirium in the suvorexant group is 11.6 % compared to 30% in the placebo group. The power will be 80% if the true proportion in the suvorexant group is 13.7%. If there are occurrences of delirium after randomization but prior to the first dose of study medication, then the number of randomized participants will be increased to account for such participants.

Previous researches show that delirium was observed at least in 10% – 20% of elderly hospitalized patients hospitalized for surgery or internal diseases (See Section 2). Since this study will enroll participants with higher risk of delirium than the general elderly hospitalized patients, it is anticipated that the incidence of delirium will be greater and the true proportion of participants with delirium is assumed to be 30% in the placebo group. Furthermore, the studies which prospectively assessed the treatment effect of suvorexant for delirium prevention [Azuma K, et al. 2018] [Hatta K, et al. 2017] resulted in treatment differences of ~17% - 18% versus the control group, and it is assumed that this study will have a similar treatment effect.

The table below provides true proportions of participants with delirium in the suvorexant group required to provide 90 (80) % power, under varying assumptions for the true proportion of participants with delirium in the placebo group.

Table 7 True Proportion of Participants With Delirium in the Suvorexant and Placebo Groups Required to Provide 90 (80) % Power (N =100 / arm)

% delirium in Placebo	% delirium in MK-4305 required to provide 90 (80) % Power
25%	8.1% (10.0%)
30%	11.6% (13.7%)
35%	15.3% (17.6%)
40%	19.2% (21.8%)
45%	23.4% (26.1%)
50%	27.8% (30.6%)
Farrington and Manning method, α=0.05 (two-sided)	

9.9.2 Sample Size and Power for Safety Analyses

Table 8 summarizes the percentage point differences between the 2 treatment groups that could be detected with ~80% probability for a variety of hypothetical underlying incidences of an adverse event. These calculations assume 100 participants in each group and are based

on a 2-sided 5% alpha level. The calculations are based on an asymptotic method proposed by Farrington and Manning [Farrington CP, et al. 1990], with no multiplicity adjustments.

Table 8 Differences in Incidence of Adverse Events Between the 2 Treatment Groups That Can be Detected With an ~80% Probability (N =100 / arm)

Incidence of Adverse Event		Risk Difference
Suvorexant (%) (N =100)	Placebo (%) (N =100)	Percentage Point
7.7	0.1	7.6
12.1	2.0	10.1
17.4	5.0	12.4
24.9	10.0	14.9
37.8	20.0	17.8
49.3	30.0	19.3
Based on an asymptotic method proposed by Farrington and Manning, α=0.05 (two-sided)		

9.10 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 endpoint will be estimated for the following subgroups using the unstratified Miettinen and Nurminen method.

- Hospitalization reason (acute disease, elective surgery)
- Age category (<75 years, ≥75 years)

Additional subgroup analyses will be described in the sSAP.

9.11 Compliance (Medication Adherence)

Participants are to take 1 tablet of study medication per day. A day within the study will be considered an "On-Therapy" day if the participant takes 1 tablet of study medication. 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 participant [which is the day before the last assessment visit (Visit 4)].

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

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

Summary statistics will be provided on percent compliance by treatment group for the FAS population.

9.12 Extent of Exposure

The distribution of the number of participants with respect to the number of days on study medication will be tabulated by treatment for the APaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, 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 participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD 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 that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

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 MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

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

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud,

scientific/research misconduct or serious GCP-non-compliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. 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 such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). 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. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants 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.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD 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

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

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

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 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 IRB, IEC, 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 study 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.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant 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 participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. 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.

10.1.4 Committees Structure

10.1.4.1 Clinical Adjudication Committee (CAC)

A CAC will evaluate the following events for the purposes of confirming them according to the criteria in Section 9, 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 (cataplexy or cataplexy-like event) or,

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

Falls 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 study intervention allocation throughout the study.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study 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 study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

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

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

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

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

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study 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 or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 9 will be performed by the central laboratory.
- Local laboratory results are required for the assessment of eligibility. Even if a local sample will be collected at the scheduled visit that the collection of the central laboratory samples is required, it is important that the sample for central analysis has to be obtained in addition to a local sample.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 9 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit		WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)	Total bilirubin
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)	Total Protein
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	CK
	LDH	Magnesium	Uric acid	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, and urobilinogen			
Other Screening Tests	All study-required laboratory assessments will be performed by a central laboratory, with the exception of the assessment of eligibility, e.g., APACHE II and exclusionary laboratory criteria (refer to Table 1).			

The investigator must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. **Results in death**

b. **Is life-threatening**

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing 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 an SAE.) A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer
- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant

number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

    - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).

    - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).

    - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE 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 product and the AE 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 AE:

    - **Exposure:** Is there evidence that the participant 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 studies 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.

- **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 study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

  - 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 study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND 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 PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention 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.

- 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:

        - Participant 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 participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

This section is not applicable to this study.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

This section is not applicable to this study.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

This section is not applicable to this study.

10.7 Appendix 7: Country-specific Requirements

This section is not applicable to this study.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
AE	adverse event
ALT	alanine aminotransferase
APACHE II	Acute Physiology and Chronic Health Evaluation II
APaT	All-Participants-as-Treated
AST	aspartate aminotransferase
CAC	clinical adjudication committee
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSR	Clinical Study Report
DILI	drug-induced liver injury
DRS-R-98	Delirium Rating Scale-Revised-98
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
ECI	event of clinical interest
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic Case Report Form
EDC	electronic data collection
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	interactive response technology
LDH	lactate dehydrogenase
MCQ	Modified Cataplexy Questionnaire
NIMP	Non-Investigational Medicinal Product
NM Scale	Nishimura Mental State Scale for the Elderly
PK	pharmacokinetic
PP	per-protocol
RCSQ	Richards Campbell Sleep Questionnaire
SAE	serious adverse event
SoA	schedule of activities
sSAP	supplemental Statistical Analysis Plan
VAS	Visual Analog Scale
WBC	white blood cell

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