

Official Protocol Title:	Phase II study, Randomized, Double-Blind, Placebo-Controlled 4-Week Clinical Study, to Evaluate the Efficacy and Safety of MK-7264 in Adult Japanese Participants with Unexplained or Refractory Chronic Cough
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Title Page

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Protocol Title: Phase II study, Randomized, Double-Blind, Placebo-Controlled 4-Week Clinical Study, to Evaluate the Efficacy and Safety of MK-7264 in Adult Japanese Participants with Unexplained or Refractory Chronic Cough

Protocol Number: 033-01

Compound Number: MK-7264

Sponsor Name and Legal Registered Address:

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

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Regulatory Agency Identifying Number(s):

EudraCT NUMBER:

Approval Date: 21-Dec-2017

Sponsor Signatory

Typed Name:
Title:

Date

Protocol-specific Sponsor Contact information can be found in the Investigator Trial 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

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 01

Overall Rationale for the Amendment:

Correction to the schedule of assessment in terms of CSD and Pharmacokinetics sample. Other clarifications required throughout, including the treatment compliance and study procedures.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
2 – Schedule of Assessments 9.2.2.2 – Cough Severity Diary	Added that CSD should be completed daily from Visit 1	CSD should be completed daily from Visit 1 in order to collect baseline data (mean weekly total score prior to first dose).
2 – Schedule of Assessments	Removed “d” from Pharmacokinetic Sample (blood) at Disc visit	Cough monitor will not be attached at Disc visit.
7.6 – Treatment Compliance	Added additional details regarding how compliance with blinded study treatment will be assessed and what steps are to be taken when there are compliance concerns.	To better clarify how compliance with blinded study treatment will be assessed and how concerns with compliance will be addressed.
9.5.5 - Spirometry	Added that spirometry is not required if done within 1 year of Screening, and during a clinically stable period.	To better clarify the requirements for spirometry assessment during Screening.

Section # and Name	Description of Change	Brief Rationale
9.5.7 – Renal and Urological Safety Procedures	Clarified procedure for evaluation of crystals and removed figure.	Based on the evaluation of crystals, decision on continued participation will be made on case-by-case basis.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarized.

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1. Synopsis

Protocol Title:

Phase II study, Randomized, Double-Blind, Placebo-Controlled 4-Week Clinical Study, to Evaluate the Efficacy and Safety of MK-7264 in Adult Japanese Participants with Unexplained or Refractory Chronic Cough

Short Title:

MK-7264 Phase II in Japanese adult participants with unexplained or refractory chronic cough

Objectives/Hypotheses and Endpoints:

This is an estimation study and there are no hypotheses in this study. In this study, the objectives and endpoints below will be evaluated in adult participants with unexplained or treatment refractory chronic cough as follows:

Objective	Endpoint
Primary	
<ul style="list-style-type: none">To evaluate the safety and tolerability of MK-7264	<ul style="list-style-type: none">Number of participants experiencing adverse events (AEs)Number of participants discontinuing study treatment due to AEs
Secondary	
<ul style="list-style-type: none">To estimate the efficacy of MK-7264 in reducing cough frequency as measured over a 24-hour period	<ul style="list-style-type: none">24-hour coughs per hour at Week 4
<ul style="list-style-type: none">To estimate the efficacy of MK-7264 in reducing cough frequency while awake during a 24-hour period	<ul style="list-style-type: none">Awake coughs per hour at Week 4

Overall Design:	
Study Phase	Phase II
Clinical Indication	Treatment of unexplained or refractory chronic cough
Population	Japanese adult participants at least 20 years of age with unexplained or refractory chronic cough
Study Type	Interventional
Type of Design	Parallel
Type of Control	Placebo
Study Blinding	Double-blind
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 months from the time the first participant signs the informed consent until the last participant's last study-related phone call or visit.

Number of Participants:

Approximately 20 participants will be enrolled.

Treatment Groups and Duration:

Treatment Groups	Participants will be randomized in a 1:1 ratio to either oral MK-7264 45 mg BID or placebo.
Duration of Participation	Each participant will participate in the study for approximately up to 8 weeks from the time the participant signs the Informed Consent Form (ICF) through the final contact. After a screening phase of up to approximately 2 weeks each participant will be receiving assigned treatment for approximately 4 weeks. After the end of treatment each participant will be followed for 2 weeks.

Study governance considerations are outlined in Appendix 1. A list of abbreviations used in this document can be found in Appendix 7.

2. Schedule of Activities (SoA)

Study Period	Screening	Baseline	Treatment				Follow-up	Disc	Notes
	Visit 1	Visit 2	Visit 3	TC	Visit 4	Visit 5	Visit 6		
Scheduled Day	Day -14 to Day -7	Day 0	Day 1	Day 14	Day 28	Day 29	Day 42		
Scheduling Window	NA	NA	NA	±3 dys	±3 dys	The next day of V4	14 dys after last dose +3 dys		
Scheduled Week	Wk -2 to Wk -1	Wk 0	Wk 1	Wk 2	Wk 4	Wk 4	Wk 6		
Administrative Procedures									
Informed Consent	X								
Informed Consent for Future Biomedical Research	X								
Participant Identification Card	X								
Inclusion/Exclusion Criteria	X	X							
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	
Demographics and Medical History	X	X							
Treatment Randomization ^a			X						
MK-7264/Placebo Distribution			X						
MK-7264/Placebo Accountability				X	X	X		X	At TC (Day 14), general treatment compliance will be checked
Efficacy Procedures									
Attach Cough Monitor		X			X				Cough monitor should be attached before 11 am and worn for 24 hours during each assessment
Collect Cough Monitor			X			X			

Study Period	Screening	Baseline	Treatment				Follow-up	Disc	Notes
Visit Number	Visit 1	Visit 2	Visit 3	TC	Visit 4	Visit 5	Visit 6		
Scheduled Day	Day -14 to Day -7	Day 0	Day 1	Day 14	Day 28	Day 29	Day 42		
Scheduling Window	NA	NA	NA	±3 dys	±3 dys	The next day of V4	14 dys after last dose +3 dys		
Scheduled Week	Wk -2 to Wk -1	Wk 0	Wk 1	Wk 2	Wk 4	Wk 4	Wk 6		
LCQ		X			X				
Cough Severity VAS	X	X			X				
CSD	Daily								
Safety Procedures									
Chest Radiograph or CT Thorax	X								Not required if done in past 5 years
Physical examination	X					X		X	
Height	X								
Weight	X					X		X	
Vital Signs	X	X	X			X	X	X	
12-lead ECG	X					X		X	
Spirometry	X								Spirometry performed within the past year is acceptable (see Section 6.2)
Urine Pregnancy Test (WCBP only)	X								Pregnancy testing (after V1) will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected (see Appendix 3).
Serum Pregnancy Test (WCBP only)	X								Only if urine test is positive.
Hematology and Chemistry	X					X		X	

Study Period	Screening	Baseline	Treatment				Follow-up	Disc	Notes
	Visit 1	Visit 2	Visit 3	TC	Visit 4	Visit 5	Visit 6		
Scheduled Day	Day -14 to Day -7	Day 0	Day 1	Day 14	Day 28	Day 29	Day 42		
Scheduling Window	NA	NA	NA	±3 dys	±3 dys	The next day of V4	14 dys after last dose +3 dys		
Scheduled Week	Wk -2 to Wk -1	Wk 0	Wk 1	Wk 2	Wk 4	Wk 4	Wk 6		
Urinalysis (w/Microscopy)	X					X		X	Dipstick to be performed at the study site.
AE/SAE review	X	X	X	X	X	X	X	X	
Pharmacokinetics/ Biomarkers									
Blood for Genetic Analysis			X						Collected from randomized participants only; See Section 9.8. and 9.9
Pharmacokinetic Sample (blood)			X ^b		X ^c	X ^d		X	

Abbreviations: AE = adverse event; CSD = cough severity diary; CT = computed tomography; Disc = discontinuation; dys = days; ECG = electrocardiogram; LCQ = Leicester Cough Questionnaire; NA = not applicable; TC=telephone contact; V = visit; VAS = visual analogue scale; WK = week

^a Treatment randomization (prescription) can be done at V2 only if a participant has been confirmed to meet the all entry criteria and the study site has schedule conflict to randomize (prescribe) at V3.

^b Sample should be drawn prior to dosing and after removing cough monitor.(V3, Day 1)

^c Sample should be drawn prior to dosing and before attaching cough monitor.(V4, Day 28)

^d Sample should be drawn after removing cough monitor.(V5, Day 29)

3. Introduction

Cough is one of the most common presenting symptoms for patients seeking care from primary care specialists, allergists, otolaryngologists, or pulmonologists worldwide. The importance of cough as a clinical problem globally has led to multiple societies publishing guidelines on the diagnosis and management of cough [Morice, A. H., et al 2004] [Irwin, R. S., et al 2006] [Morice, A. H., et al 2006] [The committee for The Japanese Respiratory Society guidelines 2006] [Kardos, P., et al 2010]. In these clinical guidelines, including Japan, cough is categorized based upon the duration of the cough; within each category (acute, sub-acute, and chronic) are likely diagnostic possibilities [Irwin, R. S., et al 2006]. Acute cough is present for less than 3 weeks and most often due to acute viral upper respiratory tract infection (URTI). A cough that has been present longer than 3 weeks is either sub-acute (3 to 8 weeks) or chronic (> 8 weeks).

It is reported in Japan that the prevalence of the chronic cough is approximately 2% of the population and the most common underlying condition is asthma/cough-variant asthma followed by sinobronchial syndrome, atopic cough, gastroesophageal reflux disease (GERD) and postinfections. Most of the patients with cough could be effectively managed by optimizing therapy for the underlying condition. However, a minority of patients with a potential underlying co-morbid condition cannot be effectively managed by optimizing therapy for the condition and are considered to have refractory chronic cough. Also, the cause of chronic cough remains unexplained in ~10% of patients seeking medical attention specific to their cough [Gibson, P., et al 2016]. This protocol aims to study participants with either refractory chronic cough or unexplained chronic cough.

Professional guidelines describe systematic approaches to the evaluation and management of chronic cough. These guidelines are based largely on consensus opinion and observational data from the medical literature. There are currently no treatments approved by the United States Food and Drug Administration, European Medicines Agency or Japan Ministry of Health, Labour and Welfare for the treatment of chronic cough. Given the prolonged nature, significant morbidity, and the lack of effective treatment, unexplained or refractory chronic cough is a major unmet medical need.

Mechanism of Cough

Each cough occurs through the stimulation of a complex reflex arc. Cough is initiated following activation of airway sensory nerves in the upper and lower respiratory tract. Airway sensory nerves are tailored to detect changes in the physical and chemical environment, and if required elicit protective reflex events such as cough. These reflexes are normally protective, however, in disease, airway reflexes can become hyper-sensitized, leading to an increase in symptoms and a pathologic cough.

P2X3 receptors are ligand-gated ion channels that respond to adenosine triphosphate (ATP) and are almost exclusively localized on C-fiber sensory neurons, which innervate the upper and lower airways and are the main nerve fibers responsible for cough. ATP is released by damaged, stressed, and inflamed tissues. The action of ATP at sensory neurons in the periphery and spinal cord contributes to neural excitability and may cause hypersensitivity through binding to P2X3-containing receptors and stimulating of C-fiber neurons [North, R. A. 2004] [Khakh, B. S. 2006]. Antagonism of P2X3-containing receptors is predicted to

normalize afferent sensitivity, based on data from P2X3 knock-out mice and the effects of small interfering ribonucleic acid (RNA) knock-down and pharmacological antagonists [Barclay, J., et al 2002] [Cockayne, D. A., et al 2000] [Souslova, V., et al 2000]. ATP and P2X3-containing receptors have been shown to be involved in airways sensitization and their involvement provides a rationale for P2X3 antagonism in the treatment of cough.

Cough Hypersensitivity Syndrome

Recently, the term cough hypersensitivity syndrome has been proposed to describe a group of patients with chronic cough and similar clinical characteristics [Chung, K. F. 2014]. These similar clinical characteristics include irritation in the throat or upper chest, cough triggered by non-tussive stimuli, increased cough sensitivity to inhaled stimuli, and cough paroxysms. A potential biologic explanation for cough hypersensitivity syndrome suggests an underlying sensory neuropathy characterized by afferent nerve hyper-sensitization. Sensory afferent nerves are susceptible to sensitization by neuroactive mediators and altered expression of ion channels which regulate afferent nerve excitability to many chemical stimuli. As described above, the action of ATP at sensory neurons may cause hypersensitivity through binding to P2X3-containing receptors and contribute to the pathophysiology of patients with chronic cough. As described elsewhere in the protocol, the data from Protocol 012 support the role of P2X3 inhibition in the treatment of patients with treatment refractory or unexplained chronic cough.

3.1 Study Rationale

The purpose of this study is to evaluate the efficacy and safety of MK-7264, an orally available P2X3 antagonist, in adult Japanese participants, at least 20 years of age, who have either unexplained or refractory chronic cough.

Current therapies for cough (narcotic, non-narcotic, and over-the-counter medications) have limited efficacy and an undesirable side effect profile. There are no therapies which were proven their efficacy for chronic cough.

Previous studies have demonstrated dose-related efficacy and acceptable safety and tolerability for MK-7264 in adult non-Japanese participants who have chronic cough (refer to the Investigator's Brochure Edition 16, 2017). This study will evaluate the safety and efficacy of MK-7264 in adult Japanese participants with unexplained or refractory chronic cough.

3.2 Background

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

3.2.1 Pharmaceutical and Therapeutic Background

MK-7264, a P2X3 receptor antagonist, has been evaluated in clinical studies for the treatment of chronic cough, interstitial cystitis/bladder pain syndrome, osteoarthritis pain, and asthma. MK-7264 has also been evaluated in an extensive nonclinical program.

MK-7264 is an oral treatment provided as a film coated tablet. The MK-7264 tablets provided for this study contain MK-7264 45 mg. The placebo tablets provided in this study are indistinguishable from the MK-7264 tablet in appearance. The placebo tablets contain no MK-7264, but contain the same inactive excipients as those included in the active tablets.

3.2.2 Clinical Studies in Japan

In single and multiple dose study in Japanese healthy subjects (Protocol 024), the safety, tolerability and PK of MK-7264 was evaluated following MK-7264 (15, 30, 50 and 100 mg/ N=8 [MK-7264: 6, PBO: 2]) as a single dose under fasting conditions in Part 1 and following repeated MK-7264 (15, 30 and 50 mg/ N=8 [MK-7264: 6, PBO: 2] in each dose) BID dosing for 15 days (morning dose only at Day 15) administration under fed conditions in Part 2. The results suggest that there is no specific safety concern in Japanese and no major difference in PK profile between Japanese and non-Japanese.

3.3 Benefit/Risk Assessment

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

MK-7264 has been evaluated in an extensive nonclinical program. To date, there is little evidence from nonclinical studies that MK-7264 has any direct cellular or direct target organ toxicity

In the completed and ongoing clinical studies, no major safety concerns have been noted. Across studies, taste-related adverse events (AEs) were the most frequent reported AEs. The rationale for taste modification exists with P2X2/3 antagonism because of the putative participation of ATP, acting via this receptor, in transducing taste signals from taste buds cells to gustatory afferents. The taste-related AEs are considered mechanism based non-serious adverse drug reactions expected for MK-7264. To date, they have been fully and rapidly reversible after discontinuation of the drug.

Overall, based on growing clinical evidence supporting the efficacy of MK-7264 in participants with refractory or unexplained chronic cough described in Investigator's Brochure (IB) and the lack of significant safety findings in completed and ongoing nonclinical and clinical studies, the benefit risk balance of MK-7264 is assessed as positive.

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

4. Objectives/Hypotheses and Endpoints

This is an estimation study and there are no hypotheses in this study. In this study, the objectives and endpoints below will be evaluated in Japanese adult participants with unexplained or treatment refractory chronic cough as follows:

Objective	Endpoint
Primary	
<ul style="list-style-type: none"> To evaluate the safety and tolerability of MK-7264 	<ul style="list-style-type: none"> Number of participants experiencing an adverse event (AE) Number of participants discontinuing study treatment due to AE
Secondary	
<ul style="list-style-type: none"> To estimate the efficacy of MK-7264 in reducing cough frequency as measured over a 24-hour period 	<ul style="list-style-type: none"> 24-hour coughs per hour at Week 4
<ul style="list-style-type: none"> To estimate the efficacy of MK-7264 in reducing cough frequency while awake during 24-hour period 	<ul style="list-style-type: none"> Awake coughs per hour at Week 4
Exploratory	
<ul style="list-style-type: none"> To estimate the efficacy of MK-7264 in cough specific quality of life 	<ul style="list-style-type: none"> LCQ total score at Week 4
<ul style="list-style-type: none"> To estimate the efficacy of MK-7264 in improving self-rated cough severity 	<ul style="list-style-type: none"> Mean weekly CSD total score at Week 4 Cough Severity VAS score at Week 4
<ul style="list-style-type: none"> 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. 	<ul style="list-style-type: none"> Germline genetic variation
<ul style="list-style-type: none"> To explore the relationship between MK-7264 plasma concentrations and safety and efficacy data 	<ul style="list-style-type: none"> Plasma concentrations of MK-7264

5. Study Design

5.1 Overall Design

This is a randomized, placebo-controlled, parallel group, multi-site, double-blind, study of MK-7264 in adult Japanese participants with unexplained or refractory chronic cough. Approximately 20 participants who meet entry criteria will enter the study. The duration of study period for each participant is as follows:

- Screening Period: a minimum of 7 days and up to 14 days
- Baseline: 1 day (including 24 hours of objective measurement of cough)
- Treatment Period: 28 days
- Follow-Up Period: 14 days

Individual participation is expected to be approximately up to 8 weeks from Screening through the Follow-up period.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the Study SoA - Section 2. Details of each procedure are provided in Section 9 – Study Assessments and Procedures.

5.1.1 Study Diagram

The study design is depicted in [Figure 1](#).

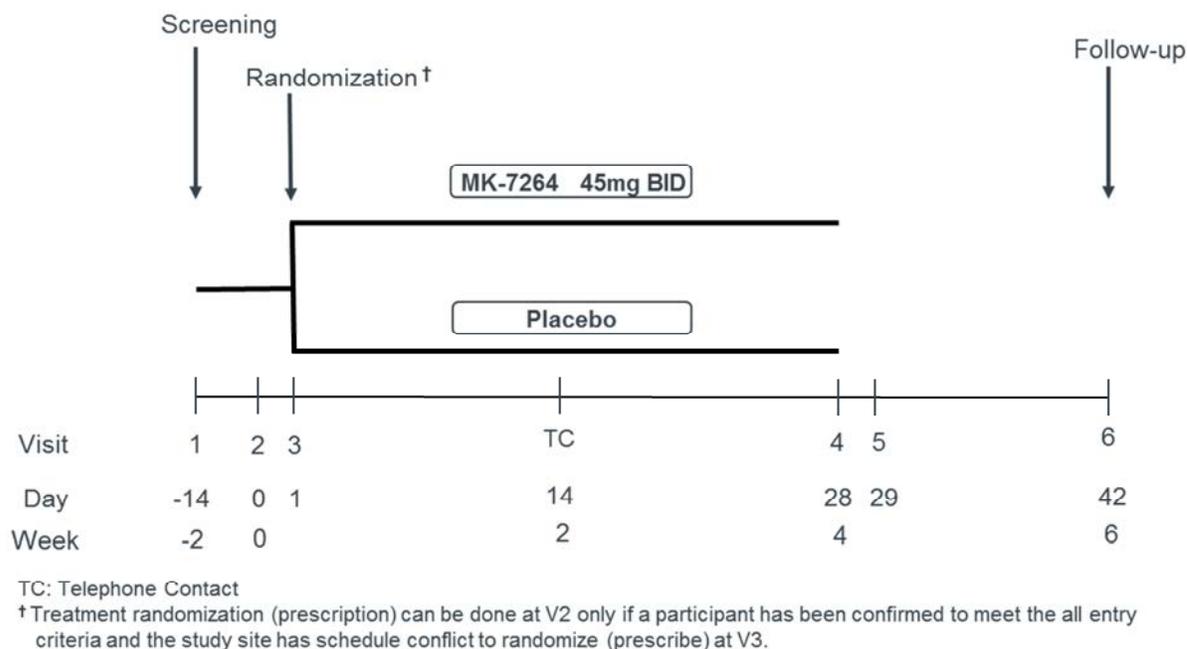


Figure 1 Study Design

There will be one randomization for the entire study. Participants will be randomized in a 1:1 ratio to MK-7264 45 mg BID or placebo.

A safety follow-up visit will be conducted 14 days (+ 3 days) after Visit 4 or after last dose of study treatment (for participants who discontinue from treatment and continue in the study). Please refer to details in Section 9.10.5.

5.2 Number of Participants

Approximately 20 participants will be randomized in this study as described in section 10.9.

5.3 Beginning and End of Study Definition

The overall study begins when the first participant signs the informed consent form (ICF). The overall study ends when the last participant completes the last study-related phone-call or visit, withdraws from the study or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

5.3.1 Clinical Criteria for Early Study Termination

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

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for Endpoints

5.4.1.1 Safety Endpoints

The safety data for MK-7264 to date has been described in detail in the IB

In support of the safety objective to evaluate the safety and tolerability profile of MK-7264 in Japanese adults, the safety and tolerability endpoints will be assessed by clinical evaluation of adverse events and inspection of other study parameters including vital signs, physical examination, and standard laboratory safety tests at time points specified in the SoA. Adverse events are graded and recorded according to Section 9.3 and Appendix 4.

5.4.1.2 Efficacy Endpoints

The first secondary endpoint of this study is the 24-hour coughs per hour (i.e., average hourly cough frequency based on 24-hour sound recordings) at Week 4. Cough counts will be measured using a digital recording device (VitaloJAK™, Vitalograph, Buckingham, United Kingdom). Worn similar to a Holter monitor, with microphones affixed to the participant's chest wall and attached to the participant's clothing, the device provides high fidelity recordings and facilitates signal processing to accurately identify and quantify cough. Digital recordings will be processed in Vitalograph's centralized reading center, where recordings are condensed using a computer algorithm before human analysts identify and tag individual coughs. The output of this process is a count of coughs for each 24-hour recording period, as well as cough counts for portions of the day when the participant is awake and asleep.

The preliminary efficacy of MK-7264 in the treatment of unexplained or refractory chronic cough in Japanese adults will be estimated, as evidenced by a change (reduction) from baseline at Week 4 in 24-hour coughs per hour in MK-7264 relative to placebo. Utilizing 24-hour coughs per hour as the efficacy endpoint is further supported with successful data from MK-7264 Protocol 012. Results from MK-7264 Protocol 012 demonstrated statistically significant reduction, in change from baseline in 24-hour coughs per hour, with 50 mg MK-7264 BID compared to placebo at Week 12. This reduction was observed from Week 4 through Week 8 and Week 12 with statistically significant difference in all time points.

The awake coughs per hour at Week 4 is included as second secondary endpoint. As described above, the 24 hour period can be divided into periods of awake and asleep. In Protocol 012, awake baseline cough rates were numerically higher than 24 hour baseline cough rates and higher than sleep cough rates. Based on these data, awake time may be a meaningful time period for refractory and unexplained chronic cough participants. Therefore awake coughs per hour will be evaluated as a secondary endpoint in this study

An assessment of cough from the participant's perspective is also important for evaluating the response to therapy. Patient-reported outcomes (PRO) associated with cough can be measured in terms of cough-specific quality of life, cough frequency, intensity, disruption due to cough and cough severity. To supplement information obtained from cough counting, the following measures will be included:

1. Leicester Cough Questionnaire (LCQ).
2. Cough Severity Diary (CSD);
3. Cough Severity Visual Analog Scale (VAS);

As validated PRO measures of cough-specific health-related quality of life and cough severity, data obtained from the LCQ, CSD, and Cough Severity VAS, will provide important information relevant to the efficacy of MK-7264 in participants with unexplained or refractory chronic cough.

In regards to Japanese translated version, LCQ has been validated for the use in Japanese chronic cough patients [Kanemitsu, Y., et al 2016]. On the other hand, there is no experience of using Japanese translated version of CSD and Cough Severity VAS. Both PROs will be linguistically validated.

The impact of chronic cough on health-related quality of life (HRQoL) as assessed by the LCQ is included as the exploratory endpoint.

The LCQ is a 19-item cough-specific health-related quality of life (HRQoL) questionnaire which contains three domains (physical, psychological and social), calculated as a mean score for each domain ranging from 1 to 7 and total score ranging from 3 to 21. Each item on the LCQ assesses symptoms or the impact of symptoms on HRQoL over the past two weeks using a 7-point Likert scale ranging from 1 to 7. Higher scores indicate better HRQoL. Data obtained from the LCQ will provide information on the impact of chronic cough on patients' daily lives, beyond objective cough counts and severity, which is valuable information for assessing the full benefit of effective cough control.

The CSD is a 7-item, disease-specific PRO measure completed daily in the evening, with a recall period of “today”. The measure evaluates frequency of cough (3 items), intensity of cough (2 items) and disruption (2 items); each item is rated on an 11-point scale ranging from 0 to 10 with higher scores indicating greater severity. A CSD total score and 3 domain scores (frequency, intensity, disruption) can be calculated.

As part of the psychometric assessment of the CSD in Protocol 012, distribution- and anchor-based analyses were conducted to determine a clinically meaningful change in the mean weekly CSD total score between baseline and Week 4. Results of the distribution-based analyses combined with the anchor-based analyses indicate that a reduction of ≥ 1.3 points and ≥ 2.7 (on the 0 to 10-point scale) are appropriate to define clinically meaningful improvements in the CSD total score.

The Cough Severity VAS is a single-item question asking the participant to rate the severity of their cough over the past 24 hours using a 100 mm VAS anchored with “No Cough” at 0 and “Extremely Severe Cough” at 100. Similar to the well-established use of VAS scales in chronic pain, the Cough Severity VAS measure provides a quick, valid and easily-interpreted subjective assessment useful for clinicians to monitor improvement of their chronic cough patients following treatment.

Based on the results from MK-7264 Protocol 012, analyses to define a clinically meaningful reduction in cough severity indicated that a reduction of ≥ 30 mm was found to be predictive of patient-reported improvement in cough as rated on the Patient Global Impression of Change (PGIC) questionnaire. This cut-point is also consistent with the provisional benchmarks outlined by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials which recommends that an improvement of approximately 30% on a 0 to 10 numeric rating scale can be considered clinically meaningful [Dworkin, R. H., et al 2009].

5.4.1.3 Pharmacokinetic Endpoints

Plasma samples for pharmacokinetic analyses will be drawn and concentrations of MK-7264 will be summarized. Exploratory population pharmacokinetic (PK) analyses may be conducted to understand the exposure-response relationships between MK-7264 and efficacy and safety data.

5.4.1.4 Pharmacodynamic Endpoints

No PD biomarkers that will require modeling are planned for this study.

5.4.1.5 Planned Exploratory Biomarker Research

5.4.1.5.1 Planned Genetic Analysis

Genetic variation may impact a participant’s response to therapy, susceptibility to, and 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 will be used for research related to the study treatment(s), the disease under study and related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases and study drug(s). Genetic research may consist of the analysis of one or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome.

DNA samples will be analyzed for variation across the entire genome. Analyses 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.

5.4.1.6 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on DNA specimens for which consent was provided during this clinical study.

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 sub-study are presented in Appendix 2 – Collection and Management of Specimens for Future Biomedical Research.

5.4.2 Rationale for the Use of Placebo

A placebo is included in this study to maintain the study blinding, allowing for an unbiased assessment of efficacy and safety. Participants may discontinue the study treatment at any time. Given that there is no approved treatment for chronic cough, use of a placebo is justified.

5.5 Justification for Dose

5.5.1 Starting Dose for This Study

The dose for this study will be either MK-7264 45 mg BID or placebo as determined by the individual allocation per the assigned treatment group (see Section 7).

The known mechanism of action of MK-7264 and related clinical study results support that the efficacy of MK-7264 in decreasing cough, and the prevalence of the most common AE, dysgeusia, are both dose related. The exposure -response model was developed from the previously conducted studies and simulations were performed to characterize the dose-response profile. 45 mg BID was selected to achieve a high benefit/risk ratio; likely to maximize the cough frequency reduction in conjunction with acceptable tolerability. Considering that the PK profiles of Japanese and non-Japanese were expected to be similar and there has been no report suggesting an ethnic difference in P2X3 receptor expression, it would be difficult to conclude that the exposure - response relationship would differ between Japanese and non-Japanese. Therefore, a 45 mg BID is selected to evaluate preliminary efficacy and safety of MK-7264 in Japanese participants with unexplained or refractory chronic cough.

5.5.2 Maximum Dose/Exposure for This Study

The maximum dose/exposure for this study will be at 45 mg BID. Participants will be exposed to MK-7264 for approximately 28 days (see Section 7).

5.5.3 Rationale for Dose Interval and Study Design

In this study, MK-7264 will be orally administered as MK-7264 45 mg BID based on the safety and pharmacokinetic efficacy results observed to date.

Based on pharmacokinetic studies, MK-7264 is rapidly absorbed with a median time to reach maximum plasma concentration (T_{max}) of 1.0 to 2.0 hours. In addition, the a half-life of MK-7264 is approximately 7 to 10 hours and consistent with a BID dosing schedule.

In protocol 012, evidence of a reduction in the 24-hour Cough Frequency at the 50 mg dose was also observed at Week 4, which was sustained through Week 12.

For this study, 4 weeks duration of treatment was selected to evaluate efficacy, safety and tolerability of MK-7264 in the treatment of refractory or unexplained chronic cough.

6. Study Population

This study will enroll male and female participants with chronic cough ≥ 1 year and a diagnosis of unexplained or refractory chronic cough according to the American College of Chest Physician (ACCP) guidelines. For the purposes of this study, refractory chronic cough is defined as participants who have had a clinical evaluation that suggested a comorbid condition that may be related to cough (eg, gastroesophageal reflux disease [GERD], asthma, or upper airway cough syndrome), the participant has received appropriate diagnostic work-up and therapy according to ACCP guidelines, and the participant continues to cough. Also for the purposes of this study, unexplained chronic cough is defined as participants who have had a clinical evaluation of their cough per ACCP guidelines and this evaluation has not suggested a comorbid condition that may be related to cough. Participants with refractory chronic cough or unexplained chronic cough and who are at least 20 years of age 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.

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of Participant and Disease Characteristics

1. Chest radiograph or computed tomography scan of the thorax (within 5 years of Screening/Visit 1 and after the onset of chronic cough) not demonstrating any abnormality considered to be significantly contributing to the chronic cough or any other clinically significant lung disease in the opinion of the principal investigator or the sub-investigator.
2. Have chronic cough for ≥ 1 year and a diagnosis of refractory chronic cough or unexplained chronic cough.
3. Have a score of ≥ 40 mm on the Cough Severity VAS at both the Screening and Baseline visits.

Demographics

4. Japanese women and men at least 20 years of age at the time of informed consent.

Female participants:

5. A female participant is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:
 - a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 3OR
 - b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the study period and for at least 14 days after the last dose of study treatment.

Informed Consent

6. The participant is able to provide written informed consent for the study on their own behalf. The participant may also provide consent for Future Biomedical Research. However the participant may participate in the main study without participating in Future Biomedical Research.

Study Participation

7. The participant is willing and able to comply with all aspects of the protocol including demonstrating an ability to follow study procedures (including use of the digital cough recording device) [VitaloJAKTM], and completion of the Cough Severity VAS, CSD, and LCQ) to the satisfaction of the investigator/qualified designee prior to randomization.

6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Current smoker.
2. Individuals who have given up smoking within 12 months of Screening/Visit 1.
3. Former smokers with a pack-year history greater than 20 pack-years.
4. Forced expiratory volume in 1 second (FEV₁)/ forced vital capacity (FVC) ratio <60% (spirometry performed within the past year is acceptable if the investigator confirms that spirometry was done during a period where the participant was clinically stable (eg, not during an upper respiratory infection).
5. History of upper or lower respiratory tract infection or recent clinically significant change in pulmonary status within 4 weeks of Screening/Visit 1.
6. History of chronic bronchitis, defined as a cough that produces a clinically significant amount of sputum (greater than approximately 1 tablespoon of phlegm) that occurs every day for at least 3 months in a row, with those periods occurring at least 2 years in a row.
7. Individuals who are currently taking an angiotensin converting enzyme inhibitor or have taken an angiotensin converting enzyme inhibitor within 3 months of Screening/Visit 1.
8. Estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m² (using the Japanese Equation for Estimating GFR [Japanese Society of Nephrology]) at Screening/Visit 1.
9. Has a history of malignancy ≤ 5 years prior to signing informed consent except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.
10. Is, at the time of signing informed consent, a user of recreational or illicit drugs or has had a recent history (within the last year) of drug or alcohol abuse or dependence in the opinion of the principal investigator or the sub-investigator.
11. Screening systolic blood pressure >160 mm Hg or a diastolic blood pressure >90 mm Hg.
12. History of cutaneous adverse drug reaction to sulfonamides with or without systemic symptoms or history of anaphylaxis to sulfonamides.
13. Has a known allergy/sensitivity or contraindication to MK-7264 or its excipients. (note: refer to the IB for details regarding excipients for MK-7264)
14. Has donated or lost ≥1 unit of blood (approximately 300 mL) within 8 weeks prior to the first dose of MK-7264.
15. A WOCBP who has a positive urine and serum pregnancy test at Visit 1. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required.

Prior/Concomitant Therapy

16. Requiring treatment with a therapy that does not adhere to the guidance parameters specified in Section 7.7.

Prior/Concurrent Clinical Study Experience

17. Has previously received MK-7264.
18. Is currently participating in or has participated in an interventional clinical study with an investigational compound or device within 30 days of participating in this current study.

Diagnostic Assessments

19. Significantly abnormal laboratory tests at Screening (see Sections 9.5.6 and 9.5.7), including:
 - a. alkaline phosphatase (AP), alanine aminotransferase (ALT, SGPT), aspartate aminotransferase (AST, SGOT) >200% of the upper limit of normal, or bilirubin >150% of the upper limit of normal.
 - b. hemoglobin <10 gm/dL, white blood cell count (WBC) <2500 mm³, neutrophil count <1500 mm³, platelet count <100 × 10³/mm³.
20. Has history or current evidence of any condition, therapy, laboratory abnormality or other circumstance that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator or Sponsor, would make the participant inappropriate for entry into this study.
21. 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.

6.3 Lifestyle Restrictions

6.3.1 Meals and Dietary Restrictions

No restrictions are required.

6.3.2 Caffeine Alcohol, and Tobacco Restrictions

Participants who currently smoke, who have given up smoking within the past 12 months, as well as participants who are former smokers with a pack/year history greater than 20 pack-years will not be permitted in the study. Smoking is also not permitted during the course of the trial (from Screening/Visit 1 through completion of Treatment period/Visit 5).

Based on known metabolism of MK-7264, there are no effect of alcohol and caffeine associated with the study treatment and therefore no related restrictions. However, participants will refrain from consumption of alcohol 24 hours prior to and after the all study visits(including the PK sampling visits).

On intermediate days, and at all other times, 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.

6.3.3 Activity

Participants should abstain from strenuous exercise and avoid noisy environments (eg, hair dryer, lawn equipment, open windows while driving, cinemas, listening to music, etc.) while the VitaloJAK™ monitor is attached over a 24 hour period. However, participants may participate in light recreational activities (eg, watching television at a low volume, reading).

Participants will also avoid getting the VitaloJAK™ device, microphone, or chest sensor wet. Thus, they must avoid bathing or showering for the duration of the 24 hour recording.

The chest sensor will be applied to the participant's chest with an adhesive (sticky pad). If the participant has a known allergic sensitivity/reaction to adhesives, and in the opinion of the investigator the sensitivity/reaction is severe enough to impact the ability of the participant to complete the study, the participant should not be enrolled in this study.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. Participants identified as screen failures can be rescreened once (within 45 days of original Screening Visit) for possible participation, and only with Sponsor consultation. Any participant who is re-screened will retain the original screening number assigned at the initial screening visit. If the Cough Severity VAS inclusion criterion is not met at screening at Visit 1, the participant will not be allowed to be rescreened. If the Cough Severity VAS criterion is not met at Visit 2 (Baseline), the participant may be re-screened only with Sponsor consultation. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any adverse events or serious adverse events (SAE) meeting reporting requirements as outlined in the data entry guidelines.

6.5 Participant Replacement Strategy

A participant who discontinues from study treatment or withdraws from the study will not be replaced.

7. Treatments

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

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

7.1 Treatments Administered

The study treatment(s) to be used in this study are outlined below in [Table 1](#).

Table 1 Study Treatment(s)

Study Treatment Name:	MK-7264	Placebo
Dosage Formulation:	Film coated tablet	Film coated tablet
Unit Dose Strength(s):	45 mg	0 mg
Dosage Level(s):	1 tablet BID	1 tablet BID
Route of Administration:	Oral	Oral
Sourcing:	Provided centrally by the Sponsor	Provided centrally by the Sponsor

All supplies indicated in [Table 1](#) will be provided per the ‘Sourcing’ row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to Section 9.1.8 for details regarding administration of the study treatment.

7.2 Dose Modification

No dose modification is allowed in this study.

7.3 Method of Treatment Assignment

Treatment allocation/randomization will occur centrally using an interactive response technology (IRT) system. There are 2 study treatment arms. Participants will be assigned randomly in a 1:1 ratio to MK-7264 45mg BID and placebo, respectively.

7.3.1 Stratification

Treatment allocation/randomization will be stratified according to the following factor:

1. Gender (Male; Female)

7.4 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. The participant, the investigator and Sponsor personnel or delegate(s) who are involved in the study treatment administration or clinical evaluation of the participants are unaware of the group assignments.

See Section 9.1.10 for a description of the method of unblinding a participant during the study, should such action be warranted.

7.5 Preparation/Handling/Storage/Accountability

7.5.1 Dose Preparation

The rationale for selection of doses to be used in this study is provided in Section 5.5 – Background. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant.

7.5.2 Handling, Storage and Accountability

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

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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 treatment 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 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 treatments in accordance with the protocol and any applicable laws and regulations.

7.6 Treatment Compliance

Records of treatment compliance for each participant will be kept during the study. The clinical research associates (CRAs) will review treatment compliance during investigational site visits and at the completion of the study. Compliance should be based on participant reporting and confirmed by tablet count where possible. Issues with compliance should be discussed with the participant and addressed as deemed appropriate by the investigator.

Interruptions from the protocol specified treatment plan of <80% compliance between visits, based on the review with the participant require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

7.7 Concomitant Therapy

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

For participants who receive study treatment, any medication (including over-the-counter medications) or therapy administered to the participant during the course of the study will be recorded on the Prior and Concomitant Therapy case report form (CRF). Treatments for chronic cough received by the participant within 1 year prior to Screening will also be recorded. The Investigator(s) will record any AE on the AEs CRF for which a concomitant therapy was administered.

Listed below are specific restrictions for prior/concomitant therapy during the course of the study:

1. Opioids (including codeine) for the treatment of cough are not allowed from 1 week prior to Screening/Visit 1 through Randomization/Visit 3. Participants should not initiate therapy with opioids (including codeine) for the treatment of cough from Randomization/Visit 3 through completion of Treatment period/Visit 5.

Opioids (including codeine) for indications other than chronic cough are permitted provided the participant is receiving a stable dose for at least 1 week prior to Screening/Visit 1 and in the opinion of the investigator, is likely to remain on the stable dose through completion of Treatment period/Visit 5..

2. Pregabalin, gabapentin, or amitriptyline for the treatment of cough is not allowed from 2 weeks prior to Screening/Visit 1 through Randomization/Visit 3. Participants should not initiate therapy with pregabalin, gabapentin, or amitriptyline for the treatment of cough from Randomization/Visit 3 through completion of Treatment period/Visit 5.

Pregabalin, gabapentin, or amitriptyline for indications other than chronic cough are permitted provided the participant is receiving a stable dose for at least 2 weeks prior to Screening/Visit 1 and in the opinion of the investigator, is likely to remain on the stable dose through completion of s Treatment period/Visit 5.

3. Dextromethorphan, guaifenesin, benzonatate and any other over the counter or prescription for the treatment of cough are not allowed from 2 weeks prior to Screening/Visit 1 through Randomization/Visit 3. Participants should not initiate therapy with any over the counter or prescription treatments for cough from Randomization/Visit 3 through completion of Treatment period/Visit 5.

4. Treatments for conditions such as GERD, asthma, sinobronchial syndrome (SBS), or atopic cough, associated with chronic cough are permitted provided that participants are receiving a stable dose for at least 2 weeks prior to Screening/Visit 1 and in the opinion of the investigator, are likely to remain on the stable dose through completion of Treatment period/Visit 5. Possible treatments are provided in Table 2. Note, this list is not meant to be comprehensive. Sponsor to be consulted for further information.

Table 2 Example of Concomitant Treatments Permitted in the Study

Condition	Treatment
GERD	Anti-reflux therapy (proton pump or H2 blockers), and/or pro-kinetic agents
Asthma	Bronchodilators, inhaled corticosteroids, and/or other anti-inflammatory agents
SBS	14-membered ring macrolides (e.g. erythromycin)
Atopic cough	Antihistamine

5. Non-pharmacologic treatments (eg, physiotherapy, speech and language therapy) for cough are not allowed from 3 months prior to Screening/Visit 1 through completion of Treatment period/Visit 5.

7.7.1 Rescue Medications and Supportive Care

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

7.8 Treatment After the End of the Study

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

7.9 Clinical Supplies Disclosure

The emergency unblinding call center will use the treatment allocation/randomization schedule for the study to unblind participants and to unmask study treatment identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 9.1.10 - Participant Blinding/Unblinding, for a description of the method of unblinding a participant during the study, should such action be warranted.

8. Discontinuation/Withdrawal Criteria

8.1 Discontinuation of Study Treatment

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

As certain data on clinical events beyond study treatment 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 treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 2 - Schedule of Activities and Section 9.10.4– Discontinued Participants Continuing to be Monitored in the Study.

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 9.10.4 – Discontinued Participants Continuing to be Monitored in the Study..

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

- The participant requests to discontinue study treatment.
- The participant’s treatment assignment has been unblinded by the investigator, Merck Sharp & Dohme, Inc subsidiary, or through the emergency unblinding call center.
- 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 treatment (including recommendation to discontinue participant from study treatment as part of monitoring for crystalluria/urolithiasis, see Section 9.5.7– Renal and Urological Safety Procedures)..
- The participant has a confirmed positive serum pregnancy test.
- In case of clinically significant and potentially drug related rash or signs and/or symptoms consistent with anaphylaxis to study treatment.
- Chronic failure to comply with the dosing, evaluations, or other requirements of the study, despite documentation at the site of repeated efforts to reinforce compliance.

For participants who are discontinued from study treatment but continue to be monitored in the study, see Section 2 – Schedule of Activities (SoA), and Section 9.10.4– Discontinued Participants Continuing to be Monitored in the Study for those procedures to be completed at each specified visit.

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

8.2 Withdrawal from the Study

A participant must be withdrawn from the study if the participant withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study treatment 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 9.1.9 – Withdrawal/Discontinuation. 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 8.3 – Lost to Follow Up.

8.3 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, phone 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 pre-specified statistical data handling and analysis guidelines.

9. 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 assuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- 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, etc.), 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, including any extra assessments that may be required, will not exceed approximately 40 mL.

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

9.1 Administrative and General Procedures

9.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential participant 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 qualified designee must ensure the appropriate consent is in place.

9.1.1.1 General Informed Consent

Consent must be documented by the participant'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 IRB/IEC's approval/favorable opinion in advance of use. The participant 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.

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.

9.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

9.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the study. Inclusion and exclusion criteria for this study are defined in Sections 6.1 – Inclusion Criteria and 6.2 – Exclusion Criteria, respectively.

9.1.3 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 utilized 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 treatment allocation/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 treatment in emergency situations where the investigator is not available.

9.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee (refer to electronic CRF [eCRF] entry guidelines).

9.1.5 Prior and Concomitant Medications Review

9.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use prior to screening (see Section 7.7 – Concomitant Therapy and refer to eCRF entry guidelines).

9.1.5.2 Concomitant Medications

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

9.1.6 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 one screening number. Screening numbers must not be re-used for different participants.

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

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 9.10.1

9.1.7 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 allocation/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.

9.1.8 Treatment Administration

Study treatment will be administered at the study site at Visit 3. This first dose of study treatment at Visit 3 should be administered as a witnessed dose after the cough counter is removed, after the pre-dose PK sample collection. Subsequent dosing will be performed by the participant (ie, unsupervised at his/her home) BID, approximately 12 hours apart at approximately the same time each day. However, at Visit 4, the morning dose should *not* be taken at home and instead will be administered as a witnessed dose at the study site, after the pre-dose PK sample collection, and before approximately 11 AM. The cough monitor should be attached prior to dosing and TURNED ON immediately AFTER dosing. The last dose of study treatment will be administered at the evening of Visit 4 (Day 28).

9.1.8.1 Timing of Dose Administration

Study treatment will be administered orally, BID, approximately 12 hours approximately 28 days (4 weeks) during the treatment period.

9.1.9 Discontinuation and Withdrawal

Participants who discontinue study treatment prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.

When a participant withdraws from participation in the study, all applicable activities scheduled for the discontinuation visit should be performed (at the time of withdrawal). Any adverse events which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 9.3 - Adverse Events, Serious Adverse Events, and Other Reportable Safety Events..

9.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for Future Biomedical Research. Participants may withdraw consent at any time by contacting the principal 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.

9.1.10 Participant Blinding/Unblinding

When the investigator or delegate needs to identify the drug used by a participant and the dosage administered in case of emergency eg, the occurrence of serious adverse events, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or delegate 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 treatment assignment, the investigator or delegate must enter the intensity of the adverse events observed, the relation to study drug, the reason thereof, etc., in the medical chart etc.

Participants whose treatment assignment has been unblinded by the investigator/delegate and/or non-study treating physician must be discontinued from study drug, but should continue to be monitored in the study.

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

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. Only the principal investigator or delegate and the respective participant's code should be unblinded. Other study site personnel and Sponsor personnel directly associated with the conduct of the study should not be unblinded.

9.1.11 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 is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

Critical equipment for this trial includes:

- VitaloJAK™ cough monitor. Operational and maintenance instructions are provided separately in a study site manual. Use should be performed according to the manufacturer's specifications. No calibration required.
- Spirometer – performed locally. The spirometer must be calibrated according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines. Calibration checks should be performed (ie, with a 3-liter syringe) at a minimum of each day that a study participant performs a spirometry assessment.
- ECG device – sourced locally; use and calibration should be performed according to the manufacturer's specifications.

9.2 Efficacy Assessments

Compliance with the efficacy and safety assessments (along with study treatment use) is essential, and any non-compliance noted by the investigator or designee should result in consultation with the participant on corrective measures needed to ensure compliance.

9.2.1 24-Hour Coughs Per Hour

The assessment of 24-hour coughs per hour (ie, average hourly cough frequency based on 24-hour sound recordings) will be evaluated using the VitaloJAK™ cough monitor, a 510k approved (Premarket Notification per the US Food, Drug and Cosmetic Act) that has been implemented successfully in clinical studies of potential cough therapies, including two Phase 2 studies of MK-7264.

The VitaloJAK™ cough monitor is a digital recording device that uses two input channels. The first records sounds from the lungs and trachea through a chest contact sensor, which is attached to the skin at the top of the sternum. The second channel captures ambient sounds through a lapel air microphone. Sounds are stored on a high-capacity compact flash card. The device will be carried in a cloth belt bag worn around the participants' waist, and it will record all sounds the participant makes during cough monitoring.

When the digital recording arrives at the central reading center, a human analyst uses standardized criteria to identify transitions between awake and asleep states. To reduce review time, the 24-hour recordings are processed through a computerized algorithm that removes periods of silence and a high proportion of non-cough sounds. A cough analyst then evaluates the abbreviated recording by listening to both audio channels and inspecting the visual wave form of potential cough sounds. The analyst tags the explosive portion of each cough using software built for analysis and annotation of sound recordings (Vitalograph Web Portal). Cough counts are then tallied automatically from the annotated audio file.

The cough monitor will be attached to the participant before approximately 11 AM and worn for 24 hours (see VitaloJAK site manual for further details). The participant should not remove the cough monitor during the 24 hour period; the monitor will be removed at the clinic, by site staff the next day. Attachment of the monitor will be managed by study site staff.

At Visit 3, the first dose of study treatment is to be administered after the cough monitor is removed, after the pre-dose PK sample collections.

At Visit 4, the dose of study treatment is to be administered after the pre-dose PK sample collections, and before approximately 11 AM. The cough monitor should be attached prior to dosing and TURNED ON immediately AFTER dosing.

If cough data is not usable, it may be repeated upon consultation with the Sponsor.

Participants who discontinue study treatment early will continue to be monitored in the study and should be encouraged to continue to complete the assessment of 24-hour coughs per hour at Day 28 (Visit 4) and Day 29 (Visit 5) as outlined in the SoA.

9.2.2 Patient-reported Outcomes

At Screening (Visit 1) and Baseline (Visit 2), each participant will be properly trained and instructed on the PRO measures. Participants should be contacted and reminded to do so (eg, by phone) before the next study site visit.

Participants who discontinue study treatment early will continue to be monitored in the study and should be encouraged to continue to complete the PRO measures as outlined in the SoA.

9.2.2.1 Leicester Cough Questionnaire

Participants will be asked to complete the 19-item LCQ to assess the impact of their cough severity on physical, social and psychological functioning.

Participants will complete the LCQ at the study site visits outlined in the SoA.

9.2.2.2 Cough Severity Diary

Participants will be asked to record their cough frequency, intensity, and disruption due to cough using the 7-item CSD. Participants will rate each item using an 11-point scale ranging from 0 to 10 with higher scores indicating greater severity.

Participants will complete the CSD, daily, at the same time every evening on Screening visit and during treatment period (beginning in the evening on the day of Visit 1 until the evening on the day of Visit 4).

9.2.2.3 Cough Severity Visual Analog Scale

Participants will be asked to rate the severity of their cough over the past 24 hours using a 100 mm Cough Severity VAS single-item questionnaire with the response ranging from 0 (“No Cough”) to 100 (“Extremely Severe Cough”).

Participants will complete the Cough Severity VAS at the study site visit at Screening, Baseline and Visit 4.

In order to confirm participant eligibility, study site staff will be required to review/confirm the:

- Participant met the Screening Cough Severity VAS criteria from the measurement done at Visit 1.
- Participant met the Baseline Cough Severity VAS criteria from the measurement done at Visit 2

A score of ≥ 40 mm on the Cough Severity VAS, at both the Screening and Baseline visits is required for randomization into the study.

9.3 Adverse Events (AE), Serious Adverse Events (SAE) and Other Reportable Safety Events

The definitions of an adverse event (AE) or serious adverse event (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 4.

AE, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver or surrogate).

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, 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 AE, SAEs and other reportable safety events for outcome according to Section 9.3.3.

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

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

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

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

Investigators are not obligated to actively seek AE or SAE 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 treatment 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 timeframes as indicated in [Table 3](#).

Table 3 Reporting Time Periods and Timeframes 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	Timeframe to Report Event and Follow-up Information to SPONSOR:
Non-Serious 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
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential DILI - Require regulatory reporting	Not required	Within 24 hours of learning of event
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

Type of Event	<u>Reporting Time Period:</u> Consent to Randomization/ Allocation	<u>Reporting Time Period:</u> Randomization/ Allocation through Protocol-Specified Follow-up Period	<u>Reporting Time Period:</u> After the Protocol Specified Follow-up Period	Timeframe to Report Event and Follow-up Information to SPONSOR:
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

9.3.2 Method of Detecting AE, SAE and Other Reportable Safety Events

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

9.3.3 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 AE, SAE and other reportable safety events including pregnancy and exposure during breastfeeding, ECI, 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 8.3). In addition, the investigator will make every attempt to follow all non-serious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 4.

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

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) 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 Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.3.5 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

There are no disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

9.3.6 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered adverse events, 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.

9.3.7 Events of Clinical Interest (ECI)

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

Events of clinical interest for this study include:

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

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

9.4 Treatment of Overdose

In this study, an overdose is any dose higher than the amount of study treatment taken outside the treatment assignment (Section 5.5.1 – Starting Dose for This Trial)

No specific information is available on the treatment of overdose. Oral doses of up to 1800 mg BID for 14 days were explored in earlier clinical studies without any untoward clinical effects (refer to IB Edition 16, 2017). Overdose should be treated according to the participant's clinical signs and symptoms.

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

9.5 Safety

Details regarding specific safety procedures/assessments to be performed in this study are provided below. The total amount of blood to be drawn over the course of the study, including approximate blood/ volumes drawn can be found in Section 9.

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

9.5.1 Chest Radiography/Computed Tomography Thorax Scan

A chest radiograph or computer tomography scan of the thorax should be performed locally for participants, at Screening, if this has not been done within the last 5 years and after the onset of chronic cough. The chest radiograph or computer tomography scan of the thorax should not demonstrate any abnormality considered to be significantly contributing to the chronic cough or any other clinically significant lung disease in the opinion of the principal investigator (or sub-investigator, see inclusion criterion 1, Section 6.1 – Inclusion Criteria).

9.5.2 Physical Examinations

A complete physical 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.

Clinically significant changes after Screening will be recorded as AEs.

A brief directed physical examination 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 directed) can be performed at any unscheduled visit if deemed necessary by the investigator.

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

9.5.3 Vital Signs and Weight and Height Measurements

Vital sign measurements, including systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), heart rate (beats per minute), respiratory rate (breaths per minute), and oral or tympanic body temperature (in centigrade) will be collected as outlined in the SoA. All blood pressure measurements should be performed on the same arm, preferably by the same person.

Height (cm) and weight (kg) will also be collected as per the SoA

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

9.5.4 Electrocardiograms

A 12-lead ECG will be performed at Screening and Visit 5 or Discontinuation Visit using local standard procedures. Any clinically significant abnormal findings after Visit 1 should be recorded in the AE eCRF.

9.5.5 Spirometry

A spirometry assessment will be performed locally at Screening using a calibrated spirometer. Assessments will include FEV₁, FVC and FEV₁/FVC ratio.

Spirometry performed within the past year of Screening is acceptable if the investigator confirms that spirometry was done during a period where the participant was clinically stable (eg, not during an upper respiratory infection)

9.5.6 Clinical Safety Laboratory Assessments

Refer to Appendix 5 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 5, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol 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 treatment, 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.

9.5.7 Renal and Urological Safety Procedures

Additional safety assessments will be performed in all participants in order to monitor renal and urological safety. Urinalysis (including microscopy) will be collected as outline in the SoA. Participants will be monitored for hematuria using urinary dipstick (performed at the study site). In addition, participants will simultaneously be evaluated further for urinary crystals.

Participants who have either crystals or unexplained hematuria will be further evaluated. Hematuria detected in the context of menstrual bleeding or urinary tract infection, for example, would not be considered “unexplained”, and would not warrant an evaluation. 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 Sponsor.

9.6 Pharmacokinetics

The date and time for the last dose of study treatment taken prior to the study visit on which the PK sample was collected should be recorded in the eCRF. In addition, the date and time of the PK sample collection should also be recorded in the eCRF.

9.6.1 Blood Collection for Plasma MK-7264

Blood samples will be collected at several visits during the study for determination of MK-7264 as outlined in the SoA. Samples will be collected pre-dose at the specified study site visits. At Visit 4 (Day 28), the morning dose of study treatment will be taken after the PK sample is collected. The last dose of study treatment will be administered at the evening of Visit 4 (Day 28).

MK-7264 plasma concentrations will be determined using a validated LC-MS/MS assay.

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

9.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

9.8 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:

- Blood for genetic analysis

9.8.1 Planned Genetic Analysis Sample Collection

The Planned Genetic Analysis 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 participant signs the Future Biomedical Research consent. If the planned genetic analysis is not approved, but Future Biomedical Research is approved and consent is given, this sample will be collected for the purpose of Future Biomedical Research.

The blood for genetic analysis sample should be collected only once per randomized participant, at pre-dose.

9.9 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

9.10 Visit Requirements

Visit requirements are outlined in Section 2 – Schedule of Activities (SoA). Specific procedure-related details are provided above in Section 9 – Study Assessments and Procedures.

9.10.1 Screening

Potential participants will be evaluated at Screening to determine if they fulfill the entry requirements as set forth in Section 6.1 – Inclusion Criteria and Section 6.2 – Exclusion Criteria. If any participant fails to meet the study entry criteria, screening procedures may be repeated within 7 to 45 days or based on investigator judgment after initial screening, and after consultation with the Sponsor. However, participants will not be permitted to rescreen if inclusion criteria for the Cough Severity VAS was not met at Visit 1.

9.10.2 Baseline

The Baseline visit must be scheduled between 7 days and 14 days after Screening.

Cough assessments will begin at Visit 2. The cough monitor should be attached before approximately 11 AM and worn for 24 hours.

9.10.3 Treatment Period

Participants will be required to be seen in the clinic at Visit 3 to have the cough monitor removed that was attached at Visit 2. Blood for PK assessments will also be collected during Visit 3. Additionally, at Visits 4, participants should return to the clinic to have the cough monitor attached. Cough monitors will be removed at study site at Visits 5. Refer to the vendor's site manual for additional details. Patient-reported outcome measures will be completed as outlined in the SoA.

9.10.4 Discontinued Participants Continuing to be Monitored in the Study

If a participant is discontinued from the study treatment early, all applicable activities scheduled for the Discontinuation Visit should be performed (at the time of discontinuation of study treatment).

It is intended that all participants should be followed through completion of the study, regardless of premature discontinuation of treatment, unless the participant withdraws consent. Thus, participants who discontinue from study treatment prior to completion of the study should continue to be monitored to obtain relevant information through the end of the study. Clinic visits/phone calls should be made at timepoints that correspond to each remaining study visit. Such contacts will allow collection of follow-up information, limited to AEs, concomitant medication use, objective cough counting and PROs assessments as outlined in the SoA (Section 2).

Concomitant therapies specifically prohibited (see Section 7.7 – Concomitant Therapy) while the patient was on study treatment are no longer prohibited after discontinuation of study treatment.

For these participants who have discontinued study treatment early, sites will be instructed to exert diligent efforts to continue to contact them. To enable sites to reach participants, the participants should provide primary and secondary contact information (eg, home phone, work phone, mobile phone). Sites must document the outcome of the telephone contact(s), to demonstrate diligent efforts have been made. If a participant does not agree to be contacted for follow-up for each of the remaining visits (as described in Section 8.1 -Discontinuation of Study Treatment), the participant should be encouraged to accept a telephone contact at least at the date of Visit 5.

Additionally, the ICF will explain the importance of continued data collection from participants, including the use of continued contact by phone.

9.10.5 Post-Study

All participants will be required to clinic approximately 14 days (+ 3 days) after the last dose of study treatment for the post-study visit to determine if any AEs have occurred since discontinuing study treatment.

10. Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post-hoc exploratory analyses will be clearly identified in the CSR.

10.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized below. The comprehensive plan is provided in Sections 10.2-10.12. This is an estimation/exploratory study, no hypothesis testing will be performed (and therefore no multiplicity adjustments will be made).

Study Design Overview	Phase II study, Parallel, randomized, double-blind, placebo-controlled, 4-week clinical study, to evaluate the efficacy and safety of MK-7264 in adult Japanese participants with unexplained or refractory chronic cough
Treatment Assignment	Participants will be randomized in a 1:1 ratio to either MK-7264 45 mg BID or placebo treatment group, stratified by gender.
Analysis Populations	Efficacy: Full Analysis Set (FAS) population. Safety: All Participants as Treated (APaT) population
Primary Endpoint	<ul style="list-style-type: none"> • Number of participants experiencing adverse events (AEs) • Number of participants discontinuing study treatment due to AEs
Statistical Methods for Key Efficacy Analyses	<p>The primary analysis will be based on the FAS population. The primary analysis approach will be conducted utilizing the analysis of covariance (ANCOVA) model. In this model, the response vector consists of the change from baseline in (natural) log-transformed 24-hour coughs per hour at post-baseline. The model will include factors for treatment, gender, and the log-transformed baseline value as a covariate. The model will use all available 24-hour coughs per hour data at baseline and on Week 4. The least-squares (LS) mean change from baseline (in log scale) with the associated standard errors (SEs) will be displayed for each treatment group. Estimated treatment differences (MK-7264 – placebo) along with corresponding 95% confidence intervals (CIs) (no multiplicity adjustment) will also be presented for MK-7264 45 mg BID treatment group.</p> <p>The percent difference change between MK-7264 and placebo will be estimated by $100*(e^{\text{diff}} - 1)$, where diff is the difference provided by the analysis of the log transformed variable.</p>
Statistical Methods for Key Safety Analyses	AEs will be summarized by the number and percentage of the subjects who experienced respective events. Taste-related AEs and Oral paraesthesia/hypoesthesia will be evaluated 95% CIs within treatment group. Change from baseline in laboratory tests, vital signs and ECG will be summarized by descriptive statistics.
Interim Analyses	No interim analysis is planned in this trial.
Multiplicity	No multiplicity adjustment is planned in this Phase II trial.

Sample Size and Power	The planned sample size is 20 participants. Assuming 5% dropout rate, this will provide approximately 9 evaluable participants per treatment group. With 9 evaluable participants per treatment group, the precision of the point estimate in terms of half-width of the 95% confidence interval (CI) is summarized for a range of relative reduction and common standard deviations (SDs) of difference in 24-hr coughs per hour between MK-7264 45 mg BID and placebo groups in section 10.9.
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10.2 Responsibility for Analyses/In-House Blinding

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

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

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment.

10.3 Hypotheses/Estimation

There is no hypotheses for this study.

10.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for are presented in Section 4 followed by the descriptions of the derivations of selected endpoints.

10.4.1 Efficacy Endpoints

Secondary Efficacy Endpoint

- 24-hour coughs per hour at Week 4.
- Awake coughs per hour at Week 4

Exploratory Efficacy Endpoints

- LCQ total score at Week 4
- Mean weekly CSD total score at Week 4
- Cough Severity VAS score at Week 4

10.4.2 Safety Endpoints

Safety endpoints are stated in Section 4.

10.4.3 Derivations of Efficacy Endpoints

Baseline for efficacy variable is defined as the last non-missing value prior to the first study treatment.

Data Handling Rules for Cough Data

In general, each 24-hour session starts with awake status and is composed of an awake monitoring period and a sleep monitoring period. If a participant did not have a sleep time available before the end of the recording session, it will be considered that the participant was awake during the entire session. The last monitoring period of a session will be censored after the end time of the session.

The cough data will contain all cough events occurring during that 24-hour monitoring period as well as the information about “sleep time” and “awake time”. Any session with duration of recording <20 hours will be considered as missing. If a session has duration less than 24 hours but no less than 20 hours, the 24-hour coughs per hour will be based on the actual duration of the session.

On each collection day, the cough counts, the actual cough monitoring duration (in hours), and the coughs per hour will be derived for the total 24-hour period, the awake period, and the sleep period, respectively.

24-hour Coughs Per Hour

The 24-hour coughs per hour at baseline and post-baseline visit are calculated as follows:

24-hour coughs per hour = (Total number of cough events during the monitoring period (24-hour interval))/24 (where the denominator may be different, as noted above, if the recording period is actually <24 hours but ≥ 20 hours).

As the change from baseline in 24-hour coughs per hour may have a skewed and wide distribution, the data will be (natural) log-transformed prior to analysis for the primary approach. The variable of change from baseline in log-transformed 24-hour coughs per hour will be used in the analysis of this endpoint. For post-baseline, the efficacy variable of analysis is defined as following:

Change from baseline in log-transformed 24-hour coughs per hour

= Log (24-hour coughs per hour at post-baseline) – Log (24-hour coughs per hour at baseline).

The primary analysis of this endpoint will be on the natural log scale of the cough rate data.

Awake Coughs Per Hour

Awake is time between waking up and sleep during the 24-hour monitoring period. The awake coughs per hour are defined as follows:

Awake Coughs per Hour = Total number of cough events during the monitoring period (24-hour interval) the participant is awake/Total duration (in hours) for the monitoring period the participant is awake.

Similar to the 24-hour coughs per hour variable, change from baseline in (natural) log-transformed awake coughs per hour will be used in the analysis and defined as below:

Change from baseline in log-transformed awake coughs per hour

= Log (Awake coughs per hour at post-baseline) – Log (Awake coughs per hour at baseline).

PRO Endpoints

- LCQ total score

Change from baseline in LCQ total score = LCQ total score at post-baseline – LCQ total score at baseline.

- Mean weekly CSD total score

Change from baseline in mean weekly CSD total score = mean weekly CSD total score at each post-baseline week – mean weekly CSD total score at baseline.

- Cough Severity VAS score

Change from baseline in Cough Severity VAS score = Cough Severity VAS score at post-baseline – Cough Severity VAS score at baseline.

10.5 Analysis Populations

10.5.1 Efficacy Analysis Population

The FAS population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all randomized participants who have taken at least one dose of study medication and provided at least one baseline and one post-baseline endpoint observations during the treatment period. Participants will be analyzed according to the treatment group to which they are randomized.

Participants will be included in the treatment group to which they are randomized for the analysis of efficacy data using the FAS populations. Details on the approach to handling missing data are provided in Section 10.6 Statistical Methods.

10.5.2 Safety Analysis Population

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received at least one dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. For most participants this will be the treatment group to which they are randomized.

Participants who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received.

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

10.5.3 Pharmacokinetic Analysis Population

The evaluable PK population for PK data analysis is defined as all participants with one measurable PK sample.

10.6 Statistical Methods

Statistical testing and inference for efficacy and safety analyses are described in Sections 10.6.1 and 10.6.2.

10.6.1 Statistical Methods for Efficacy Analyses

The analysis of efficacy endpoints will be based on the FAS population.

Secondary Efficacy Analysis

Cough monitoring is conducted for baseline and 24 hours after administration of the study treatment on Week 4. As the change from baseline in 24-hour coughs per hour may have a skewed and wide distribution, the data will be (natural) log-transformed prior to analysis for the primary approach.

The primary analysis will be based on the FAS population. The primary analysis approach will be conducted utilizing the ANCOVA model. In this model, the response vector consists of the change from baseline in log-transformed 24-hour coughs per hour at post-baseline. The model will include factors for treatment, gender, and the log-transformed baseline value as a covariate. The model will use all available 24-hour coughs per hour data at baseline and on Week 4. The least-squares (LS) mean change from baseline (in log scale) with the associated standard errors (SEs) will be displayed for each treatment group. Estimated treatment differences (MK-7264 – placebo) along with corresponding 95% CIs (no multiplicity adjustment) will also be presented for MK-7264 45 mg BID treatment group.

In addition, the geometric mean of the 24-hour coughs per hour will be presented by treatment and by visit. The percent difference in the change from baseline between MK-7264 and placebo will be estimated by $100 * (\text{ediff} - 1)$, where diff is the difference provided by the analysis of the log-transformed variable.

An observation of zero coughs per hour will be replaced by a cough rate of 0.1/hour for the calculation of geometric means. If this rule is used, the table will have a footnote detailing the participant(s) and treatment group(s) that had observations of zero coughs per hour.

Awake coughs per hour will be analyzed using the same ANCOVA model as used for the 24-hour coughs per hour primary analysis.

As the change in awake coughs per hour may have a skewed and wide distribution, the data will be log-transformed (natural log) prior to analysis. The variable of change from baseline in log-transformed awake coughs per hour will be used in the analysis.

Table 4 summarizes key analysis strategy of the secondary efficacy endpoints.

Table 4 Analysis Strategy for Secondary Efficacy Endpoints

Endpoint/Variable (At Week 4)	Approach	Statistical Method	Analysis Population	Missing Data Approach
Secondary				
24-hour coughs per hour	P	ANCOVA	FAS	Observed data only
Awake coughs per hour	P	ANCOVA	FAS	Observed data only
ANCOVA = Analysis of covariance; FAS = Full Analysis set.; P = Primary				

Handling of Missing Data

All analyses will be conducted based on the observed data only.

10.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, vital signs, and electrocardiogram (ECG) measurements.

All safety analyses will be based on APaT population.

AEs and other safety events will be summarized using the number and percentage of the subjects who experienced respective events.

Taste-related AEs (including dysgeusia, ageusia, and hypogeusia, as well as other related terms) and Oral paraesthesia/hypoesthesia are considered as interested AEs, which will be evaluated via point estimates and 95% CIs using the exact binomial method proposed by Clopper and Pearson (1934) since there are small number of participants. Any AE, Any Serious AE, Any Drug-Related AE, Any Serious and Drug-Related AE and predefined limits of change will be also evaluated via point estimates and 95% CIs.

Continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters will be summarized using descriptive statistics.

Summary statistics for baseline, on treatment, and change from baseline values will be provided by treatment group in table format.

Table 5 summarizes analysis strategy for safety parameters.

Table 5 Analysis Strategy for Safety Parameters

Safety Endpoint [†]	95% CI within Treatment group	Descriptive Statistics
Taste-related AE	X	X
Oral paraesthesia/hypoesthesia	X	X
Any AE	X	X
Any Serious AE	X	X
Any Drug-Related AE	X	X
Any Serious and Drug-Related AE	X	X
PDLCs	X	X
Discontinuation due to AE		X
Specific AEs by preferred term		X
SOCs		X
Change from baseline results (Labs, ECGs, Vital Signs)		X
[†] Adverse Experience references refer to both Clinical and Laboratory adverse events. AE = adverse event; ECG = electrocardiogram; SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.		

10.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Demographic and Baseline Characteristics

The number and percentage of participants screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed.

Demographic variables (including age, gender, weight, and height), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables. The comparability of the treatment groups for each relevant characteristic will be assessed by the summary tables. No statistical hypothesis tests will be performed on these characteristics.

10.7 Interim Analyses

No interim analysis is planned in this trial.

10.8 Multiplicity

No multiplicity adjustment is planned in this Phase II trial.

10.9 Sample Size and Power Calculations

A total of 20 participants (10 per treatment group) will be randomized in a 1:1 ratio to either MK-7264 45 mg BID or placebo. Assuming 5% dropout rate, this will provide approximately 9 evaluable participants per treatment group.

With 9 evaluable participants per treatment group, the precision of the point estimate in terms of half-width of the 95% confidence interval (CI) is summarized for a range of relative reduction and common standard deviations (SDs) of difference in 24-hr coughs per hour between MK-7264 45 mg BID and placebo groups in [Table 6](#). Assumption is based on Protocol 012 data.

Table 6 Half-width of the 95% CI for Different Common Standard Deviations (SDs)

Expected Common SD (Log scale)	Expected Relative Reduction (MK-7264 45 mg BID vs. Placebo)	
	30%	25%
0.7	53%	57%
0.8	62%	67%
0.9	72%	77%

10.10 Subgroup Analyses

Analysis for 24-hour coughs per hour will be provided for the following subgroups of baseline factors:

- Gender (Male, Female);
- Age group (<60 years, ≥60 years);
- Duration of cough (in years) (<10 years, ≥10 years);
- Baseline Cough Severity VAS (<60 mm, ≥60 mm);
- Baseline 24-hour coughs per hour (<20 coughs/hr, ≥20 coughs/hr).

For each subgroup, summary statistics including mean, SD will be provided for each treatment group.

10.11 Compliance (Medication Adherence)

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

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

A day within the study will be considered an “On-Therapy” day if the participant takes all required medication as instructed in Section 9 – Study Assessments and Procedures. When a participant takes less than or more than the required medication on a day, that day is not considered an On-Therapy day.

For participants who are followed for the entire study period, the “Number of Days Should be on Therapy” is the total number of days from the first scheduled treatment day to the last scheduled treatment day. For participants who discontinue from the study permanently, the “Number of Days Should Be on Therapy” is the total number of days from the first scheduled treatment day to the last dose day.

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

10.12 Extent of Exposure

The duration of treatment for each participant will be evaluated by calculating the number of days on therapy. Exposure to study medication will be summarized using descriptive statistics (mean, SD, median, minimum, and maximum) for the APaT population.

11. References

- | | | |
|-------------------------------|--|--------|
| [Barclay, J., et al 2002] | Barclay J, Patel S, Dorn G, Wotherspoon G, Moffatt S, Eunson L, et al. Functional downregulation of P2X3 receptor subunit in rat sensory neurons reveals a significant role in chronic neuropathic and inflammatory pain. <i>J Neurosci.</i> 2002 Sep 15;22(18):8139-47. | 04JQYJ |
| [Chung, K. F. 2014] | Chung KF. Approach to chronic cough: the neuropathic basis for cough hypersensitivity syndrome. <i>J Thorac Dis.</i> 2014 Oct;6(Suppl 7):S699-707. | 04R3SD |
| [Cockayne, D. A., et al 2000] | Cockayne DA, Hamilton SG, Zhu QM, Dunn PM, Zhong Y, Novakovic S, et al. Urinary bladder hyporeflexia and reduced pain-related behaviour in P2X3-deficient mice. <i>Nature.</i> 2000 Oct 26;407(6807):1011-5. | 04K6LW |
| [Dworkin, R. H., et al 2009] | Dworkin RH, Turk DC, McDermott MP, Peirce-Sandner S, Burke LB, Cowan P, et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. <i>Pain.</i> 2009 Dec;146(3):238-44. | 03Z3YR |
| [Gibson, P., et al 2016] | Gibson P, Wang G, McGarvey L, Vertigan AE, Altman KW, Birring SS. Treatment of Unexplained Chronic Cough: CHEST Guideline and Expert Panel Report. <i>Chest.</i> 2016 Jan;149(1):27-44. | 04MMZ9 |
| [Irwin, R. S., et al 2006] | Irwin RS, Baumann MH, Bolser DC, Boulet LP, Braman SS, Brightling CE, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. <i>Chest.</i> 2006 Jan;129(1 Suppl):1S-23S. | 04KW7B |
| [Kanemitsu, Y., et al 2016] | Kanemitsu Y, Niimi A, Matsumoto H, Iwata T, Ito I, Oguma T, et al. Gastroesophageal dysmotility is associated with the impairment of cough-specific quality of life in patients with cough variant asthma. <i>Allergol Int.</i> 2016 Jul;65(3):320-6. | 04SV2L |

[Kardos, P., et al 2010]	Kardos P, Berck H, Fuchs KH, Gillissen A, Klimek L, Morr H, et al. Guidelines of the German Respiratory Society for diagnosis and treatment of adults suffering from acute or chronic cough. <i>Pneumologie</i> . 2010 Nov;64(11):701-11.	04KQP6
[Khakh, B. S. 2006]	Khakh BS, North RA. P2X receptors as cell-surface ATP sensors in health and disease. <i>Nature</i> . 2006 Aug 3;442(7102):527-32.	04JRKF
[Morice, A. H., et al 2004]	Morice AH, Fontana GA, Sovijarvi AR, Pistolesi M, Chung KF, Widdicombe J, et al. The diagnosis and management of chronic cough. <i>Eur Respir J</i> . 2004 Sep;24(3):481-92.	04KQPD
[Morice, A. H., et al 2006]	Morice AH, McGarvey L, Pavord I, on behalf of the British Thoracic Society Cough Guideline Group. Recommendations for the management of cough in adults. <i>Thorax</i> 2006;61(Suppl 1):i1-i24.	03QMXM
[North, R. A. 2004]	North RA. P2X3 receptors and peripheral pain mechanisms. <i>J Physiol</i> . 2004 Jan 15;554(Pt 2):301-8.	04JRR8
[Souslova, V., et al 2000]	Souslova V, Cesare P, Ding Y, Akopian AN, Stanfa L, Suzuki R, et al. Warm-coding deficits and aberrant inflammatory pain in mice lacking P2X3 receptors. <i>Nature</i> . 2000 Oct 26;407(6807):1015-7.	04K76C
[The committee for The Japanese Respiratory Society guidelines 2006]	The committee for The Japanese Respiratory Society guidelines for management of cough. Concept and use of guidelines. <i>Respirology</i> . 2006;11(Suppl 4):S135-S136	04KW9M

12. Appendices

12.1 Appendix 1: Study Governance Considerations

Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

A. IRB/IEC review

All clinical trials will be reviewed and approved by an independent IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/IEC prior to implementation, except that changes required urgently to protect participant safety and well-being may be enacted in anticipation of IRB/IEC approval. For each site, the IRB/IEC and Merck 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. Participants are never denied access to appropriate medical care based on participation in a Merck clinical trial.

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll 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.

Merck does not pay for participant referrals. However, Merck 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 Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/IEC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

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.

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 which 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.

Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/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.

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 in order to verify worksheet/case report form data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form 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.

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.

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.

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 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.

Compliance with Law, Audit and Debarment

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

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

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

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

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

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 regulatory authority as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/case report forms.

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.

Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. 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 may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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.

12.2 Appendix 2: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

- a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.¹
- b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.²
- c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.²
- d. DNA: Deoxyribonucleic acid.
- e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 9.9 – Future Biomedical Research Sample Collection will be used in various experiments to understand:

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

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 electronic Case Report Forms (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 treatment outcomes are critical to understanding clinical context of analytical results.

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

At the clinical 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 sub-study. 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 principal 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 e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute: <https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618>
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; Available from: <http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html>
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at <http://i-pwg.org/>
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at <http://i-pwg.org/>

12.3 Appendix 3: Contraceptive Guidance and Pregnancy Testing

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

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

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 hormonal 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 non-hormonal 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.

Contraception Requirements

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use one of the contraception methods described in [Table 7](#) consistently and correctly during the protocol-defined time frame in Section 6.1.

Table 7 Contraceptive Methods

<p>Highly Effective Contraceptive Methods That Are User Dependent ^a <i>Failure rate of <1% per year when used consistently and correctly.</i></p> <ul style="list-style-type: none"> ● Combined (estrogen- and progestogen- containing) hormonal contraception <ul style="list-style-type: none"> ○ Oral ● Progestogen-only hormonal contraception <ul style="list-style-type: none"> ○ Oral
<p>Highly Effective Methods That Have Low User Dependency <i>Failure rate of <1% per year when used consistently and correctly.</i></p> <ul style="list-style-type: none"> ● Intrauterine hormone-releasing system (IUS) ● Intrauterine device (IUD) ● Bilateral tubal occlusion ● Vasectomized partner A vasectomized partner 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. ● 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 treatment. 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.)
<p>Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.</p> <p>a) Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly).</p>

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.

12.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment.
- 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 treatment.
- NOTE: for purposes of AE definition, study treatment (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, 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, or are 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 treatment 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 treatment or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated adverse event, the AE term should reflect the clinical symptoms or abnormal test result. An overdose of study treatment without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer or progression of existing cancer.

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to section 9.3.5 for protocol specific exceptions

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- in offspring of participant taking the product regardless of time to diagnosis

f. Other important medical events:

● Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one 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.

Additional Events Reported

Additional Events which require reporting

- In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.
- Is a cancer;
- Is associated with an overdose.

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 Adverse Event case report forms/worksheets at each examination.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- An event is defined as ‘serious’ when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:
 - Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. (for pediatric studies, awareness of symptoms, but easily tolerated)
 - Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities. (for pediatric studies, definitely acting like something is wrong)
 - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of Causality

- Did the Sponsor's product cause the adverse event?
 - The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the adverse event based upon the available information
 - **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:
 - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
 - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?
 - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

- If yes, did the AE resolve or improve?
 - If yes, this is a positive dechallenge.
- If no, this is a negative dechallenge.

(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study); or (4) Sponsor's product(s) is/are only used one time.)

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

- If yes, did the AE recur or worsen?
 - If yes, this is a positive rechallenge.
- If no, this is a negative rechallenge.

(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study); or (3) Sponsor's product(s) is/are used only one time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.

- **Consistency with Study treatment Profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
 - Yes, there is a reasonable possibility of Sponsor's product relationship:
There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
 - No, there is not a reasonable possibility of Sponsor's product relationship:
Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also

<p>entered for a participant with overdose without an associated AE.)</p> <ul style="list-style-type: none">● For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.● There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.● The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.● The causality assessment is one of the criteria used when determining regulatory reporting requirements
<p>Follow-up of AE and SAE</p> <ul style="list-style-type: none">● 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.

Reporting of AE, SAE, and Other Reportable Safety Events to the Sponsor

<p>AE, SAE, and Other Reportable Safety Event Reporting to Sponsor via Electronic Data Collection Tool</p> <ul style="list-style-type: none">● The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.<ul style="list-style-type: none">● 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.<ul style="list-style-type: none">● Reference section 9.3.1 – Time Period and Frequency for Collecting AE and SAE and Other Reportable Safety Event Information 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 electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
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- 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 electronic data collection 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 Trial File Binder (or equivalent).

SAE Reporting to the Sponsor via Paper CRF

- If the electronic data collection 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 Trial File Binder (or equivalent).

12.5 Appendix 5: Clinical Laboratory Tests

- The tests detailed in [Table 8](#) will be performed
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 – Study Population 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 8 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet Count	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	RBC Count		
	Hemoglobin		
	Hematocrit		
Chemistry	Electrolytes	Sodium Potassium Chloride Bicarbonate Calcium Phosphorous	
	Liver function tests	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT) Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT) Alkaline phosphatase Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)	
	Renal function parameters	Blood Urea Nitrogen Creatinine eGFR calculation eGFR will be calculated with each serum creatinine measurement (using the Japanese Equation for Estimating GFR [Japanese Society of Nephrology])	
	Other	Glucose (nonfasting) Albumin Total Protein	

Laboratory Assessments	Parameters
Routine Urinalysis	<ul style="list-style-type: none">• Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick (performed at site)• Microscopic examination (all crystals will be characterized)
Other Screening Tests	<ul style="list-style-type: none">• Serum or urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for women of childbearing potential)<ul style="list-style-type: none">a. Urine pregnancy test will be performed at site in women of child-bearing potential. Refer to SoA in Section 2.

Investigators must document their review of each laboratory safety report.

12.6 Appendix 6: Abbreviations and Trademarks

Abbreviation	Term
ACCP	American College of Chest Physican
AE	adverse event
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
ANCOVA	analysis of covariance
APaT	all participants as treated
ATP	adenosine triphosphate
ATS	American Thoracic Society
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
BID	twice daily
CFR	Code of Federal Regulations
CI	confidence interval
CRF	case report form
CSD	Cough Severity Diary
CSR	clinical study report
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
EMA	European Medicines Agency
ERS	European Respiratory Society
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FDAAA	Food and Drug Administration Amendments Act
FEV ₁	forced expiratory volume in 1 second
FVC	forced vital capacity
GERD	gastroesophageal reflux disease
GCP	Good Clinical Practice(s)
HIV	human immunodeficiency virus
IB	Investigator's brochure
ICH	International Council on Harmonisation
IEC	independent ethics committee

Abbreviation	Term
IRB	institutional review board
IRT	interactive response technology
LCQ	Leicester Cough Questionnaire
NSAE	non-serious adverse event
PGIC	Patient Global Impression of Change
PK	pharmacokinetic
PRO	patient reported outcome
RBC	red blood cell (count)
RNA	ribonucleic acid
SAE	serious adverse event
SD	standard deviation
SoA	Schedule of Activities
sSAP	supplemental Statistical Analysis Plan
UACS	upper airway cough syndrome
VAS	visual analog scale
WBC	white blood cell (count)
WOCBP	women of child bearing potential