Official Protocol Title:	A Randomized Double Blind Clinical Trial to Evaluate the Effects of MK-7264 in Participants with Obstructive Sleep Apnea
NCT number:	NCT03882801
Document Date:	02-APR-2019

Title Page

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Protocol Title: A Randomized Double Blind Clinical Trial to Evaluate the Effects of MK-7264 in Participants with Obstructive Sleep Apnea

Protocol Number: 039-02

Compound Number: MK-7264

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

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Regulatory Agency Identifying Number(s):

IND	141,037
EudraCT	2018-004099-37

Approval Date: 02 April 2019

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 02	02-APR-2019	Update prohibited concomitant medications.
Amendment 01	30-JAN-2019	The MK-7264 45 mg assessment was removed.
Original Protocol	11-DEC-2018	Not Applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendments:

Following publication of Protocol 039-01, new in vitro data suggesting transporter inhibition by MK-7264 became available. Based on this information, pitavastatin has been added to the list of prohibited medications.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page	Added IND into Regulatory Agency table to align with the IND number	The revisions reflect the clarification of the IND number in the Regulatory Agency table.
Section 1.3: Schedule of Activities (SoA)	Added a line for blood and urine collections for in clinic PSG days	The revisions reflect clarification of the SoA.
Section 1.3: Schedule of Activities (SoA)	Added additional flexibility for timing of admission arrival and procedures.	The revision is to accommodate patient and site schedules.
Section 1.3: Schedule of Activities (SoA)	Added that patient allocation number will be added to the Participant ID Card at randomization.	The revisions reflect clarification of the SoA.
Section 2.3: Pharmaceutical and Therapeutic Background	Added updated in vitro MK-7264 transporter inhibition data.	The revisions reflect the inclusion of newly available in vitro transporter inhibition data.

Section # and Name	Description of Change	Brief Rationale
Section 5.2: Exclusion Criteria	Added pitavastatin to list of prohibited medications.	The revisions reflect the updated prohibited medications list based on newly available in vitro transporter inhibition data.
Section 5.2: Exclusion Criteria	Added history of allergy to sulfonamide-containing drugs to the exclusion criteria.	The revision reflects the updated allergy exclusion criterion.
Section 5.2: Exclusion Criteria	Updated eGFR criterion	The revisions reflect the updated eGFR exclusion criterion.
Section 5.3.1.1: Diet Restrictions	Clarified diet restrictions for assessment visits.	The revisions reflect the clarification of diet restrictions.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Randomized Double Blind Clinical Trial to Evaluate the Effects of MK-7264 in Participants with Obstructive Sleep Apnea

Short Title: MK-7264 Trial in Participants with Obstructive Sleep Apnea

Acronym:

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

Male/Female participants with moderate to severe obstructive sleep apnea between the ages of 18 and 75 years (inclusive) will be enrolled in this trial.

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Treatment of Obstructive Sleep Apnea
Population	Male and female adults with moderate to severe obstructive sleep apnea (OSA) who do not use positive airway pressure (PAP) therapy.
Study Type	Interventional
Intervention Model	Cross-over This is a multi-site study in the US and Europe.
Type of Control	Placebo
Study Blinding	Double-blind
Masking	Investigator
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 9 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 16 participants will be allocated/randomized.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Administration</th><th>Treatment Period</th></tr>
<tr><td rowspan="2">All participants</td><td>MK-7264</td><td>180 mg</td><td>QHS x 7 days</td><td>Oral</td><td>Period 1 or 2</td></tr>
<tr><td>Placebo</td><td>0 mg</td><td>QHS x 7 days</td><td>Oral</td><td>Period 1 or 2</td></tr>
<tr><td colspan="6">Abbreviations:
QHS: daily at bedtime</td></tr>
</table>
</td></tr>
<tr><td>Total Number</td><td>There will be a total of 2 treatment sequences as outlined below. Both sequences will have 8 participants.
<table>
<tr><th>Treatment Sequence</th><th>Period 1</th><th>Period 2</th></tr>
<tr><td>1
(n=8)</td><td>Placebo</td><td>MK-7264 180 mg</td></tr>
<tr><td>2
(n=8)</td><td>MK-7264 180 mg</td><td>Placebo</td></tr>
</table>
</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study for approximately 10 weeks from the time the participant signs the Informed Consent Form (ICF) through the final contact.</td></tr>
</table>

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 10.1.	

Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 10.11.

1.2 Schema

The study design is depicted in Figure 1

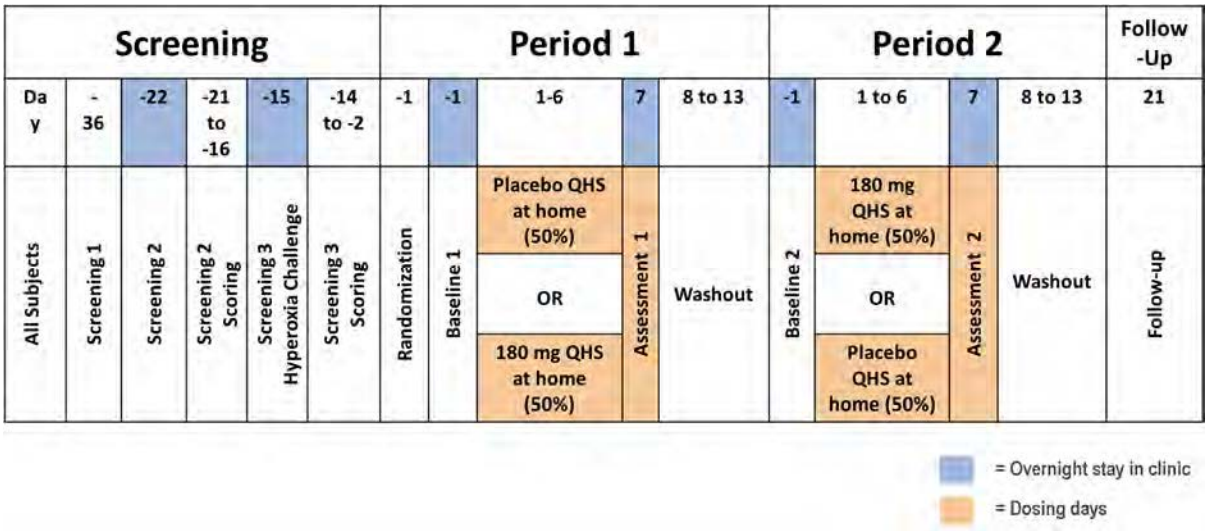

Figure 1 Study Design

1.3 Schedule of Activities (SoA)

Study Period	Screening				Periods 1 and 2				Follow-up	Notes
Scheduled Visit	Screening 1	Screening 2	Screening 3	Randomization	Baseline	At-Home Dosing	Assessment	At-Home Washout	Post-study Visit	Procedures scheduled for Randomization occur in Period 1 only
Study Days	Day -36	Day -22	Day -15	Day -1	Day -1	Days 1-6	Day 7	Days 8-13	Day 21 (After Period 2 only)	
Visit Window (days)	*+13*	*+/- 3*	*+/- 5*		*+ 3*		*+ 2*		*+/- 2*	Visit Windows denote flexibility of certain scheduled Visits. "+" means Visit can be delayed by X days; "-" means Visit can be scheduled ahead by X days.
Administrative Procedures										
Assignment of Screening Number	X									
Informed Consent	X									
Informed Consent for Future Biomedical Research	X									
Participant Identification Card	X			X						Allocation number will be added to the Participant ID Card at Randomization
Inclusion/Exclusion Criteria	X	X	X	X						
Medical History	X									
Prior/Concomitant Medication Review	X ---------- X									
Assignment of Treatment/Randomization Number				X						Site should refer to Study Operations Manual for details on participant assignment. All safety procedures should be completed prior to treatment assignment.
Dosing and Other Related Procedures										
MK-7264/Placebo and Study Intervention Diary Dispensing					X					
MK-7264/Placebo Administration (at home)						X				Participants should take the assigned treatment as instructed by the site

Study Period	Screening				Periods 1 and 2				Follow-up	Notes
Scheduled Visit	Screening 1	Screening 2	Screening 3	Randomization	Baseline	At-Home Dosing	Assessment	At-Home Washout	Post-study Visit	Procedures scheduled for Randomization occur in Period 1 only
Study Days	Day -36	Day -22	Day -15	Day -1	Day -1	Days 1-6	Day 7	Days 8-13	Day 21 (After Period 2 only)	
Visit Window (days)	*+13*	*+/- 3*	*+/- 5*		*+ 3*		*+ 2*		*+/- 2*	Visit Windows denote flexibility of certain scheduled Visits. "+" means Visit can be delayed by X days; "-" means Visit can be scheduled ahead by X days.
Study Intervention Reminder Contact						X				Participants will be contacted and reminded to self-administer study intervention.
Study Intervention Diary (at home)						X				Participants should complete the study intervention diary after each dosing at home
MK-7264/Placebo Administration (in clinic)							X			
Collection of MK-7264 / Placebo bottles and Study Intervention Diary as applicable							X			
Standard Meals		X	X		X		X			
Efficacy/Pharmacodynamic Procedures										
Hyperoxia Challenge			X							
Polysomnography (PSG)		X	X		X		X			See sub-flow chart below for detailed timing of procedures on PSG/in-clinic days
Epworth Sleepiness Scale (ESS)			X		X		X			
Morning Sleep Questionnaire (MSQ) Dispensing					X					
Morning Sleep Questionnaire (MSQ)			X		X	X	X			MSQ should be completed within 15 minutes of rising as instructed by the site
Collection of Completed MSQ							X			
Functional Outcomes of Sleep Questionnaire (FOSQ)			X		X		X			

Study Period	Screening				Periods 1 and 2				Follow-up	Notes
Scheduled Visit	Screening 1	Screening 2	Screening 3	Randomization	Baseline	At-Home Dosing	Assessment	At-Home Washout	Post-study Visit	Procedures scheduled for Randomization occur in Period 1 only
Study Days	Day -36	Day -22	Day -15	Day -1	Day -1	Days 1-6	Day 7	Days 8-13	Day 21 (After Period 2 only)	
Visit Window (days)	*+13*	*+/- 3*	*+/- 5*		*+ 3*		*+ 2*		*+/- 2*	Visit Windows denote flexibility of certain scheduled Visits. "+" means Visit can be delayed by X days; "-" means Visit can be scheduled ahead by X days.
Emerald Device Sleep Data Capture		X	X		X		X			Emerald device will be included for US sites only as described in Section 8.2.2.
Safety Procedures										
Full Physical Examination	X								X	
Focused Physical Exam		X	X	X[a]	X		X			
Height	X									
Weight	X									
Vital Signs (BP/HR/RR/Body Temperature)	X			X	X		X		X	SpO2 will be assessed at Screening Visit 1 for I/E Criteria
12-lead ECG	X			X					X	
Urine or Serum Pregnancy Test (WOCBP only)	X			X[a]	X				X	
HIV, Hepatitis B and C Screen (per site SOP)	X									
Urine Drug Screen (UDS) (per site SOP)	X			X[a]	X					
Laboratory Safety Tests (Chemistry, Hematology, Urinalysis (with microscopy))	X			X[a]	X		X		X	
AE/SAE review	X ---------- X									

Study Period	Screening				Periods 1 and 2				Follow-up	Notes
Scheduled Visit	Screening 1	Screening 2	Screening 3	Randomization	Baseline	At-Home Dosing	Assessment	At-Home Washout	Post-study Visit	Procedures scheduled for Randomization occur in Period 1 only
Study Days	Day -36	Day -22	Day -15	Day -1	Day -1	Days 1-6	Day 7	Days 8-13	Day 21 (After Period 2 only)	
Visit Window (days)	*+13*	*+/- 3*	*+/- 5*		*+ 3*		*+ 2*		*+/- 2*	Visit Windows denote flexibility of certain scheduled Visits. "+" means Visit can be delayed by X days; "-" means Visit can be scheduled ahead by X days.
Pharmacokinetics										
Blood for Plasma MK-7264							X			Blood for MK-7264 PK will be collected at the following time points: Day 7 of each Period: predose, 30 minutes post dose, and lights on.
Biomarkers										
Blood (DNA) for Planned Genetic Analysis[b, c]					X					Collect from randomized participants at Period 1 only.
Blood (serum and plasma) for Clinical Biomarkers [c]					X		X			
Urine for Clinical Biomarkers[c]					X		X			

[a] Events that are marked for both Randomization (Day -1) and Period 1 Baseline (Day -1) should only be performed once. They should not be duplicated.
[b] This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the participant signs the future biomedical research consent. If the planned genetic analyses are not approved, but future biomedical research is approved, and consent is given, this sample will be collected for the purpose of future biomedical research
[c] Leftover from these samples are subject to FBR as described in Section 8.11.

Detailed Schedule of Activities for In Clinic PSG Days

Note: the purpose of the table below is to provide details on the timing in relation of the procedures on PSG days. Not every single procedure is scheduled for each PSG day. Please refer to the Schedule of Activities above to see which procedures are applicable during each visit.

	Arrival (within -6 hours)	Within -4 hours	-1.5 hour	-1.0 hour	'Lights Off' 0 hour		'Lights On' 8 hour	1 hour post 'Lights On'	Discharge
Randomization Procedures (as described in SoA above, Period 1 Baseline only)	X								
Collection of MK-7264/Placebo Bottles, Study Intervention Diary, and MSQ (only on assessment days)	X								
Safety Procedures (Focused Physical Exam[d], Vital Signs)	X								
Vital Signs			X				X		
Blood Collection for MK-7264 PK [a] (only on assessment days)			X	X			X [b]		
MK-7264/Placebo Administration (only on assessment days)			X						
Standard Meal		X						X	
PSG Set-Up			X----------X						
PSG including Finger Pulse Oximetry (SaO_2 monitoring)					X----------X				
Hyperoxia Challenge (Screening Visit 3 only)					X----------X				
Emerald Device Sleep Data Capture					X----------X				
Laboratory Safety Tests (Chemistry, Hematology, Urinalysis)							X [b]		
Clinical Biomarker Sample Collection (urine & blood)							X [b]		
Morning Sleep Questionnaire (MSQ) [c]								X	
Epworth Sleepiness Scale (ESS)								X	
Functional Outcomes of Sleep Questionnaire (FOSQ)								X	
Dispense study medication / Drug Diary, Morning Sleep Questionnaire (MSQ)									X

	Arrival (within -6 hours)	Within -4 hours	-1.5 hour	-1.0 hour	'Lights Off' 0 hour		'Lights On' 8 hour	1 hour post 'Lights On'	Discharge
[a] Blood for MK-7264 PK will be collected at the following time points: Days 7 of each Period: predose, 30 minutes postdose, and lights on. [b] Blood and urine collection for biomarker/PK samples collected at "lights-on" should be drawn at the same time. PGA sample collected at Baseline, Period 1 may also be collected at this time. [c] MSQ should be completed within 15 minutes of rising as instructed by the site. [d] Physical exam may be performed within 1 hour of "Lights-On".									

2 INTRODUCTION

Approximately twenty six percent of American adults suffer from obstructive sleep apnea (OSA) [Peppard, P. E., et al 2013]. Patients with OSA are at increased risk for multiple co-morbidities, including, but not limited, to hypertension, diabetes, stroke, depression, and early mortality [Young, T., et al 2009] [Pagel, J. F. 2007] [Hale, C. S. 2005] [Parish, J. M., et al 2007]. This burden is amplified by the fact that health care utilization and costs among OSA patients are double those of age, body mass index (BMI), and gender matched controls [Pagel, J. F. 2007]. The first-line treatment for OSA is a positive airway pressure (PAP) device, which reduces but does not eliminate the co-morbidities associated with OSA [Pagel, J. F. 2007]. Unfortunately, PAP is cumbersome and poorly tolerated, leading to low long-term adherence rates of approximately 50% [Weaver, T. E., et al 1997] [Means, M. K., et al 2004] [Rotenberg, B. W., et al 2016] [Rotenberg, B. W., et al 2016]. Thus, an oral pharmacological treatment that can either increase the efficacy of PAP or supplant the need for PAP completely would be a significant medical advance for OSA patients.

Pathophysiology of OSA: OSA is a heterogeneous syndrome that results from obstructive (mechanical/anatomic), central (absence of inspiratory effort) or mixed (obstructive plus central) features. In all cases of OSA, there is dysregulation of respiratory motor drive to upper airway muscles, which can lead to airways that either have ineffective dilation or prematurely collapse [Dempsey, J. A., et al 2014] (Figure 2). Additional factors that contribute to OSA are low arousal threshold, prolonged circulation time and High Loop Gain (HLG). HLG is an engineering term applied in respiratory research to describe the relationship of the magnitude of a ventilatory response evoked by a ventilatory disturbance [Dempsey, J. A., et al 2014]; HLG describes a situation in which the ventilatory response is inappropriately high relative to the ventilatory disturbance. The exaggerated response to the levels of O2 and CO2 by the peripheral chemoreceptors in the carotid body (e.g. from poor circulation or autonomic dysregulation) can lead to high ventilatory drive in patients with HLG such that, following even a brief, mild apneic event, the airways open and hyperventilation occurs. This in turn restarts the cycle of hypocapnia and a paradoxical apnea or hypopnea. In patients with HLG, supplemental oxygen increases SaO2 and effectively reduces the disconnect between the perception of hypoxia by peripheral chemoreceptors and the actual gas levels in the periphery. In a subgroup of patients with oxygen responsive or *chemoreflex-dependent* OSA (high loop gain and milder pharyngeal collapsibility), lowering loop gain (with supplemental O_2) greatly improves OSA severity; approximately 25% of patients lowered Apnea-Hypopnea Index (AHI) by > 50% and 1 in 6 patients had no OSA on treatment [Sands, S. A., et al 2018]. HLG is found in approximately 33% of patients with OSA, including those with mechanical obstruction, and contributes to the pathophysiology by causing exaggerated oscillation between hyper- and hypoventilation [Dempsey, J. A., et al 2014].

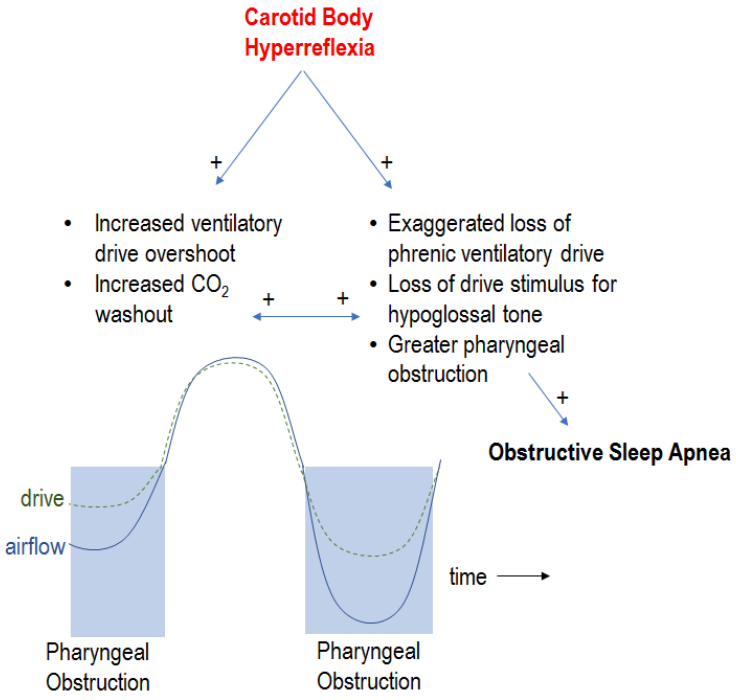

Figure 2 Putative mechanism of contribution of carotid body activation and HLG to OSA

This response results in respiratory instability and recurrent cycles of hypopnea and/or apnea during sleep [Dempsey, J. A., et al 2014] [Younes, M. 2014] (Figure 2). Antagonism of the carotid body afferents could normalize HLG and treat OSA [Paton, J. F. R., et al 2013].

2.1 Study Rationale

The inability of patients to receive maximal benefit from PAP supports the development of new drug treatments for OSA that can either replace or supplement PAP by increasing its clinical efficacy. Drug treatments for OSA have been sought for many years, but effective agents remain to be identified. A series of proof-of-principle studies have been performed using the respiratory stimulant acetazolamide, a carbonic anhydrase inhibitor [Edwards, B. A., et al 2012] [Edwards, B. A., et al 2012] [Nussbaumer-Ochsner, Y., et al 2012]. Acetazolamide produces a metabolic acidosis, which increases the baseline ventilatory drive in patients with OSA. This response can lower loop gain and the AHI [Edwards, B. A., et al 2012]. However, chronic acetazolamide treatment is not a viable long-term therapy as it leads to harmful metabolic changes. These studies support the hypothesis that lowering loop gain pharmacologically can have a beneficial impact on patients with OSA.

This trial is a Phase 1b proof of concept (PoC) placebo-controlled, double-blind, crossover study that will test the hypothesis that MK-7264 will reduce OSA severity (AHI) in chemoreflex-dependent patients with OSA. A positive outcome of this study would support further study of agents, such as MK-7264, that normalize carotid body inputs in patients with OSA.

2.2 Background

Refer to the Investigator's Brochure (IB) for detailed background information on MK-7264.

2.3 Pharmaceutical and Therapeutic Background

MK-7264 is a P2X3 receptor antagonist. P2X3 is a ligand-gated ion channel that is primarily expressed on afferent sensory c-fibers and that opens in response to extracellular ATP released by cell damage in inflamed tissues or released as a neurotransmitter from presynaptic vesicles. P2X3 receptors can be homotrimer (containing only P2X3) or heterotrimer (containing P2X2/3). MK-7264 is a selective P2X3 receptor antagonist and is a potent inhibitor with an IC50 of 20-70 nM for P2X3 and 150-300 nM for P2X2/3, with at least 100-fold selectivity over other P2X channels [North, R. A. 2004].

In vitro studies assessing the potential for MK-7264 to inhibit the human transporters Organic Anion Transporting Polypeptide 1B1 (OATP1B1), OATP1B3, Organic Cation Transporter 1 (OCT1), OCT2, Organic Anion Transporter 1 (OAT1), OAT3, Multidrug and Toxin Extrusion Protein 1 (MATE1), MATE2K, Breast Cancer Resistance Protein (BCRP), and Bile Salt Extrusion Pump (BSEP) were performed.

No clinically meaningful inhibition of OCT2, OAT1, OAT3, BCRP and BSEP was measured. At an in vitro concentration approximately equivalent to that achieved with a 180 mg QD dose, MK-7264 has the potential to inhibit OATP1B1- and OATP1B3-mediated hepatic uptake, with in vitro IC50 values of 35 µM and 97 µM, and calculated R-values (the predicted ratio of the victim drug's AUC in the presence and absence of perpetrator drug) of 1.5 and 1.2 for OATP1B1 and -1B3, respectively. MK-7264 also has the potential to inhibit OCT1-mediated hepatic uptake (IC50=17.2 µM, R=1.9), MATE1 (IC50=34.7 µM; Cmax,u/IC50=0.07), and MATE2K (IC50=31.5 µM; Cmax,u/IC50=0.08) mediated apical efflux in renal proximal tubule cells. Based on these observations, the likelihood of a clinically significant DDI with substrates of OATP1B1, OATP1B3, OCT1, MATE1 and MATE2K is considered to be low, but cannot be excluded.

2.4 Preclinical and Clinical Studies

Aberrant sympathetic nervous system excitation is linked to the pathology and morbidity of a variety of cardiorespiratory disorders, and one factor contributing to sympathoexcitation is OSA [Taylor, K. S., et al 2018]. Additionally, OSA can exacerbate ventilatory instability [Younes, M. 2014]. It has been shown that supplemental oxygen can treat ventilatory instability by reducing the sensitivity of the carotid bodies, resulting in a reduction of the AHI [Edwards, B. A., et al 2014]. In dogs, carotid body denervation reduced apneas and periodic breathing resulting from transient hyperventilations and hypercapnia [Nakayama, H., et al 2003]. An animal model of heightened sympathetic activity, the spontaneously hypertensive rat (SHR), was used to demonstrate the role of P2X3 in peripheral chemoreceptors in the carotid body [Paton, J. F. R., et al 2013] [Pijacka, W., et al 2016]. In this series of studies, electrophysiological recordings from the carotid sinus nerve innervating the carotid body demonstrated the exaggerated response to hypoxia in SHRs relative to

Wistar rat controls. This hyperreflexic response to hypoxia in the SHR was restored to the normal magnitude of response seen in the Wistar through pharmacological blockade with a selective P2X3/P2X2/3 antagonist ('AF-353', a close analogue to MK-7264). Additionally, treatment with MK-7264 significantly reduced renal sympathetic nerve activity [Pijacka, W., et al 2016].

The apneas of prematurity that occur in newborn rats is a model for OSA [Bairam, A., et al 2013]. In this model, blockade of P2X3 and P2X2/3 by 'AF-454' (another close analogue of MK-7264) had no effect on breathing under normoxic conditions but dramatically reduced hypoxia-induced hyperventilation and significantly reduced the frequency of apneas as measured by plethysmographic recordings [Katayama, P. L., et al 2017]. These pre-clinical studies support the hypothesis that P2X3 antagonism could treat sleep disordered breathing in patients with OSA.

As of 31-AUG-2018, MK-7264 has been administered to 360 study subjects in 12 completed and 2 ongoing (clinically complete) Phase 1 clinical trials. Single oral doses, 10 to 1800 mg, and multiple oral doses, 7.5 mg to 1800 mg BID for up to 14 days, were administered to healthy subjects. The efficacy of MK-7264 has been investigated in 11 completed Phase 2 clinical trials. Eight of these trials included subjects with chronic cough; 2 studies were conducted in subjects with idiopathic pulmonary fibrosis (IPF) related cough. Efficacy of MK-7264 was also evaluated in other indications, such as osteoarthritis pain, interstitial cystitis/bladder pain syndrome, and asthma. Across studies, MK-7264 was well tolerated, the most common AEs being dose-dependent effects on taste sensation - eg, dysgeusia, ageusia, hypogeusia. Subjects also described oral paresthesia (tingling sensation in the mouth and/or throat) and oral hypoesthesia (numbness/reduced sensitivity often limited to a specific place in mouth, eg, side of the tongue, lip, back of throat). The taste disturbances and oral paresthesia/hypoesthesia were fully and rapidly reversible after discontinuation of the drug.

Pharmacokinetics of MK-7264 has been evaluated in a wide dose range from 7.5 mg to 1800 mg. MK-7264 is rapidly absorbed, with a median T_{max} of 1.0 to 2.0 hours, and has a half-life of approximately 7 to 10 hours. The exposure to MK-7264 increases in proportion to the dose until 450 mg and it increase in a less than dose proportional manner beyond it. Steady state appears to be achieved within 2 to 3 days of BID dosing, with accumulation ratio of approximately 1.2- to 1.4 fold in the clinical dose range. However, with once daily administration the accumulation is expected to be minimal. Elimination of MK-7264 occurs primarily via renal excretion of intact MK-7264 as approximately 64% of the MK-7264 dose was recovered as parent drug in urine. Metabolism is a relatively minor pathway of elimination, with approximately 15% of an oral dose appearing in urine and feces as metabolites in healthy adult male subjects. The exposure of MK-7264 is inversely related to renal function. Based on linear regression analyses between eGFR and PK parameters, AUC was predicted to be 2.74 and 3.68 times higher and C_{max} 1.70 and 1.99 times higher in subjects with moderate and severe impairment, respectively, compared with healthy subjects with normal renal function.

No studies have been conducted so far to support the OSA indication.

2.5 Ongoing Clinical Studies

Approximately 2300 participants are to be enrolled in the ongoing MK-7264 clinical trials: 2 Phase 1 studies (clinically complete), 3 Phase 2 studies (1 clinically complete), and 3 Phase 3 studies.

Two ongoing Phase 1 studies are being conducted to evaluate the safety, tolerability, and PK of MK-7264 in 46 healthy adult male Japanese subjects, and to characterize the PK performance of different formulations of MK-7264, respectively.

Three Phase 2 studies are currently ongoing; one is evaluating the efficacy of MK-7264 in the treatment of endometriosis related pain (ERP); one is evaluating the efficacy, safety and tolerability of MK-7264 on acute cough in participants with induced viral upper respiratory tract infection, and the last one is evaluating the efficacy and safety of MK-7264 in adult Japanese participants with unexplained or refractory chronic cough.

There are three on-going Phase 3 studies of MK-7264. Two ongoing Phase 3 studies, in which oral doses of 15 and 45 mg BID for 52 weeks are administered to over 2000 participants with chronic cough, are being conducted to evaluate the efficacy of MK-7264 in patients with chronic cough. A third on-going Phase 3 study (in Japan only) is being conducted to evaluate the long-term safety of MK-7264.

For more information, please refer to the MK-7264 Investigator's Brochure.

2.6 Benefit/Risk Assessment

This study is the first to test the potential efficacy of MK-7264 in treating participants with moderate and severe OSA and will provide critical insights into the benefits and risks of MK-7264 compared to placebo. The benefits for participants with OSA from treatment with MK-7264 are unknown. The risk of OSA participants taking MK-7264 is also unknown. However, it is not anticipated that new safety signals will emerge in this population. Additional details regarding specific benefits and risks for participants in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

Male/Female participants with moderate to severe obstructive sleep apnea between the ages of 18 and 75 years (inclusive) will be enrolled in this study.

Objectives	Endpoints
Primary	
• Primary Objective: • To evaluate the effect of multiple dose administration of MK-7264 on the Apnea Hypopnea Index (AHI) in participants with moderate to severe OSA without Positive Airway Pressure (PAP). • Primary Hypothesis: • Multiple dose administration of MK-7264 in participants with moderate to severe OSA reduces the AHI relative to placebo. A 30% reduction in AHI as compared to placebo is expected.	• Apnea-Hypopnea Index (AHI) change from baseline compared with placebo as calculated from polysomnography (PSG)
Secondary	
• To evaluate the safety and tolerability of MK-7264 in participants with moderate to severe OSA.	• Adverse events, safety laboratory assessments, ECGs and vital signs.
Exploratory	
• To evaluate the pharmacokinetics of MK-7264 QHS in participants with moderate to severe OSA.	• MK-7264 (plasma PK): Cmax, AUC0-24, CL and t1/2
• To evaluate arousal index following multiple dose administration of MK-7264 in participants with moderate to severe OSA.	• Arousal Index
• To evaluate the proportion of stage N1 non-REM sleep to TST following multiple dose administration of MK-7264 in participants with moderate to severe OSA.	• Duration of stage N1 non-REM sleep to TST
• To estimate mean SaO2 during total sleep time (TST), NREM, REM, and awake time following the administration of multiple doses of MK-7264 in participants with moderate to severe OSA.	• Mean SaO2 during TST, NREM, REM and awake time

Objectives	Endpoints
• To evaluate the proportion of the night during TST and sleep stages in which SaO2 is less than 90% following multiple dose administration of MK-7264 in participants with moderate to severe OSA	• Proportion of the night during TST and sleep stages in which SaO2 is less than 90%
• To evaluate loop gain following multiple dose administration of MK-7264 in participants with moderate to severe OSA.	• Loop gain
• To evaluate morning systolic and diastolic blood pressure following multiple dose administration of MK-7264 in participants with moderate to severe OSA.	• Morning systolic and diastolic blood pressure
• To evaluate daytime sleepiness following multiple dose administration of MK-7264 in participants with moderate to severe OSA.	• Morning Sleep Questionnaire • Epworth Sleepiness Scale (ESS) score (0-24), units on a scale. • Functional Outcomes of Sleep Questionnaire (5-20).
• To evaluate the performance of the Emerald Device to capture sleep data	• Emerald Device sleep data
• To evaluate blood and urine biomarkers	• Exploratory biomarkers
• To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study	• Germline genetic variation

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, crossover, double-blind multi-site study of MK-7264 in participants with OSA.

The majority of study assessments and procedures for each participant will be conducted during the 6 overnight clinic visits. Eligible participants from Screening 1 will be asked to arrive at the clinic on Day -22 for Screening 2. The participants will have a PSG recording during Screening 2 where their diagnosis of OSA is confirmed.

The participants with confirmed OSA from Screening 2 will be asked to return to the clinic on Day -15 for Screening 3. During Screening 3, the participants will undergo a second PSG with supplemental inspired oxygen to assess whether their sleep apnea is "chemoreflex dependent". While asleep during the PSG, supplemental oxygen will be delivered via face mask (40% inspired oxygen) as an addition to the standard sleep study [Narkiewicz, K., et al 2016] [Sands, S. A., et al 2018]. In some participants the addition of supplemental oxygen will decrease carotid body hyperreflexia thereby lowering loop gain and leading to reduced AHI in those with "chemoreflex dependent" OSA. The number of AHI episodes, as verified by a central reader will be determined. If the participant has a $\geq$ 30 percent decrease in AHI events as well as airflow-based hypopnea events (>30% reduction in airflow) that do not meet normal criteria (3% desaturation or arousal) compared to Screening 2 (see Operations Manual for details), he/she will be eligible to be randomized into the study and may return to the clinic on Day -1 for Period 1 of the study.

During Periods 1 and 2 participants will have a baseline PSG and will receive study intervention for at-home dosing. Participants will begin self-administering study drug at-home (in the evening) for 6-days. Participants will return to the clinic on Day 7 for the last day study drug administration and an assessment PSG. Study drug will be discontinued for a 7-day washout at home before the second period.

Following completion of Period 2, participants will return to the clinic 14 days following the last study drug administration for a follow-up visit.

Because this is a Phase 1 assessment of MK-7264 in humans, the pharmacokinetic (PK), pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is therefore written with flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Refer to Section 8.12 for examples of modifications permitted within the protocol parameters.

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

4.2 Scientific Rationale for Study Design

This study is designed to test the efficacy and safety of MK-7264 in participants with chemoreflex-dependent (i.e. responsive to hyperoxia) OSA. These participants are specifically predicted to respond to MK-7264 based on the shared underlying biological pathways of the hyperoxia and MK-7264 interventions. To select for this population, screening PSG studies will be performed to confirm that each participant has OSA (Screening 2) and that the OSA is responsive to hyperoxia (Screening 3) prior to randomization.

A two-period crossover design was selected so that each participant receives both MK-7264 and placebo in the study, thus permitting for within-subject assessment of treatment effect. A baseline PSG is included in each period to control for any period and/or carryover effects that may be present. A dosing duration of approximately 7 days in each period was selected based on the observation that this compound demonstrated maximal inhibition of chronic cough, believed to have a similar mechanism of action as OSA, after 4 days of dosing (See Investigator's Brochure).

A single high MK-7264 dose (discussed in Section 4.3) was selected to test the P2X3 mechanism in OSA.

Rationale for Amendment 039-01: The original protocol, 039-00, included a lower dose of MK-7264 of 45 mg to further assess dose-response. However, the 180 mg dose proposed was deemed sufficient to assess the objectives of the study. With the removal of the low dose, the study design was altered to a 2 period cross over study with decreased number of PSGs as well as other study related activities which improves the operational feasibility.

Rationale for Amendment 039-02: Following publication of Protocol 039-01, new data on in vitro testing of transporter inhibition by MK-7264 became available. These data are described in Section 2.3 and indicate the potential for inhibition of OATP1B1/3, MATE1/2K and OCT1 at the 180 mg dose level of MK-7264. Based on this information, pitavastatin has been added to the list of prohibited medications.

MK-7264 is a weak inhibitor of OATP1B1/3 and corresponding increases in OATP1B1/3 substrates are predicted to be modest. Pitavastatin is excluded as a concomitant medication from the protocol as its elimination is believed to be primarily dependent on OATP1B1/3. Other statins are permitted without dose adjustment based upon the presence of alternate elimination pathways (including OAT3 for rosuvastatin and pravastatin, CYP3A for simvastatin and atorvastatin, etc.).

Potent MATE1/2K inhibitors result in less than three-fold increases in exposures of the substrate metformin. As MK-7264 is a weak inhibitor in vitro, any effect of MK-7264 would be predicted to be significantly less (below two-fold), and therefore there are no exclusions or dose adjustments of MATE1/2K substrates. Potent inhibition of OCT1 has been reported to reduce metformin efficacy without increases in metformin exposure. MK-7264 is a weak inhibitor of OCT1 in vitro and any potential effect would be anticipated to be minimal and not clinically significant in this study.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy and Safety Endpoints

One goal of the clinical development program for MK-7264 is to demonstrate its efficacy in the treatment of OSA. The primary efficacy endpoint is the change from baseline in AHI. For this PoC study, the primary efficacy endpoint addresses a quantitative measurement of improved sleep that is calculated from data obtained from the PSG studies. This endpoint has been published as the primary endpoint in many trials in clinical development programs for OSA [Wellman, A., et al 2008] [Edwards, B. A., et al 2014] [Younes, M. 2014] [Paton, J. F. R., et al 2013] [Edwards, B. A., et al 2012] [Sands, S. A., et al 2018].

The secondary objective is to evaluate the safety and tolerability of MK-7264 in participants with moderate to severe OSA. This is the first-time patients with known OSA are being dosed with MK-7264. These patients can have multiple co-morbidities as well as medications that may influence the safety of MK-7264. Therefore, adverse events, safety laboratory assessments, ECGs and vital signs will be captured (see Section 8 for details).

The first exploratory objective will evaluate the pharmacokinetics of MK-7264 QHS in participants with moderate to severe OSA. Due to the extensive experience with dosing MK-7264 in healthy volunteers and trial participants a well-established PK model is available. PK measurement in this study will help to develop PK/PD relationships for various efficacy and safety endpoints.

The second exploratory endpoint is to evaluate the frequency of nighttime arousals (as defined by the arousal index) following multiple dose administration of MK-7264 in participants with moderate to severe OSA without PAP. Nighttime arousals in patients with OSA occur as a result of profound apnea and are a reflexive response to re-initiate breathing [Dempsey, J. A., et al 2014]. If MK-7264 ameliorates the number and/or severity (duration and extent of hypoxia) of apnea events, then a decrease in nighttime arousals should occur. The number of nighttime arousals is associated with the overall restorative capacity of sleep and can correlate with daytime sleepiness, a significant quality of life measure for patients with OSA [Peppard, P. E., et al 2013] [Young, T., et al 2009] [Dempsey, J. A., et al 2014].

The third exploratory endpoint is to evaluate the proportion of stage N1 non-REM sleep following multiple dose administration of MK-7264 in participants with moderate to severe OSA without PAP. In participants with OSA, apneas are more common and severe during Stage N1 non-REM sleep [Sands, S. A., et al 2018]. Defining the proportion of TST a participant is in stage N1 non-REM and the number/severity of AHI events will be important to assess the efficacy of MK-7264 in treating OSA.

The fourth exploratory endpoint is to estimate mean oxygen saturation (SaO_2) during total sleep time (TST), NREM, REM, and awake time following the administration of multiple doses of MK-7264 in participants with moderate to severe OSA. SaO2 is a clinically relevant measurement for potential abnormal gas exchange in OSA patients. As MK-7264 is anticipated to normalize, not block, sympathetic tone and decrease hyperventilation due to

HLG, it is important to compare SaO2 during TST following administration of MK-7264 and placebo.

The fifth exploratory endpoints will evaluate the effect of multiple dose administration of MK-7264 in participants with moderate to severe OSA on the proportion of the total sleep time and sleep stage in which SaO2 is less than 90%. MK-7264 should normalize carotid body tone and minimize hyperventilation. By normalizing carotid body tone, MK-7264 should decrease the number of reflective apneas that occur due to hypocarbia after hyperventilation. Decreasing the number and/or duration of the apnea events should decrease the extent of hypoxia the participant experiences while treated with MK-7264.

The sixth exploratory endpoint is to evaluate loop gain following multiple dose administration of MK-7264 in participants with moderate to severe OSA without PAP. Loop gain will be calculated from PSG data, and it reflects carotid body tone.

The seventh exploratory endpoint is to evaluate morning systolic and diastolic blood pressure following multiple dose administration of MK-7264 in participants with moderate to severe OSA without PAP. As sympathetic overdrive can contribute to hypertension, MK-7264 treatment could have an added benefit of normalizing blood pressure.

The eighth exploratory endpoint is to evaluate daytime sleepiness following multiple dose administration of MK-7264 in participants with moderate to severe OSA without PAP. Daytime sleepiness is a significant morbidity associated with OSA [Dempsey, J. A., et al 2014]. If MK-7264 can decrease AHI and nighttime arousals, it should decrease the symptoms of daytime sleepiness. Changes in daytime sleepiness using the Epworth Sleepiness Scale (ESS), Morning Sleep Questionnaire and Functional Outcomes of Sleep Questionnaire (FOSQ) will be captured.

The ninth exploratory endpoint is to evaluate sleep endpoints using data gathered by the Emerald Device (Section 8.2.2). These may include sleep staging, respiratory rate, AHI, and total sleep time.

The tenth exploratory endpoint is to evaluate blood and urine biomarkers. These may include, but are not limited to, renin, angiotensin II, and vanillylmandelic acid.

4.2.1.2 Pharmacokinetic Endpoints

The relationship between MK-7264 plasma concentrations/exposure and AHI /side effects will be explored (as described above). Exploratory population PK analyses will be conducted to obtain the exposure data in order to understand the exposure-response relationships between MK-7264 and efficacy and safety data.

4.2.1.3 Pharmacodynamic Endpoints

No pharmacodynamics biomarkers are planned for this study.

4.2.1.4 Planned Exploratory Biomarker Research

4.2.1.4.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome. Analysis may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

4.2.1.5 Future Biomedical Research

The Sponsor will conduct future biomedical research on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (ribonucleic acid [RNA]), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of this future biomedical research substudy are presented in Appendix 6.

4.2.2 Rationale for the Use of Placebo

A placebo period is included in this study to maintain the study blinding, allowing for an unbiased assessment of efficacy and safety. It will also serve as comparator to MK-7264 for assessing PSG endpoints. Participants may discontinue the study intervention at any time. Since there are no oral treatments for OSA available on the market, the use of a placebo is justified.

4.3 Justification for Dose

As this is a Phase 1 assessment of example in humans, and the PK, pharmacodynamic and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants. Details of allowed modifications are provided in Section 8.12.6.

The dose of MK-7264 that might have efficacy in OSA is currently unknown. To select the dose for treatment of sleep apnea, prior exposure–response (cough rate reduction and taste disturbance) experience was leveraged, keeping in mind that increasing the dose of MK-7264 will increase the likelihood for increased incidence rate of taste disturbance, which could lead to participant non-acceptance, noncompliance and study drop-out. The dose selected for the current study was based on the assumption: i) similarity of the P2X3-related mechanism of action for hypersensitivity in conditions including sleep apnea and cough; ii) similar exposure-response between cough and sleep apnea and; iii) as well as to mitigate potential rightward shift of exposure-response for sleep apnea to cough (ie, potential that sleep apnea is less sensitive than cough reflex). In efficacy assessments of MK-7264 for cough to date, 45 mg BID was found to have near-maximal efficacy with an acceptable taste disturbance profile. To assess the efficacy of MK-7264 for the treatment of sleep apnea, 180 mg qHS was selected which provides ~3 fold higher Cmax relative to 45 mg BID, and a modest increase (100%) in AUC on a 24 hour basis. The expected Cmax following 180 mg (1593 ng/mL) is approximately 40% of that observed following 900 mg BID in a 14 day multiple dose study (Cmax of 3960 ng/mL). The assumption with this qHS dose is that it provides higher exposure in the night time when the efficacy is most desirable and yet it maintains the concentrations that will be similar to 45 mg BID during the day hours. The dynamic concentration range with this dose relative to 45 mg BID dose is not expected to substantially increase the likelihood of higher taste incidence, as higher concentrations will be limited to only night time when the subjects are asleep.

The appropriateness of the 180 mg QHS dose is also supported by preclinical data, as the concentration range of 170-793 ng/mL was found to be efficacious in preclinical models for neuropathic, arthritic and inflammatory conditions and overlaps with the expected steady state concentration in humans.

This dose will additionally provide important information on taste disturbance following QHS dosing regimen. The taste disturbance information available thus far is with BID dosing regimen and will not be relevant to extrapolate for the sleep apnea indication, as the time course of the drug exposure will be different with the proposed QHS regimen compared to BID regimen.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws

from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

A study may be paused during review of newly available preclinical/clinical safety, PK, pharmacodynamic, efficacy, or biologic data or other items of interest, prior to a final decision on continuation or termination of the study. It may be necessary to keep the study open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the study. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. If the decision has been made to end the study following this review period, the study end will be defined as the date of the Sponsor decision, and this end of study date supersedes the definitions outlined above. The Competent Authority(ies) and Institutional Review Board(s)/Independent Ethics Committee(s) [IRB(s)/IEC(s)] will be apprised of the maximum duration of the study beyond the last participant out and the justification for keeping the study open.

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

Male/Female participants with moderate to severe obstructive sleep apnea between the ages of 18 and 75 years (inclusive) will be enrolled in this study.

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

5.1 Inclusion Criteria

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

1. Has an International Classification of Sleep Disorders (ICSD-3) diagnosis of Obstructive Sleep Apnea, based on:
    i. Investigator's assessment of the OSA history and diagnostic interview, which must include: Documented sleep study (i.e. nighttime diagnostic PSG in a sleep lab or home sleep testing (HST)) in the past that confirmed the OSA diagnosis without significant prior medical intervention including but not limited to: weight loss surgery or other surgical interventions to improve sleep quality.
2. Has AHI ≥ 20 events/hour at Screening 2.
3. Has not used positive airway pressure device (PAP) within the preceding 1 month or a dental appliance within the preceding 7 days prior to Screening 2 Visit, and is not allowed to use PAP or a dental appliance throughout the study (including washout intervals between treatment periods) and until the poststudy visit.

4. Has hyperoxia response as assessed during Screening 3 hyperoxia challenge with a reduction in AHI of ≥30% as well as airflow-based hypopnea events (>30% reduction in airflow) that do not meet normal criteria (3% desaturation or arousal) upon supplemental oxygen therapy.

5. Has a baseline SpO2 ≥ 94% at Screening 1 to ensure that carotid body response to hyperoxia is not impaired.

6. Has a Body Mass Index (BMI) ≤ 35 kg/m2 at the pre-study (Screening 1) visit.

7. Is judged to be in good health based on medical history, physical examination, vital sign measurements, and laboratory safety tests (see Appendix 10.2) performed at the pre-study (Screening 1, 2 or 3) visit and/or Baseline 1. Participants with hypertension, Type 2 diabetes, or hypothyroidism may be included if well-controlled on stable doses of appropriate therapy for ≥ 1 month prior to Screening Visit 2.

8. Has no clinically significant abnormality on electrocardiogram (ECG) performed at the pre-study (Screening 1) visit and/or prior to administration of the initial dose of study drug.

Demographics

9. Is male or female, from 18 years to 75 years of age inclusive, at the time of signing the informed consent.

Male Participants

10. Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female Participants

11. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

  - Is not a woman of childbearing potential (WOCBP)

    OR

- Is a WOCBP and using an acceptable contraceptive method, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 10.5 during the intervention period and for at least 1 week after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (urine as required by local regulations) within 72 hours before the first dose of study intervention.

- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 5.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

12. Provides written informed consent/assent for the study. The participant may also provide consent/assent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

Additional Categories

13. Has a consistent sleep-wake schedule that is not subject to any other unusual changes in sleeping routine (i.e., bedtimes and wake times do not vary more than 1-2 hours except on rare occasions).

14. Is able to maintain sleep for at least 4 consecutive hours based on self-report.

5.2 Exclusion Criteria

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

Medical Conditions

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

2. 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
    - Chronic kidney disease
    - Kidney transplant

3. 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
    - Direct bilirubin > 1.5 x ULN
    - Serum Creatinine of > 2 mg/dL

    See Appendix 2 for an algorithm for assessing out-of-range laboratory values.

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

    - Narcolepsy (with or without cataplexy) or Idiopathic Hypersomnia
    - 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
- Chronic Insomnia

5. Is a WOCBP who has a positive urine or serum pregnancy test within 24 hours before the Baseline 1 of study intervention (see Appendix 10.5). If the urine test cannot be confirmed as negative, a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

6. Has a history of clinically significant or poorly-controlled endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases. Participants with a remote history of uncomplicated medical events (eg, uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma) may be enrolled in the study at the discretion of the investigator.

7. Is mentally or legally incapacitated, has significant emotional problems at the time of prestudy (screening 1) visit or expected during the conduct of the study or has a history of clinically significant psychiatric disorder. Participants who have had situational depression may be enrolled in the study at the discretion of the investigator.

8. Has, in the opinion of the investigator, 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 participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate. Examples of excluded disorders include, but are not limited to: active endocrine disorders (however, participants 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).

9. 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

10. Has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (ie, systemic allergic reaction) to prescription or non-prescription drugs or food.

11. Has a history of anaphylaxis or cutaneous adverse drug reaction (with or without systemic symptoms) to sulfonamide antibiotics or other sulfonamide-containing drugs.

12. Is positive for hepatitis B surface antigen, hepatitis C antibodies or HIV.

13. Has a history of cancer (malignancy).

    Exceptions: (1) Adequately treated nonmelanomatous skin carcinoma or carcinoma in situ of the cervix or; (2) Other malignancies that have been successfully treated with appropriate follow up and therefore unlikely to recur for the duration of the study, in the opinion of the investigator and with agreement of the Sponsor (e.g., malignancies that have been successfully treated ≥10 years prior to the prestudy [screening] visit).

14. Has an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 based on the Cockcroft-Gault (CG) Equation.

Cockcroft-Gault Equation:

$$Cl_{Cr} = \frac{(140\text{-age[yr]})(\text{body wt [kg]})}{(72)(\text{serum creat [mg/dL]})}$$

[When creatinine is measured in micromole/litre, use this formula]

$$Cl_{Cr} = \frac{(140\text{-age[yr]})(\text{body wt[kg]})}{(72)(\text{serum creatinine [micromol/L] x 0.0113})}$$

For females, multiple the result by 0.85.

At the discretion of the investigator a measured creatinine clearance, as determined by a 24-hour urine collection, may be used in place of, or in conjunction with, the estimate of the creatinine clearance.

Participants who have a measured creatinine clearance of up to 10% below 60 mL/min may be enrolled in the study at the discretion of the investigator.

Prior/Concomitant Therapy

15. Is unable to refrain from or anticipates the use of certain medications, including prescription and nonprescription drugs or herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to Screening 1, throughout the study (including washout intervals between treatment periods), until the poststudy visit. There may be certain medications that are permitted (see Section 6.5). A list of prohibited medications is provided in the table below. The table below is not all inclusive and the participant may be excluded if taking other medications based on the discretion of the Sponsor or the Investigator.

Table 1 Prohibited Medications and Specified Washout Period

Treatment	Interval*
Investigational compounds	4 weeks prior to Screening 1 or 5 half-lives (see exclusion below)
Antihistamines (sedating)	2 weeks
Hypnotics (OTC as well as prescriptions)	2 weeks or 5 half-lives** prior to Screening 1
Other Psychotropics:	
Antidepressants (other than fluoxetine)	2 weeks
Fluoxetine	4 weeks
Anticonvulsants	2 weeks
Antipsychotics	2 weeks or 5 half-lives
Anxiolytics (benzodiazepines, non-benzodiazepines)	2 weeks or 5 half-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	2 weeks
Systemic glucocorticoids	2 weeks
Isotretinoin	2 weeks
Diet pills	2 weeks
Pitavastatin	1 week

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

** The indicated hypnotic/anxiolytic washout applies to intermittent use only (defined as use of < 4 times/week). For those participants chronically using a hypnotic or anxiolytic (defined as use of ≥ 4 times/week) a 4-week washout (or 5 half-lives, whichever is greater) must **occur prior to completion of Screening 1.** Please see Section 6.5 for more information.

Prior/Concurrent Clinical Study Experience

16. Has participated in another investigational study within 4 weeks prior to the prestudy (screening 1) visit. The window will be derived from the date of the last visit in the previous study.

Diagnostic Assessments

None

Other Exclusions

17. Is under the age of legal consent.

18. Has a need for more than 3 toilet visits during the night.

19. Has traveled across 3 or more time zones in the last 1 week prior to study start. Participant should not anticipate traveling across 3 or more time zones during the study.

20. Consumes greater than 3 glasses of alcoholic beverages (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Participants who consume 4 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator.

21. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.

22. Is an excessive smoker (i.e., more than 10 cigarettes/day) and is unwilling to restrict smoking to ≤10 cigarettes per day or is unwilling to follow the smoking restrictions defined by the CRU. Participants who smoke ≤10 cigarettes per day may be enrolled as long as they do not have significant lung disease related to their smoking.

23. Has had upper airway surgery for obstructive sleep apnea.

24. 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 1) 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 1 visit of the current study.

25. Is a regular user of cannabis, any illicit drugs or has a history of drug (including alcohol) abuse within approximately 3 months. Participants must have a negative urine drug screen (UDS) prior to randomization.

26. Presents any concern by the investigator regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.

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

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Diet Restrictions

Fasting requirements for study procedures, such as but not limited to laboratory safety evaluations are specified in Section 8.0.

On PSG Assessment Visits**,** participants will fast from all food and drinks except water between study drug administration and the next scheduled meal the following morning. Water will be provided during study drug administration. Water will be restricted 1 hour prior to and 1 hour after study drug administration only on PSG Assessment Visits.

On all visits, meals and snack(s) will be provided by the investigator at time points indicated in the study flow chart. Participants will fast from all food and drinks except water between meals and snacks. At all other times and while at home, meals and snacks will be unrestricted in caloric content, composition and timing.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

Participants can consume caffeinated beverages or xanthine-containing products at their normal daily amount but not to exceed more than 6 units per day amounts (1 unit = 120 mg of caffeine). Participants should avoid drinking caffeinated beverages 4 hours before their anticipated bedtime at home. Caffeinated beverages will not be served to participants at the clinic prior to sleep study. Participants should not drink any caffeinated beverages up to 10 hours prior to their scheduled in-clinic sleep study.

5.3.2.2 Alcohol Restrictions

Alcohol consumption is limited to no more than approximately 3 alcoholic beverages or equivalent (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Participants should avoid drinking alcoholic beverages 4 hours before their anticipated bedtime at home. Alcoholic beverages will not be served to participants at the clinic. Participants should not drink any alcoholic beverages on the day of their scheduled in-clinic sleep study.

5.3.3 Tobacco Restrictions

Smoking should be limited to ≤ 10 cigarettes per day and follow the smoking restrictions defined by the CRU while on site.

5.3.4 Activity Restrictions

Participants will avoid unaccustomed strenuous physical activity (ie, weight lifting, running, bicycling, etc.) from the prestudy (Screening 1) visit until administration of the initial dose of study drug, throughout the study (including washout intervals between treatment periods) and until the poststudy visit.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information may be included, as outlined in the electronic case report forms (eCRF) entry guidelines. Minimal information may include demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements.

5.5 Participant Replacement Strategy

If a participant discontinues from study intervention OR withdraws from the study prior to completion of Period 2 a replacement participant may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement participant will generally receive the same intervention or intervention sequence (as appropriate) as the participant being replaced. The replacement participant will be assigned a unique treatment/randomization number. The study site should contact the Sponsor for the replacement participant's treatment/randomization number.

The replacement participant may begin dosing at the subsequent period/dose, based on investigator and Sponsor review and discussion.

6 STUDY INTERVENTION

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

Clinical supplies MK-7264 and placebo will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 2.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administra -tion	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Placebo	Other	Placebo Matching MK-7264	Other	Tablet	0 mg	4 tablets QHS	Oral	Period 1, or 2	Placebo	IMP	Provided centrally by the Sponsor
MK-7264	Experi mental	MK-7264	Drug	Tablet	45 mg	4 tablets QHS	Oral	Period 1, or 2	Experimental	IMP	Provided centrally by the Sponsor
Definition Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.											

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

6.2.2 Handling, Storage, and Accountability

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

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

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

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants will be assigned randomly to one of two treatment sequences according to a computer-generated allocation schedule.

The sample allocation schedules are shown below in Table 3:

Table 3 Sample Allocation Schedule

Subjects	Period 1	Period 2
N=8	Pbo	MK-7264
N=8	MK-7264	Pbo
[a] The suggested doses may be adjusted downward based on evaluation of safety, tolerability, and/or pharmacodynamics data. Note: Subjects who drop out will be replaced.		

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. MK-7264 and placebo will be packaged identically so that blind is maintained. **If applicable** for certain site(s), MK-7264 and placebo will be packaged as open label bulk supplies and will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study site personnel. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment plan require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

If a participant does not discontinue all prohibited medications in Table 1, he/she may be included in the study if the investigator can rationalize that the specific use of a prior medication is either medically required or not clinically relevant within the context of the study.

Concurrent use of any prescription or nonprescription medication, or concurrent vaccination, during the ongoing study (ie, after randomization or intervention allocation) must first be discussed between the investigator and Sponsor prior to administration, unless appropriate medical care necessitates that therapy or vaccination should begin before the investigator and Sponsor can consult. The participant will be allowed to continue in the study if both the Sponsor and the investigator agree. The subject may be asked to repeat a period or skip a period due to any medical issues or concomitant medication use.

Paracetamol/acetaminophen or low dose non-steroidal anti-inflammatory drugs (ibuprofen/naproxen) may be used for minor ailments without prior consultation with the Sponsor.

6.5.1 Rescue Medications and Supportive Care

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

6.6 Dose Modification

Not Applicable

6.6.1 Stopping Rules

The following stopping rules will be employed during the conduct of this study.

If the below stopping rule is met, the study will be paused and no further dosing will occur until the Sponsor has reviewed the totality of data available. In order to continue the study (upon joint agreement with the Sponsor and investigators), a substantial amendment will be submitted for approval.

1. An individual participant reports a Serious Adverse Event considered related to the study drug by the investigator.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention allocation/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period/vaccination regimen will still continue to participate in the study as specified in Section 1.3 and Section 8.1.9, or if available, a protocol clarification letter.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Sections 8.1.9 and 8.12.3.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant's treatment assignment has been unblinded by the investigator, MSD subsidiary, or through the emergency unblinding call center.
- The participant interrupts study intervention administration for more than 2 consecutive days or has 4 cumulative missed doses.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention (including recommendation to discontinue participant from study treatment as part of monitoring for crystalluria/urolithiasis, see Section 8.4.6–Renal and Urological Safety Procedures).
- The participant has a confirmed positive serum pregnancy test.
- The participant has a positive urine drug screen (confirmed by recheck) at any time during the course of the study.

Discontinuation from study intervention is "permanent." Once a participant is discontinued, he/she shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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

The maximum amount of blood collected from each participant over the duration of the study will not exceed 235 mL (Appendix 10.8).

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study or future biomedical research.If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative'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 participant before participation in the study.

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant must receive the Institutional Review Board/Independent Ethics Committee's (IRB/IEC's) approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the

study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the future biomedical research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the future biomedical research substudy. A copy of the informed consent will be given to the participant.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 14 days before starting the study (Screening Visit 1).

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

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

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Administration of study intervention will occur at home and in-clinic as described in Section 1.3 Schedule of Activities.

The distribution of study intervention will be witnessed by the investigator and/or qualified designee at the study visits. Participants will receive one bottle of study intervention at each baseline visit. Each bottle will contain MK-7264 45 mg or placebo matched to 45 mg MK-7264. Participants will be instructed on how to administer study intervention by the site staff.

Participants will be provided with study intervention at the beginning of each period and will receive enough study intervention to last between study site visits. Study intervention should begin on the day following the baseline visit in each period. Participants will be contacted by the site and instructed to self-administer study intervention in the evening approximately one and a half hours before bedtime. Subsequent doses should occur at approximately the same time each evening. Participants will record time of dosing in a drug diary.

Participants will return to clinic at the end of each period for the assessment visit. If the visit assessment is delayed by 1-2 days as allowed in the Visit Window, the participant should continue study intervention as instructed by the site. During the assessment visit, participants will receive the assigned study intervention in the evening, approximately one and a half hour before bedtime. Administration of study intervention during in-clinic assessments will be witnessed by the investigator and/or study staff.

Water will be provided during study drug administration.

While taking the study intervention at home, participants who vomit after dosing or miss a dose should be instructed to continue with the next scheduled dose. However, on clinic PSG days, if the participant vomits within 1 hour of study drug administration, the participant should take an additional dose of study intervention.

8.1.8.1 Timing of Dose Administration

Study intervention will be administered orally in the evening approximately one and a half hours prior to bedtime.

8.1.9 Discontinuation and Withdrawal

The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study. If a participant discontinues for any reason at any time during the course of the study, the participant may be asked to return to the clinic (or be contacted) for a poststudy visit as per the number of days described in Section 8.12.4 (approximately 14 days post the last dose of study intervention for a poststudy visit) to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up time frame as specified in Section 8.4.1, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.4.1) to confirm if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

8.1.10 Participant Blinding/Unblinding

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

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

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

Once an emergency unblinding has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention, but should continue to be monitored in the study.

8.1.11 Domiciling

Participants will be instructed to report to the sleep center on the evening of scheduled baseline and assessment visits as described in Section 1.3. Participants will remain in the clinic overnight and will be discharged upon completion of assessments as described in Section 1.3.

8.1.12 Calibration of Equipment

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

8.2 Efficacy Assessments

8.2.1 Polysomnography

PSG is a diagnostic sleep study that collects EEG, EOG, EMG, ECG, airflow, respiratory effort, oximetry, and sleep position. The PSG will be used to assess entry into the study and will be used as an efficacy assessment at the time points indicated in the SoA. The details of the PSG procedure including participant preparation and lead placement will be described in the study operations manual.

Sleep parameters including, but not limited to, total sleep time (TST), Sleep Latency (SL), Stage of Sleep (i.e. REM, non-REM), Arousal Index (AI), oxygen saturation (SaO_2), Apnea-Hypopnea Index (AHI), and others will be calculated by a central reader as described in the study operations manual.

The time of bedtime in the lab should approximate the participant's bedtime at home (median habitual bedtime), where "bedtime" is defined as the time when the participant intends/attempts to fall asleep, e.g., lying down or reclining with eyes closed. The median bedtime reported by the participant at Screening 1 (within ±1 hour) will be used as the bedtime ("Lights-Off") for all subsequent PSGs. During "Lights-On", a trained study staff will enter the room to wake the patient (if applicable), stop the PSG recording, and turn on the light.

Hyperoxia Challenge and Assessment of Loop Gain

At Screening Visit 3 the PSG described above will be augmented using continuous supplemental inspired oxygen. The hyperoxia challenge is the addition of inhaled 40% oxygen delivered through a face mask. The AHI will be scored as described above and compared to the number of AHI events as well as airflow-based hypopnea events (>30% reduction in airflow) that do not meet normal criteria (3% desaturation or arousal) (see Operations Manual for details) recorded at Screening Visit 2. If the AHI and/or airflow-based hypopnea events decreases by 30% between the two screening visits the participant will have a confirmed hyperoxia response.

8.2.2 Emerald Device Sleep Data Capture

For US sites with IRB approval (ex-US site(s) excluded) the Emerald device will be included during standard PSG for sleep data capture at screening, baseline, and assessment visits as described in the SoA. This device uses passive monitoring of radio wireless local area network (Wi-Fi) signals in combination with machine learning algorithms to determine respiratory signal, sleep stages, and periods of apnea. The concordance between Emerald-derived endpoints and PSG measures will be explored. The details of the Emerald device procedure will be described in the Study Operations Manual.

8.2.3 Morning Sleep Questionnaire (MSQ)

In each treatment period participants will be required to complete a morning sleep questionnaire to record items related to the previous night's sleep. The MSQ should be completed in the morning, within 15 minutes of rise time or as instructed by the site.

Exact clock time must be recorded on the MSQ (hour and minute). The participants will be asked to complete the morning sleep questionnaire as indicated in the SoA.

Participants will bring the completed questionnaires to clinic at assessment visits and the contents will be reviewed. Any participant 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 morning.

8.2.4 Epworth Sleepiness Scale (ESS)

The ESS is a self-administered questionnaire designed to measure sleep propensity in a subjective but standardized way. The ESS consists of 8 questions that take approximately 5 minutes to answer. Participants will be asked to rate, on a 4-point scale (0-3), their chances of dozing off or falling asleep while engaged in eight different situations that involve low levels of stimulation. The ESS score (the sum of 8 item scores, 0-3) can range from 0 to 24. The higher the ESS score, the higher that person's average sleep propensity in daily life (ASP). The participants will be asked to complete the ESS as indicated in the SoA.

8.2.5 Functional Outcomes of Sleep Questionnaire (FOSQ)

The FOSQ is a 30 item self-administered questionnaire which determines functional status in adults; measures are designed to assess the impact of disorders of excessive sleepiness on multiple activities of everyday living and the extent to which these abilities are improved by effective treatment [Weaver, T. E., et al 1997]. The participants will be asked to complete the FOSQ as indicated in the SoA.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in Appendix 8.

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

8.4 Physical Examinations

8.4.1 Complete Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. At a minimum, the

examination will include assessments of the following: general appearance; skin and lymphatic; eyes, ears, nose, throat; cardiovascular system; respiratory system; abdomen/gastrointestinal system; urological system; musculoskeletal and neurological systems. Other body systems may be examined. Height (cm) and weight (kg) will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.4.2 Focused Physical Examinations

A brief focused physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. At a minimum, the examination will include assessments of the following: cardiovascular system, respiratory system, abdomen/gastrointestinal system, and extremities. Other body systems may be examined.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

A brief focused physical exam may be performed at any study site visit that does not already include a physical exam if deemed necessary by the investigator due to signs/symptoms. A physical exam (complete or focused) can be performed at any unscheduled visit if deemed necessary by the investigator.

8.4.3 Calculate Body Mass Index

BMI will be calculated (weight/height^2 in kg/m^2) by the investigator or qualified designee based on participant's height and weight at Screening Visit 1 to ensure the participant meets study Inclusion Criteria (see Section 5.1).

8.4.4 Vital Signs

Vital signs will be measured in a sitting position after approximately 5 minutes rest and will include oral or tympanic temperature (in centigrade), systolic and diastolic blood pressure (mm Hg), respiratory rate, and heart rate (beats per minute). Vital signs should be performed prior to any blood draws at the same timepoint. All blood pressure measurements during the study should be performed on the same arm, preferably by the same person.

Any clinically significant abnormalities in vital signs noted after Screening Visit 1 will be recorded as AEs in the eCRF.

8.4.5 Electrocardiograms

For screening purposes, a single 12-lead electrocardiogram (ECG) will be obtained using local standard procedures and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA.

8.4.6 Renal and Urological Safety Procedures

Urinalysis (including microscopy) will be collected as outlined in the SoA. Participants who have either crystals or unexplained hematuria will be further evaluated. The decision regarding continuing treatment with MK-7264 and/or continued participation in the study will be made on a case-by-case basis in consultation with the Sponsor.

8.4.7 Pregnancy Testing

Urine or serum pregnancy testing will be performed at the investigator site as indicated in the SoA.

8.4.8 Exploratory Blood and Urine Clinical Biomarkers

Exploratory blood and urine for biomarkers will be collected as indicated in the SoA.

8.5 Clinical Safety Laboratory Assessments

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

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

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

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

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

8.6 Other Assessments

8.6.1 Study Intervention Diary

In each treatment period participants will be required to complete a diary to record at-home administration of study intervention. The diary should be completed after each evening dose of study drug. The exact clock time of each dosing must be recorded on the diary. Participants will bring the diary to clinic at assessment visits and the contents will be reviewed. Any participant 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 evening.

8.7 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 10.3.

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

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

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

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

AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before intervention allocation/randomization, must be reported by the investigator for randomized participants only if the event is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

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

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

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

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

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

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
Nonserious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 24 hours of learning of event

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 10.3.

8.7.4 Regulatory Reporting Requirements for SAE

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

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

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

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

8.7.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

Not Applicable

8.7.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.8, that is not associated with clinical symptoms or abnormal laboratory results.

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

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that must trigger an additional evaluation for an underlying etiology. The study site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this study.

8.8 Treatment of Overdose

The participant has taken (accidentally or intentionally) any drug administered as part of the protocol that exceeds 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, in consultation with the Sponsor.

8.9 Pharmacokinetics

8.9.1 Blood Collection for Plasma MK-7264

Sample collection, storage, and shipment instructions for plasma samples will be provided in the study operations manual.

8.10 Planned Genetic Analysis Sample Collection

This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be provided in the operations/laboratory manual.

8.11 Future Biomedical Research Sample Collection

If the participant signs the future biomedical research consent, the following specimens will be obtained as part of future biomedical research:

- Leftover DNA for future research
- Leftover main study urine from clinical biomarkers assay
- Leftover main study serum from clinical biomarkers assay
- Leftover main study plasma from clinical biomarkers assay

8.12 Visit Requirements

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

8.12.1 Screening

Approximately 5 weeks prior to intervention randomization, potential participants will be evaluated over multiple screening visits to determine that they fulfill the entry requirements as set forth in Section 5.

Screening Visit 1 will assess medical history, vital signs, concomitant medications, ECG, and laboratory safety tests as described in Section 1.3

During Screening Visit 2 participants will undergo a PSG to confirm diagnosis of moderate to severe sleep apnea. Participants must demonstrate AHI ≥ 20 events/hour to continue in the study.

During Screening Visit 3 participants will undergo a PSG with hyperoxia challenge to confirm presence of loop gain. Participants demonstrating a 30% reduction in AHI during hyperoxia challenge will be randomized into the study.

Participants may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures listed in the SoA, including consent review.

8.12.2 Treatment Period

The trial will consist of three treatment periods.

During Periods 1 and 2, participants will have a baseline PSG and will receive study intervention for at-home dosing. Participants will begin self-administering study drug at-home (in the evening) for 6-days. Participants will return to the clinic on Day 7 for the last day study drug administration and an assessment PSG. Study drug will be discontinued for a 7-day washout at home before the next period.

Following completion of Period 2, participants will return to the clinic 14 days following the last study drug administration for a follow-up visit.

8.12.3 Discontinued Participants Continuing to be Monitored in the Study

At any point if a participant discontinues from treatment but continues to be monitored in the study, a subset of study procedures specified in the SoA may be completed at the discretion of the investigator and with Sponsor agreement. The subset of study procedures completed will be communicated in a PCL.

8.12.4 Poststudy

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

8.12.5 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the PSG is the critical procedure.

At any postdose time point, the PSG needs to be started as close to the exact start time relative to dosing as possible. All other procedures should be performed as close to the prescribed/scheduled time as possible. Study procedures can be performed prior or after the prescribed/scheduled time.

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

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

The following variance in procedure collection times will be permitted.

- PSG Lights-Off Time for Baseline and Assessment Visits (+/- 1 hour)
- Predose PK Collection: - 60 minutes from scheduled time within PSG day
- Postdose PK Collection: + 60 minutes from scheduled time within PSG day
- Laboratory Safety Tests: +120 minutes from scheduled time within PSG day
- Predose Vital Signs: - 60 minutes from scheduled time within PSG day
- Postdose Vital Signs: +120 minutes from scheduled time within PSG day

8.12.6 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

This is a Phase 1 assessment of MK-7264 in sleep apnea participants, and the PK, 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 1 clinical studies. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants.

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 may not exceed those currently outlined in the protocol.

- Entire period(s) may be omitted or repeated
- Decrease in the duration of study intervention administration (eg, number of days)
- Lengthening of the wash-out period between doses
- Addition of trial pause to assess efficacy and/or safety
- Instructions to take study intervention with or without food or drink may be modified based on newly available data
- Modification of the sample processing and shipping details based on newly available data
- Modification or removal of the Emerald Sleep Capture Device
- Modification, removal, or decision not to analyze the clinical biomarkers
- Maximum Body Mass Index (BMI) for inclusion criteria may be reduced

If necessary, a participant must be discontinued for the reasons described in Section 7.

If it is determined that incomplete or aberrant data has been captured during the baseline and/or assessment PSG at any post-randomization study visit, the participant may be asked to repeat the baseline and/or assessment PSG or the entire treatment period.

The window between screening visits, the window between Screening Visit 3 and baseline, and the wash-out between Period 1 and Period 2 may be increased for individual participants by mutual agreement of the Sponsor and investigator.

The evaluation to determine whether the PSG or treatment period is to be repeated will be done on an individual participant basis, and the decision will be reached by mutual agreement of the Sponsor and investigator. Up to 2 PSGs or 1 treatment period per participant may be repeated. Repeating treatment periods may result in an increase of the

participant's cumulative exposure and/or may increase the total blood volume by 74 mL per repeated period and 37 mL per repeated PSG. The resulting exposure or blood volume increases will be deemed acceptable by the Sponsor and investigator for that participant. The total blood volume should remain <500 mL. If there are >2 failed PSGs or >1 failed treatment period for a certain participant, the participant may be discontinued from the study intervention and replaced.

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 letter to the Study File and forwarded to the investigator for retention. The letter may be forwarded to the IRB/IEC at the discretion of the investigator.

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

The analysis for the primary endpoint will be on the natural log scale of the AHI data. Natural log-transformed fold change from baseline values for AHI will be analyzed using a linear mixed effects model. The dependent variable is natural log (treatment/baseline), and the independent variables in the model include terms for treatment, sequence, and period. In addition, the between-treatment difference in baseline AHIs (Xdiff_AB = ln(baseline of MK-7264/baseline of Placebo)) will be used as a covariate in the model, along with a treatment by Xdiff_AB interaction; the latter term allows for the fact that the correlation between change from baseline and baseline may differ by treatment. An unstructured covariance matrix will be used to allow for unequal treatment variances and to model the correlation between treatment measurements within each subject via the REPEATED statement in SAS PROC MIXED. Least square means and 95% confidence intervals will be calculated for each treatment. These least square means and 95% CIs will be exponentiated to obtain the geometric mean fold change from baseline for each treatment. The least square mean treatment differences (MK-7264 - Placebo) and corresponding 90% CIs in natural log transformed change from baseline will be calculated from the model. The treatment differences and CIs will be exponentiated to obtain the geometric mean treatment fold differences (MK-7264/placebo) and corresponding CIs. If the upper limit of this 90% CI is less than 1.00, then it will be concluded that the administration of MK-7264 has statistically significantly lowered the AHI, thus satisfying the primary hypothesis.

9.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the Early Clinical Development Statistics Department in collaboration with the Quantitative Pharmacology and Pharmacometrics Department and Translational Pharmacology Department 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.

9.3 Hypotheses/Estimation

Primary:

Hypothesis: Multiple dose administration of MK-7264 in participants with moderate to severe OSA reduces the AHI relative to placebo. A 30% reduction in AHI as compared to placebo is expected.

Secondary:

Objective: To evaluate the safety and tolerability of MK-7264 following multiple dose administration of MK-7264.

Exploratory Objectives:

- To evaluate the pharmacokinetics of MK-7264 in participants with moderate to severe OSA.
- To evaluate arousal index following multiple dose administration of MK-7264 in participants with moderate to severe OSA.
- To evaluate the proportion of stage N1 non-REM sleep following multiple dose administration of MK-7264 in participants with moderate to severe OSA.
- To estimate mean SaO2 during total sleep time (TST), NREM, REM, and awake time following the administration of multiple doses of MK-7264 in participants with moderate to severe OSA.
- To evaluate the proportion of the night during TST and sleep stages in which SaO2 is less than 90% following multiple dose administration of MK-7264 in participants with moderate to severe OSA
- To evaluate loop gain following multiple dose administration of MK-7264 in participants with moderate to severe OSA.
- To evaluate morning systolic and diastolic blood pressure following multiple dose administration of MK-7264 in participants with moderate to severe OSA.
- To evaluate daytime sleepiness following multiple dose administration of MK-7264 in participants with moderate to severe OSA.
- To evaluate the performance of the Emerald Device to capture sleep data
- To evaluate blood and urine biomarkers

- To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study

9.4 Analysis Endpoints

Primary:

AHI, which is sum of the apnea and hypopnea indices, is the primary outcome measure. The apnea index for each participant will be calculated as the number of apneas divided by the total sleep time. The hypopnea index for each participant is calculated as the number of hypopneas divided by the total sleep time. The AHI will be calculated as the number of apneas and hypopneas divided by the total sleep time. Baseline AHI for each period are obtained on Day-1. Individual AHI fold-change from baseline in each treatment period will be calculated as the ratio (on-treatment AHI/baseline AHI).

Secondary:

Adverse experiences and other safety measurements (e.g., vital signs, ECGs, laboratories)

Exploratory Endpoints:

- MK-7264 (plasma PK): Cmax, AUC0-24, CL, and t1/2
- Arousal Index for TST, REM, and NREM
- Mean SaO2 for TST, REM, NREM, and Awake time. Baseline mean SaO2 for each period is obtained on Day-1. Individual mean SaO2 fold-change from baseline in each treatment period will be calculated as the ratio (on-treatment mean SaO2/baseline mean SaO2).
- Proportion of the night during TST, REM, NREM, and Awake time in which SaO2 <90%.
- Proportion of stage N1 non-REM to TST
- Loop Gain at various sleep stages
- Change in Systolic and Diastolic blood pressure (BP at Lights on – BP at -1.5 hr)
- ESS, Morning Sleep Questionnaire (MSQ), and FOSQ scores
- Emerald Device sleep data (Not in the scope of the current analysis plan. A separate statistical analysis plan will be drafted, and a separate memo will be prepared)

9.5 Analysis Populations

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

All Participants as Treated (ASaT): The All Participants as Treated Population consists of all participants who received at least one dose of treatment. This population will be used for assessments of safety and tolerability.

Per-Protocol (PP): The Per-Protocol Population consists of the set of data generated by the subset of participants 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 important protocol deviations. Important protocol deviations will be identified to the extent possible prior to unblinding by individuals responsible for data collection/compliance, and its analysis and interpretation. Any participants 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 participants who are compliant with the study procedure as aforementioned and have available data from at least one treatment will be included in the Per-Protocol dataset. This population will be used for the PK and efficacy analyses.

9.6 Statistical Methods

Primary Endpoint

The analysis for the primary endpoint AHI will be on the natural log scale. Natural log-transformed fold change from baseline values for AHI will be analyzed using a linear mixed effects model and the following step wise procedure.

The primary hypothesis will be evaluated by first comparing 180mg MK-7264 versus placebo using data from all two periods. The dependent variable is natural log (treatment/baseline), and the independent variables in the model include terms for treatment, sequence, and period. In addition, the between-treatment difference in log-baseline AHIs (Xdiff_AB = ln(baseline of MK-7264/baseline of Placebo)) will be used as a covariate in the model, along with a treatment by Xdiff_AB interaction; the latter term allows for the fact that the correlation between change from baseline and baseline may differ by treatment. An unstructured covariance matrix will be used to allow for unequal treatment variances and to model the correlation between treatment measurements within each subject via the REPEATED statement in SAS PROC MIXED. If the model fails to converge a simpler covariance structure, Type=CS, will be used. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR). Least square means and 95% confidence intervals will be calculated for MK-7264 and placebo. These least squares means and 95% CIs will be exponentiated to obtain the geometric mean fold change from baseline for each treatment. The least squares mean treatment difference (MK-7264 - Placebo) and corresponding 90% CI in natural log transformed change from baseline will be calculated from the model. The treatment difference and CI will be

exponentiated to obtain the geometric mean treatment fold difference (MK-7264/placebo) and corresponding CI. If the upper limit of this 90% CI is less than 1.00, then it will be concluded that the administration of 180 mg MK-7264 has statistically significantly lowered the AHI, thus satisfying the primary hypothesis. This CI will be examined for the containment of 0.70 which translates into a 30% reduction in AHI with treatment.

```
PROC MIXED DATA=all;
  CLASS seq prd trt subjid;
  MODEL log(value/base) =seq  trt  prd  xdiff_AB  xdiff_AB*trt/ ddfm=kr;
  REPEATED trt/SUBJECT= subjid(seq) TYPE=UN;
  LSMEANS trt/AT xdiff_AB=0 DIFF CL ALPHA=0.1;
RUN;
```

The posterior probability that the true mean percent reduction in AHI after multiple doses of MK-7264 compared to placebo exceeds 10, 20, 30, 40 and 50% will also be obtained, assuming normality and a non-informative prior.

Secondary Endpoints

Safety and tolerability will be evaluated following multiple doses of MK-7264 administered to the participants with OSA by clinical assessment of adverse experiences and other safety measurements (vital signs, ECGs, laboratories). Summary statistics will be provided as appropriate.

Exploratory Endpoints

Population pharmacokinetics approach will be utilized for evaluating MK-7264 plasma PK parameters, Cmax, AUC0-24, CL, and t1/2. The population PK results will be presented in a separate memo.

Mean SaO2: The analysis for the mean SaO2 will be on the natural log scale. Natural log-transformed fold change from baseline values for mean SaO2 will be analyzed using the above described model. Baseline is defined as the mean SaO2 during total sleep time on day-1 for each period. The mean SaO2 during REM, NREM and Awake time will be analyzed in a similar fashion.

Proportion of the Night SaO2 <90%: Summary statistics will be provided for the percentage of participants who experience a SaO2 level less than 90% during the TST by treatment. Summary statistics will also be provided for the proportion of the night during total sleep time in which SaO2 is <90% by treatment. The proportion of the night SaO2<90% during various sleep stages, REM, NREM, and Awake time will also be summarized.

Descriptive summary statistics will be provided for the following exploratory endpoints including arousal index, loop gain at various sleep stages, and proportion of stage N1 NREM to TST. Some of these parameters may also be analyzed in models as previously described to explore the effect of MK-7264 on these parameters.

To assess the day time sleepiness and quality of life improvement, descriptive statistics will be provided for ESS, MSQ, and FOSQ scores. The relationship between the AHI and loop gain at different sleep stages and the relationship of AHI and various scores (ESS, MSQ, and FOSQ) will be explored graphically.

To explore the effect of MK-7264 on diastolic (DBP) and systolic blood pressure (SBP), the difference (BP at Lights on – BP at -1.5 hr) will be computed on the original scale. Summary statistics for this difference in the BP for both diastolic and systolic blood pressure readings will be computed.

Analysis of the sleep data from Emerald device will not be a part of the current analysis plan. A separate statistical plan will be drafted, and the results of the analysis will be presented in a separate memo.

Analysis of blood and urine biomarkers and the evaluation of the relationship of genetic variation and response to the treatment and mechanism of disease will not be a part of current analysis plan. Results of these analysis may be presented in a separate memo.

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.

Individual listings for each of the endpoints by treatment will be provided. Baseline summary statistics will also be provided.

9.7 Interim Analyses

No Interim analyses are planned

9.8 Multiplicity

No multiplicity adjustment procedure will be applied, as there is only one hypothesis to be tested

9.9 Sample Size and Power Calculations

Primary endpoint: AHI

A study with 16 completing subjects in a 2-period crossover design has ~92% probability to detect (alpha=0.05, 1-sided) a statistically significant difference between treatments if the true underlying geometric-mean ratio, GMR (MK7264/Placebo), is 0.70 (which translates into a 30% reduction in AHI after treatment with MK-7264 compared to placebo). This estimate is based on 2000 simulated trials of size N=16 in which individual AHI values were generated assuming a true reduction in AHI of 30%, total variance of 0.36 (natural log scale) and between-measurement correlation of 0.75. These variance estimates were obtained from MK-4305 P036. Fold-change from baseline was then calculated for each trial and analyzed

with the above-described linear mixed effects model. The power was obtained as the percentage of trials showing a statistically significant between-treatment difference.

Power calculations

Sample size	GMR=0.70 30% reduction Correlation=0.75	GMR=0.70 30% reduction Correlation=0.60	GMR=0.70 30% reduction Correlation=0.50
N=16	92	78	71

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing, in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

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

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

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Publication Policy

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

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

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

10.1.5 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.6 Compliance with Law, Audit, and Debarment

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

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

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

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

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

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in

conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.7 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible,

contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

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

10.1.9 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 5 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 5 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen (BUN)/Urea	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate	Chloride	Phosphorus
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose nonfasting	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] • Microscopic examination			
Other Screening Tests	• Follicle-stimulating hormone (as needed in women of nonchildbearing potential only) • Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) if applicable • Urine/Serum β human chorionic gonadotropin (β hCG) pregnancy test (as needed for WOCBP) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)			
NOTES:				

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

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

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Events NOT meeting the AE definition

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

10.3.2 Definition of SAE

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

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

1. Results in death

2. Is life-threatening

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

3. Requires inpatient hospitalization or prolongation of existing hospitalization

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

4. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

5. Is a congenital anomaly/birth defect

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

6. Other important medical events

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

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

10.3.3 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

- Is a cancer (that is not a condition of the study)
- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

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

Assessment of intensity/toxicity

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

Assessment of causality

Follow-up of AE and SAE

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

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

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

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

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

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

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

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

Not Applicable

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.

Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Female Participants

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant[b,c] • Intrauterine hormone-releasing system (IUS)[c,d] • Intrauterine device (IUD) • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen- containing) hormonal contraception[c,d] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c,d] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Acceptable Contraceptive Methods *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)[e]

a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.

b. Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly).

c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation

d. IUS is a progestin-releasing IUD.

e. A combination of male condom with either cap, diaphragm, or sponge with spermicide are considered acceptable, but not highly effective, birth control methods.

Note: The following are not acceptable methods of contraception:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM).
- Male and female condom should not be used together (due to risk of failure with friction).

10.5.3 Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

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

Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 8.11 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

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

3. Summary of Procedures for Future Biomedical Research.

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in the future biomedical research substudy

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research

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

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

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this substudy. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

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

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The

specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants

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

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

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

12. Questions

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

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10.7 Appendix 7: Country-specific Requirements

Not Applicable

10.8 Appendix 8: Blood Volume Table

	Pre-study	Treatment Periods	Post-study	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests (Chemistry, Hematology, Urinalysis)	1	4	1	6	12.5	75
HIV/Hepatitis Screen (at the discretion of the investigator)	1			1	3.5	3.5
Blood for Planned Genetic Analysis	1				8.5	8.5
Blood (Plasma and Serum) for Clinical Biomarkers		4		4	20	80
Blood for MK-7264		6		6	3	18
Total Blood Volume per Participant[a]						185 mL

[a] If additional pharmacokinetic/pharmacodynamic/efficacy and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained.

10.9 Appendix 9: 12-Lead Electrocardiogram Abnormality Criteria

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria	Potentially Significant Post-randomization Findings (clarification on action to take)
RHYTHM		
Sinus Tachycardia	>110 bpm	HR >110 bpm and HR increase of ≥25 bpm from baseline
Sinus Bradycardia	<40 bpm	HR <40 bpm and HR decrease of ≥5 bpm from baseline
Sinus Pause/Arrest	>2.0 seconds	>2.0 seconds
Atrial Premature Complex	> 1 beat	≥ 3 beats
Ventricular Premature Complex	All	≥ 3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation (newly diagnosed and untreated)	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB With Left Anterior Hemiblock (LAHB)	New Onset LAHB
Right Axis Deviation	RBBB With Left Posterior Hemiblock (LPHB)	New Onset LPHB
CONDUCTION		
1st Degree AV Block	PR ≥230 ms	PR ≥ 230 ms + Increase of >15 ms; or PR Increase of >25%
2nd Degree AV Block	Mobitz Type II	Mobitz Type II
3rd Degree AV Block	All	All
LBBB	All	All
RBBB	RBBB With LAHB/LPHB as Defined Above	New Onset RBBB (Not Including Rate-related)
Incomplete Right BBB (ICRBBB) (QRS <120 ms)	No Exclusion	Nothing
Short PR/ Preexcitation Syndrome	Delta Wave + PR <120 ms	Delta Wave + PR <120 ms
Other Intra-Ventricular Conduction Delay	QRS ≥130 ms	QRS ≥130 ms + Increase of ≥10 ms
QTc (F)		
Male	QTc ≥470 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
Female	QTc ≥480 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria	Potentially Significant Post-randomization Findings (clarification on action to take)
HYPERTROPHY		
Atrial Abnormalities	Definite Evidence of P Mitrale or P Pulmonale	Definite Evidence of P Mitrale or P Pulmonale
Ventricular Abnormalities	Voltage Criteria for LVH Plus Strain Pattern	Voltage Criteria for LVH Plus Strain Pattern
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old	All	All
ST/T MORPHOLOGY		
ST Elevation Suggestive of Myocardial Injury	In 2 or more contiguous leads	In 2 or more contiguous leads
ST Depression Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Non-specific ST-T Changes (In 2 or More Leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	All	All
Baseline is defined as Predose Day -1; ms=milliseconds, mm=millimeter		

10.10 Appendix 10: Algorithm for Assessing Out of Range Laboratory Values

For all laboratory values obtained at prestudy (screening) visit and/or predose evaluation:

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

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

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

   i. The participant may be excluded from the study;

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

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

   OR

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

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

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

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

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
ADL	activities of daily living
AHI	Apnea-Hypopnea Index
AE	adverse event
BDS	blood drug screen
CAC	Clinical Adjudication Committee
CNS	central nervous system
CRF	Case Report Form
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
eCTA	exploratory Clinical Trial Application
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EEG	electroencephalogram
EMA	European Medicines Agency
EMG	electromyography
EOC	Executive Oversight Committee
EOG	electrooculography
FDAAA	Food and Drug Administration Amendments Act
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
MTD	maximum tolerated dose
NDA	New Drug Application
NOAEL	no observed adverse effect level
OSA	Obstructive sleep apnea
PET	positron emission tomography
PK	pharmacokinetic
PSG	Polysomnography
QP2	department of quantitative pharmacology and pharmacometrics
RNA	ribonucleic acid
SAC	Scientific Advisory Committee
SAE	serious adverse event
siDMC	Standing Internal Data Monitoring Committee
SoA	schedule of activities

Abbreviation	Expanded Term
SUSAR	suspected unexpected serious adverse reaction
UDS	urine drug screen
WOCBP	woman/women of childbearing potential

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