Table S1. Mean SpO_2 by hour of the night

		Suvorexant		Placebo		Difference (Suvorexant – Placebo) of Least Squares Means (90% CI)
Endpoint	Day	N	Least Square Mean (95% CI)	N	Least Square Mean (95% CI)	
Mean SpO_2 in Hour 1 (%)	1	26	94.23 (93.53, 94.93)	24	94.26 (93.54, 94.98)	-0.03 (-0.59, 0.53)
	4	26	94.54 (93.81, 95.26)	25	94.71 (93.98, 95.45)	-0.18 (-0.65, 0.30)
Mean SpO_2 in Hour 2 (%)	1	26	94.00 (93.26, 94.74)	24	93.64 (92.88, 94.40)	0.36 (-0.18, 0.90)
	4	26	93.88 (93.15, 94.62)	25	94.10 (93.35, 94.85)	-0.22 (-0.88, 0.45)
Mean SpO_2 in Hour 3 (%)	1	26	93.88 (93.15, 94.62)	24	94.21 (93.46, 94.97)	-0.33 (-0.87, 0.21)
	4	26	93.88 (93.18, 94.59)	25	93.70 (92.99, 94.42)	0.18 (-0.30, 0.66)
Mean SpO_2 in Hour 4 (%)	1	26	93.92 (93.04, 94.80)	24	94.19 (93.27, 95.11)	-0.27 (-1.12, 0.58)
	4	26	94.31 (93.68, 94.93)	25	94.24 (93.61, 94.87)	0.07 (-0.43, 0.57)
Mean SpO_2 in Hour 5 (%)	1	26	93.96 (93.19, 94.73)	24	94.43 (93.64, 95.23)	-0.47 (-1.07, 0.13)
	4	26	94.23 (93.56, 94.90)	25	94.30 (93.62, 94.98)	-0.07 (-0.47, 0.33)
Mean SpO_2 in Hour 6 (%)	1	26	94.23 (93.56, 94.90)	24	94.32 (93.63, 95.00)	-0.09 (-0.51, 0.34)
	4	26	94.50 (93.85, 95.15)	25	94.20 (93.54, 94.86)	0.30 (-0.12, 0.72)
Mean SpO_2 in Hour 7 (%)	1	26	94.50 (93.88, 95.12)	24	94.57 (93.92, 95.22)	-0.07 (-0.66, 0.52)
	4	26	94.35 (93.66, 95.03)	25	94.22 (93.53, 94.92)	0.12 (-0.41, 0.66)
Mean SpO_2 in Hour 8 (%)	1	26	94.58 (93.89, 95.26)	24	94.88 (94.16, 95.60)	-0.31 (-1.09, 0.47)
	4	26	94.77 (94.13, 95.41)	25	94.60 (93.94, 95.25)	0.17 (-0.37, 0.72)

Table S2. Results of assessments of next-day residual effects

						Difference from Placebo	
Endpoint	Day	Treatment	N	Mean	(95 % CI)	Mean	(90 % CI)
Immediate recall score*	1	Placebo	25	9.26	(8.19, 10.33)	.	
		Suvorexant	26	9.15	(8.10, 10.21)	-0.11	(-0.90,0.68)
	4	Placebo	25	10.66	(9.59, 11.73)	.	
		Suvorexant	26	10.31	(9.25, 11.36)	-0.35	(-1.14,0.44)
Delayed recall score*	1	Placebo	25	7.67	(6.44, 8.89)	.	
		Suvorexant	26	7.31	(6.09, 8.52)	-0.36	(-1.32,0.60)
	4	Placebo	25	9.19	(7.96, 10.41)	.	
		Suvorexant	26	8.69	(7.48, 9.91)	-0.49	(-1.46,0.47)
Digit Symbol Substitution Test Total Correct*	1	Placebo	25	54.69	(49.75, 59.64)	.	
		Suvorexant	26	55.15	(50.24, 60.07)	0.46	(-2.29, 3.21)
	4	Placebo	25	53.77	(48.83, 58.72)	.	
		Suvorexant	26	54.62	(49.70, 59.53)	0.84	(-1.91, 3.59)
Bond and Lader VAS[1]							
Alertness	1	Placebo	25	20.55	(18.47, 22.64)	.	
		Suvorexant	26	21.59	(19.52, 23.67)	1.04	(-0.06, 2.15)
	4	Placebo	24	19.08	(16.98, 21.17)	.	
		Suvorexant	26	20.66	(18.59, 22.73)	1.58	(0.46, 2.71)
Calmness	1	Placebo	25	4.84	(4.41, 5.28)	.	
		Suvorexant	26	4.65	(4.22, 5.08)	-0.19	(-0.50, 0.11)
	4	Placebo	24	4.58	(4.14, 5.01)	.	
		Suvorexant	26	4.72	(4.29, 5.15)	0.14	(-0.17, 0.46)
Contentedness	1	Placebo	25	10.54	(9.33, 11.75)	.	
		Suvorexant	26	11.00	(9.80, 12.20)	0.46	(-0.12, 1.04)
	4	Placebo	24	10.08	(8.86, 11.29)	.	
		Suvorexant	26	10.50	(9.30, 11.70)	0.43	(-0.16, 1.01)

*Lower values are associated with impairment.

[1] Alertness Factor Scale: 0 (most alert) to 28.79 (least alert); Calmness Factor Scale: 0 (most calm) to 7.01 (least calm); Contentedness Factor Scale: 0 (most content) to 16.25 (least content)

Table S3. Body Sway test results

Endpoint	Day	Treatment	N	Geometric Mean	(95 % CI)	Geometric Mean Ratio – Suvorexant/Placebo (90 % CI)	
A95 Eyes Closed (cm^2)	1	Placebo	25	0.40	(0.30, 0.53)	.	
		Suvorexant	25	0.45	(0.34, 0.59)	1.12	(0.95, 1.33)
	4	Placebo	25	0.40	(0.30, 0.53)	.	
		Suvorexant	23	0.42	(0.32, 0.56)	1.06	(0.89, 1.26)
A95 Eyes Open (cm^2)	1	Placebo	25	0.34	(0.25, 0.46)	.	
		Suvorexant	25	0.36	(0.27, 0.49)	1.07	(0.82, 1.38)
	4	Placebo	25	0.36	(0.27, 0.49)	.	
		Suvorexant	23	0.44	(0.32, 0.60)	1.20	(0.92, 1.56)
COP_Length Eyes Closed (cm)	1	Placebo	25	21.86	(19.86, 24.06)	.	
		Suvorexant	25	21.79	(19.80, 23.98)	1.00	(0.94, 1.05)
	4	Placebo	25	21.80	(19.81, 23.99)	.	
		Suvorexant	23	21.57	(19.58, 23.77)	0.99	(0.94, 1.05)
COP_Length Eyes Open (cm)	1	Placebo	25	18.39	(15.68, 21.57)	.	
		Suvorexant	25	17.63	(15.03, 20.68)	0.96	(0.79, 1.16)
	4	Placebo	25	18.25	(15.55, 21.40)	.	
		Suvorexant	23	22.90	(19.39, 27.06)	1.26	(1.03, 1.53)

Higher values associated with impairment.
A95, the area of the 95% confidence ellipse enclosing the center of pressure; COP, center of pressure.

Supplemental Data. Study protocol (following pages)

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036-01

A Study to Evaluate the Effects of MK-4305 in Patients with Obstructive Sleep Apnea

Product: MK-4305
Protocol/Amendment No.: 036-01

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TITLE:

A Study to Evaluate the Effects of MK-4305 in Patients with Obstructive Sleep Apnea

INVESTIGATOR:

PRIMARY:

CLINICAL PHASE: I

US IND NUMBER: 101,847

SITE:

INSTITUTIONAL REVIEW BOARD/ETHICS REVIEW COMMITTEE:

Product: MK-4305 1
Protocol/Amendment No.: 036-01

SUMMARY OF CHANGES

PRIMARY REASON FOR THIS AMENDMENT:

The purpose of this amendment to is to incorporate the exclusion criteria for the Columbia-Suicide Severity Risk Scale (C-SSRS). This has been added to Section 2.3, Exclusion Criteria, as follows:

y. **The subject is at imminent risk of self-harm or harm to others in the investigator's opinion, based on clinical interview and responses provided on the Columbia-Suicide Severity Risk Scale (C-SSRS). Subjects must be excluded if they report suicidal ideation with intent, with or without a plan in the past 2 months or suicidal behavior in the past 6 months, as measured by the C-SSRS at Screening or Baseline.**

Conduct of the C-SSRS (detailed in Section 1.7 Study Flow Chart), and the C-SSRS forms (Appendix 6.10), were included in the original protocol. Conduct of the C-SSRS is considered appropriate for assessment of drugs with central nervous system activity.

OTHER CHANGES INCLUDED IN THE AMENDMENT:

1) In Section 2.2, Patient Inclusion Criteria: inclusion criteria "b." was updated where the lower limit of the BMI criteria was removed.

2) In Section 2.2, Patient Inclusion Criteria: inclusion criteria "f." was updated where a screening NPSG is required for all patients to confirm OSA diagnosis.

3) In Section 2.3, Exclusion Criteria: the order of the lettering for the listed exclusion criteria was corrected.

4) In Section 2.3, Patient Exclusion Criteria: exclusion criteria "w." was updated so that patient is excluded if they are not able to avoid nightshift work for **2** weeks prior to each treatment period.

5) In Section 2.3, Patient Exclusion Criteria: exclusion criteria "x." was updated so that patient is excluded if that have traveled across 3 or more time zones (transmeridian travel) in the last **1** weeks prior to study start.

6) In Sections, 2.7 List of Safety Measurements and 3.4.1 Clinical and Laboratory Measurements for Safety, details on how to handle positive and significant findings related to the Columbia Suicide Severity Rating Scale (C-SSRS) have been added.

7) The terminology "throughout the night" was changed to "during total sleep time" throughout the following sections: 2.1 Objectives and Hypotheses, 2.5 List of Pharmacodynamic Measurement, 2.8 Statistical Analysis Plan Summary, and 3.5 Statistical Analysis Plan.

8) In Section 3.5.2, Analysis Endpoints: the scoring rules for apneic and hypopneic events have been updated and will be based on the 2007 AASM definition.

    a. The original definitions for apneic and hypopneic events that were originally cited in the protocol were (same as that in the 2007 Ramelteon OSA study [3]):

        - -hypopnea: 25%-50% reduction in airflow or tidal volume
        - -apnea: >50% reduction in airflow or tidal volume

    b. The 2007 AASM definitions for apneic and hypopneic events that are now cited and to be used in the protocol are [1, 28]:

        - -hypopnea: ≥ 50% airflow reduction and ≥ 3% desaturation or arousal.
        - -apnea: > 90% reduction in flow

9) In Section 5, List of References: the references citing the scoring rules and baseline definitions for apneic and hypopneic events based on the 2007 AASM definition have been added as: [1, 28].

10) In Section 5, List of References: the reference citing The Columbia Suicide Severity Rating Scale (C-SSRS) has been added as: [27].

11) In Section 5, List of References: the order and the numbering for the listed references has been corrected.

All additions to the protocol are bolded indicating revisions that are required to accommodate this amendment.

PROTOCOL

A Study to Evaluate the Effects of MK-4305 in Patients with Obstructive Sleep Apnea

TABLE OF CONTENTS

Contents	Application Starting Page
SUMMARY OF CHANGES	3
Primary Reason For This Amendment:	3
Other Changes Included In The Amendment:	3
1. SUMMARY	11
1.1 Title	11
1.2 Indication	11
1.3 Summary of Rationale	11
1.4 Summary of Study Design	11
1.5 Sample	13
1.6 Dosage/Dosage Form, Route, and Dose Regimen	13
1.7 Study Flow Chart	14
2. CORE PROTOCOL	18
2.1 Objectives and Hypotheses	18
2.1.1 Primary	18
2.1.2 Secondary	18
2.1.3 Exploratory	19
2.2 Patient Inclusion Criteria	19
2.3 Patient Exclusion Criteria	21
2.4 Study Design and Duration	26
2.4.1 Summary of Study Design	26
2.4.2 Treatment Plan	29
2.4.3 Protocol Modifications Allowed During the Conduct of the Study	30
2.5 List of PHARMACODYNAMIC Measurements	30

TABLE OF CONTENTS (CONT.)

Contents	Application Starting Page
2.6 List of PHARMACOKINETIC Measurements	30
2.7 List of Safety Measurements	31
2.8 Statistical Analysis Plan Summary	31
3. PROTOCOL DETAILS	34
3.1 BACKGROUND AND Rationale	34
3.1.1 Background	34
3.1.2 Product Description and Formulation	35
3.1.3 Clinical Experience in Humans	35
3.1.3.1 Clinical Safety of MK-4305	35
3.1.3.2 Clinical Study Information Not in the IB	35
3.1.3.2.1 Completed MK-4305 Studies	35
3.1.3.2.1.1 Protocol 027-02 Multiple Dose Elderly Safety Study (Updated Study Information- unblinded)	35
3.1.3.2.1.2 Protocol 016-00 Digoxin DDI Study	41
3.1.3.2.1.3 Protocol 017-00 Single Dose in Hepatic Insufficiency Patients Study	46
3.1.3.2.1.4 Protocol 023-00 Renal Insufficiency Study	48
3.1.3.2.1.5 Protocol 022-01 QTc Study	51
3.1.3.2.1.6 Protocol 024-00 Warfarin Interaction Study	57
3.1.3.2.2 Ongoing studies	59
3.1.4 Rationale for This Study	60
3.1.5 Rationale for Study Design	61
3.1.6 Rationale for Dose Regimen	61
3.1.7 Rationale for End Points	64
3.1.7.1 Safety Endpoints	65
3.1.8 Rationale for Optional Specimen Collection for Genetic and Other Biomedical Research	65
3.2 Study Procedures	66

TABLE OF CONTENTS (CONT.)

Contents	Application Starting Page
3.2.1 Concomitant Medication(s)/Treatment(s)	66
3.2.2 Diet/Activity/Other	68
3.2.2.1 Diet	68
3.2.2.2 Fruit Juice Restrictions	69
3.2.2.3 Alcohol Restrictions	69
3.2.2.4 Caffeine Restrictions	69
3.2.2.5 Smoking Restrictions	69
3.2.2.6 Activity Restrictions	69
3.2.2.7 Contraception	69
3.2.2.8 Pregnancy Testing	70
3.2.2.9 Median Sleep Time Determination and Sleep History Diary Completion	70
3.2.2.10 Bedtime (″Lights-Off″):	70
3.2.2.11 Outpatient Study Diary Completion	71
3.2.2.12 Telephone Call	71
3.2.3 Procedures	71
3.2.3.1 Prestudy	73
3.2.3.2 Screening Nighttime Polysomnography (NPSG) Visit and Pharmacodynamic Practice Assessments	75
3.2.3.3 Treatment (Periods 1 and 2)	76
3.2.3.3.1 Pre-Dose Procedures (Periods 1 and 2)	76
3.2.3.3.2 Post-dose Procedures (Periods 1 and 2)	77
3.2.3.4 Washout Period	80
3.2.3.5 Post-study	80
3.2.3.6 Volume of Blood Drawn During the Study	81
3.2.3.7 Study Design/Procedures Modifications Permitted Within Protocol Parameters	81
3.2.3.8 Informed Consent	83

TABLE OF CONTENTS (CONT.)

Contents	Application Starting Page
3.2.3.8.1 General Informed Consent	83
3.2.3.8.2 Consent and Collection of Specimens for Genetic and Other Biomedical Research	83
3.2.3.9 Assignment of Baseline Number	84
3.2.3.10 Randomization/Allocation	84
3.2.3.11 Blinding/Unblinding	84
3.2.3.12 Discontinuation/Withdrawal from Study	85
3.2.3.13 Study Completion and Termination	85
3.3 Efficacy/Pharmacokinetic/Immunogenicity, etc. Measurements	86
3.3.1 Clinical and Laboratory Measurements for Efficacy/Pharmacokinetic/ Immunogenicity, etc.	86
3.3.2 Pharmacodynamic Measurements	86
3.4 Safety Measurements	87
3.4.1 Clinical and Laboratory Measurements for Safety	87
3.4.2 Recording Adverse Experiences	88
3.4.3 Definition of an Overdose for This Protocol	89
3.4.3.1 Reporting of Overdose to SPONSOR	89
3.4.4 Reporting of Pregnancy to SPONSOR	89
3.4.5 Immediate Reporting of Adverse Experiences to the SPONSOR	89
3.4.5.1 Serious Adverse Experiences	89
3.4.5.2 Selected Nonserious Adverse Experiences (if applicable)	90
3.4.6 Evaluating Adverse Experiences	90
3.4.7 SPONSOR Responsibility for Reporting Adverse Experiences	93
3.5 Statistical Analysis Plan (SAP)	93
3.5.1 Hypothesis	93
3.5.2 Analysis Endpoints	94
3.5.3 Approaches to Analyses	94

TABLE OF CONTENTS (CONT.)

Contents	Application Starting Page
3.5.4 Statistical Methods	95
3.5.5 Assumptions	97
3.5.6 Multiplicity	97
3.5.7 Power	97
3.6 Labeling, Packaging, Storage, Dispensing, and Return of Clinical Supplies	98
3.6.1 Patient and Replacements Information	98
3.6.2 Product descriptions	99
3.6.3 Primary Packaging and Labeling Information	99
3.6.4 Clinical Supplies Disclosure	99
3.6.5 Storage and Handling Requirements	100
3.6.6 Standard Policies / Return of Clinical Supplies	100
3.7 Data Management	101
3.8 Biological Specimens	101
4. ADMINISTRATIVE AND REGULATORY DETAILS	102
4.1 Confidentiality	102
4.1.1 Confidentiality of Data	102
4.1.2 Confidentiality of Subject/Patient Records	102
4.1.3 Confidentiality of Investigator Information	102
4.2 Compliance with Law, Audit, and Debarment	103
4.3 Compliance with Financial Disclosure Requirements	104
4.4 Quality Control and Quality Assurance	105
4.5 Compliance with Information Program on Clinical Trials for Serious or Life Threatening Conditions	105
4.6 Publications	105
5. LIST OF REFERENCES	107
6. APPENDICES	110

TABLE OF CONTENTS (CONT.)

Contents		Application Starting Page
6.1	Laboratory Analyses for Safety and Screening	110
6.2	Algorithm for Assessing Out-of-Range Laboratory Values	111
6.3	Blood Volume Requirements	112
6.4	Plasma for MK-4305 Assay -- Biological Sample Collection, Handling, and storage	113
6.5	Modified Cataplexy Questionnaire (MCQ) - Single Episode	116
6.6	Immediate Word Recall and Delayed Word Recall (IDWR)	120
6.7	Digit Symbol Substitution Test (DSST)	121
6.8	Instructions for Bond and Lader Visual Analog Scale (VAS)	123
6.9	Body Sway	124
6.10	Columbia Suicide Severity Rating Scale (C-SSRS) and Columbia - Classification Algorithm of Suicide Assessment (C-CASA) Scores	125
6.11	Sleep history Diary	143
6.12	Outpatient study diary for Self-Administration of study drug	144
7.	ATTACHMENTS	149
8.	SIGNATURES	371
8.1	SPONSOR'S REPRESENTATIVE	371
8.2	INVESTIGATOR	371

1. SUMMARY

1.1 TITLE

A Study to Evaluate the Effects of MK-4305 in Patients with Obstructive Sleep Apnea

1.2 INDICATION

Insomnia

1.3 SUMMARY OF RATIONALE

Redacted

1.4 SUMMARY OF STUDY DESIGN

This is a multi-center, randomized, double-blind, 2-period, cross-over study in patients with OSA to evaluate the safety, tolerability, and effect of multiple doses of MK-4305 on respiratory function compared to administration with placebo. Adult male and female patients with confirmed mild to moderate OSA, between the ages of 18 to 65 years, will participate in this study to complete approximately 24 evaluable patients. Patients will first be evaluated to determine if they fulfill the entry requirements as set forth in Sections 2.2 and 2.3, and approximately 12 of the 24 evaluable patients enrolled will have confirmed moderate OSA.

Following an initial pre-study visit, patients who meet the initial pre-study inclusion/exclusion criteria will undergo a Screening Nighttime Polysomnography (NPSG) Visit (~7 to 10 days prior to Day 1 in Period 1). A sleep history diary will be used to establish habitual median bedtime for at least 5 nights prior to the Screening NPSG visit. The median bedtime established during this period (±1 hour) will be used as the bedtime ("Lights-Off") for the Screening NPSG visit and PSG collection on Day 1 and 4 in both Periods 1 and 2 (See Sections 3.2.2.9 and 3.2.2.10 for median habitual bedtime determination and timing of "lights-off").

The Screening NPSG Visit will further define patient eligibility [specifically Apnea Hypopnea Index (AHI), limb movement, and other sleep disorders] through PSG assessment. A pharmacodynamic assessment practice visit will also occur at the Screening NPSG Visit to allow patients to become familiar with the Immediate and Delayed Word Recall (IDWR), Digit Symbol Substitution Test (DSST), Bond-Lader Visual Analog Scale (VAS), and Body Sway assessments. An outpatient diary for use during the treatment phase of the study will be presented. Patients who meet the

Screening NPSG eligibility criteria, and fulfill the entry requirements as set forth in Sections 2.2 and 2.3, will be enrolled and randomized into the study.

Following the Screening NPSG Visit, patients will be enrolled to receive 2 different treatments, Treatment A and Treatment B, in a randomized crossover design. In each period, patients will receive a 40 mg oral dose of MK-4305 (Treatment A) or matching placebo (Treatment B) once daily for 4 consecutive days. In both treatments, study drug will be administered in the evening (PM, ~0.5 hour before "Lights-Off"). "Lights-off" should be within ±1 hour of the patient's establish habitual median bedtime. On Days 1 and 4 only, study drug will be administered following approximately a four hour fast.

In both Periods 1 and 2, patients will be admitted to the clinical research unit (CRU) on Day 1 for PSG recording and SaO_2 monitoring. Study drug will be administered in the evening (PM, ~0.5 hour before "Lights-Off"). "Lights-off" should be within ±1 hour of the patient's establish habitual median bedtime. PSG recording will commence ~0.5 hour after study drug has been administration at the time of "Lights-off", and will continue overnight for 8 hours. Sparse PK sampling for determination of plasma MK-4305 concentrations will be collected at selected time points, and safety will be closely monitored through clinical and laboratory evaluations. Following pharmacodynamic assessments at approximately 9 hours postdose, at the discretion of the investigator, patients may be discharged in the morning on Day 2 after all study procedures are completed. In the morning of Day 2, the investigator will determine if it is safe for the patient to continue in the study and self-administer study drug at home on Days 2 to 3. Should preliminary review of the Day 1 SaO_2 data show an observed SaO_2 decrease of < 85% for more than 5 consecutive minutes, or if the investigator has any concern of patient safety, the patient will be required to remain in the clinical research unit (CRU) on Days 2 to 3 for dosing and additional observation and monitoring. Otherwise, patients will be discharged in the morning on Day 2 after all study procedures are completed. Patients will be returned to their home or their place of work by private service (e.g. taxi) or a designated relative and/or responsible adult known to the patient.

On Days 2 to 3, patients will continue to take study drug at home (self-administration) each evening before bed. All doses will be taken at ~0.5 hour before bedtime ("Lights off"). Patients will be required to complete the outpatient paper diary following each dose of study drug. Additionally, on Day 3, patients will receive a phone call from the CRU staff daily to confirm that study drug was self-administered as required and for adverse experience (AE) reporting purposes.

In the evening on Day 4, patients will be admitted to the CRU for PSG recording and SaO_2 monitoring. Study drug will be administered in the evening (PM, ~0.5 hour before "Lights-Off"). "Lights-off" should be within ±1 hour of the patient's establish habitual median bedtime. PSG recording will commence ~0.5 hour after study drug administration at the time of "Lights-off", and will continue overnight for 8 hours. Sparse PK sampling for determination of plasma MK-4305 concentrations will be collected at selected time points, and safety will be closely monitored through clinical and laboratory evaluations. Following pharmacodynamic assessments at approximately 9

hours postdose, at the discretion of the investigator, patients will be discharged in the morning on Day 5 after all study procedures are completed, and patients will be returned to their home or their place of work by private service (e.g. taxi) or a designated relative and/or responsible adult known to the patient.

Following the completion of Period 1, patients will return for Period 2 on Day 1 (PM). There will be a minimum 5 day washout between the last dose of MK-4305/placebo on Day 4 in Period 1 and the first dose of MK-4305/placebo in Period 2.

The duration of this study is approximately 9 weeks including pre-study and post-study evaluations.

1.5 SAMPLE

Adult male and female patients with confirmed mild to moderate OSA, between the ages of 18 to 65 years (inclusive), will participate in this study to complete approximately 24 evaluable patients. Approximately 12 of the 24 evaluable patients enrolled will have confirmed moderate OSA.

1.6 DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN

MK-4305 will be provided to the site as tablets in a 40-mg potency, with placebo to match, for this study.

During each period, patients will be administered a 40 mg oral dose of MK-4305 (as 1 x 40-mg tablet) or matching placebo, once daily for 4 consecutive days in the evening (PM, ~0.5 hour before lights off, which should be within one hour of the patient's usual bed time).

On Days 1 and 4, study drug will be administered with ~240 mL of water, in the fasted state (after approximately a four hour fast), with water restricted 1 hour prior and 1 hour after study drug administration. Patients will continue to fast for at least ~2 hours after study drug administration on Days 1 and 4 in each period. On Days 2 to 3, there will be no restriction with regard to food and water and study drug administration. The order in which MK-4305 and placebo are administered will be determined by a computer generated allocation schedule. There will be a minimum 5 day washout between the last dose of MK-4305/placebo on Day 4 in Period 1 and the first dose of MK-4305/placebo in Period 2.

1.7 STUDY FLOW CHART

PRESTUDY and NPSG SCREENING/PHARMACODYNAMIC PRACTICE ASSESSMENTS

Procedures	Pre-study[a]	PSG Screening and PD Practice Assessments[b]	
		PM	AM
Informed Consent / Genetic Consent[c]	X		
Medical history	X		
Physical exam [d]	X		
12-lead ECG [e]	X		
Semi-recumbent vital signs (heart rate (HR) & blood pressure (BP))[e]	X		
Orthostatic vital signs (HR and BP) [f]	X		
Respiration rate (RR) [e]	X		
Oral/tympanic temperature (T)	X		
Finger pulse oxymetry (SaO_2 monitoring)		X----------X	
Immediate and Delayed Word Recall (IDWR; Refer to Appendix 6.6) [g]	X		X
Body Sway (Refer to Appendix 6.9) [g]	X		X
Bond and Lader Visual Analog Scale (VAS; Refer to Appendix 6.8) [g]	X		X
Digit Symbol Substitution Test (DSST; Refer to Appendix 6.7) [g]	X		X
Urine drug screen	X	X	
Alcohol screen	X	X	
Laboratory safety tests [h]	X		
Pregnancy β-hCG test [i]	X		
Serum FSH (if applicable) [j]	X		
HIV/Hepatitis Screen [k]	X		
Columbia Suicide Severity Rating Scale (C-SSRS) [l]	X		
Sleep history diary (Appendix 6.11) [m]	X----------X		
PSG recording [n]		X----------X	

4305, Protocol 036-01 Issue Date: 15-Mar-2011

[a]	Pre-study evaluations to be performed approximately 2 to 3 weeks prior Period 1.
[b]	PSG screening visit/PD practice visit is to take place ~7 to 10 days prior to Day 1, Period 1.
[c]	Obtain informed consent prior to any study mandated procedures; signing of genetic consent/participating in genetic sampling is not necessary to participate in the study.
[d]	Includes height and weight.
[e]	Patients should be in a resting semi-recumbent position for ≥10 minutes before measurements are taken.
[f]	Orthostatic vital signs (BP and HR) should be obtained after the semi-recumbent vital sign measurements are collected. Patients should remain standing for 2 minutes prior to obtaining the orthostatic measurements.
[g]	Pharmacodynamic practice tests will occur at the time of the NPSG visit. The Digit Symbol Substitution Test (DSST) should be repeated 3 times at the NPSG visit using the same form, so that they become familiar with the test, with no scoring is needed.
[h]	Includes chemistry, hematology, and urinalysis. Samples are to be collected after a minimum 8-hr fast.
[i]	For females of child-bearing potential.
[j]	For female Patients of non-childbearing potential a blood sample serum FSH will be collected to confirm postmenopausal status.
[k]	At the discretion of the Investigator
[l]	The C-SSRS will be conducted by the Investigator or delegate at pre-study. Subjects who at any time spontaneously report AEs of suicidal thoughts or ideation must be assessed by the Investigator or delegate using the C-SSRS. See Appendix 6.10.
[m]	A sleep history diary will be used to establish habitual median bedtime for at least 5 nights prior to the Screening NPSG visit.
[n]	An extended PSG recording (NPSG screening visit only) will be conducted for 8 hours.

4305, Protocol 036-01 Issue Date: 15-Mar-2011

PERIOD 1 AND 2 (P.M. DOSING) and POST-STUDY

Procedures	Hours Postdose[a]													
	Day 1						Days 2 to 3	Day 4						
	Pre-dose	0 hr	0.5 hr	9 hr	10 hr	10.5 hr	0 hr	Pre-dose	0 hr	0.5 hr	9 hr	10 hr	10.5 hr	Post-study[b]
Physical exam[c]														X
12-lead ECG[d]	X													X
Semi-recumbent vital signs (heart rate (HR) & blood pressure (BP))[d]	X			X		X		X			X		X	X
Orthostatic vital signs (HR and BP)[e]														X
Respiration rate (RR)[d]	X					X		X					X	X
Oral/tympanic temperature (T)														X
Immediate and Delayed Word Recall (IDWR; Refer to Appendix 6.6)				X							X			
Body Sway (Refer to Appendix 6.9)				X							X			
Bond and Lader Visual Analog Scale (VAS; Refer to Appendix 6.8)				X							X			
Digit Symbol Substitution Test (DSST; Refer to Appendix 6.7)				X							X			
Laboratory safety tests (Appendix 6.1)[f]	X													X
Pregnancy β-hCG test[g]	X							X						X
Urine drug screen	X							X						
Alcohol screen	X							X						
MK-4305/placebo administration[h]		X					X		X					
Outpatient Diary (Appendix 6.12)[i]							X							
Columbia Suicide Severity Rating Scale (C-SSRS)[j]	X												X	X
Standardized meals[k]	X				X			X				X		
PSG recording[l]			X----------X							X----------X				
Finger pulse oxymetry (SaO_2 monitoring)[l]	X[m]		X----------X			X[n]		X[m]		X----------X			X[n]	
Blood for MK-4305 assay	X			X				X			X			
Blood for genetic sampling[o]	X													

[a] There will be a minimum 5 day washout between Period 1 and Period 2.

[b] Post-study evaluations to be performed approximately 14 days after last dose administered in Period 2.

[c] Includes weight at post-study only.

[d] Patients should be in a resting semi-recumbent position for ≥10 minutes before measurements are taken.

[e] Orthostatic vital signs (BP and HR) should be obtained after the semi-recumbent vital sign measurements are collected. Patients should remain standing for 2 minutes prior to obtaining the orthostatic measurements.

[f] Includes chemistry, hematology, and urinalysis. May be collected within 24 hours of dosing; samples are to be collected after a ≥4-hr fast. At post-study samples are to be collected after a minimum 8-hr fast

[g] For females of child-bearing potential.

[h] On Days 1 and 4, study drug is to be administered after a ≥ 4-hour fast with 240 mL of water in the fasted state with water restricted 1 hour prior and 1 hour after study drug administration. Timing of all subsequent procedures will be relative to study drug administration. On Days 2 to 3, patients will self-administer study drug at home in the evening (PM) before bed, within 1 hour of the time study drug was administered in the CRU on Day 1 and should be taken ~0.5 hour before lights off .

[i] Patients will be required to complete the paper diary following each dose of study drug. Additionally, patients will receive a phone call from the CRU staff on Day 3 to confirm that study drug was self-administered as required and for adverse experience (AE) reporting purposes.

[j] The (C-SSRS) will be conducted by the Investigator or delegate at the following time points: predose Day 1, prior to discharge at 10.5 hours postdose Day 4, and at the post-study visit. Subjects who at any time spontaneously report AEs of suicidal thoughts or ideation must be assessed by the Investigator or delegate using the C-SSRS. See Appendix 6.10.

[k] A standard dinner will be served ~4.5 hrs prior to dosing. Standard breakfast to be provided following completion of PSG recording and other study procedures at ~10 hr postdose.

[l] PSG and SaO_2 monitoring will be recorded for 8 hours (0.5 to 8.5 hours postdose). Lights are to be turned off after ~0.5 hour postdose procedures have been completed. Lights are to be turned on after the 8 hour PSG recording is completed. Should a patient remain in-house for dosing on Days 2 and 3, SaO_2 monitoring will be conducted to monitor the patient.

[m] Predose SaO_2 monitoring should be begin 15 minutes prior to dosing.

[n] At the time of discharge, patients should have a SaO_2 value of 90% or above.

[o] Sample is optional and is only taken once during study. Sample may be collected anytime during the study after randomization. Separate informed consent is required.

4305, Protocol 036-01 Issue Date: 15-Mar-2011

2. CORE PROTOCOL

2.1 OBJECTIVES AND HYPOTHESES

2.1.1 Primary

Objectives:

1. To evaluate the safety and tolerability of multiple doses of MK-4305 in patients with mild to moderate OSA.

2. To evaluate the effect of multiple doses of MK-4305 on mean Apnea-Hypopnea Index (AHI) overnight as measured by PSG.

Hypothesis:

Multiple doses of MK-4305 do not produce a clinically significant increase in AHI in patients with mild to moderate OSA, as compared to placebo. Specifically, the true mean AHI treatment difference (MK-4305 – Placebo) on Night 4 is less than 5.

2.1.2 Secondary

Objectives:

1. To evaluate the effect of multiple dose administration of MK-4305 on mean arterial blood oxygen saturation (SaO_2) **during total sleep time** as measured by pulse oxymetry.

2. To evaluate the proportion of the night **during total sleep time** in which SaO_2 is less than 90%, 85% and 80% following multiple dose administration of MK-4305 and placebo.

3. To compare mean SaO_2 of different sleep stages (awake, NREM, REM) following multiple dose administration of MK-4305 and placebo.

4. To evaluate the effect of single dose administration of MK-4305 on the apnea/hypopnea index (AHI), mean oxygen saturation (SaO_2) **during total sleep time** and during each sleep stage (awake, NREM, REM), and the proportion of the night **during total sleep time** in which SaO_2 is less than 90%, 85% and 80%.

Hypotheses:

1. Multiple doses of MK-4305 do not produce a clinically significant reduction of mean SaO_2 **during total sleep time** in patients with mild to moderate OSA, as compared to placebo. Specifically, the true mean SaO_2 treatment difference (MK-4305 – Placebo) on Night 4 is greater than -2%.

2. **Estimation**: The proportion of the night **during total sleep time** in which SaO_2 is less than 90%, less than 85% and less than 80% following multiple dose administration of MK-4305 and placebo will be estimated.

3. **Estimation**: The mean SaO2 for each sleep stage (awake, NREM, REM) following multiple dose administration of MK-4305 and placebo will be estimated.

4. A single dose of MK-4305 does not produce a clinically significant increase in AHI in patients with mild to moderate OSA, as compared to placebo. Specifically, the true mean AHI treatment difference (MK-4305 – Placebo) after single dose administration (Night 1) is less than 5.

2.1.3 Exploratory

Objectives:

1. To explore the effects of MK-4305 on objective sleep parameters (e.g. LPS, WASO, TST, SEI, etc) in patients with mild to moderate OSA as assessed by PSG.

2. To explore the next-day residual effect of MK-4305 on psychomotor performance tests (e.g. Delayed Word Recall (IDWR), Digit Symbol Substitution Test (DSST)), Bond-Lader Visual Analog Scale (VAS) and Body Sway).

2.2 PATIENT INCLUSION CRITERIA

Demographics

a. Patient is a male or female 18 to 65 years of age at the pre-study (screening) visit.

   1. Female patients of reproductive potential must demonstrate a serum β-hCG level consistent with the nongravid state at the pre-study (screening) visit and agree to use (and/or have their partner use) two (2) acceptable methods of birth control beginning at the pre-study visit throughout the study (including washout intervals between treatment periods/panels) and until 2 weeks after the last dose of study drug in the last treatment period. Acceptable methods of birth control two (2) of the following: intrauterine device (IUD-with or without local hormone release), diaphragm, spermicides, cervical cap, contraceptive sponge, and /or condoms. Abstinence is an alternative life style and Patients practicing abstinence may be included in the study.

   2. Women who are postmenopausal without menses for at least 1 year **and** an FSH value in the postmenopausal range upon pre-study (screening) evaluation, and/or are status post hysterectomy, oophorectomy or tubal ligation may participate.

      - Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure otherwise the

patient will be excluded. Information must be captured appropriately within the site's source documents.

b. The patient has a Body Mass Index (BMI) ≤ 40 kg/m^2 at the pre-study (screening) visit. BMI is calculated by taking the Patient's weight in kg and dividing by the Patient's height in meters, squared.

Medical history, physical examination, laboratory safety test and ECG measurements

c. Patient is judged to be in good health based on medical history, physical examination, vital sign measurements, and laboratory safety tests (see Appendix 6.1 and 6.2) performed at the pre-study (screening) visit and/or prior to administration of the initial dose of study drug.

d. Patient has no clinically significant abnormality on electrocardiogram (ECG) performed at the pre-study (screening) visit and/or prior to administration of the initial dose of study drug.

e. Patient has an International Classification of Sleep Disorders diagnosis of Obstructive Sleep Apnea Syndrome (see Attachments for ICSD criteria), based on:

   1. Investigator's assessment of the OSA/HS history and diagnostic interview;

   and

   2. Documented sleep study (i.e. nighttime diagnostic PSG in a sleep lab) within the past 5 years that confirmed the OSA/HS diagnosis

f. Patient has confirmed mild **or** moderate obstructive sleep apnea [defined as mild OSA **with AHI =** ≥ 5 and < 15, and moderate OSA **with AHI** = ≥ 15 and < 30] based on the screening NPSG.

g. Patient must be in stable physical health for at least 2 weeks prior to entering the study.

Diet/Activity/Other

h. Patient has a usual bedtime between 20:00 (8:00 PM) and 00:30 (12:30 AM) and is not subject to any other unusual changes in sleeping routine.

i. Subject must complete a sleep history diary for at least 5 consecutive days and up to 21 days prior to the screening PSG visit.

j. Patient sleeps for 4 hours or more per night.

k. Patient understands the study procedures and agrees to participate in the study by giving written informed consent.

l. Patient is reliably able to perform the study assessments; demonstrates the ability to understand task instructions and is physically capable (e.g., adequate manual dexterity, vision and hearing) of performing study tasks.

m. Patient has been a nonsmoker and/or has not used nicotine or nicotine-containing products for at least approximately 6 months; Patients who have discontinued smoking or the use of nicotine/nicotine containing products for at least approximately 3 months may be enrolled in the study at the discretion of the investigator.

n. Patient is willing to comply with the study restrictions (see Section 3.2. for a complete summary of study restrictions).

2.3 PATIENT EXCLUSION CRITERIA

Medical History, Physical Examinations, Laboratory Safety Tests and ECG Measurements

a. Patient has used continuous positive airway pressure devise (CPAP) or a dental appliance within the preceding 7 days prior to Screening NPSG Visit, or is required to use CPAP or a dental appliance during course of the study (7 days prior to the screening NSPG, throughout the study (including washout intervals between treatment periods), and until the poststudy visit) .

b. Other than OSA, patient has evidence of another clinically significant, active pulmonary disorder such as bronchiectasis, emphysema, or asthma documented by history, physical examination, or chest x-ray.

c. Patient has either a history within the past 6 months prior to the prestudy visit or current evidence of an unstable or clinically significant cardiovascular disorder, including but not limited to:

- Acute coronary syndrome
- Unstable angina
- Congestive heart failure
- Cardiogenic syncope
- Cardiomyopathy
- Any symptomatic arrhythmia
- Orthostatic hypotension
- Uncontrolled hypertension

d. Patient has abnormal pre-randomization laboratory values per the guidance below or other clinically significant, unexplained laboratory abnormality in the opinion of the investigator:

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

- Serum Creatinine of > 2 mg/dL

See Appendix 6.2 for an algorithm for assessing out-of-range laboratory values.

e. Patient has a history or diagnosis of any of the following conditions, in the opinion of the investigator:

- Narcolepsy
- Cataplexy (familial or idiopathic)
- Circadian Rhythm Sleep Disorder
- Parasomnia including nightmare disorder, sleep terror disorder, sleepwalking disorder, and REM behavior disorder
- Periodic Limb Movement (PLM) Disorder
- Restless Legs Syndrome
- Primary Hypersomnia

Patients with insomnia **can be** enrolled.

f. Patient has a screening PSG recording with any of the following conditions:

1) O2 saturation <80% for ≥ 5% of the total sleep time

2) >10 PLM per hour associated with an arousal (PLMAI)

g. Patient is under the age of legal consent.

h. Patient is mentally or legally incapacitated, has significant emotional problems at the time of prestudy (screening) visit or expected during the conduct of the study or has a history of a clinically significant psychiatric disorder over the last 5 to 10 years. Patients who have had situational depression may be enrolled in the study at the discretion of the investigator.

i. Patient has any of the following:

1. Lifetime history of bipolar disorder, a psychotic disorder, or posttraumatic stress disorder; or,
2. A psychiatric condition requiring treatment with a prohibited medication; or,
3. Other psychiatric condition that, in the investigator's opinion, would interfere with the patient's ability to participate in the study.

j. Patient, in the opinion of the investigator, has a history or current evidence of any condition, therapy, lab or ECG abnormality or other circumstances that might confound the results of the study, or interfere with the patient's participation for the full duration of the study, such that it is not in the best interest of the patient to participate. Examples of excluded disorders include, but are not limited to: HIV or other relevant infections, history of acute or chronic hepatitis, history of gastric

bypass or gastric banding surgery, active endocrine disorders (however, patients with well-controlled non-insulin-dependent diabetes, or hypothyroidism are allowed if on stable doses of appropriate therapy for ≥ 1 month prior to Screening Visit 2).

k. Patient has any history of a neurological disorder, including but not limited to seizure disorder (other than single episodes of childhood febrile seizures), stroke, transient ischemic attack, multiple sclerosis, cognitive impairment, or significant head trauma with sustained loss of consciousness within the last 10 years.

l. Patient has a history of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, or genitourinary abnormalities or diseases. Patients with a history of uncomplicated kidney stones may be enrolled in the study at the discretion of the investigator.

m. Patient has a history of neoplastic disease.

   Exceptions: (1) Patients with adequately treated non-melanomatous skin carcinoma or carcinoma *in situ* of the cervix may participate in the study; (2) Patients with other malignancies which have been successfully treated ≥ 10 years prior to the prestudy (screening) visit where, in the judgment of both the Investigator and treating physician, appropriate follow-up has revealed no evidence of recurrence from the time of treatment through the time of the prestudy (screening) visit (except those cancers identified at the beginning of exclusion l.); or, (3) Patients, who, in the opinion of the Investigator, are highly unlikely to sustain a recurrence for the duration of the study.

n. Patient is a nursing mother.

o. Patient has a positive screening urine alcohol test or drug test (e.g., positive for benzodiazepines, cannabinoids, cocaine, etc.). NOTE: The screen may be repeated at investigator's discretion and as warranted by medical history and concomitant medications. A repeat drug screen must be negative prior to randomization or it must be discussed with the SPONSOR.

Diet/Activity/Other

p. Patient has a need for more than 3 toilet visits during the night.

q. Patient is taking, or plans to take, one or more of the following medications, shown below and in Table 3-9, within the specified washout period prior to the first drug administration and throughout the course of the study (a detailed list of the prohibited medications is provided in Section 3.2.1.)

Prohibited Medications and Specified Washout Period

Treatment	**Interval***
Investigational compounds	4 weeks prior to screening (see exclusion w)
Strong CYP3A4 Inhibitors and Inducers	2 weeks or 5 $t_{½}$ lives
Antihistamines (sedating)	2 weeks
Hypnotics	2 weeks or 5 $t_{½}$ lives **
Other Psychotropics:	
Antidepressants (other than fluoxetine) Fluoxetine	2 weeks 4 weeks
Anticonvulsants	2 weeks
Antipsychotics	2 weeks or 5 $t_{½}$ lives
Anxiolytics (benzodiazepines, non-benzodiazepines)	2 weeks or 5 $t_{½}$ lives**
Centrally acting anticholinergics	2 weeks
Any CNS depressants	2 weeks
Mood Stabilizers	2 weeks
Stimulants	2 weeks
Supplements with possible psychotropic effects	2 weeks
Other Medications:	
Anticoagulants, systemic glucocorticoids, isotretinoin, diet pills	2 weeks

* Interval notes minimum washout period. Washout should occur for 5 half lives or the minimum specified period (2 or 4 weeks), which ever is longer to systemically eliminate the compound.

** The indicated hypnotic/anxiolytic washout applies to intermittent use only (defined as use of < 4 times/week). For those patients chronically using a hypnotic or anxiolytic (defined as use of ≥4 times/week) a 4-week washout (or 5 t½ lives, whichever is greater) must occur prior to completion of Visit 1. Please see Section 3.2.1 for more information.

r. Patient consumes excessive amounts of alcohol, defined as greater than 3 glasses of alcoholic beverages (1 glass is approximately equivalent to: beer [284 mL], wine [125 mL/4 ounces], or distilled spirits [25 mL/1 ounce]) per day. Patients who consume 4 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator. During the study, alcohol will not be consumed 48 hours prior to the in-patient nights (Day 1, Day 4, and screening NPSG) until discharge. During the remaining study days, patients will limit alcohol consumption to 2 glasses a day and will avoid consuming alcohol at least 3 hours before going to bed.

s. Patient consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, or other caffeinated beverages per day. During the study, caffeine will be not allowed within 10 hours of bedtime prior the in-patient nights (Day 1, Day 4 and screening NPSG) until discharge. During the remaining study days, patients will be required to avoid caffeine after 4:00 pm during the treatment period. At all other times, caffeinated beverages will be limited to no more than 2 units per day amounts (>4 units: 1 unit=120 mg of caffeine).

t. Patient has had major surgery, donated or lost 1 unit of blood (approximately 500 mL) or participated in another investigational study within 4 weeks prior to the prestudy (screening) visit. The 4 week window will be derived from the date of the last study procedure (i.e. poststudy, AE follow-up, etc.) in the previous study to the prestudy/screening visit of the current study.

u. Patient has a history of significant multiple and/or severe allergies (including latex allergy), or has had an anaphylactic reaction or significant intolerability to prescription or non-prescription drugs or food.

v. Patient is currently a regular user (including "recreational use") of any illicit drugs or has a history of drug (including alcohol) abuse within approximately 2 years.

w. Patient works a night shift and is not able to avoid night shift work within **2** week before each treatment visit (or before the study start and during the study).

x. Patient has traveled across 3 or more time zones (transmeridian travel) in the last **1** weeks prior to study start.

y. **The subject is at imminent risk of self-harm or harm to others in the investigator's opinion, based on clinical interview and responses provided on the Columbia-Suicide Severity Risk Scale (C-SSRS). Subjects must be excluded if they report suicidal ideation with intent, with or without a plan in the past 2 months or suicidal behavior in the past 6 months, as measured by the C-SSRS at Screening or Baseline.**

z. There is any concern by the investigator regarding the safe participation of the patient in the study or for any other reason; the investigator considers the patient inappropriate for participation in the study.

2.4 STUDY DESIGN AND DURATION

2.4.1 Summary of Study Design

This is a multi-center, randomized, double-blind, 2-period, cross-over study in patients with OSA to evaluate the safety, tolerability, and effect of multiple doses of MK-4305 on respiratory function compared to administration with placebo. Adult male and female patients with confirmed mild to moderate OSA, between the ages of 18 to 65 years, will participate in this study to complete approximately 24 evaluable patients. Patients will first be evaluated to determine if they fulfill the entry requirements as set forth in Sections 2.2 and 2.3, and approximately 12 of the 24 evaluable patients enrolled will have confirmed moderate OSA.

Following an initial pre-study visit, patients who meet the initial pre-study inclusion/exclusion criteria will undergo a Screening Nighttime Polysomnography (NPSG) Visit (~7 to 10 days prior to Day 1 in Period 1). A sleep history diary will be used to establish habitual median bedtime for at least 5 nights prior to the Screening NPSG visit. The median bedtime established during this period (±1 hour) will be used as the bedtime ("Lights-Off") for the Screening NPSG visit and PSG collection on Day 1 and 4 in both Periods 1 and 2 (See Sections 3.2.2.9 and 3.2.2.10 for median habitual bedtime determination and timing of "lights-off").

The Screening NPSG Visit will further define patient eligibility [specifically Apnea Hypopnea Index (AHI), limb movement, and other sleep disorders] through PSG assessment. A pharmacodynamic assessment practice visit will also occur at the Screening NPSG Visit to allow patients to become familiar with the Immediate and Delayed Word Recall (IDWR), Digit Symbol Substitution Test (DSST), Bond-Lader Visual Analog Scale (VAS), Body Sway assessments. An outpatient diary for use during the treatment phase of the study will be presented. Patients who meet the Screening NPSG eligibility criteria, and fulfill the entry requirements as set forth in Sections 2.2 and 2.3, will be enrolled and randomized into the study.

Following the Screening NPSG Visit, patients will be enrolled to receive 2 different treatments, Treatment A and Treatment B, in a randomized crossover design. In each period, patients will receive a 40 mg oral dose of MK-4305 (Treatment A) or matching placebo (Treatment B) once daily for 4 consecutive days. In both treatments, study drug will be administered in the evening (PM, ~0.5 hour before "Lights-Off"). "Lights-off" should be within ±1 hour of the patient's establish habitual median bedtime. On Days 1 and 4 only, study drug will be administered following approximately a four hour fast.

In both Periods 1 and 2, patients will be admitted to the clinical research unit (CRU) on Day 1 for PSG recording and SaO_2 monitoring. Study drug will be administered in the evening (PM, ~0.5 hour before "Lights-Off"). "Lights-off" should be within ±1 hour of

the patient's establish habitual median bedtime. PSG recording will commence ~0.5 hour after study drug has been administration at the time of "Lights-off", and will continue overnight for 8 hours. Sparse PK sampling for determination of plasma MK-4305 concentrations will be collected at selected time points, and safety will be closely monitored through clinical and laboratory evaluations. Following pharmacodynamic assessments at approximately 9 hours postdose, at the discretion of the investigator, patients may be discharged in the morning on Day 2 after all study procedures are completed. In the morning of Day 2, the investigator will determine if it is safe for the patient to continue in the study and self-administer study drug at home on Days 2 to 3. Should preliminary review of the Day 1 SaO_2 data show an observed SaO_2 decrease of < 85% for more than 5 consecutive minutes, or if the investigator has any concern of patient safety, the patient will be required to remain in the clinical research unit (CRU) on Days 2 to 3 for dosing and additional observation and monitoring. Otherwise, patients will be discharged in the morning on Day 2 after all study procedures are completed. Patients will be returned to their home or their place of work by private service (e.g. taxi) or a designated relative and/or responsible adult known to the patient.

On Days 2 to 3, patients will continue to take study drug at home (self-administration) each evening before bed. All doses will be taken at ~0.5 hour before bedtime ("Lights off"). Patients will be required to complete the outpatient paper diary following each dose of study drug. Additionally, on Day 3, patients will receive a phone call from the CRU staff daily to confirm that study drug was self-administered as required and for adverse experience (AE) reporting purposes.

In the evening on Day 4, patients will be admitted to the CRU for PSG recording and SaO_2 monitoring. Study drug will be administered in the evening (PM, ~0.5 hour before "Lights-Off"). "Lights-off" should be within ±1 hour of the patient's establish habitual median bedtime. PSG recording will commence ~0.5 hour after study drug administration at the time of "Lights-off", and will continue overnight for 8 hours. Sparse PK sampling for determination of plasma MK-4305 concentrations will be collected at selected time points, and safety will be closely monitored through clinical and laboratory evaluations. Following pharmacodynamic assessments at approximately 9 hours postdose, at the discretion of the investigator, patients will be discharged in the morning on Day 5 after all study procedures are completed, and patients will be returned to their home or their place of work by private service (e.g. taxi) or a designated relative and/or responsible adult known to the patient.

Following the completion of Period 1, patients will return for Period 2 on Day 1 (PM). There will be a minimum 5 day washout between the last dose of MK-4305/placebo on Day 4 in Period 1 and the first dose of MK-4305/placebo in Period 2.

The duration of this study is approximately 9 weeks including pre-study and post-study evaluations.

A schematic representation of the study design is given below in Table 2-1.

Table 2-1

Study Design

Study Day	**Activity**
Prestudy visit	Informed consent, inclusion/exclusion, lab safety tests, etc.
At least 5 nights prior to the PSG screening visit	Completion of the sleep history diary to establish habitual median bedtime
PSG screening visit (evening)	Screening NPSG, SaO_2 and Pharmacodynamic assessment practice (~7 to 10 days prior to Day 1, Period 1)
Period 1 Day 1 (evening)	MK-4305/placebo dosing and begin SaO_2 and NPSG
Period 1 Day 2 (morning)	Release from CRU following final study procedures (including next-day pharmacodynamic assessment)
Period 1 Days 2 to 3	Daily MK-4305/placebo self-administration in PM at home and call from study staff on Day 3
Period 1 Day 4 (evening)	MK-4305/placebo dosing and begin SaO_2 and NPSG
Period 1 Day 5 (morning)	Release from CRU following final study procedures (including next-day pharmacodynamic assessment)
Washout Period = 5 days	
Period 2 Day 1 (evening)	MK-4305/placebo dosing and begin SaO_2 and NPSG
Period 2 Day 2 (morning)	Release from CRU following final study procedures (next-day pharmacodynamic assessment)
Period 2 Days 2 to 3	Daily MK-4305/placebo self-administration in PM at home and call from study staff on Day 3
Period 2 Day 4 (evening)	MK-4305/placebo dosing and begin SaO_2 and NPSG
Period 2 Day 5 (morning)	Release from CRU following final study procedures (next-day pharmacodynamic assessment)
Post study visit	~14 days following last dose of study drug

2.4.2 Treatment Plan

Patients will be randomized to receive MK-4305 or matching placebo according to a computer-generated allocation schedule. The order in which patients receive each treatment will be according to a balanced crossover design for Periods 1 and 2. Each site will receive its own range of allocation numbers for randomization. Within each site's respective range, sites will randomize in ascending order, starting with the lowest allocation number, for patients with mild OSA (for example: AN 0001, then AN 0002, then AN 0003, etc.), and will randomize in descending order, starting with the highest allocation number, for patients with moderate OSA (for example: AN 0010, then AN 0009, then AN 0008, etc.). A sample allocation scheme for the treatment plan of this study is presented in Table 2-2.

On Days 1 and 4, study drug will be administered with 240 mL of water, in the fasted state (after approximately a four hour fast), with water restricted 1 hour prior and 1 hour after study drug administration. Patients will continue to fast for at least ~2 hours after study drug administration on Days 1 and 4 in each period. On Days 2 to 3, there will be no restriction with regard to food and water and study drug administration.

In both Periods 1 and 2, patients will undergo identical NPSG procedures, SaO_2 monitoring, pharmacokinetic sampling, pharmacodynamic assessment, and safety evaluations following dose administration.

There will be at least a 5-day washout between Period 1 and Period 2. Safety will be monitored throughout the study by repeated clinical and laboratory evaluations. PSG and SaO_2 recordings will also be performed on Days 1 and 4.

Table 2-2

Sample Allocation Schedule

Treatment Sequence	Number of Patients	Period 1	Period 2
A/B	12	Treatment A	Treatment B
B/A	12	Treatment B	Treatment A
Treatment A = 40 mg MK-4305 administered once daily in the evening for 4 consecutive days. Treatment B = MK-4305 matching placebo administered once daily in the evening for 4 consecutive days.			

2.4.3 Protocol Modifications Allowed During the Conduct of the Study

Because this is a Phase I assessment of MK-4305 in humans and the pharmacokinetic, pharmacodynamic and safety profiles of the compound are still being elucidated, this protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase I clinical studies.

Please refer to Section 3.2.3.7 (Protocol Details) for examples of modifications permitted within the protocol parameters.

2.5 LIST OF PHARMACODYNAMIC MEASUREMENTS

Following evening administration of MK-4305 or matching placebo, patients will sleep in the sleep laboratory for PSG recording and SaO2 monitoring which will be collected during a defined interval of time postdose. Scoring for PSG sleep will be determined by the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events criteria into the four sleep stages [1]. **AASM rules maintain much of the Rechtschaffen and Kales framework for standardized scoring methods and criteria [2].**

The next-day effects of MK-4305 will be evaluated by Delayed Word Recall (IDWR), Digit Symbol Substitution Test (DSST), Bond-Lader Visual Analog Scale (VAS), Body Sway.

<u>Efficacy Endpoints following multiple dose administration of MK-4305 compared to placebo:</u>

- The apnea/hypopnea index (AHI) on Day 4, defined by total number of apnea and hypopnea divided by total sleep time (in minutes) multiplied by 60.

<u>Secondary Endpoints:</u>

- Mean arterial oxygen saturation (SaO2) **during total sleep time** on Day 1 and Day 4.
- The proportion of the night in which SaO_2 is less than 90%, 85% and 80% on Day 1 and Day 4.
- Mean SaO_2 of different sleep stages on Day 1 and Day 4.
- The apnea/hypopnea index (AHI) on Day 1, defined by total number of apnea and hypopnea divided by total sleep time (in minutes) multiplied by 60.

2.6 LIST OF PHARMACOKINETIC MEASUREMENTS

In Periods 1 and 2, plasma for PK determinations will be measured predose, and at 9 hours postdose on Days 1 and 4.

2.7 LIST OF SAFETY MEASUREMENTS

Safety and tolerability will be closely monitored throughout the study via physical examinations, vital signs, 12-lead electrocardiograms (ECGs), and laboratory safety evaluations (hematology, blood chemistry, and urinalysis). Patients will be assessed for adverse experiences throughout the study. All patients in this study will be monitored for activities of daily living by the clinical staff, who will also implement fall precautions.

The Columbia Suicide Severity Rating Scale (C-SSRS) will be utilized as an assessment for suicidal ideation and potential behavior. Subjects will be assessed for adverse events during the study. Any safety procedures may be done at unscheduled time points, if deemed necessary by the investigator.

These procedures may also be performed at various unscheduled time points, if deemed clinically necessary by the Investigator.

2.8 STATISTICAL ANALYSIS PLAN SUMMARY

Methods: **Primary** AHI (Primary Hypothesis) The primary hypothesis regarding the effect of MK-4305 on AHI will be addressed by comparing the AHI following administration of MK-4305 to AHI following administration of placebo. Individual AHI values on Day 4 will be evaluated in a linear mixed-effects model appropriate for a 2-period crossover study. The model will contain fixed effects for treatment, period and sequence, and a random effect for Patient within sequence. Using an appropriate linear contrast, a two-sided 90% confidence interval (equivalent to a one-sided upper 95% confidence interval) for the true mean difference (MK-4305 – Placebo) in AHI will be calculated using the mean square error from the model and referencing a t-distribution. If the upper bound of the confidence interval is less than 5, then the hypothesis that multiple oral doses of MK-4305 do not produce a clinically significant increase in AHI in patients with mild to moderate OSA, as compared to placebo, will be supported. Day 1 results will be analyzed in a similar fashion as above. Safety Safety and tolerability will be evaluated following multiple doses of MK-4305 administered to patients with OSA by clinical assessment of adverse experiences and other safety measurements (e.g., vital signs, ECGs, laboratories, etc.). Summary statistics will be provided as appropriate. **Secondary** Mean SaO_2 (1^{st} Secondary Hypothesis) Individual values for the mean SaO_2 on Day 4 **during total sleep time** will be analyzed in a linear mixed effects model as previously described. A two-sided 90% confidence interval (equivalent to a one-sided lower 95% confidence interval) for the true mean difference (MK-4305 – Placebo) in mean SaO_2 **during total sleep time** will be calculated using the mean square error from the model and referencing a t-distribution. If the lower bound of the confidence interval is greater than -2%, then the hypothesis that multiple oral doses of MK-4305 do not produce a clinically significant reduction of mean SaO_2 **during total sleep time** in patients with mild to moderate OSA, as compared to placebo, will be supported. Day 1 results will be analyzed in a similar fashion as above. Proportion of the Night SaO_2 < 90%, <85% and <80% (2^{nd} Secondary Estimation Hypothesis) Summary statistics will

be provided for the percentage of patients on each treatment who experience an SaO_2 level less than 90%, 85% and 80% during the night following multiple dose administration. Further, individual values for the proportion of the night **during total sleep time** in which SaO_2 is less than 90% following multiple dose administration of MK-4305 and placebo (Day 4) may be analyzed in a linear mixed effects model as previously described if a sufficient number of patients have a nonzero proportion of the night in which SaO_2 is less than 90%. A two-sided 90% confidence interval for the true mean difference (MK-4305 – Placebo) would be calculated using the mean square error from the model and referencing a t-distribution to estimate the effect of MK-4305 on the proportion of the night in which SaO_2 is less than 90%. The proportion of the night **during total sleep time** that SaO_2 is less than 85% and 80% will be estimated in a similar fashion if a sufficient number of patients have a nonzero proportion of the night in which SaO_2 is less than 85% and 80%. Day 1 results will be analyzed in a similar fashion as above. SaO_2 During REM, NREM, Awake Stages (3rd Secondary Estimation Hypothesis) Mean SaO_2 for each of the different sleep stages (awake, NREM, REM) following multiple doses of MK-4305 and placebo will be analyzed in a similar fashion as above. Day 1 results will be analyzed in a similar fashion as above. AHI (4th Secondary Hypothesis) Individual AHI values on Day 1 will be analyzed in a linear mixed effects model as previously described. If the upper bound of the 90% confidence interval for the true mean AHI treatment difference (MK-4305 – Placebo) is less than 5, then the hypothesis that a single dose of MK-4305 does not produce a clinically significant increase in AHI in patients with mild to moderate OSA, as compared to placebo will be supported. **Exploratory** Exploratory PSG endpoints will be analyzed in models as previously described to explore the effect of MK-4305 on these parameters. Summary statistics will be provided from IDWR, DSST, Bond & Lader VAS and Body Balance tests.

Power: **Primary** AHI (Primary Hypothesis) Assuming a true within-patient variance of 14.62 for AHI pooled from [**3, 4**], a total of 24 patients completing the crossover study, and significance level alpha=0.05, there is 0.92 probability that the upper bound of the 90% confidence interval for the true mean difference in AHI (MK-4305 – Placebo) on Day 4 will be less than 5, given the true difference is 1.5. The true difference can be as high as 2.17 and still have 80% power to support the hypothesis. **Secondary** Mean SaO_2 (1st Secondary Hypothesis) Assuming a true within-patient variance of 0.763 $\%^2$ for Mean SaO_2 as observed in [2], a total of 24 patients completing the crossover study, and significance level alpha=0.05, there is 0.99 probability that the lower bound of the 90% confidence interval for the true mean difference in Mean SaO_2 (MK-4305 – Placebo) on Day 4 will be greater than -2%, given the true difference is -1%. The true difference can be as low as -1.35% and still have 80% power to support the hypothesis. AHI (4th Secondary Hypothesis) Assuming a true within-patient variance of 14.62 for AHI pooled from [2, 3], a total of 24 patients completing the crossover study, and significance level alpha=0.05, there is 0.92 probability that the upper bound of the 90% confidence interval for the true mean difference in AHI (MK-4305 – Placebo) on Day 1 will be less than 5, given the true difference is 1.5. The true difference can be as high as 2.17 and still have 80% power to support the hypothesis. Other Secondary Endpoints The precision of the estimates of the mean treatment difference (MK-4305 - Placebo) in the additional

secondary endpoints of interest can be assessed by calculating the half-width of the 90% confidence interval expected for the given sample size (N=24) and assumed variability. Estimates of within patient variability, expected confidence interval half-widths and example confidence intervals are provided in Table 2-3.

Table 2-3

Precision Estimates for Secondary Endpoints

Parameter	MSE	CI ½ width	Example 90% CI if Observed Difference=0
Proportion of Night SaO_2 <90%†	60.73%^{2}	3.86%	(-3.86%, 3.86%)
Proportion of Night SaO_2 <85%†	2.51%^{2}	0.79%	(-0.79%, 0.79%)
Proportion of Night SaO_2 <80%‡	0.374%^{2}	0.30%	(-0.30%, 0.30%)
SaO_2 During REM‡	1.50%^{2}	0.61%	(-0.61%, 0.61%)
SaO_2 During NREM‡	0.618%^{2}	0.39%	(-0.39%, 0.39%)
SaO_2 During Awake Stage‡	0.923%^{2}	0.48%	(-0.48%, 0.48%)

† Variance pooled from Gabaxadol Protocol 045 and [**5**]
‡ Variance obtained from [**3**]

3. PROTOCOL DETAILS

3.1 BACKGROUND AND RATIONALE

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Product: MK-4305 2
Protocol/Amendment No.: 036-01

Redacted

Product: MK-4305 3
Protocol/Amendment No.: 036-01

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Product: MK-4305 8
Protocol/Amendment No.: 036-01

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Product: MK-4305 9
Protocol/Amendment No.: 036-01

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Product: MK-4305 10
Protocol/Amendment No.: 036-01

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Product: MK-4305 11
Protocol/Amendment No.: 036-01

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Product: MK-4305 13
Protocol/Amendment No.: 036-01

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Product: MK-4305 14
Protocol/Amendment No.: 036-01

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Product: MK-4305 15
Protocol/Amendment No.: 036-01

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Product: MK-4305 16
Protocol/Amendment No.: 036-01

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Product: MK-4305 17
Protocol/Amendment No.: 036-01

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Product: MK-4305 18
Protocol/Amendment No.: 036-01

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Product: MK-4305 19
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Product: MK-4305 20
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Protocol/Amendment No.: 036-01

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Protocol/Amendment No.: 036-01

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Product: MK-4305 25
Protocol/Amendment No.: 036-01

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Product: MK-4305 26
Protocol/Amendment No.: 036-01

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Product: MK-4305 27
Protocol/Amendment No.: 036-01

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Product: MK-4305 28
Protocol/Amendment No.: 036-01

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Protocol/Amendment No.: 036-01

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Product: MK-4305 30
Protocol/Amendment No.: 036-01

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Product: MK-4305 31
Protocol/Amendment No.: 036-01

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Product: MK-4305 32
Protocol/Amendment No.: 036-01

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3.2 STUDY PROCEDURES

3.2.1 Concomitant Medication(s)/Treatment(s)

The list of prohibited medicines below is not intended to be comprehensive, but to help guide the investigator's medical judgment in cases where a patient presents with a medication not included in the following list. Investigators are encouraged to confer with the SPONSOR if any clarification is needed.

Patients being withdrawn from prohibited medications such as benzodiazepines, barbiturates or other medications that are likely to precipitate a withdrawal reaction or intolerance should not be abruptly discontinued from these medications. Instead, patients should be withdrawn from these medications in a manner that is consistent with labeling recommendations and conventional medical practice. Investigators should allow sufficient time to taper patients off these agents, i.e., up to several weeks prior to entry.

Table 3-9 presents the list of prohibited medications/treatments. Patients must washout of the prohibited medications for 2 or 4 weeks as indicated in Table 3-9 below. The use of these compounds is prohibited during the course of the study:

Table 3-9

Prohibited Medications and Specified Washout Period

Treatment	Interval*
Investigational compounds	4 weeks prior to screening (see exclusion w)
Strong CYP3A4 Inhibitors and Inducers	2 weeks or 5 $t_{½}$ lives
Antihistamines (sedating)	2 weeks
Hypnotics	2 weeks or 5 $t_{½}$ lives **
Other Psychotropics:	
Antidepressants (other than fluoxetine) Fluoxetine	2 weeks 4 weeks
Anticonvulsants	2 weeks
Antipsychotics	2 weeks or 5 $t_{½}$ lives
Anxiolytics (benzodiazepines, non-benzodiazepines)	2 weeks or 5 $t_{½}$ lives**
Centrally acting anticholinergics	2 weeks
Any CNS depressants	2 weeks
Mood Stabilizers	2 weeks
Stimulants	2 weeks
Supplements with possible psychotropic effects	2 weeks
Other Medications:	
Anticoagulants, systemic glucocorticoids, isotretinoin, diet pills	2 weeks

* Interval notes minimum washout period. Washout should occur for 5 half lives or the minimum specified period (2 or 4 weeks), which ever is longer to systemically eliminate the compound.

** The indicated hypnotic/anxiolytic washout applies to intermittent use only (defined as use of < 4 times/week). For those patients chronically using a hypnotic or anxiolytic (defined as use of ≥4 times/week) a 4-week washout (or 5 t½ lives, whichever is greater) must occur prior to completion of Visit 1. Please see Section 3.2.1 for more information.

NOTE: While listed here as prohibited medications, please note that some of these medications are additionally associated with excluded medical disorders, e.g., excluded cardiovascular disease, stroke, psychotic disorders, and relevant infections, such as H.I.V. infection. Patients should not be withdrawn from medically necessary medications (e.g., warfarin, psychotropics, antivirals) in order to participate in this study, but rather such patients should be excluded from the study both due to their medical condition and due to the requirement for these therapies.

Concurrent therapy (including vaccines) with any medication during the course of the protocol (after randomization) including both prescription and nonprescription drugs must first be discussed with the investigator and Sponsor Medical Monitor prior to administration, unless appropriate medical care necessitates that therapy should begin before the investigator and Sponsor Medical Monitor can be consulted.

Use of concurrent therapy (including vaccines) after randomization will be discussed with the Sponsor Medical Monitor. The patient will be allowed to continue in the study if both the Sponsor Medical Monitor and the investigator agree.

Paracetamol/acetaminophen may be used for minor ailments without prior consultation with the Sponsor Medical Monitor.

3.2.2 Diet/Activity/Other

3.2.2.1 Diet

On Day 1 and Day 4 in each treatment period, patients will fast from food for ~4 hours prior to dosing. Study drug will be administered with ~ 240 mL of water with water restricted 1 hour prior to and 1 hour after study drug administration. Patients will continue to fast for at least ~2 hours after study drug administration on Days 1 and 4 in each period. On Days 2 to 3, there will be no restriction with regard to food and water and study drug administration.

On Days 1 and 4 of each treatment period, study drug will be administered in the evening (PM, ~0.5 hour before "Lights-off"). On Days 2 to 3, patients will continue to take study drug at home (self-administration)/or in the CRU each evening before bed. All doses will be taken in the evening (PM) and should be taken ~0.5 hour before "Lights-off".

Predose on Days 1 and 4 in each treatment period, a standard dinner will be served ~4.5 hrs prior to dosing. Postdose Days 1 and 4 (Study Days 2 and 5), a standard breakfast will be provided following completion of PSG recording and pharmacodynamic assessments at ~10 hr postdose. The caloric content and composition of meals will be the same in each treatment period. After the 10.5 hour postdose procedures have been completed, subsequent meals and snacks will be unrestricted in caloric content and composition and timing.

On outpatient days (Days 2 to 3), patients should avoid alteration in their regular dietary pattern from the prestudy (screening) visit until administration of the initial dose of study drug, throughout the study, and until the poststudy visit.

3.2.2.2 Fruit Juice Restrictions

Patients will refrain from consumption of grapefruit juice, grapefruits and grapefruit products beginning approximately 2 weeks prior to administration of the initial dose of study drug, throughout the study (including the washout interval between treatment periods) and until the poststudy visit.

Patients also will refrain from consumption of all juices 12 hours prior to and 8 hours after administration of study drug on Day 1 and Day 4**.** On Days 2 to 3 consumption of all juices (except for grapefruit juices) is allowed.

All fruits except for grapefruits are allowed on all days of the study.

3.2.2.3 Alcohol Restrictions

On Days 1 and 4, patients will refrain from consumption of alcohol from 48 hours prior to and until discharge in each treatment period and for 24 hours prior to the prestudy and poststudy visits. At all other times (such as the washout period), alcohol consumption is limited to no more than approximately 2 alcoholic beverages or equivalent (beer [284 mL], wine [125mL] or distilled spirits [25 mL]) per day and will avoid consuming alcohol at least 3 hours before going to bed.

3.2.2.4 Caffeine Restrictions

On Day 1 and Day 4, patients will refrain from consumption of caffeinated beverages from 10 hours prior to dosing and until the time of discharge in each treatment period. On Days 2 to 3 patients will be required to avoid caffeine after 4:00 pm during the treatment period. At all other times, caffeinated beverages will be limited to no more than 2 units per day amounts (>4 units: 1 unit=120 mg of caffeine).

3.2.2.5 Smoking Restrictions

Smoking or nicotine containing products are not permitted during the study.

3.2.2.6 Activity Restrictions

Patients will avoid unaccustomed strenuous physical activity (*i.e.,* weight lifting, running, bicycling, *etc.*) from the prestudy (screening) visit until administration of the initial dose of study drug, throughout the study (including washout intervals between treatment periods) and until the poststudy visit.

3.2.2.7 Contraception

Women of childbearing potential can be enrolled. However, two (2) acceptable methods of barrier contraception must be used beginning at the pre-study visit, throughout the study (including washout intervals between treatment periods/panels) and until 2 weeks after the last dose of study drug in the last treatment period. Acceptable methods of birth control are two (2) of the following: intrauterine device (IUD-with or without local hormone release), diaphragm, spermicides, cervical cap, contraceptive sponge, and/or

condoms. Abstinence is an alternative life style and patients practicing abstinence may be included in the study.

Oral contraceptives are not allowed as a method of birth control in this study.

Patients must be completely informed of the unknown risks of pregnancy and agree not to become pregnant during the time they are participating in this study.

If there is any question that a patient will not be reliable in the use of appropriate contraceptive methods, they should not be entered into the study.

3.2.2.8 Pregnancy Testing

Female patients of childbearing potential will be tested for serum β-human chorionic gonadotropin (hCG) at pre-study and post-study, and for serum or urine β-human chorionic gonadotropin (hCG) pre-dose in each treatment period. In the case of a positive or borderline serum β-hCG pregnancy test at the pre-study visit, the patient must not enter the study; in the case of a positive or borderline serum or urine β-hCG pregnancy test during the study, a serum pregnancy test should be repeated and confirmed positive. If the pregnancy has been confirmed the patient must be discontinued from the study immediately and the Sponsor Medical Monitor must be contacted within 24 hours. The site will contact the patient at least monthly and update the SPONSOR until the pregnancy has been terminated or completed. The outcome of the pregnancy will be reported to the SPONSOR without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion [spontaneous or elective], congenital anomaly, birth defect, or other disabling or life-threatening complication to the mother or newborn).

3.2.2.9 Median Sleep Time Determination and Sleep History Diary Completion

Patients will be required to complete a sleep history diary to establish the habitual median bedtime for this study (See Appendix 6.11). The patient's time to bed at home should be recorded for at least 5 nights prior to the Screening NPSG visit. The median will be the midpoint value after ordering all the data points from lowest to highest (50% of the observations will fall below the median and 50% will fall above the median). If the number of data points is even, the midpoint value will be the average of the 2 middle values.

3.2.2.10 Bedtime ("Lights-Off"):

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

The median habitual bedtime will be based on at least 5 days of diary data accumulated up to Screening NPSG visit. The median bedtime established during this period (within

±1 hour) will be used as the bedtime ("Lights-Off") for the Screening NPSG visit and PSG collection on Day 1 and Day 4 in both Periods 1 and 2

3.2.2.11 Outpatient Study Diary Completion

In each treatment period patients will be required to complete the paper diary on Day 2 and Day 3 of the study (Appendix 6.12). The diary should be completed after each daily dose of study drug. The exact clock time of each dosing must be recorded on the diary, as well as the time the patient went to bed and awoke, and to report any adverse experiences. Patients will bring the diary to the CRU on Day 4 and the contents will be reviewed with the study coordinator, or designee.

Patient compliance with the diary should be reviewed at the Day 4 visit. Any patient who demonstrates non-compliance in completing the diary in Period 1 should receive additional diary training with emphasis on the importance of completing the diary each day.

3.2.2.12 Telephone Call

In each treatment period patients will receive a telephone call from the CRU staff on Day 3 to assess drug administration compliance, diary completion compliance, and to also assess potential adverse experiences that may have occurred.

3.2.3 Procedures

For this study PSG recording and SaO_2 monitoring are the critical parameters.

At any **postdose timepoint** the PSG recording and SaO_2 monitoring needs to be collected as close to the exact timepoint as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Study procedures can be done prior or after the prescribed/scheduled time.

1. PSG recording and SaO_2 monitoring
2. Blood sample collection MK-4305 PK sampling
3. Pharmacodynamic assessments (to be performed in the following order):
    a. Immediate Word Recall (IWR)
    b. Digit Symbol Substitution Test (DSST)
    c. Bond-Lader Visual Analog Scale (VAS)
    d. Body Sway
    e. Delayed Word Recall (DWR)
4. Laboratory safety tests

5. 12-lead ECG
6. Vital signs
7. Physical examinations

The order of priority can be changed during the study with joint agreement of the investigator and the Sponsor Clinical Monitor.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

Weight and Height

Body weight and height will be obtained with the patients shoes off, jacket or coat removed.

Body Mass Index (BMI)

BMI equals a person's weight in kilograms divided by height in meters squared. (BMI=kg/m2). Body weight and height will be obtained with the patients shoes off, jacket or coat removed.

Body Temperature

Body temperature will be measured with an oral or tympanic thermometer. The same method (e.g., oral or tympanic) must be used for all measurements for each individual patient and should be the same for all patients.

Laboratory Safety Tests (Appendix 6.1)

Laboratory safety tests will be performed after an 8-hour fast at the prestudy and poststudy visits.

Laboratory safety tests will be performed after a 4-hour fast predose on Days 1 and 4 in each treatment period.

Vital Sign Measurements (Heart Rate, Blood Pressure and Respiratory Rate)

Patients should be resting in a semi-recumbent position for at least 10 minutes prior to having vital sign measurements obtained. Semi-recumbent vital signs will include heart rate (HR), blood pressure (BP) and respiratory rate (RR). The correct size of the blood pressure cuff and the correct positioning on the patient's arm is essential to increase the accuracy of blood pressure measurements.

Orthostatic vital signs (HR and BP) will also be obtained. Patients should be semi-recumbent for at least 10 minutes and then stand upright for 2 minutes prior to measurement of orthostatic vital signs.

The same method (e.g., manual or automated) must be used for all measurements for each individual patient and should be same for all patients.

12-Lead ECG

Special care must be taken for proper lead placement. Patients may need to be shaved to ensure proper lead placement. Female patients may need to remove their bra.

Patients should be resting in a semi-recumbent position for at least 10 minutes prior to having ECG readings obtained. If repeat ECGs are required the clinical site will decide to either leave the electrodes in place or mark the position of the electrodes for subsequent ECGs.

Other Procedures

PSG, SaO2 monitoring, Body Sway, Bond-Lader Visual Analog Scale (VAS), Digit Symbol Substitution Test (DSST), and Immediate and Delayed Word Recall (IDWR) assessments will be conducted at times specified in the Study Flow Chart (Section 1.7).

3.2.3.1 Prestudy

Within approximately 4 weeks prior to administration of the initial dose of study drug in Period 1, potential patients will be evaluated to determine that they fulfill the entry requirements set forth in Sections 2.2 and 2.3. The investigator will discuss with each patient the nature of the study, its requirements, and its restrictions. Written informed consent will be obtained. A unique baseline number will be assigned for identification purposes.

All patients will be given a card identifying them as participants in a research study. The card will contain contact information (including direct telephone numbers) to be utilized in the event of an emergency.

Patients will be instructed about the restrictions for diet, activity, concomitant medications, alcohol, caffeine, grapefruit/fruit juice, contraception and smoking as noted in the Diet/Activity/Other Section (Section 3.2.2.) above.

Patients will be required to complete a sleep history diary to establish the habitual median bedtime for this study. The patient's time to bed at home should be recorded for at least 5 nights prior to the Screening NPSG visit.

Pre-study procedures are listed in Table 3-10.

Table 3-10

Pre-study Procedures

Study Informed Consent/genetic informed consent [a]
Medical history
Physical examination (including weight and height)
12-Lead Electrocardiogram [b]
Oral/tympanic temperature
Respiratory rate [b]
Semi-recumbent vital signs (heart rate (HR) & blood pressure (BP)) [b]
Orthostatic vital signs (HR and BP) [c]
Laboratory safety tests (hematology, chemistry, urinalysis) [d]
Serum β-hCG test (females Patients of reproductive potential only)
Serum FSH test (if applicable for females of non-childbearing potential only) [e]
HIV/Hepatitis Screen (at discretion of the investigator)
Urine Drug Screen
Alcohol Screen
Immediate and Delayed Word Recall (IDWR; Refer to Appendix 6.6)
Body Sway (Refer to Appendix 6.9)
Bond and Lader Visual Analog Scale (VAS; Refer to Appendix 6.8)
Digit Symbol Substitution Test (DSST; Refer to Appendix 6.7)
Columbia Suicide Severity Rating Scale (C-SSRS) [f]
Sleep history diary (Appendix 6.11) [g]
[a] Obtain informed consent prior to performing any study mandated procedures; signing of genetic consent/participating in genetic sampling is not necessary to participate in the study.
[b] Patients should be semi-recumbent for ≥ 10 minutes prior to 12-lead electrocardiogram (ECG) and vital sign measurements (HR and BP), and respiratory rate .
[c] Orthostatic vital signs (BP and HR) should be obtained after the semi-recumbent vital sign measurements are collected. Patients should remain standing for 2 minutes prior to obtaining the orthostatic measurements.
[d] Patients will fast, with the exception of water, for at least 8 hours prior to collection of samples (Appendix 6.1 and 6.2).
[e] For female patients of non-childbearing potential a blood sample serum FSH will be collected to confirm postmenopausal status.
[f] The C-SSRS will be conducted by the Investigator or delegate at pre-study. Subjects who at any time spontaneously report AEs of suicidal thoughts or ideation must be assessed by the Investigator or delegate using the C-SSRS. See Appendix 6.10.
[g] A sleep history diary will be used to establish habitual median bedtime for at least 5 nights prior to the Screening NPSG visit.

3.2.3.2 Screening Nighttime Polysomnography (NPSG) Visit and Pharmacodynamic Practice Assessments

Following an initial pre-study visit, patients who meet the initial pre-study inclusion/exclusion criteria will undergo a Screening Nighttime Polysomnography (NPSG) Visit (~7 to 10 days prior to Day 1 in Period 1). The Screening NPSG Visit will further define patient eligibility [specifically Apnea Hypopnea Index (AHI), limb movement, and other sleep disorders] through an expanded PSG assessment. A pharmacodynamic assessment practice visit will also occur at the Screening NPSG Visit to allow patients to become familiar with the Immediate and Delayed Word Recall (IDWR), Digit Symbol Substitution Test (DSST), Bond-Lader Visual Analog Scale (VAS), and Body Sway assessments. An outpatient diary for use during the treatment phase of the study will be presented. Patients who meet the Screening NPSG eligibility criteria, and fulfill the entry requirements as set forth in Sections 2.2 and 2.3, will be enrolled and randomized into the study. The following NPSG Screening procedures will be performed (Table 3-11).

Table 3-11

NPSG Screening and Pharmacodynamic Practice Assessment Procedures [a]

Procedure	Time
Urine Drug Screen	PM (prior to PSG)
Alcohol Screen	PM (prior to PSG)
Polysomnography (PSG Recording)[b]	collected over 8 hours (PM to AM)
Finger pulse oxymetry (SaO_2 monitoring)	collected over 8 hours (PM to AM)
Immediate and Delayed Word Recall (IDWR; Refer to Appendix 6.6) [c]	AM (after PSG)
Body Sway (Refer to Appendix 6.9) [c]	AM (after PSG)
Bond and Lader Visual Analog Scale (VAS; Refer to Appendix 6.8) [c]	AM (after PSG)
Digit Symbol Substitution Test (DSST; Refer to Appendix 6.7) [c]	AM (after PSG)

[a] PSG screening visit/PD practice visit is to take place ~7 to 10 days prior to Day 1, Period 1.
[b] An extended PSG is to be performed.
[c] Pharmacodynamic practice tests will occur at the time of the NPSG visit. The Digit Symbol Substitution Test (DSST) should be repeated 3 times at the NPSG visit using the same form, so that they become familiar with the test, with no scoring is needed.

3.2.3.3 Treatment (Periods 1 and 2)

After the pre-dose procedures in Period 1 have been completed, prior to study drug administration, qualified patients will be assigned to treatment according to an allocation schedule and assigned a unique allocation number.

3.2.3.3.1 Pre-Dose Procedures (Periods 1 and 2)

On Days 1 and 4 of each treatment period, patients will report to the clinical research unit at a time specified by the Investigator.

On Days 2 to 3, patients will self administer study drug at home on an outpatient basis. In the morning of Day 2, the investigator will determine if it is safe for the patient to continue in the study and self-administer study drug at home on Days 2 to 3. Should preliminary review of the Day 1 SaO_2 data show an observed SaO_2 decrease of < 85% for more than 5 consecutive minutes, or if the investigator has any concern of patient safety, the patient will be required to remain in the clinical research unit (CRU) on Days 2 to 3 for dosing and additional observation and monitoring. Otherwise, patients will be discharged in the morning on Day 2 after all study procedures are completed at the discretion of the investigator.

On Days 1 and 4, patients will fast from all food and drink, except for water, for approximately 4 hours prior to dosing. Water will be restricted 1 hour prior to dosing to and 1 hour after dosing.

Predose Day 1 and Day 4 procedures to be performed in both Period 1 and Period 2 are shown in Table 3-12.

Table 3-12

Predose Day 1 and Day 4 Procedures (Periods 1 and 2)

12-Lead Electrocardiogram (predose on Day 1 only) [a]
Respiratory rate [a]
Semi-recumbent vital signs (heart rate (HR) & blood pressure (BP)) [a]
Finger pulse oxymetry (SaO_2 monitoring) [b]
Laboratory safety tests (hematology, chemistry, urinalysis) (predose on Day 1 only) [c]
Serum/Urine β-hCG test (females Patients of reproductive potential only)
Urine Drug Screen
Alcohol Screen
Blood for MK-4305 assay
Blood for genetic sampling [d]
Standard meal [e]
Columbia Suicide Severity Rating Scale (C-SSRS) (Predose Day1 only) [f]

[a] Patients should be semi-recumbent for ≥ 10 minutes prior to 12-lead electrocardiogram (ECG) and vital sign measurements (HR and BP), and respiratory rate .

[b] Predose SaO_2 monitoring should be begin 15 minutes prior to dosing.

[c] Patients will fast, with the exception of water, for at least 4 hours prior to collection of samples (Appendix 6.1 and 6.2).

[d] Sample is optional and is only taken once during study in either Period 1 or Period 2. Sample may be collected anytime during the study after randomization. Separate informed consent is required.

[e] A standard dinner will be served ~4.5 hrs prior to dosing

[f] The C-SSRS will be conducted by the Investigator or delegate at predose Day 1 only. Subjects who at any time spontaneously report AEs of suicidal thoughts or ideation must be assessed by the Investigator or delegate using the C-SSRS. See Appendix 6.10.

3.2.3.3.2 Post-dose Procedures (Periods 1 and 2)

On Days 1 and 4 of each treatment period, patients will be administered study drug in the evening (PM) ~0.5 hour before "Lights-Off". "Lights-off" should be within ±1 hour of the patient's establish habitual median bedtime. Study drug will be taken with ~240 mL of water. The exact clock time of dosing should be recorded. Water will be restricted 1 hour after study drug administration. Lights will be turned off in the CRU approximately ~0.5 hour following study drug administration, and turned back on after the 8 hour PSG

recording is completed. In the morning, patients will complete additional safety and pharmacodynamic assessments and they be offered a breakfast. Patients will be discharged from the CRU after the completion of the ~10.5 hour post-dose assessments at the investigator's discretion, and will be returned to their home or their place of work by private service (e.g. taxi) or a designated relative and/or responsible adult known to the patient

On study Days 2 to 3, patients will self-administer study drug on an out-patient basis. At discretion of the investigator, patients may be required to remain in the unit on Day 2 to 3 for dosing and observation. All doses will be taken in the evening (PM) and should be taken ~0.5 hour before "Lights-Off". Patients will be required to complete the paper outpatient diary following each dose of study drug. Each patient must record the exact clock time of each dose of study drug in his/her diary, time and the time the he/she went to bed and awoke. Patients will be required to bring their diaries to the CRU on Day 4 for review of the contents with CRU staff for compliance. Any patient who demonstrates non-compliance in completing the diary in Period 1 should receive additional diary training with emphasis on the importance of completing the diary each day. Additionally, on Day 3, patients will receive a phone call from the CRU staff daily to confirm that study drug was self-administered as required and for adverse experience (AE) reporting purposes.

Postdose Day 1 and 4 procedures to be performed in both Period 1 and Period 2 are shown in Table 3-13.

Day 2 to Day 3 procedures to be performed in both Period 1 and Period 2 are shown in Table 3-14.

Table 3-13

Postdose Day 1 and Day 4 Procedures (Periods 1 and 2)

Procedures	Time Relative to MK-4305/Placebo Administration
Semi-recumbent vital signs (heart rate (HR) & blood pressure (BP)) [a]	9 and 10.5 hours post-dose
MK-4305/placebo administration [b]	0 hour
Standard meal [c]	10 hours postdose
Immediate and Delayed Word Recall (IDWR; Refer to Appendix 6.6)	9 hours postdose
Body Sway (Refer to Appendix 6.9)	9 hours postdose
Bond and Lader Visual Analog Scale (VAS; Refer to Appendix 6.8)	9 hours postdose
Digit Symbol Substitution Test (DSST; Refer to Appendix 6.7)	9 hours postdose
PSG recording [d]	0.5 to 8.5 hours post-dose
Finger pulse oxymetry (SaO_2 monitoring)[d]	0.5 to 8.5 hours post-dose, and 10.5 hours post-dose [e]
Blood for MK-4305 assay	9 hours post-dose
Columbia Suicide Severity Rating Scale (C-SSRS) [f]	10.5 hours post-dose Day 4 only

a Patients should be semi-recumbent for ≥ 10 minutes prior to vital sign measurements (HR and BP).
b On Days 1 and 4, study drug is to be administered after a ≥ 4-hour fast with 240 mL of water in the fasted state with water restricted 1 hour prior and 1 hour after study drug administration. Timing of all subsequent procedures will be relative to study drug administration.
c Standard breakfast to be provided following completion of PSG recording and other study procedures at ~10 hr postdose.
d PSG and SaO2 monitoring will be recorded for 8 hours. Lights are to be turned off after ~0.5 hour postdose procedures have been completed. Lights are to be turned on after the 8 hour PSG recording is completed.
e At the time of discharge, patients should have a SaO_2 value of 90% or above.
f The C-SSRS will be conducted by the Investigator or delegate at 10.5 hrs postdose Day 4 only. Subjects who at any time spontaneously report AEs of suicidal thoughts or ideation must be assessed by the Investigator or delegate using the C-SSRS. See Appendix 6.10.

Table 3-14

Day 2 to Day 3 Procedures (Periods 1 and 2)

Procedure	Time (Hours Postdose)
MK-4305/placebo self-administration [a]	Time = 0
Outpatient Diary	Daily Days 2 to 3
Phone call from the CRU	Day 3
[a] Patient self-administration of study drug should be taken ~0.5 hour before "Lights-off".	

3.2.3.4 Washout Period

There will be a minimum washout of 5 days from the last dose of study drug on Day 4 in Period 1 to the first dose of study drug on Day 1 in Period 2. During the washout period, patients are considered active study participants and should continue to honor all study obligations and restrictions.

3.2.3.5 Post-study

Patients will be required to return to clinic approximately 14 days after the last dose of study drug for the post-study visit. If the post-study visit occurs less than 14 days after the last dose of study drug, a subsequent follow-up phone call should be made to determine if any adverse experiences have occurred since the post-study clinic visit.

If a patient discontinues at any time during the course of the study, the patient may be asked to return to the clinic (or be contacted) for a post-study visit (approximately 14 days after the last dose of study drug) to have the applicable procedures conducted. However, the investigator may decide to perform the post-study procedures at the time of discontinuation or as soon as possible after discontinuation. If the post-study visit occurs prior to 14 days after the last dose of study drug, the investigator should perform a follow up phone call to determine if any adverse experiences have occurred since the post-study clinic visit.

Patients will fast from all food and drink, except water, for 8 hours prior to the blood and urine collections for laboratory safety tests. Post-study evaluations will include those listed in Table 3-15.

Table 3-15

Post-study Procedures

Procedure
Physical examination (including weight)
12-lead ECG [a]
Oral/tympanic temperature
Respiratory rate [a]
Semirecumbent vital signs (BP and HR) [a]
Orthostatic vital signs (HR and BP) [b]
Laboratory safety tests (hematology, chemistry, urinalysis) [c]
Serum β-hCG test [d]
Columbia Suicide Severity Rating Scale (C-SSRS) [e]
[a] Patient should be semi-recumbent at least 10 minutes before measurements are taken. [b] Orthostatic vital signs (BP and HR) should be obtained after the semi-recumbent vital sign measurements are collected. Patients should remain standing for 2 minutes prior to obtaining the orthostatic measurements. [c] See Appendix 6.1 and 6.2 for laboratory safety analyses; to be performed after an 8-hour fast. [d] For female patients of reproductive potential only. [e] The C-SSRS will be conducted by the Investigator or delegate at poststudy. Subjects who at any time spontaneously report AEs of suicidal thoughts or ideation must be assessed by the Investigator or delegate using the C-SSRS. See Appendix 6.10.

3.2.3.6 Volume of Blood Drawn During the Study

The total amount of blood to be drawn over the course of the study (from pre-study to post-study visits) will be approximately 122 mL per patient (see Appendix 6.3).

3.2.3.7 Study Design/Procedures Modifications Permitted Within Protocol Parameters

This is a Phase I assessment of MK-4305 in humans, and the pharmacokinetic, pharmacodynamic and safety profiles of the compound is still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase I clinical studies. Modifications to the dose, dosing regimen and/or clinical or laboratory procedures currently outlined below may be required to achieve the scientific

goals of the study objectives and/or to ensure appropriate safety monitoring of the study patients.

As such, some alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum daily dose and maximum cumulative exposure may not exceed those currently outlined in the protocol.

- Decrease in the dose of the study drug administered
- Decrease in the duration of study drug administration (e.g. number of days)
- Adjustment of the dosing interval (e.g. divided doses [QD to BID, TID or vice versa])

  Note: Total daily dose/exposure will remain the same or be lower than outlined in the protocol
- Lengthening of the wash-out period between doses

If it is determined that incomplete or aberrant data has been captured during the Day 1 or Day 4 PSG and SaO_2 measurements, the patient may be asked repeat the treatment period. The evaluation to determine whether the treatment period is to be repeated will be done on an individual basis per patient and the decision will be reached by mutual agreement of the SPONSOR and Investigator. Up to two (2) treatment periods per patient may be repeated. Repeating treatment periods may result in an increase of the patient's cumulative exposure and/or may increase the total blood volume with 36 mL per repeated period. The resulting exposure or blood volume increases will be deemed acceptable by the SPONSOR and Investigator for that patient. If there are >2 failed treatment periods for a certain patient, the patient may be discontinued from the study and replaced.

Instructions to take study drug with or without food or drink may also be modified based on newly available data.

The pharmacokinetic/pharmacodynamic sampling scheme currently outlined in the protocol may be modified during the study based on newly available pharmacokinetic or pharmacodynamic data (e.g., to obtain data closer to the time of peak plasma concentrations). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

Up to additional 50 mL blood may be drawn for safety, pharmacokinetic, and/or pharmacodynamic analyses. The total blood volume withdrawn from any single patient will not exceed the maximum allowable volume during his/her participation in the entire study (Appendix 6.3).

The timing of procedures for assessment of safety parameters (e.g., vital signs, ECG, safety laboratory tests, etc.) currently outlined in the protocol may be modified during the

study based on newly available safety, tolerability, pharmacokinetic or pharmacodynamic data (e.g., to obtain data closer to the time of peak plasma concentrations). These changes will not increase the number of study procedures for a given patient during his/her participation in the entire study.

It is understood that the current study may employ some or none of the alterations described above. Any alteration made to this protocol to meet the study objectives must be detailed by the Sponsor in a memo to the Study File and forwarded to the Investigator for retention. The memo may be forwarded to the IRB/ERC at the discretion of the Investigator.

3.2.3.8 Informed Consent

3.2.3.8.1 General Informed Consent

The investigator must obtain documented consent from each potential patient in biomedical research or when an investigational drug is administered to the patient in a clinical study, prior to any study related procedures being performed.

Consent must be documented by the patient's dated signature on a Consent Form along with the dated signature of the person conducting the consent discussion. A copy of the signed and dated consent form should be given to the patient before participating in the trials.

3.2.3.8.2 Consent and Collection of Specimens for Genetic and Other Biomedical Research

During this study, a separate signed informed consent will be administered to cover the conduct of genetic and other biomedical research, including 1) optional blood specimen(s) and 2) specimens remaining after the main study is completed (e.g., blood, body fluids and/or tissue).

Review committees (IRBs/ERCs) and/or individual sites may choose not to participate, and in some cases local regulations may prevent conduct of genetic and other biomedical research on collected specimens. Under such circumstances, this information should be communicated to Merck Research Laboratories by the local study representative of the associated agencies and/or IRBs/ERCs, when initial submission takes place. Such declaration will not lead to protocol amendment. However, a Protocol Clarification Letter could be issued by the MRL clinical team.

Only those subjects who have consented to allow the genetic and other biomedical research may have additional, optional blood specimen(s) drawn. The investigator or designate is responsible for explaining the optional nature of the conduct of genetic and other biomedical research and that participation in the associated clinical study is not dependent upon giving consent or additional samples for such research. The investigator or designate is also responsible for verifying the subject's written consent before obtaining any additional blood specimens for such research. Collection of the additional specimens may occur at any visit after the corresponding consent has been signed.

In some cases, the approval of this consent form and the associated protocol procedures (e.g., collection of blood specimens) may proceed independently from the associated main clinical study through review (by Agencies, IRBs/ERCs, Independent Ethical Committees, Privacy Committees, etc.). In such cases, the Clinical Study approval should not be delayed by the consent approval process for the optional specimen collection for genetic and other biomedical research. If the latter consent is denied, additional blood specimens for genetic and other biomedical research will not be collected and main study specimens will not be used for that purpose. If the consent for optional specimen collection for genetic and other biomedical research is delayed, the additional blood specimens must not be collected and main study specimens will not be used for genetic and other biomedical research until approval is granted. In either event, specimen testing defined as part of the main study would not be affected by the consent process for genetic and other biomedical research.

For additional background information, see Attachments "Privacy Protection of Optional Specimens for Genetic and Other Biomedical Research Collected from Clinical Trials Sponsored by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.: A Guideline for Clinicians and Privacy Board Members," and "Pharmacogenomics Informational Brochure for IRBs/IECs & Investigational Site Staff."

3.2.3.9 Assignment of Baseline Number

A baseline or screening number is assigned to the patient upon signing the consent form to identify the patient for all procedures that occur prior to randomization. Each baseline or screening number will be assigned to only one patient.

3.2.3.10 Randomization/Allocation

A single patient/Patient cannot be assigned more than 1 allocation number.

In a situation where rerandomization of the Patients/patients is planned (e.g., study extension periods), the rerandomization is done based on a new allocation schedule, however each Patient/patient retains his/her original allocation number. Only the treatment regimen associated with the rerandomization period or phase may change.

3.2.3.11 Blinding/Unblinding

In the event of an emergency, the patient's treatment can be unblinded. **Except for an emergency when the information could influence medical care, the investigator should not unblind a patient's treatment without prior approval from Merck.** If unblinding of the investigational product(s) should occur (e.g., accidental unblinding, emergency unblinding for a serious adverse experience), the investigator must promptly document the circumstances and immediately notify the Merck Clinical Monitor. If unblinding occurs, only the principal investigator or delegate and the respective patient's code should be unblinded. Site personnel and Merck personnel directly associated with the conduct of the study should not be unblinded. The unblinding should be documented in the unblinding log provided by Merck.

3.2.3.12 Discontinuation/Withdrawal from Study

Patients/patients may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a Patient/patient may be withdrawn by the investigator or the SPONSOR if he/she violates the study plan or for administrative and/or other safety reasons. The investigator or study coordinator must notify the SPONSOR immediately when a Patient/patient has been discontinued/withdrawn due to an adverse experience (telephone or FAX). When a Patient/ patient discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse experiences which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in section 3.4 SAFETY MEASUREMENTS - DETAILS.

Subjects/patients who optionally donate blood, body fluids and/or tissue for genetic and other biomedical research analyses may request that their specimen(s) be removed from storage and destroyed in accordance with the terms outlined in the associated consent form. Subjects/patients should be informed that withdrawal from the main study does not cause the withdrawal and destruction of the optional specimens for genetic and other biomedical research. Requests for withdrawal and destruction of the optional specimens for genetic and other biomedical research should be made in writing to the investigator. In turn, the investigator must promptly inform MRL so that appropriate follow-up can be initiated. The investigator will be informed when the associated specimens are destroyed and should notify the subject/patient that specimen destruction is complete.

Subjects/patients who discontinue from the study will be replaced as required for the study to meet its objectives. The decision to remove a subject/patient and to replace dropouts will be made jointly by the investigator, SPONSOR Clinical Monitor, and SPONSOR study statistician. The replacement will generally receive the same treatment or treatment sequence (as appropriate) as the allocation number replaced. Both the replacement and originally allocated number will be unique numbers.

Biological specimens obtained prior to subject/patient discontinuation can be analyzed unless consent is withdrawn.

3.2.3.13 Study Completion and Termination

Definition of Study Completion

Study completion is defined as the date the last patient completes the final visit in the study.

Given the unpredictable nature of early Phase I studies, it may exceptionally be necessary to keep the study open for gathering/reviewing additional supportive data (preclinical and/or clinical) to optimally complete the objective(s) of the study. In this case the competent authority(ies) and the ethics committee(s) will be appraised of the maximum

extension of the duration of the study beyond the last patient out and the justification for keeping the study open. If necessary, the appropriate amendments to the protocol will be generated.

Definition of Study Termination

Study termination is defined as a permanent discontinuation of the study due to unanticipated concerns of safety to the study patients or availability of other new data (pharmacokinetic, pharmacodynamic, efficacy, biologic etc.) arising from clinical or preclinical studies with this study drug. A study may be paused during review of newly available preclinical/clinical safety, pharmacokinetic, pharmacodynamic, efficacy, or biologic data, or other issues of interest or potential concern prior to a final decision for continuation or termination of the study.

3.3 EFFICACY/PHARMACOKINETIC/IMMUNOGENICITY, ETC. MEASUREMENTS

3.3.1 Clinical and Laboratory Measurements for Efficacy/Pharmacokinetic/ Immunogenicity, etc.

The decision as to which plasma and/or urine samples collected will be assayed for evaluation of pharmacokinetics/pharmacodynamics will be collaboratively determined by the Departments of Drug Metabolism and Clinical Pharmacology, (e.g., samples at lower doses may not be assayed if samples at higher doses reveal undetectable drug concentrations). If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

Plasma for MK-4305 Assay

Blood samples (4 mL) for MK-4305 concentrations will be obtained during the study. Blood will be drawn at specified time points according to the study flow chart. All post-dose collection time points are relative to the administration of study drug. For biological collection, sample handling, storage and shipment instructions see Appendix 6.4.

3.3.2 Pharmacodynamic Measurements

The approximate order of PD measurements is as follows:

Immediate word recall
Digit Symbol Substitution Test
Bond and Lader VAS
Body Sway
Delayed Word Recall

Changes to the order of the PD measurements can be made during the study with joint agreement of the investigator and the Sponsor Clinical Monitor.

Immediate and Delayed Word Recall

A list of 15 words is read aloud to the volunteer 5 times for the volunteer to remember. The volunteer is then given 1 minute to recall as many of the words as possible without seeing the words again.

Bond-Lader VAS of Mood and Alertness

This questionnaire of 16 analogue scales derives 3 factors that assess change in Self-rated Alertness, Self-rated Calmness and Self-rated Contentment.

DSST

Digit Symbol Substitution Test (DSST) is a neuropsychological test contained within the Wechsler Adult Intelligence Scale, that measures relative changes in a subject's cognitive ability which consists of digit-symbol pairs (e.g. 1/-,2/⊥ ... 7/Λ,8/X,9/=) followed by a list of digits. Under each digit the subject should write down the corresponding symbol as fast as possible. The number of correct symbols within the allowed time (90 sec) is measured.

Body Sway

The stationary postural stabilometry platform (AccuSway, Advanced Mechanical Technology, Inc., Watertown, Massachusetts, U.S.A.) will assess the effects of drugs on body sway in the 'eyes open' and 'eyes closed' states. In this system, subjects stand on a force platform, and strain gauges under the platform provide input that is used to calculate the center of pressure (COP). The extent of movement of the COP directly relates to the subject's ability to maintain balance. The AccuSway system derives the length of the COP and the area of the 95% confidence ellipse enclosing the COP (A95). Body sway area (A95) or length (CoP length) is an objective, non-invasive, reliable method for assessing the effects of sedative drugs, and these parameters are increased by alcohol over 0.5 g/kg and sedatives. The exploratory endpoint of this study will be A95; increases in the A95 reflect increased body sway, which indicates impairment [6].

3.4 SAFETY MEASUREMENTS

3.4.1 Clinical and Laboratory Measurements for Safety

Safety and tolerability will be closely monitored throughout the study via physical examinations, vital signs, 12-lead electrocardiograms (ECGs), and laboratory safety evaluations (hematology, blood chemistry, and urinalysis). Patients will be assessed for adverse experiences throughout the study. All patients in this study will be monitored for activities of daily living by the clinical staff, who will also implement fall precautions.

These procedures may also be performed at various unscheduled time points, if deemed clinically necessary by the Investigator.

The Columbia Suicide Severity Rating Scale (C-SSRS) will also be performed at time points specified in the Study Flow Chart (Refer to Section 1.7).

The Columbia Suicide Severity Rating Scale (C-SSRS) is a semi-structured interview which provides a detailed assessment of suicidality (suicidal ideation and/or behavior) [27]. The C-SSRS is completed by the investigator or delegate at time points indicated in the study flow chart. In addition, subjects who at any time during this study spontaneously report AEs of suicidal ideation or behavior, either between visits or during visit interviews, or whose responses to the C-SSRS are suggestive of suicidal ideation, must be assessed by the Investigator or delegate and referred for further mental health evaluation. Subjects with evidence of suicidality at screening or throughout the study must be evaluated by a psychiatrist or other trained mental health professional who is a licensed psychologist, social worker, or nurse practitioner (or comparable professional qualification in countries outside the United States). Only subjects whose suicidal ideation is passive, who expressly deny any intent to act, and who, after evaluation, are judged not to be at serious risk for self-harm during the course of the study may continue in the study at the discretion of the investigator; others must be discontinued from study participation and receive appropriate clinical follow-up care to assure their safety. Sites will assure availability of health care professionals responsible for acute care on-site and for referral centers(s) to be used for further evaluation. All reports of suicidal ideation or behavior must be reported as an ECI. Please refer to Section 3.4.5.2 for additional information on ECIs.

3.4.2 Recording Adverse Experiences

An adverse experience is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the SPONSOR's product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the SPONSOR's product, is also an adverse experience.

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

Adverse experiences may occur in the course of the use of a Merck product in clinical studies or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse, and from withdrawal.

Adverse experiences may also occur in screened Patients/patients during any preallocation baseline period as a result of a protocol-specified intervention including washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

Such events will be recorded at each examination on the Adverse Experience Case Report Forms/Worksheets.

3.4.3 Definition of an Overdose for This Protocol

The patient has taken, accidentally or intentionally, any drug administered as part of the protocol, and exceeding the dose as prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, but Merck personnel have the authority to upgrade the determination, if deemed appropriate. Before upgrading a report, it is necessary for Merck personnel to communicate with the investigator and reach a consensus.

3.4.3.1 Reporting of Overdose to SPONSOR

If an adverse experience(s) is associated with ("results from") the overdose of test drug or vaccine, the adverse experience(s) is reported as a serious adverse experience, even if no other criteria for serious are met.

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

All reports of overdose with and without an adverse experience must be reported within 24 hours to one of the individuals listed on the sponsor contact information page found in the Administrative Binder.

3.4.4 Reporting of Pregnancy to SPONSOR

Although not considered an adverse experience, it is the responsibility of investigators or their designees to report any pregnancy in a Patient/patient (spontaneously reported to them) which occurs during the study or within 14 days of completing the study. All Patients/patients who become pregnant must be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported to one of the individuals listed on the SPONSOR Contact Information page found in the Administrative Binder.

3.4.5 Immediate Reporting of Adverse Experiences to the SPONSOR

3.4.5.1 Serious Adverse Experiences

Any serious adverse experience, including death due to any cause, which occurs to any Patient/patient entered into this study or within 14 days following cessation of treatment or within the established off therapy follow-up period for safety described in the protocol, whether or not related to the investigational product, must be reported within 24 hours to one of the individual(s) listed on the contact information page.

Additionally, any serious adverse experience considered by an investigator who is a qualified physician to be possibly, probably, or definitely related to the investigational

product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to one of the individuals listed on the sponsor contact information page found in the administrative binder.

All Patients/patients with serious adverse experiences must be followed up for outcome.

3.4.5.2 Selected Nonserious Adverse Experiences (if applicable)

These selected non-serious adverse experiences are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Experience Case Report Forms/Worksheets.

The ECI's below must be recorded in both Periods 1 and 2.

- Cataplexy (The Modified Cataplexy Questionnaire will be used to assess a single episode of a patient's spontaneously reported cataplexy-like behavior in conjunction with ECI reporting of the event, see Appendix 6.5)
- Hypnagogic or hypnopompic hallucinations
- Sleep paralysis; sleep onset paralysis
- Falls
- Suicidal ideation and/or behaviors
- Complex sleep-related behaviors
- Selected events associated with potential for abuse:
    - Depersonalization
    - Derealization
    - Dissociation
    - Euphoric Mood
    - Hallucination
    - Mania
    - Potential Study Medication Misuse
- Adverse Experiences Associated with Traffic/Motor Vehicle Accidents

A supplemental document will be provided.

3.4.6 Evaluating Adverse Experiences

Refer to Table 3-16 for instructions in evaluating adverse experiences.

Table 3-16

An investigator who is a qualified physician, will evaluate all adverse experiences as to:

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

Relationship to test drug (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the dose of test drug discontinued or 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 test drug; or (3) the study is a single-dose drug study.)
	Rechallenge	Was the Patient/patient reexposed to the test drug 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.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE TEST DRUG, OR IF REEXPOSURE TO THE TEST DRUG POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PATIENT/PATIENT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Study Drug Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the test drug or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a drug relationship).**
Yes, there is a reasonable possibility of drug relationship.		There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to the administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. **Depending on data collection method employed, drug relationship may be further graded as follows:**
	Definitely related	There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge is positive. Rechallenge (if feasible) is positive. The AE shows a pattern consistent with previous knowledge of the test drug or test drug class.
	Probably related	There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge (if performed) is positive.
	Possibly related	There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE could have been due to another equally likely cause. Dechallenge (if performed) is positive.
No, there is not a reasonable possibility of drug relationship		Patient did not receive the test drug OR temporal sequence of the AE onset relative to administration of the test drug is not reasonable OR there is another obvious cause of the AE. (Also entered for a Patient with overdose without an associated AE.) **Depending on data collection method employed, drug relationship may be further graded as follows:**
	Probably not related	There is evidence of exposure to the test drug. There is another more likely cause of the AE. Dechallenge (if performed) is negative or ambiguous. Rechallenge (if performed) is negative or ambiguous.
	Definitely not related	The Patient/patient did not receive the test drug. OR Temporal sequence of the AE onset relative to administration of the test drug is not reasonable. OR There is another obvious cause of the AE.

3.4.7 SPONSOR Responsibility for Reporting Adverse Experiences

All adverse experiences will be reported to regulatory agencies, IRB/IECs, and investigators in accordance with all applicable global laws and regulations.

3.5 STATISTICAL ANALYSIS PLAN (SAP)

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the Clinical Pharmacology Statistics Department in collaboration with the Drug Metabolism and Pharmacokinetics and Clinical Pharmacology Departments of the Sponsor.

If, after the study has begun, changes are made to the statistical analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the Clinical Study Report.

3.5.1 Hypothesis

Primary

Multiple doses of MK-4305 do not produce a clinically significant increase in AHI in patients with mild to moderate OSA, as compared to placebo. Specifically, the true mean AHI treatment difference (MK-4305 – Placebo) is less than 5.

Secondary

1. Multiple doses of MK-4305 do not produce a clinically significant reduction of mean SaO_2 **during total sleep time** in patients with mild to moderate OSA, as compared to placebo. Specifically, the true mean SaO_2 treatment difference (MK-4305 – Placebo) is greater than -2%.

2. Estimation: The proportion of the night **during total sleep time** in which SaO_2 is less than 90%, less than 85% and less than 80% following multiple dose administration of MK-4305 and placebo will be estimated.

3. Estimation: The mean SaO2 for each sleep stage (awake, NREM, REM) following multiple dose administration of MK-4305 and placebo will be estimated.

4. A single dose of MK-4305 does not produce a clinically significant increase in AHI in patients with mild to moderate OSA, as compared to placebo. Specifically, the true mean AHI treatment difference (MK-4305 – Placebo) after single dose administration is less than 5.

3.5.2 Analysis Endpoints

Primary

AHI on Day 4, which is sum of the apnea and hypopnea indices, is the primary outcome measure. The apnea index for each patient is calculated as the number of apneas divided by the total sleep time. The hypopnea index for each patient is calculated as the number of hypopneas divided by the total sleep time. **Scoring of apneic and hypopneic events will be based on the 2007 AASM definition [1, 28].**

Primary safety endpoints will include all types of adverse experiences, in addition to laboratory safety tests and vital signs.

Secondary

Secondary endpoints of interest include the mean oxygen saturation **during total sleep time** (SaO_2), as well as during REM, NREM and awake stages on Day 4. The proportion of the night **during total sleep time** on Day 4 that SaO_2 is less than 90%, less than 85% and less than 80% are also of secondary interest. Corresponding endpoints on Day 1 are also of secondary interest.

Exploratory

Exploratory pharmacodynamic (PD) endpoints of interest include objective sleep parameters as measured by PSG, including latency to persistent sleep (LPS), wake after sleep onset (WASO), total sleep time (TST) and sleep efficiency index (SEI). Additional exploratory PD endpoints include cognitive and psychomotor performance tests (IDWR, DSST, Bond & Lader VAS, Body Balance) used to assess next-day residual effects.

Due to the sparse sampling, pharmacokinetic parameters will not be calculated. Plasma concentration values at individual time points are of interest.

3.5.3 Approaches to Analyses

The following populations are defined for the analysis and reporting of data. All patients will be reported, and their data analyzed, according to the treatment(s) they actually received.

All Patients as Treated (AST) - All patients who received at least one dose of the investigational drug. This population will be used for assessments of safety and tolerability.

Per-Protocol (PP) – The set of data generated by the subset of patients who comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol violations. Major protocol violators will be identified to the extent possible prior to unblinding by individuals responsible for data collection/compliance,

and its analysis and interpretation. Any patients or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all patients who are compliant with the study procedure as aforementioned and have available data from at least one treatment will be included in the primary analysis dataset. This population will be used for the PD (including AHI and SaO_2) analyses.

3.5.4 Statistical Methods

Primary

AHI (Primary Hypothesis)

The primary hypothesis regarding the effect of MK-4305 on AHI will be addressed by comparing the AHI following administration of MK-4305 to AHI following administration of placebo. Individual AHI values on Day 4 will be evaluated in a linear mixed-effects model appropriate for a 2-period crossover study. The model will contain fixed effects for treatment, period and sequence, and a random effect for Patient within sequence. Using an appropriate linear contrast, a two-sided 90% confidence interval (equivalent to a one-sided upper 95% confidence interval) for the true mean difference (MK-4305 – Placebo) in AHI will be calculated using the mean square error from the model and referencing a t-distribution. If the upper bound of the confidence interval is less than 5, then the hypothesis that multiple oral doses of MK-4305 do not produce a clinically significant increase in AHI in patients with mild to moderate OSA, as compared to placebo, will be supported.

Day 1 results will be analyzed in a similar fashion as above.

Safety

Safety and tolerability will be evaluated following multiple doses of MK-4305 administered to patients with OSA by clinical assessment of adverse experiences and other safety measurements (e.g., vital signs, ECGs, laboratories, etc.). Summary statistics will be provided as appropriate.

Secondary

Mean SaO_2 (1^{st} Secondary Hypothesis)

Individual values for the mean SaO_2 on Day 4 during total sleep time will be analyzed in a linear mixed effects model as previously described. A two-sided 90% confidence interval (equivalent to a one-sided lower 95% confidence interval) for the true mean difference (MK-4305 – Placebo) in mean SaO_2 during total sleep time will be calculated using the mean square error from the model and referencing a t-distribution. If the lower bound of the confidence interval is greater than -2%, then the hypothesis that multiple oral doses of MK-4305 do not produce a clinically significant reduction of mean SaO_2 during total sleep time in patients with mild to moderate OSA, as compared to placebo, will be supported.

Day 1 results will be analyzed in a similar fashion as above.

Proportion of the Night SaO_2 <90%, <85%, <80% (2nd Secondary Estimation Hypothesis)

Summary statistics will be provided for the percentage of patients on each treatment who experience an SaO_2 level less than 90%, 85% and 80% during the night following multiple dose administration.

Further, individual values for the proportion of the night **during total sleep time** in which SaO_2 is less than 90% following multiple dose administration of MK-4305 and placebo (Day 4) may be analyzed in a linear mixed effects model as previously described if a sufficient number of patients have a nonzero proportion of the night in which SaO_2 is less than 90%. A two-sided 90% confidence interval for the true mean difference (MK-4305 – Placebo) would be calculated using the mean square error from the model and referencing a t-distribution to estimate the effect of MK-4305 on the proportion of the night in which SaO_2 is less than 90%.

The proportion of the night during total sleep time that SaO_2 is less than 85% and less than 80% will be estimated in a similar fashion if a sufficient number of patients have a nonzero proportion of the night in which SaO_2 is less than 85% or 80%.

Day 1 results will be analyzed in a similar fashion as above.

SaO_2 During REM, NREM, Awake Stages (3rd Secondary Estimation Hypothesis)

Mean SaO_2 for each of the different sleep stages (awake, NREM, REM) following multiple doses of MK-4305 and placebo will be analyzed in a similar fashion as above. Day 1 results will be analyzed in a similar fashion as above.

AHI (4th Secondary Hypothesis)

Individual AHI values on Day 1 will be analyzed in a linear mixed effects model as previously described. If the upper bound of the 90% confidence interval for the true mean AHI treatment difference (MK-4305 – Placebo) is less than 5, then the hypothesis that a single dose of MK-4305 does not produce a clinically significant increase in AHI in patients with mild to moderate OSA, as compared to placebo will be supported.

Exploratory

Exploratory PSG endpoints will be analyzed in models as previously described to explore the effect of MK-4305 on these parameters.

Summary statistics will be provided from IDWR, DSST, Bond & Lader VAS and Body Balance tests.

3.5.5 Assumptions

All data will be examined for departures from the assumptions of the model(s), i.e., heteroscedasticity, outliers, and non-independence and nonnormality of the error terms. Suitable data transformations may be applied. Distribution-free methods may be used if a serious departure from the assumptions of the model(s) is observed.

3.5.6 Multiplicity

Since there is only one primary hypothesis, no multiplicity adjustment is required.

3.5.7 Power

AHI (Primary Hypothesis)

Assuming a true within-patient variance of 14.62 for AHI pooled from [2, 3], a total of 24 patients completing the crossover study, and significance level alpha=0.05, there is 0.92 probability that the upper bound of the 90% confidence interval for the true mean difference in AHI (MK-4305 – Placebo) on Day 4 will be less than 5, given the true difference is 1.5. The true difference can be as high as 2.17 and still have 80% power to support the hypothesis.

Secondary

Mean SaO_2 (1st Secondary Hypothesis)

Assuming a true within-patient variance of 0.763 $\%^2$ for Mean SaO_2 as observed in [2], a total of 24 patients completing the crossover study, and significance level alpha=0.05, there is 0.99 probability that the lower bound of the 90% confidence interval for the true mean difference in Mean SaO_2 (MK-4305 – Placebo) on Day 4 will be greater than -2%, given the true difference is -1%. The true difference can be as low as -1.35% and still have 80% power to support the hypothesis.

AHI (4th Secondary Hypothesis)

Assuming a true within-patient variance of 14.62 for AHI pooled from [2, 3], a total of 24 patients completing the crossover study, and significance level alpha=0.05, there is 0.92 probability that the upper bound of the 90% confidence interval for the true mean difference in AHI (MK-4305 – Placebo) on Day 1 will be less than 5, given the true difference is 1.5. The true difference can be as high as 2.17 and still have 80% power to support the hypothesis.

Other Secondary Endpoints

The precision of the estimates of the mean treatment difference (MK-4305 - Placebo) in the additional secondary endpoints of interest can be assessed by calculating the half-width of the 90% confidence interval expected for the given sample size (N=24) and assumed variability. Estimates of within patient variability, expected confidence interval half-widths and example confidence intervals are provided in Table 3-17.

Table 3-17

Precision Estimates for Secondary Endpoints

Parameter	MSE	CI ½ width	Example 90% CI if Observed Difference=0
Proportion of Night SaO_2 <90%†	60.73%^{2}	3.86%	(-3.86%, 3.86%)
Proportion of Night SaO_2 <85%†	2.51%^{2}	0.79%	(-0.79%, 0.79%)
Proportion of Night SaO_2 <80%‡	0.374%^{2}	0.30%	(-0.30%, 0.30%)
SaO_2 During REM‡	1.50%^{2}	0.61%	(-0.61%, 0.61%)
SaO_2 During NREM‡	0.618%^{2}	0.39%	(-0.39%, 0.39%)
SaO_2 During Awake Stage‡	0.923%^{2}	0.48%	(-0.48%, 0.48%)

† Variance pooled from Gabaxadol Protocol 045 and [**5**]
‡ Variance obtained from [**3**]

3.6 LABELING, PACKAGING, STORAGE, DISPENSING, AND RETURN OF CLINICAL SUPPLIES

3.6.1 Patient and Replacements Information

Clinical supplies will be packaged to support enrollment of approximately 120 subjects (24 per site). No replacement subjects will be packaged.

Clinical supplies will be packaged according to an allocation schedule generated by the SPONSOR**.**

3.6.2 Product descriptions

Investigational materials will be provided by the SPONSOR as summarized in Table 3-18.

Table 3-18

Product Descriptions

Product Name & Potency	Dosage Form
MK-4305 40 mg	Film Coated Tablet
Placebo to match MK-4305 40 mg	

3.6.3 Primary Packaging and Labeling Information

Each patient will receive two bottles. (One bottle for Period 1 and then one bottle for Period 2). Supplies will be packaged in HDPE bottles as described in Table 3-19 below.

Table 3-19

Packaging of Clinical Supplies

Interval ID	Product Name & Potency	Fill Count	Dosing Instructions
Period 1	MK-4305 40 mg or placebo	7 tablets	Take as Directed
Period 2	MK-4305 40 mg or placebo	7 tablets	

Container label text may include the following:

• Lot Trace ID • Allocation # • Fill Count & Dosage Form • Interval ID (Period 1 or Period 2) • Product Name and Potency [or placebo] • Supplier (GCSO) Name and Address	• Dosing Instructions • Storage Conditions • Compound ID - Protocol # • Country regulatory requirements • SPONSOR address (If applicable)

3.6.4 Clinical Supplies Disclosure

Supplies will be provided with blinded envelopes containing drug disclosure information. The SPONSOR will provide one sealed envelope to the investigator for each allocation number for each interval ID.

Disclosure envelopes must be received by a designated person at the study site and kept in a secured location to which only the investigator and designated assistants have access. The envelope should be opened only in the case of an emergency. Drug identification information is to be unmasked ONLY if necessary for the welfare of the patient. Every effort should be made not to unblind the patient unless necessary. Prior to unblinding, the investigator will attempt to contact the clinical monitor. Any unblinding that occurs at the site must be documented and the unblinded envelope retained at site. At the end of the study, disclosure envelopes are to be returned to the SPONSOR.

Envelope information may include the following:

- Allocation number
- Lot Trace ID
- Interval ID (Period X (1 or 2))
- Protocol # - Compound ID
- Drug identity (inside the envelope)

3.6.5 Storage and Handling Requirements

Clinical supplies should be kept in a secured location at controlled room temperature. Do not store above 30ºC and protect from moisture.

The clinical supplies storage area at the site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range specified in this protocol or in the product label attached to the protocol. Documentation of temperature monitoring should be maintained

3.6.6 Standard Policies / Return of Clinical Supplies

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Clinical supplies are to be dispensed only in accordance with the protocol. The investigator is responsible for keeping accurate records of the clinical supplies received from the SPONSOR, the amount dispensed to and returned by the subjects/patients, and the amount remaining at the conclusion of the study. In accordance with Good Pharmacy Practices, gloves should always be worn by study personnel if directly handling tablets or capsules that are returned (i.e., when counting returns). The Clinical Monitor should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all clinical supplies including partial and empty containers must be returned as indicated on the Contact Information page(s).

U.S. sites should follow instructions for the Clinical Supplies Return Form (R464) and contact your SPONSOR representative for review of shipment and form before shipping.

3.7 DATA MANAGEMENT

Information regarding Data Management procedures for this protocol will be provided by the SPONSOR.

3.8 BIOLOGICAL SPECIMENS

Information regarding biological specimens for this protocol will be provided by the SPONSOR.

Product: MK-4305 1
Protocol/Amendment No.: 036-01

4. ADMINISTRATIVE AND REGULATORY DETAILS

4.1 CONFIDENTIALITY

4.1.1 Confidentiality of Data

For Studies Conducted Under the U.S. IND

Particular attention is drawn to the regulations promulgated by the Food and Drug Administration under the Freedom of Information Act providing, in part, that information furnished to clinical investigators and Institutional Review Boards will be kept confidential by the Food and Drug Administration only if maintained in confidence by the clinical investigator and Institutional Review Board.

For All Studies

By signing this protocol, the investigator affirms to the SPONSOR that information furnished to the investigator by the SPONSOR will be maintained in confidence and such information will be divulged to the Institutional Review Board, Ethics Review Committee, 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.

4.1.2 Confidentiality of Subject/Patient Records

For All Studies

By signing this protocol, the investigator agrees that the SPONSOR (or SPONSOR representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject/patient agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject/patient will be identified by unique code only; full names/initials will be masked prior to transmission to the SPONSOR.

For Studies Conducted Under the U.S. IND

By signing this protocol, the investigator agrees to treat all patient data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations, including all applicable provisions of the Health Insurance Portability and Accountability Act and its implementing regulations, as amended from time to time. ("HIPAA").

4.1.3 Confidentiality of Investigator Information

For All Studies

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site

personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number, and email address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

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

For Multicenter Studies
In order to facilitate contact between investigators, the SPONSOR may share an investigator's name and contact information with other participating investigators upon request.

4.2 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 Good Clinical Practice; 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 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., is attached.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review, and regulatory agency inspection of trial-related documents and procedures and provide for direct access to all study-related source data and documents.

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

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Clinical Practice standards and applicable federal, state, and local laws, rules and regulations; and, for each subject/patient participating in the study,

provide all data, and upon completion or termination of the clinical study submit any other reports to the SPONSOR as required by this protocol or as otherwise required pursuant to any agreement with the SPONSOR.

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

International Conference of Harmonization Good Clinical Practice guidelines (Section 4.3.3) recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

According to European legislation, a SPONSOR must designate a principal or coordinating investigator (CI) to review the report (summarizing the study results) and confirm that to the best of his/her knowledge the report accurately describes conduct and results of the study. The SPONSOR may consider one or more factors in the selection of the individual to serve as the CI (e.g., thorough understanding of clinical trial methods, appropriate enrollment of subject/patient cohort, timely achievement of study milestones, availability of the CI during the anticipated review process).

The investigator will promptly inform the SPONSOR of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on clinical studies by any court or regulatory agency 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.

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

4.3 COMPLIANCE WITH FINANCIAL DISCLOSURE REQUIREMENTS

By signing this protocol, the investigator agrees to provide to the SPONSOR accurate financial information to allow the SPONSOR to submit complete and accurate certification and disclosure statements as required by U.S. Food and Drug Administration regulations (21 CFR Part 54). The investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. This requirement also extends to subinvestigators. The investigator also consents to the transmission of this information to Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. in the United States for

these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

4.4 QUALITY CONTROL AND QUALITY ASSURANCE

By signing this protocol, the SPONSOR agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written SOPs to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

4.5 COMPLIANCE WITH INFORMATION PROGRAM ON CLINICAL TRIALS FOR SERIOUS OR LIFE THREATENING CONDITIONS

Under the terms of The Food and Drug Administration Modernization Act (FDAMA), the SPONSOR of the study is solely responsible for determining whether the study is subject to the requirements for submission to the Clinical Trials Data Bank, http://clinicaltrials.gov/. Merck, as SPONSOR of this study, will review this protocol and submit the information necessary to fulfill this requirement. Merck entries are not limited to FDAMA mandated trials. Merck's voluntary listings, beyond those mandated by FDAMA, will be in the same format as for treatments for serious or life-threatening illnesses. Information posted will allow patients to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligation under FDAMA is that of the SPONSOR and agrees not to submit any information about this study to the Clinical Trials Data Bank.

4.6 PUBLICATIONS

This study is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The SPONSOR will work with the authors to submit a manuscript describing study results within 12 months after the last data become available, which may take up to several months after the last patient visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC studies. For studies intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the study results until the SPONSOR notifies the investigator that all relevant regulatory requirements on the study drug have been fulfilled with regard to pediatric-related regulatory filings. Merck will post a synopsis of study results for approved products on www.clinicalstudyresults.org and www.clinicaltrials.gov by 12 months after the last patient's last visit or within 7 days of product approval in any major markets (United States, Europe or Japan), whichever is later. These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties.

Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement.

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

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

The SPONSOR must have the opportunity to review all proposed abstracts, manuscripts, or presentations regarding this study 60 days prior to submission for publication/presentation. Any information identified by the SPONSOR as confidential must be deleted prior to submission. SPONSOR review can be expedited to meet publication timelines.

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