Official Protocol Title:	A Phase 3, Randomized, Double-blind Clinical Study to Evaluate the Longterm Safety and Efficacy of MK-7264 in Japanese Adult Participants with Refractory or Unexplained Chronic Cough
NCT number:	NCT03696108
Document Date:	26-SEP-2018

Title Page

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Protocol Title: A Phase 3, Randomized, Double-blind Clinical Study to Evaluate the Long-term Safety and Efficacy of MK-7264 in Japanese Adult Participants with Refractory or Unexplained Chronic Cough

Protocol Number: 038-01

Compound Number: MK-7264

Sponsor Name:

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

Legal Registered Address:

One Merck Drive

P.O. Box 100

Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

Approval Date: 26-SEP-2018

Sponsor Signatory

Typed Name: Date
Title:

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

Investigator Signatory

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

Typed Name: Date
Title:

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 01

Overall Rationale for the Amendments:

Based on the results of a study conducted in participants with severe renal impairment and moderate renal impairment, the expected increase in exposure to MK-7264 in participants with moderate renal impairment is not anticipated to lead to an increased risk of clinically relevant adverse events. Therefore, a major update included in this amendment is to change the estimated glomerular filtration (eGFR) rate criterion for participant exclusion from a cut-off of <50 mL/min/1.73 m^2 to cut-off of <30 mL/min/1.73 m^2. Participants with an eGFR of ≥30 mL/min/1.73 m^2 and <50 mL/min/1.73 m^2 at Visit 1 with unstable renal function (defined as a ≥50% increase of serum creatinine compared to a value obtained at least 6 months prior to Visit 1) are also excluded.

Clarifications of certain sections and procedures, as detailed below, were also made in the protocol during the creation of this amendment.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.3 – Schedule of Activities	Removed explanatory text in the notes column.	Explanatory text is found in the protocol body and is now cross-referenced in the Schedule of Activities.
	Added row for contact to participant enrollment center.	For reference
	Added weight measurements to be conducted at Visit 3 and Visit 6.	Included additional visits for weight measures to better assess any changes in weight throughout the trial.
	Added specialized urine collection for crystal assay to be performed at Visits 5, 6, 8, and discontinuation.	This assessment was included to highlight the visits where specialized urine collection is required.

Section # and Name	Description of Change	Brief Rationale
5.2 – Exclusion Criteria	Exclusion #7 was updated to change the estimated glomerular filtration (eGFR) rate for participant exclusion from a cut-off of <50 mL/min/1.73 m^2 to cut-off of <30 mL/min/1.73 m^2 OR ≥30 mL/min/1.73 m^2 and <50 mL/min/1.73 m^2 at Visit 1 with unstable renal function (defined as a ≥50% increase of serum creatinine compared to a value obtained at least 6 months prior to Visit1).	To allow enrollment of participants with moderate to severe renal impairment in the study.
	Exclusion #18 was updated to include text indicating that laboratory assessments can be repeated once at the investigator's discretion.	To provide more flexibility during the screening process.
5.3.2 – Caffeine, Alcohol, and Tobacco Restrictions	Added text specifying that smoking of any kind is not permitted during the study. Examples of smoking are provided.	To better clarify that all tobacco and non-tobacco smoking items are not permitted during the study.
6.8 – Clinical Supplies Disclosure	Added cross reference for unblinding a participant during the study	For reference.
8.1.2 – Inclusion/Exclusion Criteria	Added the instruction for source documentation regarding eGFR criterion.	The source documentation of stable serum creatinine must be retained to enroll the participant with eGFR ≥30 mL/min/1.73 m^2 and <50 mL/min/1.73 m^2 at Visit 1 with stable renal function.

Section # and Name	Description of Change	Brief Rationale
8.1.10 – Participant Blinding/Unblinding	Removed the description for returning random code/disclosure envelops or lists and unblinding log to the Sponsor or designee.	This process is not applied to this study.
8.2.1– Parient-reported Outcomes (PRO)	Text updated describing training on CSD will be needed at Visit 1 and instruction on the PRO measurments at each visits.	PRO training at Visit 2 is not necessarily needed when training on CSD is conducted properly at Visit 1.
8.3.3– Vital Signs and Weight and Height Measurements	Removed the method of collection for temperature.	To allow flexibility for temperature to be collected according to local clinical practice
8.3.7 – Renal and Urological Safety Assessments	Text updated describing how participants with urinary crystals and/or hematuria should be assessed by the investigator for participation in the study and how a participant with MK-7264 crystal should be followed .	To adjust the description and and to update follow-up procedure for a participant with MK-7264 crystal.
10.5 – Appendix 5: Contraceptive Guidance and Pregnancy Testing	Added clarification that pregnancy testing will be performed at Visit 1 for women of childbearing potential (WOCBP) and after Visit 1 whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.	To provide better clarification of timing of pregnancy testing.
	Added text that male participants are not required to use a form of contraception.	To clarify contraception use in male participants during the study.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarized.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Randomized, Double-blind Clinical Study to Evaluate the Long-term Safety and Efficacy of MK-7264 in Japanese Adult Participants with Refractory or Unexplained Chronic Cough

Short Title: MK-7264 Phase 3 long-term study in Japanese adult participants with refractory or unexplained chronic cough

Acronym: Not Applicable

Hypotheses, Objectives, and Endpoints:

There are no hypothesis for this study.

In this study, the objectives and endpoints below will be evaluated by treatment group and combined in Japanese adult participants with refractory or unexplained chronic cough.

Primary Objectives	Primary Endpoints
- To evaluate the safety and tolerability of MK-7264 through 52 weeks	- Adverse event (AE) - Study treatment discontinuations due to AE
Secondary Objectives	Secondary Endpoints
- To evaluate the efficacy of MK-7264 in improving cough specific quality of life with change from baseline at Week 12 and through 52 weeks	- Leicester Cough Questionnaire (LCQ)

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Treatment of refractory or unexplained chronic cough
Population	Japanese adult participants at least 20 years of age with refractory or unexplained chronic cough
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	No Treatment Control
Study Blinding	Double-blind
Masking	Participant, Investigator
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 23 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 160 participants will be randomized and 84 participants will complete the study to evaluate the 1-year safety as described in Section 9.9.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admin.	Treatment Period	Use
MK-7264 45 mg	MK-7264 45 mg	45 mg	1 tablet BID	Oral	52 weeks	Experimental
	Placebo matched to MK-7264 15 mg	0 mg	1 tablet BID	Oral	52 weeks	Placebo
MK-7264 15 mg	MK-7264 15 mg	15 mg	1 tablet BID	Oral	52 weeks	Experimental
	Placebo matched to MK-7264 45 mg	0 mg	1 tablet BID	Oral	52 weeks	Placebo

Total Number	2
Duration of Participation	Each participant will participate in the study for approximately 56 weeks from the time the participant signs the Informed Consent Form (ICF) through the final contact. After a screening phase of up to 2 weeks, each participant will be receiving assigned intervention for approximately 52 weeks. After the end of treatment period, each participant will be followed for 2 weeks.

Study Governance Committees:

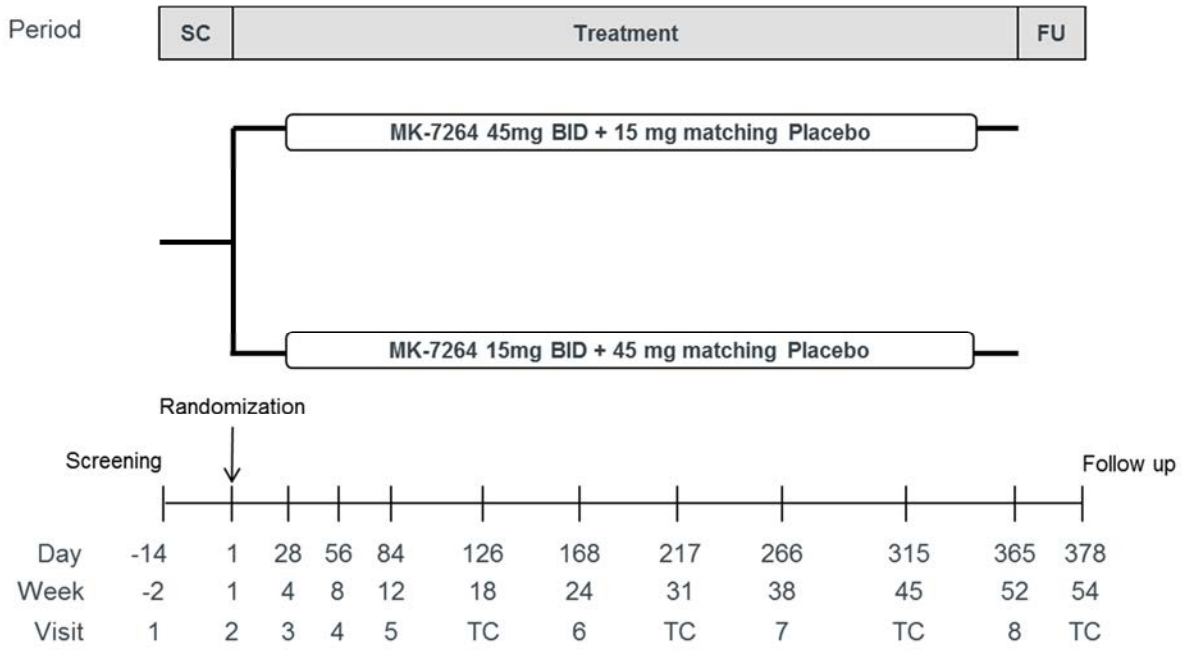
Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

Study Accepts Healthy Volunteers: No

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

1.2 Schema

The study design is depicted in Figure 1.



Abbreviations: SC=screening; FU=follow up; TC=telephone contact

Figure 1 Study Design

1.3 Schedule of Activities (SoA)

Study Period	Screening	Base line/ Randomization	Treatment Period									Follow -up	Disc.	Notes
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**TC***	**V6**	**TC***	**V7**	**TC***	**V8**	**TC**		*These TC can be conducted as site visits
Scheduled Day	**Day-14 to Day -7**	**Day 1**	**Day 28**	**Day 56**	**Day 84**	**Day 126**	**Day 168**	**Day 217**	**Day 266**	**Day 315**	**Day 365**	**Day 378**		
Schedule Window (Recommended)	**NA**	**NA**	**±4 dys**	**±4 dys**	**±4 dys**	**±7 dys**	**±7 dys**	**±14 dys**	**±14 dys**	**±14 dys**	**±14 dys**	**+7 dys**		
Scheduled Week	**Wk-2 to Wk-1**	**Wk 1**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 18**	**Wk 24**	**Wk 31**	**Wk 38**	**Wk 45**	**Wk 52**	**Wk 54**		
Administrative Procedure														
Written Informed Consent	X													See Section 4.1.
Written Informed Consent for Future Biomedical Research	X													
Inclusion/Exclusion Criteria	X	X												
Participant Identification Card	X													
Demographics, Medical & Medication History	X	X												
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	
Intervention Randomization		X												
MK-7264 Administration		<=	=	=	=	=	=	=	=	=	=>			See Section 8.1.8.
Study Treatment Accountability		X	X	X	X	X	X	X	X	X	X		X	At TC, general treatment compliance will be checked.

Study Period	**Screening**	**Base line/ Randomization**	**Treatment Period**									**Follow -up**	**Disc.**	**Notes**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**TC***	**V6**	**TC***	**V7**	**TC***	**V8**	**TC**		*These TC can be conducted as site visits
Scheduled Day	**Day-14 to Day -7**	**Day 1**	**Day 28**	**Day 56**	**Day 84**	**Day 126**	**Day 168**	**Day 217**	**Day 266**	**Day 315**	**Day 365**	**Day 378**		
Schedule Window (Recommended)	**NA**	**NA**	**±4 dys**	**±4 dys**	**±4 dys**	**±7 dys**	**±7 dys**	**±14 dys**	**±14 dys**	**±14 dys**	**±14 dys**	**+7 dys**		
Scheduled Week	**Wk-2 to Wk-1**	**Wk 1**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 18**	**Wk 24**	**Wk 31**	**Wk 38**	**Wk 45**	**Wk 52**	**Wk 54**		
Contact Participant Enrollment Center	X	X	X	X	X		X		X		X		X	
Efficacy Procedures														
LCQ		X	X	X	X		X		X		X		X	
CSD	Daily		X	X	X		X		X		X			See Section 8.2.1.2.
EQ5D-5L		X			X		X				X		X	
PGIC					X		X				X		X	
Safety Procedure														
Chest radiograph or CT Thorax	X													See Section 8.3.1.
Spirometry	X													See Section 8.3.5.
Physical examination	X				X						X		X	See Section 8.3.2.
Vital Signs	X	X	X	X	X		X		X		X		X	
Height	X													
Weight	X		X		X		X				X		X	
12-lead ECG	X													
Hematology & Chemistry	X				X		X				X		X	
Urinalysis (w/Microscopy)	X				X		X				X		X	Dipstick for hematuriaperformed for ALL paticipants at the site. Samples are also collected and sent to central laboratory for ALL participants.

Study Period	**Screening**	**Baseline/ Randomization**	**Treatment Period**									**Follow-up**	**Disc.**	**Notes**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**TC***	**V6**	**TC***	**V7**	**TC***	**V8**	**TC**		*These TC can be conducted as site visits
Scheduled Day	**Day-14 to Day -7**	**Day 1**	**Day 28**	**Day 56**	**Day 84**	**Day 126**	**Day 168**	**Day 217**	**Day 266**	**Day 315**	**Day 365**	**Day 378**		
Schedule Window (Recommended)	**NA**	**NA**	**±4 dys**	**±4 dys**	**±4 dys**	**±7 dys**	**±7 dys**	**±14 dys**	**±14 dys**	**±14 dys**	**±14 dys**	**+7 dys**		
Scheduled Week	**Wk-2 to Wk-1**	**Wk 1**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 18**	**Wk 24**	**Wk 31**	**Wk 38**	**Wk 45**	**Wk 52**	**Wk 54**		
Specialized Urine Collection for Crystal Assay					X		X				X		X	
Urine Pregnancy Test (WOCBP only)	X													See Appendix 5 for instructions on when pregnancy testing should be performed after Visit 1.
Serum β-Human Chorionic Gonadotropin	X													Only if urine pregnancy test is positive
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	See Table 3 for further details
Biomarkers														
Blood for Genetic Analysis		X												Collected from randomized participants only; See Section 8.8.1 and 8.9

Abbreviations: CSD = Cough Severity Diary; CT = computed tomography; Disc. = discontinuation; dys = days; ECG = electrocardiogram; EQ5D-5L = EuroQoL 5 Version Five Dimensions Questionnaire; LCQ = Leicester Cough Questionnaire; NA = not applicable; PGIC = Patient Global Impression of Change; TC = telephone contact; V = visit; Wk =Week

2 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, subacute, 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 may affect up to approximately 2% of the adult population and the most common underlying condition is asthma/cough-variant asthma followed by sinobronchial syndrome, atopic cough, gastroesophageal reflux disease (GERD) and postinfections[Fujimura, M. 2012]. 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 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 5% to 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 Japan Ministry of Health, Labour and Welfare, the United States Food and Drug Administration or European Medicines Agency for the treatment of chronic cough. Given the prolonged nature, significant morbidity, and the lack of effective treatment, refractory or unexplained 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-responsive, 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 hyper-responsiveness 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 sensory neuron 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 stimuli that do not normally cause cough, increased cough sensitivity to inhaled stimuli, and cough paroxysms. A potential biologic explanation for cough hypersensitivity syndrome suggests an associated sensory neuropathy characterized by sensory nerve hyper-sensitization. Sensory nerves are susceptible to sensitization by neuroactive mediators and altered expression of ion channels which regulate sensory nerve excitability to many chemical stimuli. As described above, the action of ATP at sensory neurons may cause hyper-responsiveness through binding to P2X3-containing receptors and contribute to the pathophysiology of patients with chronic cough. The data from Protocol 012 support the role of P2X3 antagonism in the treatment of patients with refractory or unexplained chronic cough.

2.1 Study Rationale

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

Current therapies for cough (narcotic, non-narcotic, and over-the-counter medications) have limited and/or unproven efficacy and an undesirable side effect profile. There are currently no approved therapies for chronic cough.

Previous Phase 2 studies have demonstrated dose-related efficacy and an acceptable safety and tolerability for MK-7264 in non-Japanese adult participants with refractory and unexplained chronic cough (refer to the Investigator's Brochure [IB]). The purpose of this study is to evaluate the long-term safety of MK-7264 with regulatory required number of Japanese refractory or unexplained chronic cough patients.

2.2 Background

Refer to the IB for detailed nonclinical and clinical background information on MK-7264.

2.2.1 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 either MK-7264 45 mg or 15 mg. The placebo tablets provided in this study are indistinguishable from the MK-7264 tablet, respectively, in appearance. The placebo tablets contain no MK-7264, but contain the same inactive excipients as those included in the active tablets.

2.2.2 Clinical Studies in Chronic Cough Patients

Two phase 3 studies (Protocol 027 and Protocol 030) are ongoing to evaluate the efficacy and safety of MK-7264 in adult participants with refractory or unexplained chronic cough. As for Japanese adult participants with refractory or unexplained chronic cough, a phase 2 study (Protocol 033) was conducted to evaluate the safety and efficacy. This study has been completed and the Clinical Study Report is not finalized.

2.3 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 disturbance 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 gustatorysensory nerves. The taste-related AEs are considered mechanism based non-serious adverse drug reactions and are 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 the 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 IB and ICF documents.

3 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

There are no hypothesis for this study.

In this study, the objectives and endpoints below will be evaluated by treatment group and combined in Japanese adult participants with refractory or unexplained chronic cough.

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of MK-7264 through 52 weeks	• Adverse event (AE) • Study treatment discontinuations due to AE
Secondary	
• To evaluate the efficacy of MK-7264 in improving cough specific quality of life with change from baseline at Week 12 and through 52 weeks	• Leicester Cough Questionnaire (LCQ)
Exploratory	
• To evaluate the efficacy of MK-7264 in improving self-rated cough severity with change from baseline at Week 12 and through 52 weeks	• Cough Severity Diary (CSD)
• To evaluate the impact of MK-7264 on generic health-related quality of life and global rating of change through 52 weeks	• EuroQoL 5 Version Five Dimensions Questionnaire (EQ5D-5L) • Patient Global Impression of Change (PGIC)
• To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study.	• Germline genetic variation

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, no treatment controlled, parallel-group, multi-site, double-blinded study of MK-7264 in Japanese adult participants with refractory or unexplained chronic cough.

Approximately 160 participants who meet entry criteria will enter the study. The study duration for each participant is as follows:

- Screening Period: a minimum of 7 days and up to 14 days. For those who need to washout therapy, the washout starts after obtaining the informed consent and the screening period starts from the completion of washout.
- Baseline/Randomization: Day 1
- Treatment period: 52 weeks
- Follow-up period: 14 days

Individual participation is expected to be approximately 56 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 SoA in Section 1.3. Details of each procedure are provided in Section 8.

At study entry, participants will be randomized in 1:1 ratio to 1 of 2 treatment groups: MK-7264 45 mg twice daily (BID) or MK-7264 15 mg BID. Participants should remain on their assigned treatment throughout the study period.

A safety follow-up telephone contact will be conducted at a minimum of 14 days (with an allowed variance of up to +7 days) after last dose of study intervention. Please refer to details in Section 8.10.6.

There will be one planned interim analysis when all the randomized participants have completed Week 24, or discontinued prior to Week 24. The initial database lock (to support the interim analysis) and all safety and efficacy analyses will be performed on the data up to Week 24. The sponsor will be unblinded at this point in order to analyze and report the data as the result will be used for the regulatory filing of MK-7264 in Japan. The study team responsible for the ongoing monitoring of the study will remain blinded to the treatment-level results of this interim analysis (safety and efficacy). The final database lock will be conducted when all participants have completed or discontinued prior to the completion of study.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Safety Endpoints

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

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 8.4 and Appendix 3.

4.2.1.2 Efficacy Endpoints

An assessment of cough from the participant's perspective is important for evaluating the response to therapy. Patient-reported outcomes (PROs) associated with cough can be measured in terms of cough-specific quality of life, cough frequency, intensity, disruption due to cough, cough severity and global rating of change in chronic cough. The following cough related measures will be included in this study as secondary and exploratory endpoints:

Secondary endpoint:

Leicester Cough Questionnaire (LCQ)

Exploratory endpoints:

Cough Severity Diary (CSD) and Patient Global Impression of Change (PGIC)

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

In regards to the LCQ, a Japanese translated version of the LCQ has been validated for the use in Japanese chronic cough patients [Kanemitsu, Y., et al 2016]. There is experience in using the Japanese translated version of the CSD in the MK-7264 development program. The CSD will be linguistically validated.

The impact of chronic cough on HRQoL as assessed by the LCQ is included as the secondary endpoint. The LCQ is a 19-item cough-specific 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 minimally important change of LCQ was defined based on the study with 52 chronic cough patients [Raj, A. A., et al 2009]. Improvement of ≥1.3 points was found to be predictive of patient-reported improvement on their cough-related symptoms, feelings as consequence of their cough, work or social life, and overall quality of life as rated on the Global Rating of Change Questionnaires.

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.

The PGIC is a single-item question asking the participant to rate the change in their chronic cough compared to the start of the study with response options ranging from "very much improved" to "very much worse"

In addition to the above cough related PROs, EuroQoL 5 Version Five Dimensions Questionnaire (EQ5D-5L) will be included in this study as exploratory endpoints to evaluate generic HRQoL:

Exploratory endpoints: EuroQoL 5 Version Five Dimensions Questionnaire (EQ5D-5L)

The EQ5D-5L is a standardized instrument for measuring generic health status used for estimating preference weights for that health status. By combining the weight with time, quality-adjusted life years can be computed. The EQ5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels and the participant will be asked to indicate their health state using a 5-level rating scale. The EQ VAS records the participant's self-rated health on vertical VAS where the endpoints are labeled "best imaginable health state" and "worst imaginable health state". This information can be used as a quantative measure of health outcomes as judged by the individual participant.

4.2.1.3 Planned Exploratory Biomarker Research

4.2.1.3.1 Planned Genetic Analysis

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

DNA samples will be used for research related to the study intervention(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 intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate).

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.

4.2.1.4 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 substudy are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator/Placebo

No comparator or placebo arm is included in this study. This study will be conducted as double dummy study and as appearance of MK-7264 45 mg and 15 mg tablets are different, matching placebos are used to maintain blinding.

4.3 Justification for Dose

4.3.1 Doses for This Study

The dose for this study will be either MK-7264 45 mg BID or MK-7264 15 mg BID as determined by the individual allocation per the assigned treatment group (see Section 6).

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. In order to allow patients and prescribers appropriate flexibility based upon individual clinical needs, the MK-7264 development program has targeted two different doses to study in the Phase 3 program.

4.3.2 Maximum Dose/Exposure for This Study

The maximum dose/exposure for this study will be at 45 mg BID. Participants who are administered MK-7264 (either 15 mg BID or 45 mg BID) will be exposed to MK-7264 for approximately 52 weeks.

4.3.3 Rationale for Dose Interval and Study Design

In this study, MK-7264 will be orally administered as MK-7264 45 mg BID or 15 mg BID based on the safety and pharmacokinetic efficacy results observed to date (refer to the IB).

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 half-life of MK-7264 is approximately 7 to 10 hours and consistent with a BID dosing schedule.

The duration of treatment is up to 1 year in order to provide a more robust assessment of the long-term safety, tolerability and efficacy of MK-7264 in the treatment of refractory or unexplained chronic cough.

4.4 Beginning and End of Study Definition

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

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

Male/Female participants with chronic cough ≥ 4 months and a diagnosis of refractory or unexplained chronic cough at least 20 years of age will be enrolled in this study. For the purposes of this study, refractory chronic cough is defined as participants who have had a clinical evaluation that suggested a co-morbid condition that may be related to cough (eg, gastroesophageal reflux disease [GERD], asthma, or upper airway cough syndrome), the participant has received appropriate diagnostic workup and therapy according to the Japanese Respiratory Society (JRS) guidelines, and the participant continues to cough despite being on therapy. Also in this study, unexplained chronic cough is defined as participants who have had a clinical evaluation of their cough per JRS guidelines and this evaluation has not suggested a co-morbid condition that may be related to cough.

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

5.1 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 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 cough for ≥ 4 months at signing informed consent and a diagnosis of refractory or unexplained chronic cough as specified in Section 5.

3. The participant has persistent cough despite of treatment in accordance with the latest guideline of cough from the Japanese Respiratory Society and is burden to the participant and need further treatment in the opinion of the principal investigator or the sub-investigator.

Demographics

4. Participant is Japanese Male or Female from 20 years of age inclusive, at the time of signing the informed consent.

Female Participants

5. A female participant is eligible to participate if she is not pregnant (Appendix 5), not breastfeeding, and at least 1 of the following conditions applies:

    a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 5.

        OR

    b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 from signing informed consent to 14 days after the last dose of study intervention.

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 completion of the patient report outcomes [PROs]) to the satisfaction of the investigator/qualified designee prior to randomization (see Section 8.1.2).

5.2 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 Visit 1.

3. Forced expiratory volume in 1 second (FEV_1)/ forced vital capacity (FVC) ratio <60% (spirometry performed within the past year and after the onset of chronic cough 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).

4. History of upper or lower respiratory tract infection or recent clinically significant change in pulmonary status within 4 weeks of Visit 1.

5. 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.

6. Individuals who are currently taking an angiotensin converting enzyme inhibitor or have taken an angiotensin converting enzyme inhibitor within 3 months of signing informed consent.

7. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 at Screening OR eGFR ≥30 mL/min/1.73 m^2 and <50 mL/min/1.73 m^2 at Visit 1 with unstable renal function (defined as a ≥50% increase of serum creatinine compared to a value obtained at least 6 months prior to Visit 1).

8. 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.

9. 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.

10. Systolic blood pressure >160 mm Hg or a diastolic blood pressure >90 mm Hg at Visit 1.

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

12. 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)

13. Has donated or lost ≥1 unit of blood (approximately 300 mL) within 8 weeks prior to the first dose of MK-7264.

14. 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

15. Requiring treatment with a therapy that does not adhere to the guidance parameters specified in Section 6.5.

Prior/Concurrent Clinical Study Experience

16. Has previously received MK-7264 (excluding participants who received MK-7264 and completed the treatment in Protocol 033).

17. 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

18. Significantly abnormal laboratory tests at Visit 1 (see Section 8.3.6), including:

    a. alkaline phosphatase (ALP), 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 g/dL, white blood cell count (WBC) <2500 /µl, neutrophil count <1500 /µl, platelet count $<10 \times 10^4$ /µl.

    For any of the above listed laboratory assessments, 1 repeat measurement will be allowed at the investigator's discretion, before being considered a screen failure.

Other Exclusions

19. 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.

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

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

No restrictions are required.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

Use of any tobacco products will not be allowed during the course of the study. For the purposes of the study, smoking is intended to include cigars, e-cigarettes, cigarettes, vapes, etc.

Based on known metabolism of MK-7264, there are no effects of alcohol and caffeine associated with the study intervention and therefore no related restrictions are required.

5.3.3 Activity Restrictions

No restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the 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 AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

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

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 1.

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP	Sourcing
MK-7264 45 mg BID	Experimental	MK-7264 45 mg	Drug	Tablet	45 mg	1 tablet BID	Oral	52 weeks	Experimental	IMP	Sponsor
MK-7264 15 mg BID	Experimental	MK-7264 15 mg	Drug	Tablet	15 mg	1 tablet BID	Oral	52 weeks	Experimental	IMP	Sponsor
MK-7264 45 mg BID	Experimental	Placebo matched to MK-7264 15 mg	Drug	Tablet	0 mg	1 tablet BID	Oral	52 weeks	Placebo	IMP	Sponsor
MK-7264 15 mg BID	Experimental	Placebo matched to MK-7264 45 mg	Drug	Tablet	0 mg	1 tablet BID	Oral	52 weeks	Placebo	IMP	Sponsor

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

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 where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc.).

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

6.1.1 Medical Devices

No medical device is used in this study.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants will be assigned randomly according to a computer-generated allocation schedule.

6.3.2 Stratification

No stratification will be used in this study.

6.3.3 Blinding

In this study double-blinding technique with in-house blinding will be used. MK-7264 45 mg and MK-7264 15 mg will be packaged identically relative to their matching placebos so that blind is maintained. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the group assignments.

The study will continue as double-blind only after Week 24 acknowledging that the sponsor will be unblinded at that point in order to analyze and report the data. The study team responsible for the ongoing monitoring of the study will remain blinded to the treatment-level results of this interim analysis (safety and efficacy).

See Section 8.1.10 for a description of the method of unblinding a participant during the study, should such action be warranted.

6.4 Study Intervention Compliance

Records of intervention compliance for each participant will be kept during the study. The clinical research associates will review intervention 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 intervention plan for compliance <80% between visits require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

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

participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

For participants who receive study intervention, 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 Visit 1 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 Visit 1 through Visit 2. Participants should not initiate therapy with opioids (including codeine) for the treatment of cough from Visit 2 through completion of the treatment period.

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

2. Pregabalin, gabapentin, or amitriptyline for the treatment of cough is not allowed from 2 weeks prior to Visit 1 through Visit 2. Participants should not initiate therapy with pregabalin, gabapentin, or amitriptyline for the treatment of cough from Visit 2 through completion of the treatment period.
   Pregabalin, gabapentin, or amitriptyline for indications other than chronic cough are permitted provided the participant is receiving a stable treatment regimen for at least 2 weeks prior to Visit 1 and in the opinion of the investigator, is likely to remain on the stable treatment regimen through completion of the treatment period.

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

4. Treatments for conditions associated with chronic cough such as GERD, asthma, sinobronchial syndrome (SBS), or atopic cough, are permitted provided that participants are receiving a stable treatment regimen for at least 2 weeks prior to Visit 1 and in the opinion of the investigator, are likely to remain on the stable treatment regimen through completion of the treatment period. Sponsor should be consulted if the treatment were to be modified. Possible treatments are provided in Table 2. Note, this list is not meant to be comprehensive. Sponsor needs 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 H_2 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. Angiotensin converting enzyme inhibitors are not allowed from 3 months prior to signing informed consent through completion of the treatment period.

6.5.1 Rescue Medications and Supportive Care

The concomitant therapy defined in Section 6.5 will be allowed for up to 3 weeks for treatment of acute cough.

6.6 Dose Modification

Dose modification is not allowed in this study.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

See Section 8.1.10 for a description of the method of unblinding a participant during the study, should such action be warranted.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-

up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.10.5.

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

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

- The participant requests to discontinue study intervention.
- The participant's treatment assignment has been unblinded by the investigator, MSD subsidiary, or through the emergency unblinding call center.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention (including recommendation to discontinue participant from study intervention as part of monitoring for crystalluria/urolithiasis, see Section 8.3.7).
- 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 allergic drug reaction or anaphylaxis to study intervention.
- 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 intervention but continue to be monitored in the study, see Section 1.3 and Section 8.10.5 for those procedures to be completed at each specified visit.

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

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant 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 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

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

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Study File Binder (or equivalent).

- All study-related medical (or dental) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).

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

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

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

The standard amount of blood collected from each participant over the duration of the study will be approximately 50 mL (Appendix 2).

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator 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.

8.1.1.1 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 Institutional Review Board/Independent Ethics Committee's (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.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator to ensure that the participant qualifies for the study. This includes assessing the participant's CSD before randomization at Visit 2 to confirm that the participant has an ability to complete the PROs during the treatment period.

Source documentation for all eligibility criteria needs to be maintained at the site. For participants with eGFR ≥30 mL/min/1.73 m^2 and <50 mL/min/1.73 m^2 at Visit 1 with stable renal function (unstable renal function is defined as a ≥50% increase of serum creatinine compared to a value obtained at least 6 months prior to Visit 1), documentation of stable serum creatinine must be retained as source documentation at the study site.

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use and record prior medication taken by the participant (see Section 6.5 and refer to eCRF entry guidelines).

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

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

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.10.2.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment 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.

8.1.8 Study Intervention Administration

Since MK-7264 45 mg and 15 mg will differ in appearance and have corresponding matching placebos, participants will receive two study intervention bottles for the treatment period (ie, either MK-7265 45 mg and placebo matched to MK-7264 15 mg OR MK-7264 15 mg and placebo matched to MK-7264 45 mg). Participant should be instructed to take one tablet from each bottle BID.

Participants will be provided with enough study intervention to last between study site visits. Prescription and distribution of study interventions are allowed at unscheduled visits as well as scheduled visits.

The first dose of study intervention will be administered at the study site at Visit 2 after completing baseline assessments. 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. The last dose will be on the day before Visit 8.

8.1.8.1 Timing of Dose Administration

Study intervention will be administered orally BID, approximately 12 hours apart for apporoximately 52 weeks during the treatment period.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention 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 AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4 .

8.1.9.1 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.

8.1.10 Participant Blinding/Unblinding

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

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

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

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

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

8.1.11 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.

8.2 Efficacy Assessments

Compliance with the efficacy assessments (along with study intervention 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.

8.2.1 Patient-reported Outcomes (PRO)

Each participant will be properly trained on CSD at Visit 1 and instructed on the PRO measurements at each visit. Participants will be contacted and reminded to complete the CSD as trained (eg, at telephone contacts).

Participants who discontinue study intervention early will continue to be monitored in the study and should be encourage to continue to complete the PROs measures as outlined in the SoA.

8.2.1.1 Leicester Cough Questionnaire (LCQ)

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 be complete the LCQ at study site visits outlined in the SoA

8.2.1.2 Cough Severity Diary (CSD)

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 every evening beginning in the evening on the day of Visit 1 to the day before Visit 2 (for a minimum of 7 days between Visit 1 and prior to Visit 2). For Visit 3, 4, 5, 6, 7, and 8, the CSD will be completed every evening beginning 1 week prior to the visits. Participant should be contacted (eg, by telephone) around 1 week prior to those visits to remind them to complete the CSD during these weeks.

8.2.1.3 EuroQoL 5 Version Five Dimensions Questionnaire (EQ5D-5L)

The EQ5D-5L is a standardized instrument for measuring generic health status used for estimating preference weights for that health status. The participant will be asked to indicate their health state using a 5-level rating scale. The participant will also be asked to complete the EQ VAS to record the participant's self-rated health on a vertical VAS.

Participants will complete the EQ5D-5L at the study site visits outlined in the SoA.

8.2.1.4 Patient Global Impression of Change (PGIC)

Participants will be asked to rate the change in their chronic cough compared to the start of the study using the PGIC with response options ranging from "very much improved" to "very much worse".

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

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided below. The total amount of blood volumes drawn can be found in Section 8.

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

8.3.1 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 investigator (see inclusion criterion 1, Section 5.1).

8.3.2 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.

A brief directed physical examination may be performed as outlined in the SoA except for Visit 1. A physical exam (complete or directed) can be performed at any unscheduled visit if deemed necessary by the investigator.

Clinically significant changes identified after randomization will be recorded as AEs in the eCRF.

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

8.3.3 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 body temperature (in centigrade) will be collected as outlined in the SoA. All blood pressure measurements should be performed on the same arm at the same positon, preferably by the same person. All body temperature should be measured by the same method.

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

Any clinically significant abnormalities in vital signs and changes in weight identified after randomization will be recorded as AEs in the eCRF.

8.3.4 Electrocardiograms

A 12-lead electrocardiogram (ECG) will be obtained at Visit 1 using local standard procedures.

8.3.5 Spirometry

A spirometry assessment will be performed locally at Visit 1 using a calibrated spirometer. Assessments will include $FEV_{1,}$ FVC, and FEV_1/FVC ratio.

Spirometry performed within the past year of Visit 1 and after the onset of chronic cough 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).

8.3.6 Clinical Safety Laboratory Assessments

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

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

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

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

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

8.3.7 Renal and Urological Safety Procedures

Safety assessments will be performed in all participants in order to monitor renal and urological safety during the course of the study. Participants will be monitored for hematuria using urinary dipstick (performed at the study site) and urinary crystals through urinalysis (performed at the central laboratory). Dipstick and urinalyses (including microscopy performed at the central laboratory) will be collected as outlined in the SoA.

If during screening, a participant has crystalluria and/or unexplained hematuria (defined as participants without a history of recent menses, urinary tract infection, or recent procedure/instrumentation that would explain the hematuria), the investigator should:

- Review and confirm if the finding is a new finding or a previously documented finding.

- Evaluate the participant's medical history to identify conditions (ie, prior renal disease, prior history of kidney stones, medications, gastrointestinal conditions) and make a clinical determination if the participant is at high or low risk of potential complications/worsening due to an associated renal/urinary condition or its treatment, or requires a change in therapy for that condition that may interfere with interpretation of safety data collected during the study.

- If high risk, the participant should not be enrolled and should be considered for further evaluation.

- If low risk, the participant may continue with screening.

If after randomization, the participant has confirmed, unexplained hematuria and/or urinary crystals, an urine sample collected via a specialized filter will be shipped to Sponsor or designee and assessed for the presence of MK-7264 urinary crystals via Raman spectroscopy. Raman spectroscopy is sensitive to the chemical structure of the molecule and MK-7264 has unique chemical structure compared to common urinary crystals. See vendor's site manual for further procedural details.

If a participant has confirmed MK-7264 urinary crystals, the Sponsor will inform the investigator and require discontinuation of the participant from study intervention with the recommendation to follow-up at approximately 2-week intervals with additional specialized urine analysis performed until resolution of MK-7264 urinary crystals.

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

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

Adverse events, 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, is 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 8.4.3.

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

All AEs, SAEs, and other reportable safety events that occur after the 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 cause 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 last study-related intervention safety follow-up phone call, all AEs, SAEs and other reportable safety events must be reported by the investigator; however, for those participants who discontinue from the study intervention but continue to be monitored, only the AEs and other reportable safety events that are shown in Table 3 need to be reported. This specific approach for reporting

starts from completion of the safety follow-up phone call/visit following cessation of intervention until the last study-related off-intervention phone call/visit.

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 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 intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 3.

Table 3 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-Specified Follow-up Period	Reporting Time Period: After the Protocol Specified Follow-up Period	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

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:
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
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

* Participants who discontinue intervention and are continuing to be monitored in the study do not require the reporting of ECIs, Pregnancy/Lactation Exposure and Overdose. Previously reported pregnancies/lactation exposure need to be followed for completion/termination; report outcome.

8.4.2 Method of Detecting AEs, SAEs, 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 nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (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 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. All AEs will be reported to regulatory authorities, IRB/IECs, and investigators in accordance with all applicable global laws and regulations (ie, per ICH Topic E6 (R2) Guidelines for Good Clinical Practice [GCP]).

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

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

8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

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

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

8.5 Treatment of Overdose

In this study, an overdose is any dose higher than the amount of study intervention taken outside the intervention assignment. Study intervention should be taken once in the morning and once in the evening. If more than the protocol-specified intervention is taken within a 1 day period (ie, >2 tablets/day from either bottle), this is regarded as an overdose.

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 (see MK-7264 IB). Overdose should be treated according to the participant's clinical signs and symptoms.

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

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 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 as specified in the SoA:

- Blood for Genetic Analysis

8.8.1 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.

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

8.9 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

8.10 Visit Requirements

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

8.10.1 Pre-screening

Participants who require washout of any therapy (see Section 6.5) should start washout after the written informed consent is obtained. The procedures scheduled at Visit 1, for participants who require washout, should be started as soon as the washout completes. Screening period, for these participants, starts from the completion of the washout of required therapy.

8.10.2 Screening

Approximately 2 weeks prior to treatment randomization, participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. If any participant fails to meet the study entry criteria, screening procedures may be repeated once based on investigator judgement after initial screening, and after consultation with the Sponsor.

8.10.3 Baseline

Visit 2 must be scheduled between 7 days and 14 days after Visit 1. The first dose is administered at the study site.

8.10.4 Treatment Period

Participants will be required to be seen in the clinic at Visit 3, 4, 5, 6, 7 and 8 and they are to be reminded to bring their CSD with them to the site for these visits. Participants will be contacted by telephone between Visit 5, 6, 7, and 8 respectively. These telephone contact can be conducted as site visits.

8.10.5 Discontinued Participants Continuing to be Monitored in the Study

If a participant is discontinued from the study intervention early, the Discontinuation Visit assessments are to be performed as soon as possible.

It is intended that all participants should be followed through completion of the study, regardless of premature discontinuation of intervention unless the participant withdraws consent. Thus, participants who discontinue from study intervention prior to completion of the study should continue to be monitored to obtain relevant information through the end of the study. Study site visits/telephone calls should be made at timepoints that correspond to each remaining study visit. The follow-up information, limited to AEs, concomitant medication use, and patient report outcomes (site visits only) will be collected as outlined in the SoA.

Concomitant therapies specifically prohibited (see Section 6.5) while the participant was on study intervention are no longer prohibited after discontinuation of study intervention.

For these participants who have discontinued study intervention 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 telephone, work telephone, mobile telephone). 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 7.1), the participant should be encouraged to accept a telephone contact at least at Visit 8 date.

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

8.10.6 Follow-up Period

All participants will be required to complete the safety follow-up telephone contact approximately 14 days (+7 days) after the last dose of study intervention to determine if any AEs have occurred since discontinuing study intervention.

9 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.

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	Phase 3 study, Randomized, Double-blind Clinical Study to Evaluate the Long-term Safety and Efficacy of MK-7264 in Japanese Adult Participants with Refractory or Unexplained Chronic Cough
Treatment Assignment	Participants will be randomized in a 1:1 ratio to either MK-7264 45 mg BID or MK-7264 15 mg BID.
Analysis Populations	Efficacy: Full Analysis Set (FAS) population. Safety: All Participants as Treated (APaT) population.
Primary Endpoint	• Adverse events (AEs) • Study treatment discontinuations due to AE
Statistical Methods for Key Efficacy Analyses	Change from baseline in LCQ total score at Week 12 and through Week 52 will be analyzed using the longitudinal analysis of covariance (ANCOVA) model. The model will include terms for treatment, visit, the interactions of treatment by visit, and baseline value as covariates. The change from baseline to each visit and 95% CIs will be estimated from this model.
Statistical Methods for Key Safety Analyses	AEs will be summarized by the number and percentage of the participants who experienced respective events. Change from baseline in laboratory tests, vital signs at respective timepoints will be summarized by descriptive statistics.
Interim Analyses	The planned interim analysis (safety and efficacy) will be performed based on the data up to Week 24 when all the randomized participants have completed Week 24 or discontinued prior to Week 24.
Multiplicity	No multiplicity adjustment is planned in this trial.
Sample Size and Power	A total of 160 participants will be enrolled. Assuming a discontinuation rate of approximately 47% at Week 52, 84 participants are expected to complete 52 weeks of treatment.

9.2 Responsibility for Analyses/In-house Blinding

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

This study will be conducted as a double-blind study under in-house blinding procedures. Double blinding technique with in-house blinding will be used until all the randomized participants have completed Week 24 or discontinued prior to Week 24 after which a double blinding only technique will be used. The official, final database will not be unblinded until

medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

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

9.3 Hypotheses/Estimation

There are no hypotheses for this study.

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoints

- Leicester Cough Questionnaire (LCQ) total score
- Mean weekly Cough Severity Diary (CSD) total score
- EuroQoL 5 Version Five Dimension Questionnaire (EQ5D-5L)
- Patient Global Impression Change (PGIC)

9.4.2 Safety Endpoints

- Adverse event (AE)
- Study treatment discontinuations due to AE
- Laboratory test
- Vital sign
- Taste related AE
- Oral paraesthesia/hypoethesia

9.5 Analysis Populations

9.5.1 Efficacy Analysis Population

The FAS population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all randomized participants who have 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 included in the treatment group to which they are randomized for the analysis of efficacy data using the FAS populations.

9.5.2 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. Discontinued participants before Week 52 will be included in 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.

9.6 Statistical Methods

The results will be provided by treatment group and total (combined treatment group). There is no plan to do between treatment group comparisons.

9.6.1 Statistical Methods for Efficacy Analyses

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

The continuous endpoints will be analyzed using the longitudinal analysis of covariance (ANCOVA) model. In this model, response variable will be change from baseline. The model will include terms for treatment, visit, and the interactions of treatment by visit and baseline value as covariates. Visit is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. This model uses the maximum likelihood principle to estimate the parameters and account for missing data in an implicit fashion. The change from baseline to each visit and 95% CIs will be estimated from this model. Baseline variable is defined as the last non-missing value prior to the treatment.

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, study treatment discontinuations due to AE, laboratory tests, vital signs 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 participants 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 AEs of interest.

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

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

9.6.3 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 comorbid conditions, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables.

9.7 Interim Analyses

All safety and efficacy analyses will be performed based on the data up to Week 24 when all the randomized participants have completed Week 24 or discontinued prior to Week 24. Regardless of the result of the interim analysis (safety and efficacy), the study will continue as planned. Double blinding only to treatment assignment will be maintained at all investigational sites after all participants have completed Week 24. The results of interim analyses (safety and efficacy) will not be shared with the investigators prior to the completion of the study. The study will continue as double-blind only after Week 24 acknowledging that the sponsor will be unblinded at that point in order to analyze and report the data. The study team responsible for the ongoing monitoring of the study will remain blinded to the treatment-level results of this interim analysis (safety and efficacy).

9.8 Multiplicity

No multiplicity adjustment is planned in this trial.

9.9 Sample Size and Power Calculations

A total of 160 participants will be enrolled. Assuming a discontinuation rate of approximately 47%, 84 participants are expected to complete 52 weeks of treatment. The discontinuation rate was estimated from previous study (Protocol 012), which was 12 weeks study.

The probability of observing at least one AE in this study depends on the number of participants treated and underlying incidence with an AE in the study population. If the underlying incidence of an AE is 2%, probability of observing at least one AE is 82% among

84 participants and 57% among 42 participants. If no participants had a specific AE, then upper bound of the 95% CI of the underlying incidence rate would be 4.3% for 84 participants and 8.4% for 42 participants. For LCQ total score, assuming a 3.7 change from baseline and a SD of 3.9 at Week 12 based on Protocol 012, a 95% confidence interval of change from baseline in LCQ total score would be (2.9, 4.5) for 84 participants and (2.5, 4.9) for 42 participants.

9.10 Subgroup Analyses

No subgroup analysis is planned in this study.

9.11 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 8 – 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 for the APaT population.

9.12 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.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Publication Policy

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

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

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

10.1.5 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.6 Compliance with Law, Audit, and Debarmen

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of 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 Code of Conduct for Clinical Studies.

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

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

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

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

10.1.7 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. 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.

10.1.9 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 4 will be performed by the central laboratory or at the study site.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator.

Table 4 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH MCHC %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
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 tests	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	
Routine Urinalysis	At site: Hematuria by dipstick Central lab: Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase, Microscopic examination (crystals and blood cell will be characterized)		
Other Screening Tests	Serum or urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for WOCBP) Urine pregnancy test will be performed at sites inWOCBP. Refer to SoA.		

Investigators must document their review of each laboratory safety report.

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

10.3.1 Definition of AE

AE definition

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

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

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, 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 intervention administration even though it may have been present before the start of the study.

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

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

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

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.7 for protocol-specific exceptions.

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

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

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

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

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

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

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

f. **Other important medical events**

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

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

10.3.3 Additional Events Reported

Additional events that require reporting

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

- Is a cancer

- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

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

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

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

Assessment of intensity

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

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

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

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

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

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

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

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

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

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

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

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

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN

ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

  - Yes, there is a reasonable possibility of Sponsor's product relationship:

  - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

  - No, there is not a reasonable possibility of Sponsor's product relationship:

  - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

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

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

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

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

Follow-up of AE and SAE

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

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

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

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

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

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

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

This appendix is not applicable for this study.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

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 hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Male Participants

Male participants are not required to use a form of contraception.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use 1 of the contraception methods described in Table 5 consistently and correctly during the protocol-defined time frame in Section 5.1.

Table 5 Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception ○ Oral
● Progestogen only hormonal contraception ○ Oral
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● 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 intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Notes: [a] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly).

10.5.3 Pregnancy Testing

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

Pregnancy testing will be performed at Visit 1 (in WOCBP) and after Visit1 whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

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

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.

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

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

d) DNA: Deoxyribonucleic acid.

e) RNA: Ribonucleic acid.

2. **Scope of Future Biomedical Research**

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

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

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

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

3. **Summary of Procedures for Future Biomedical Research.**

a) Participants for Enrollment

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

b) Informed Consent

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

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

c) eCRF Documentation for Future Biomedical Research Specimens

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

d) Future Biomedical Research Specimen(s)

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

4. **Confidential Participant Information for Future Biomedical Research**

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participant' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and 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 substudy. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the 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 emailed directly to clinical.specimen.management@merck.com.

13. **References**

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3) Industry Pharmacogenomics Working Group [Internet]: 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/

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10.7 Appendix 7: Country-specific Requirements

This appendix is not applicable to this study.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
AE	adverse event
ALP	alkaline phosphatase
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
APaT	all participants as treated
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
ATP	adenosine triphosphate
BID	twice daily
β-hCG	beta-human chorionic gonadotropin
CFR	Code of Federal Regulations
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSD	Cough Severity Diary
CT	computed tomography
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
EQ5D-5L	EuroQoL 5 Version Five Dimensions Questionnaire
eCRF	electronic Case Report Form
EDC	electronic data collection
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FAS	full analysis set
FDAAA	Food and Drug Administration Amendments Act
FEV_1	forced expiratory volume in 1 second
FSH	follicle stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	investigational medical product
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
JRS	the Japanese Respiratory Society
LCQ	Leicester Cough Questionnaire
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
NA	not applicable
NIMP	non investigational medical product
PGIC	Patient Global Impression of Change
PRO	patient reported outcome

Abbreviation	Expanded Term
RBC	red blood cell (count)
RNA	ribonucleic acid
SAE	serious adverse event
SD	standard deviation
SLAB	supplemental laboratory tests
SoA	schedule of activities
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TC	telephone contact
V	visit
WBC	white blood cell (count)
WOCBP	women of child bearing potential

11 REFERENCES

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Supplemental Statistical Analysis Plan (sSAP)

TABLE OF CONTENETS

LIST OF TABLES

1.0 INTRODUCTION

This supplemental SAP (sSAP) is a companion document to the protocol. In addition to the information presented in the protocol SAP which provides the principal features of analyses for this trial, this supplemental SAP provides additional sensitivity statistical analysis details, data derivations and documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

2.0 SUMMARY OF CHANGES

[14-Apr-2020 Amendment 2]

Sections 3.1 and 3.7

The scope of the interim analysis of safety data was expanded to include all available data up to the cutoff date for the interim database lock.

[13-Feb-2020 Amendment 1]

Section 3.6.1

The covariance structure for the longitudinal analysis of covariance was changed from Toeplitz to unstructured.

Analysis of EQ VAS was added.

Section 3.11

It was clarified that 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 for those participants who discontinued *study medication* permanently, instead of for those participants who discontinued the *study* permanently.

Appendix

The relative day ranges for body weight was modified to include the additional timepoints (Visits 3 and 6) included in the protocol amendment (038-01).

3.0 ANALYTICAL AND METHODOLOGICAL DETAILS

3.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 3.2-3.12.

Study Design Overview	Phase 3 study, Randomized, Double-blind Clinical Study to Evaluate the Long-term Safety and Efficacy of MK-7264 in Japanese Adult Participants with Refractory or Unexplained Chronic Cough
Treatment Assignment	Participants will be randomized in a 1:1 ratio to either MK-7264 45 mg BID or MK-7264 15 mg BID.
Analysis Populations	Efficacy: Full Analysis Set (FAS) population. Safety: All Participants as Treated (APaT) population.
Primary Endpoint	• Adverse events (AEs) • Study treatment discontinuations due to AE
Statistical Methods for Key Efficacy Analyses	Change from baseline in LCQ total score at Week 12 and through Week 52 will be analyzed using the longitudinal analysis of covariance (ANCOVA) model. The model will include terms for treatment, visit, the interactions of treatment by visit, and baseline value as covariates. The change from baseline to each visit and 95% CIs will be estimated from this model.
Statistical Methods for Key Safety Analyses	AEs will be summarized by the number and percentage of the participants who experienced respective events. Change from baseline in laboratory tests, vital signs at respective timepoints will be summarized by descriptive statistics.
Interim Analyses	The planned interim efficacy analysis will be performed based on the data up to Week 24 when all the randomized participants have completed Week 24 or discontinued prior to Week 24. Safety analysis will include all available data up to the cutoff date for the interim database lock.
Multiplicity	No multiplicity adjustment is planned in this trial.
Sample Size and Power	A total of 160 participants will be enrolled. Assuming a discontinuation rate of approximately 47% at Week 52, 84 participants are expected to complete 52 weeks of treatment.

3.2 Responsibility for Analyses / In-house Blinding

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

This study will be conducted as a double-blind study under in-house blinding procedures. Double blinding technique with in-house blinding will be used until all the randomized participants have completed Week 24 or discontinued prior to Week 24 after which a double blinding only technique will be used. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

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

3.3 Hypotheses / Estimation

There are no hypotheses for this study.

3.4 Analysis Endpoints

3.4.1 Efficacy Endpoints

- Leicester Cough Questionnaire (LCQ) total score
- Mean weekly Cough Severity Diary (CSD) total score
- EuroQoL 5 Version Five Dimension Questionnaire (EQ5D-5L)
- Patient Global Impression Change (PGIC)

3.4.2 Safety Endpoints

- Adverse event (AE)
- Study treatment discontinuations due to AE
- Laboratory test
- Vital sign
- Taste related AE
- Oral paraesthesia/hypoethesia

3.5 Analysis Populations

3.5.1 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 included in the treatment group to which they are randomized for the analysis of efficacy data using the FAS populations.

3.5.2 Safety Analysis Populations

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. Discontinued participants before Week 52 will be included in 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.

If a participant is found to have taken one or more incorrect doses of study medication from that to which he/she was randomized, then the participant will be counted in the higher dose arm he/she actually received; that is, if a participant was originally randomized to MK-7264 15 mg but during the course of the study has taken 1 or more doses of MK-7264 45 mg, then the participant will be included in the MK-7264 45 mg treatment arm in the safety analysis.

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.

3.6 Statistical Methods

The results will be provided by treatment group and total (combined treatment group). There is no plan to do between treatment group comparisons.

3.6.1 Statistical Methods for Efficacy Analyses

The analysis of efficacy endpoints will be based on the FAS population. Unless specified otherwise, analyses will include all follow-up efficacy data collected for those participants who discontinued treatment.

The continuous endpoints will be analyzed using the longitudinal analysis of covariance (ANCOVA) model. In this model, response variable will be change from baseline. The model will include terms for treatment, visit, and the interaction of treatment by visit and baseline value as a covariate. Visit is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. An unstructured covariance matrix will be used to model correlations among repeated measures. If the unstructured covariance structure fails to converge with the default algorithm, then the AR(1) structure can be used to provide initial values of the covariance parameters. This model uses the maximum likelihood principle to estimate the parameters and account for missing data in an implicit fashion. The change from baseline to each visit and 95% CIs will be estimated from this model. Baseline variable is defined as the last non-missing value prior to the treatment.

Categorical endpoints will be analyzed by calculating the percentage of participants in each response category at each timepoint. For some endpoints (change from baseline in LCQ total score, change from baseline in mean weekly CSD total score), percentage of participants meeting certain threshold values will also be provided. Only observed data will be included in the analysis.

Considerations for the analysis specific to the respective endpoints are provided below.

<u>LCQ total score</u>

Change from baseline in the LCQ total score will be analyzed using the longitudinal ANCOVA model above to estimate within-treatment change from baseline and corresponding 95% CI at each time point. Percentage of participants who had an increase in the total score of ≥1.3 points from baseline at each time point will also be summarized.

The Physical domain score will be considered as missing if there are 2 or more items are missing. If there is only 1 item is missing, the Physical domain score will be based on the actual non-missing items. Psychological domain score will be derived in a similar fashion. The Social domain score will be considered as missing if any item is missing. The LCQ total score will be considered as missing if any of the 3 domain scores is missing.

Mean weekly CSD total score

Change from baseline in the mean weekly CSD total score will be analyzed using the longitudinal ANCOVA model above to estimate within-treatment change from baseline and corresponding 95% CI at each time point. Percentage of participants who had a reduction in the total score of ≥1.3 and ≥2.7 points from baseline at each time point, respectively, will also be summarized.

The mean weekly total score will be considered missing if there are less than 4 non-missing days during the week prior to each visit. If there are less than 7 but at least 4 non-missing days during the week prior to a visit, the mean weekly total score will be based on the actual non-missing days of the week prior to the visit. Mean weekly subscales will be derived in a similar fashion.

EQ5D-5L

Change from baseline in the EQ5D-5L index utility score will be analyzed using the longitudinal ANCOVA model above to estimate within-treatment change from baseline and corresponding 95% CI at each time point. If a participant has a missing response to any of the five individual questions at a particular timepoint, then the entire response for that participant at that timepoint will be considered missing.

EQ VAS

Change from baseline in EQ VAS will also be analyzed using the longitudinal ANCOVA model above to estimate within-treatment change from baseline and corresponding 95% CI at each time point.

PGIC

Percentage of participants with each response to the PGIC questionnaire will be summarized at each timepoint. Percentage of participants with improvements (either "very much improved" or "much improved" on the PGIC scale) will also be summarized at each time point.

Table 1 summarizes the analysis strategy for efficacy endpoints.

Table 1 Analysis Strategy for Efficacy Endpoints

Endpoint / Variable (Description / Timepoint)	Statistical Method	Analysis Population	Missing data approach
Secondary objective			
Change from baseline in LCQ total score	Longitudinal ANCOVA†	FAS	Model-based
% of participants who had an increase in the total score of ≥1.3 points from baseline	Descriptive statistics	FAS	Data as observed
Exploratory objective #1			
Change from baseline in mean weekly CSD score	Longitudinal ANCOVA†	FAS	Model-based
% of participants who had a decrease in the total score of ≥1.3 and ≥2.7 points from baseline	Descriptive statistics	FAS	Data as observed
Exploratory objective #2			
Change from baseline in the EQ5D-5L index utility score	Longitudinal ANCOVA†	FAS	Model-based
Change from baseline in EQ VAS	Longitudinal ANCOVA†	FAS	Model-based
% of participants with each response to the PGIC questionnaire	Descriptive statistics	FAS	Data as observed
% of participants with improvements in the PGIC questionnaire	Descriptive statistics	FAS	Data as observed

† Longitudinal analysis of covariance model with terms for treatment, visit and the interaction of treatment by visit, and baseline value as a covariate

LCQ = Leicester Cough Questionnaire, CSD = Cough Severity Diary, EQ5D-5L = EuroQoL 5 Version Five Dimensions Questionnaire, PGIC = Patient Global Impression of Change, ANCOVA = analysis of covariance, FAS = Full Analysis Set.

3.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, study treatment discontinuations due to AE, laboratory tests, vital signs measurements.

All safety analyses will be based on the APaT population.

AEs and other safety events will be summarized using the number and percentage of the participants who experienced respective events. The AEs observed up to 14 days after the last dose will be included in the analysis.

Taste-related AEs (including dysgeusia, ageusia, and hypogeusia, as well as other related terms) and oral paraesthesia/hypoesthesia are considered as AEs of interest.

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

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

3.6.3 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 comorbid conditions, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables.

3.7 Interim Analyses

All efficacy analyses will be performed based on the data up to Week 24 when all the randomized participants have completed Week 24 or discontinued prior to Week 24. Safety analysis will include all available data up to the cutoff date for the interim database lock. Regardless of the result of the interim analysis (safety and efficacy), the study will continue as planned. Double blinding only to treatment assignment will be maintained at all investigational sites after all participants have completed Week 24. The results of interim analyses (safety and efficacy) will not be shared with the investigators prior to the completion of the study. The study will continue as double-blind only after Week 24 acknowledging that the sponsor will be unblinded at that point in order to analyze and report the data. The study team responsible for the ongoing monitoring of the study will remain blinded to the treatment-level results of this interim analysis (safety and efficacy).

3.8 Multiplicity

No multiplicity adjustment is planned in this trial.

3.9 Sample Size and Power Calculations

A total of 160 participants will be enrolled. Assuming a discontinuation rate of approximately 47%, 84 participants are expected to complete 52 weeks of treatment. The discontinuation rate was estimated from previous study (Protocol 012), which was a 12 week study.

The probability of observing at least one AE in this study depends on the number of participants treated and the underlying incidence with an AE in the study population. If the underlying incidence of an AE is 2%, the probability of observing at least one AE is 82% among 84 participants and 57% among 42 participants. If no participants had a specific AE, then the upper bound of the 95% CI of the underlying incidence rate would be 4.3% for 84 participants and 8.4% for 42 participants. For LCQ total score, assuming a 3.7 change from baseline and a SD of 3.9 at Week 12 based on Protocol 012, a 95% confidence interval of change from baseline in LCQ total score would be (2.9, 4.5) for 84 participants and (2.5, 4.9) for 42 participants.

3.10 Subgroup Analyses and Effect of Baseline Factors

No subgroup analysis is planned in this study.

3.11 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 8 of the Protocol – 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 medication 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 for the APaT population.

3.12 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.

Appendix: Relative day ranges

Since it is not always possible for all study participants to come in for their clinic visits on the exact day specified in the protocol schedule, the following relative day ranges will be defined for each time point.

	Scheduled day	LCQ, CSD, vital signs	EQ5D-5L, PGIC, laboratory parameters	Body weight
Baseline	1	Day ≤1	Day ≤1	Day ≤1
Week 4	28	2≤ Day ≤41	--	2≤ Day ≤55
Week 8	56	42≤ Day ≤69	--	--
Week 12	84	70≤ Day ≤125	2≤ Day ≤125	56≤ Day ≤125
Week 24	168	126≤ Day ≤216	126≤ Day ≤266	126≤ Day ≤266
Week 38	266	217≤ Day ≤315	--	--
Week 52	365	316≤ Day	267≤ Day	267≤ Day
For the analysis of safety parameters, Day at post-baseline timepoints must be ≤14 days following the last dose. The analysis week for CSD will be defined based on the day of study visit by subjects. Seven (7) days to 1 day before the study visit will be used as the measurements for the analysis week to which the study visit day belongs.				

If a subject has data on multiple days within a day range, the measurement closest to the scheduled day within the day range will be used in the analysis. If there are observations before and after the scheduled day that are equally apart from the scheduled day, then the observation after the scheduled day will be used for analysis. If two or more measurements are obtained on the same day, the average will be used as the observation for the day.

Baseline variable is defined as the last non-missing value prior to treatment. Typically this is the measurement taken at Visit 1 or Visit 2, depending on the endpoint.