Official Protocol Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 12-Month Study to Evaluate the Efficacy and Safety of MK-7264 in Adult Participants with Chronic Cough (PN030)
NCT number:	NCT03449147
Document Date:	26-APR-2019

Title Page

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This protocol amendment is applicable only to the United Kingdom, United States of America, Ukraine, Germany and Poland.

Protocol Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 12-Month Study to Evaluate the Efficacy and Safety of MK-7264 in Adult Participants with Chronic Cough (PN030)

Protocol Number: 030-04

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):

IND	123007
EudraCT	2017-003559-49

Approval Date: 26 April 2019

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:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
030-04	26-APR-2018	The overall rationale for the country-specific amendment is to add a 3-month, Off-treatment Durability Study Period to explore the impact of withdrawing MK-7264 therapy in participants who have been treated for 1 year.
030-03	18-OCT-18	Amendment was created only for China. The purpose was to add a China extension period, in order to extend Chinese enrollment beyond the global study period to achieve the locally required sample size. (Note: Editorial changes were made to original rationale.)
030-02	18-SEP-18	[redacted] 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, another major update included in this amendment is that of the estimated glomerular filtration rate (eGFR) criterion for participant exclusion; updated 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 Screening with unstable renal function (defined as a ≥50% increase of serum creatinine compared to a value obtained at least 6 months prior to the Screening Visit) were also excluded. Clarifications of certain sections and procedures, as detailed below, were also made in the protocol during the creation of this amendment.
030-01	13-DEC-17	Removal of special characters in inclusion and exclusion criteria to support study database. Other clarifications required throughout including the schedule of assessments, study population, and formatting.
030-00	16-OCT-17	Original protocol

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendments:

The overall rationale for the amendment is to add a 3-month, Off-treatment Durability Study Period to explore the impact of withdrawing MK-7264 therapy in participants who have been treated for 1 year.

Summary of Changes Table:

Primary Reason for This Amendment:

Section # and Name	Description of Change	Brief Rationale
10.7 Appendix 7: Country-specific Requirements	Added information about the Off-treatment Durability Study Period	To explore the impact of withdrawing MK-7264 therapy after 1 year of treatment

Additional Changes for This Amendment:

6 Study Intervention	Removed the following text: *When a replacement participant is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies*.	Statement removed as protocol does not allow for participants to be replaced.

Section # and Name	Description of Change	Brief Rationale
6.5 Concomitant Therapy	Updated text in bullet #3 (new text is in bold, italicized font): *Dextromethorphan, guaifenesin, benzonatate, and any other over the counter or prescription for the treatment of cough are not allowed from 2 weeks prior to Screening/Visit 1 through Randomization/Visit 3.* ***Furthermore****, participants should not initiate therapy with* ***dextromethorphan, guaifenesin, benzonatate, or*** *any over the counter or prescription treatments for cough from Randomization/Visit 3 through completion of the Main and Extension study periods.*	To clarify that dextromethorphan, guaifenesin, and benzonatate should not be initiated during the trial.
8.1.9 Study Intervention Administration	Updated "Visit 13/Discontinuation" to "Visit 13 or Discontinuation"	To clarify that study intervention supplies will be collected at either Visit 13 **or** Discontinuation
8.2.1 Objective Cough Counts	Updated statement to: *The cough monitor will be attached to the participant at Visit 2* ***and the day before*** *for Visits 4-9 and Discontinuation during the Main study period (see Section 1.3).*	To provide clarity when the cough monitor is attached by stating the exact visit numbers instead of stating "the day before **all other visits**".

Section # and Name	Description of Change	Brief Rationale
8.3.7 Renal and Urological Safety Assessments	Updated statement to: *If during screening, a participant has crystalluria and/or unexplained hematuria (defined as, for example, participants without a history of recent menses, urinary tract infection, or recent procedure/instrumentation that would explain the hematuria. Note: Any other explanation for hematuria finding must be reviewed with the Sponsor).*	To clarify that the protocol provides examples of explanations accepted for 'unexplained' hematuria and that other explanations should be reviewed with the Sponsor.
10.3.1 Definition of AE-Events Meeting the AE Definition	Text below was revised to provide clarity on which abnormal laboratory test results must be reported as an AE to the sponsor. The words "or are" were removed. *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.*	Text has been amended to more closely align with EDC data entry guidelines.
Throughout	Minor typographical errors corrected.	Minor, therefore have not been summarized

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 12-Month Study to Evaluate the Efficacy and Safety of MK-7264 in Adult Participants with Chronic Cough (PN030)

Short Title: MK-7264 Phase 3 study in adult participants with chronic cough (PN030)

Acronym: COUGH-2

Hypotheses, Objectives, and Endpoints:

In this study, the objectives/hypotheses and endpoints below will be evaluated in adult participants with refractory or unexplained chronic cough as follows:

Primary Objectives	Primary Endpoints
- Objective: To evaluate the efficacy of MK-7264 in reducing cough frequency as measured over a 24-hour period Hypothesis (H1): At least 1 MK-7264 dose is superior to placebo in reducing coughs per hour (over 24 hours) at Week 24	- 24-hour coughs per hour at Week 24
- Objective: To evaluate the safety and tolerability of MK-7264	- Number of participants experiencing an AE - Number of participants discontinuing study intervention due to an AE
Secondary Objectives	Secondary Endpoints
- Objective: To evaluate the efficacy of MK-7264 in reducing cough frequency as measured while awake during a 24-hour period Hypothesis (H2): At least 1 MK-7264 dose is superior to placebo in reducing coughs per hour (while awake during a 24-hour period) at Week 24	- Awake coughs per hour at Week 24

- Objective: To evaluate the ability of MK-7264 to provide a clinically significant improvement in cough specific quality of life Hypothesis (H3): At least 1 MK-7264 dose is superior to placebo with respect to the proportion of participants with a ≥1.3-point increase from baseline in Leicester Cough Questionnaire (LCQ) total score at Week 24	- Proportion of participants with a ≥1.3 point increase from baseline in LCQ total score at Week 24
- Objective: To evaluate the efficacy of MK-7264 based on the proportion of participants with a clinically significant reduction from baseline in 24-hour coughs per hour Hypothesis (H4): At least 1 MK-7264 dose is superior to placebo with respect to the proportion of participants with a ≥30% reduction from baseline in 24-hour coughs per hour at Week 24	- Proportion of participants with a ≥30% reduction from baseline in 24-hour coughs per hour at Week 24
- Objective: To evaluate the efficacy of MK-7264 in improving self-rated cough severity	- Proportion of participants with a ≥1.3 point reduction from baseline in mean weekly Cough Severity Diary (CSD) total score at Week 24 - Proportion of participants with a ≥2.7 point reduction from baseline in mean weekly CSD total score at Week 24 - Proportion of participants with a ≥30 mm reduction from baseline in Cough Severity Visual Analog Scale (VAS) score at Week 24

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Treatment of chronic cough
Population	Participants who are at least 18 years of age with refractory chronic cough or unexplained chronic cough
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study. This study includes a 24-week Main study period, followed by a 28-week Extension study period.
Type of Control	Placebo
Study Blinding	Double-blind
Masking	Participant Investigator
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 37 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 1290 participants will be enrolled.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Dose Strength	Dose Frequency	Route of Admin.	Regimen/ Treatment Period	Use
MK-7264 45 mg	45 mg	1 tablet BID	Oral	Main Study Period: 24 weeks Extension Study Period: 28 weeks	Exp
	0 mg matched to MK-7264 15 mg	1 tablet BID	Oral	Main Study Period: 24 weeks Extension Study Period: 28 weeks	Pbo
MK-7264 15 mg	15 mg	1 tablet BID	Oral	Main Study Period: 24 weeks Extension Study Period: 28 weeks	Exp
	0 mg matched to MK-7264 45 mg	1 tablet BID	Oral	Main Study Period: 24 weeks Extension Study Period: 28 weeks	Pbo
Placebo	0 mg matched to MK-7264 45 mg	1 tablet BID	Oral	Main Study Period: 24 weeks Extension Study Period: 28 weeks	Pbo
	0 mg matched to MK-7264 15 mg				

Admin = administration; BID = twice daily; Exp = experimental; Pbo = placebo.

Total Number	3
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 approximately 2 weeks, each participant will be receiving assigned intervention for approximately 52 weeks. Each participant will have a safety follow-up telephone call 14 days after completion, discontinuation or withdrawal of the study intervention.

Study Governance Committees:

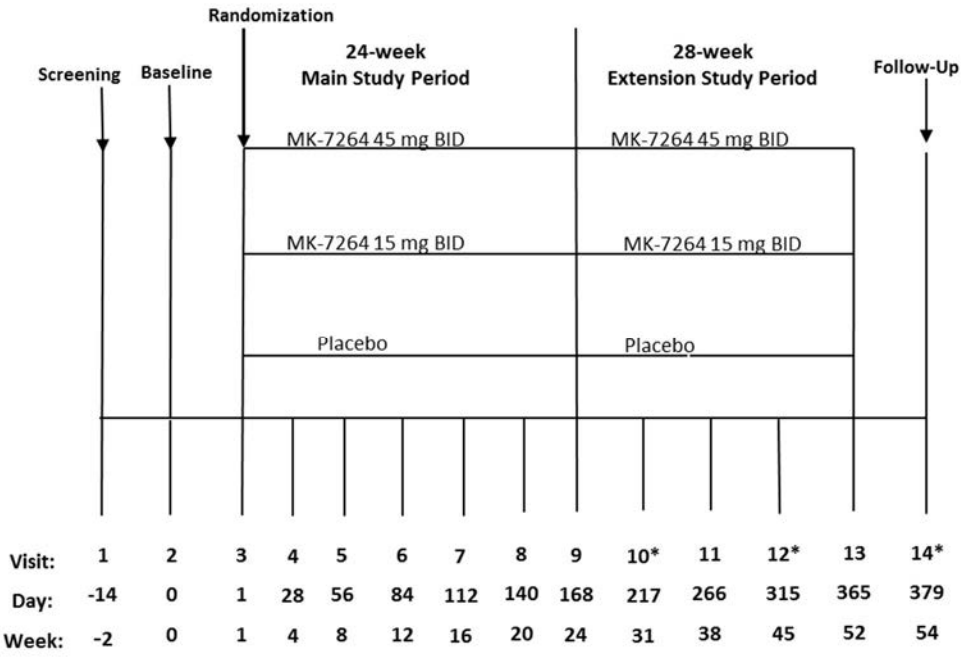
Steering Committee	No
Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Scientific Advisory Committee	Yes
Study governance considerations are outlined in Appendix 1.	

Study Accepts Healthy Volunteers: No

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

1.2 Schema

The study design is depicted in Figure 1.



**Note: Visits 10, 12, and follow-up Visit 14 will be conducted by telephone.*
BID = twice daily

Figure 1 Study Design

At study entry, participants will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups: MK-7264 45 mg twice daily (BID), MK-7264 15 mg BID, or placebo. Participants will remain on their assigned intervention at Randomization throughout the study.

A safety follow-up telephone call will be conducted at a minimum of 14 days (with an allowed variance of up to + 7 days) after Visit 13 or after last dose of study intervention (for participants who discontinue from intervention). Please refer to details in Section 8.10.6.

1.3 Schedule of Activities (SoA)

Study Period	**SCR**	**BL**	**Main Study Period**														**Extension Study Period**				**FU**	**Disc**	**Notes**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**		**Visit 5**		**Visit 6**		**Visit 7**		**Visit 8**		**Visit 9**		**Visit 10 (TC)**	**Visit 11**	**Visit 12 (TC)**	**Visit 13**	**Visit 14 (TC)**		V10, 12, and Follow-up to be conducted by telephone
Scheduled Day	**Dy –14 to Dy –7**	**Dy 0**	**Dy 1**	Dy 27	**Dy 28**	Dy 55	**Dy 56**	Dy 83	**Dy 84**	Dy 111	**Dy 112**	Dy 139	**Dy 140**	Dy 167	**Dy 168**	**Dy 217**	**Dy 266**	**Dy 315**	**Dy 365**	**Dy 379**		
Scheduling Window (Recommended)	**NA**	**NA**	**NA**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**±4 dys**	**±4 dys**	**±4 dys**	**±4 dys**	**+7 dys**		
Scheduled Week	**Wk -2 to Wk -1**	**Wk 0**	**Wk 1**	**Wk 4**		**Wk 8**		**Wk 12**		**Wk 16**		**Wk 20**		**Wk 24**		**Wk 31**	**Wk 38**	**Wk 45**	**Wk 52**	**Wk 54**		
Administrative Procedures																						
Written Informed Consent	X																					See Section 8.1.1.
Participant Identification Card	X																					
Issue/Instruct the use of Participant Comment Card			X		X		X		X		X		X		X		X					See Section 8.1.6.
Collect/Review Participant Comment Card					X		X		X		X		X		X		X		X		X (MS/ES)	
Informed Consent for Future Biomedical Research	X																					

Study Period	**SCR**	**BL**	**Main Study Period**												**Extension Study Period**				**FU**	**Disc**	**Notes**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**		**Visit 5**		**Visit 6**		**Visit 7**		**Visit 8**		**Visit 9**		**Visit 10 (TC)**	**Visit 11**	**Visit 12 (TC)**	**Visit 13**	**Visit 14 (TC)**		V10, 12, and Follow-up to be conducted by telephone
Scheduled Day	**Dy –14 to Dy –7**	**Dy 0**	**Dy 1**	Dy 27	**Dy 28**	Dy 55	**Dy 56**	Dy 83	**Dy 84**	Dy 111	**Dy 112**	Dy 139	**Dy 140**	Dy 167	**Dy 168**	**Dy 217**	**Dy 266**	**Dy 315**	**Dy 365**	**Dy 379**		
Scheduling Window (Recommended)	**NA**	**NA**	**NA**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**±4 dys**	**±4 dys**	**±4 dys**	**±4 dys**	**+7 dys**		
Scheduled Week	**Wk -2 to Wk -1**	**Wk 0**	**Wk 1**	**Wk 4**		**Wk 8**		**Wk 12**		**Wk 16**		**Wk 20**		**Wk 24**		**Wk 31**	**Wk 38**	**Wk 45**	**Wk 52**	**Wk 54**		
Inclusion/ Exclusion Criteria	X	X																				
Demographics; Medical & Medication History	X																					
Prior/Con-comitant Medications	X	X	X		X		X		X		X		X		X	X	X	X	X	X	X (MS/ES)	
Study intervention Distribution and/or Accountability			X		X		X		X		X		X		X		X		X		X (MS/ES)	See Section 8.1.9.
Contact IRT system	X		X		X		X		X		X		X		X		X		X		X (MS/ES)	
Efficacy Procedures																						
Attach Cough Monitor		X		X		X		X		X		X		X							X (MS)	See Section 8.2.1.
Collect Cough Monitor			X		X		X		X		X		X		X						X (MS)	See Section 8.2.1.
Activate ePROs		X			X		X		X		X		X		X		X		X		X (MS/ES)	See Section 8.2.2.
LCQ		X			X		X		X		X		X		X		X		X		X (MS/ES)	See Sections 8.2.2 and 8.2.2.1.

Study Period	**SCR**	**BL**	**Main Study Period**														**Extension Study Period**				**FU**	**Disc**	**Notes**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**		**Visit 5**		**Visit 6**		**Visit 7**		**Visit 8**		**Visit 9**		**Visit 10 (TC)**	**Visit 11**	**Visit 12 (TC)**	**Visit 13**	**Visit 14 (TC)**		V10, 12, and Follow-up to be conducted by telephone
Scheduled Day	**Dy –14 to Dy –7**	**Dy 0**	**Dy 1**	Dy 27	**Dy 28**	Dy 55	**Dy 56**	Dy 83	**Dy 84**	Dy 111	**Dy 112**	Dy 139	**Dy 140**	Dy 167	**Dy 168**	**Dy 217**	**Dy 266**	**Dy 315**	**Dy 365**	**Dy 379**		
Scheduling Window (Recommended)	**NA**	**NA**	**NA**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**±4 dys**	**±4 dys**	**±4 dys**	**±4 dys**	**+7 dys**		
Scheduled Week	**Wk -2 to Wk -1**	**Wk 0**	**Wk 1**	**Wk 4**		**Wk 8**		**Wk 12**		**Wk 16**		**Wk 20**		**Wk 24**		**Wk 31**	**Wk 38**	**Wk 45**	**Wk 52**	**Wk 54**		
CSD	Daily	X	Daily														X		X			See Section 8.2.2.2.
Cough Severity VAS	Daily	X	Daily														X		X			See Section 8.2.2.3.
SF-12		X							X						X						X (MS)	See Section 8.2.2.
WPAI		X							X						X						X (MS)	
EQ5D-5L		X							X						X						X (MS)	
PGIC									X						X						X (MS)	
HARQ		X																				See Section 8.2.2.8.
Safety Procedures																						
Chest Radiograph or CT Thorax	X																					Not required if done in past 5 years.
Physical Examination	X														X				X		X (MS/ES)	Complete physical exam performed only at V1; directed physical exam at all other scheduled visits.
Vital Signs	X	X	X		X		X		X		X		X		X		X		X		X (MS/ES)	
Height	X																					

Study Period	**SCR**	**BL**	**Main Study Period**														**Extension Study Period**				**FU**	**Disc**	**Notes**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**		**Visit 5**		**Visit 6**		**Visit 7**		**Visit 8**		**Visit 9**		**Visit 10 (TC)**	**Visit 11**	**Visit 12 (TC)**	**Visit 13**	**Visit 14 (TC)**		V10, 12, and Follow-up to be conducted by telephone
Scheduled Day	**Dy –14 to Dy –7**	**Dy 0**	**Dy 1**	Dy 27	**Dy 28**	Dy 55	**Dy 56**	Dy 83	**Dy 84**	Dy 111	**Dy 112**	Dy 139	**Dy 140**	Dy 167	**Dy 168**	**Dy 217**	**Dy 266**	**Dy 315**	**Dy 365**	**Dy 379**		
Scheduling Window (Recommended)	**NA**	**NA**	**NA**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**±4 dys**	**±4 dys**	**±4 dys**	**±4 dys**	**+7 dys**		
Scheduled Week	**Wk -2 to Wk -1**	**Wk 0**	**Wk 1**	**Wk 4**		**Wk 8**		**Wk 12**		**Wk 16**		**Wk 20**		**Wk 24**		**Wk 31**	**Wk 38**	**Wk 45**	**Wk 52**	**Wk 54**		
Weight	X				X				X						X				X		X (MS/ES)	
ECG (12-lead)	X																					
Spirometry	X																					Not required if done within past 1 year and during a clinically stable period.
Hematology and Chemistry	X								X						X				X		X (MS/ES)	
Urinalysis (w/Micro-scopy)	X								X						X				X		X (MS/ES)	Dipstick performed for ALL participants. Samples are also collected and sent to central laboratory for ALL participants. See Table 8.

Study Period	**SCR**	**BL**	**Main Study Period**												**Extension Study Period**				**FU**	**Disc**	**Notes**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**		**Visit 5**		**Visit 6**		**Visit 7**		**Visit 8**		**Visit 9**		**Visit 10 (TC)**	**Visit 11**	**Visit 12 (TC)**	**Visit 13**	**Visit 14 (TC)**		V10, 12, and Follow-up to be conducted by telephone
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Scheduling Window (Recommended)	**NA**	**NA**	**NA**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**±4 dys**	**±4 dys**	**±4 dys**	**±4 dys**	**+7 dys**		
Scheduled Week	**Wk -2 to Wk -1**	**Wk 0**	**Wk 1**	**Wk 4**		**Wk 8**		**Wk 12**		**Wk 16**		**Wk 20**		**Wk 24**		**Wk 31**	**Wk 38**	**Wk 45**	**Wk 52**	**Wk 54**		
Specialized Urine Collection for Crystal Assay									X						X				X		X (MS/ES)	Only if central laboratory urinalysis, after randomization, is positive for crystals and/or unexplained hematuria. See Section 8.3.7.
Urine Pregnancy Test	X																					See Appendix 5 for instructions on when pregnancy testing should be performed after Visit 1.
Serum Pregnancy Test	X																					Only if urine pregnancy test is positive.
Adverse Event Monitoring	X	X	X		X		X		X		X		X		X	X	X	X	X	X	X (MS/ES)	See Table 3 for further details.

Study Period	**SCR**	**BL**	**Main Study Period**												**Extension Study Period**				**FU**	**Disc**	**Notes**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**		**Visit 5**		**Visit 6**		**Visit 7**		**Visit 8**		**Visit 9**		**Visit 10 (TC)**	**Visit 11**	**Visit 12 (TC)**	**Visit 13**	**Visit 14 (TC)**		V10, 12, and Follow-up to be conducted by telephone
Scheduled Day	**Dy –14 to Dy –7**	**Dy 0**	**Dy 1**	Dy 27	**Dy 28**	Dy 55	**Dy 56**	Dy 83	**Dy 84**	Dy 111	**Dy 112**	Dy 139	**Dy 140**	Dy 167	**Dy 168**	**Dy 217**	**Dy 266**	**Dy 315**	**Dy 365**	**Dy 379**		
Scheduling Window (Recommended)	**NA**	**NA**	**NA**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**±4 dys**	**±4 dys**	**±4 dys**	**±4 dys**	**+7 dys**		
Scheduled Week	**Wk -2 to Wk -1**	**Wk 0**	**Wk 1**	**Wk 4**		**Wk 8**		**Wk 12**		**Wk 16**		**Wk 20**		**Wk 24**		**Wk 31**	**Wk 38**	**Wk 45**	**Wk 52**	**Wk 54**		
Pharmacodynamics/Biomarkers																						
PK Sample (blood)		X	X		X		X		X		X		X		X				X			V3: pre-dose and 2 hours post-dose. V4-V9: pre-dose only. V2, V13: no dosing.
Blood for Genetic Analysis			X																			Collected from randomized participants only; see Sections 8.8 and 8.9.

AE = adverse event; BL = Baseline; CSD = Cough Severity Diary; CT = computed tomography; Disc = discontinuation; Dy = Day; dys = days; ECG = electrocardiogram; eDiary = electronic diary; ePRO = electronic patient-reported outcome; EQ5D-5L = EuroQoL5 Version 5L dimensions questionnaire; ES = Extension study period; ET = end of treatment; FBR = future biomedical research; FU = follow-up; HARQ = Hull Airway Reflux Questionnaire; LCQ = Leicester Cough Questionnaire; MS = main study period; NA = not applicable; PGIC = Patient Global Impression of Change; PK = pharmacokinetic; SCR = screening; SF-12 = 12-item Short Form Survey; SOP = standard operating procedure; TC = telephone contact; V = visit; VAS = Visual Analog Scale; Wk = Week; WPAI = Work Productivity and Activity Impairment

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] [Chung, K. F., 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, cough is categorized based upon the duration of the cough; within each category acute, sub-acute, and chronic are likely diagnostic possibilities [Irwin, R. S., et al 2006]. Acute cough is present for less than 3 weeks and most often due to acute viral upper respiratory tract infection. A cough that has been present longer than 3 weeks is either sub-acute (3 to 8 weeks) or chronic (> 8 weeks).

Chronic cough may affect up to approximately 12% of the adult population [Chamberlain, S. A., et al 2015]. For approximately two-thirds of these patients, a potential co-morbid condition can be identified and the cough effectively managed by optimizing therapy for the condition. 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 the United States Food and Drug Administration (FDA) or European Medicines Agency (EMA) for the treatment of chronic cough. Given the prolonged nature, significant morbidity, and lack of effective treatment, unexplained or refractory chronic cough is a major unmet medical need.

Mechanism of Cough

Each cough occurs through the stimulation of a complex reflex arc. Cough is initiated following activation of airway sensory nerves in the upper and lower respiratory tract. Airway sensory nerves are tailored to detect changes in the physical and chemical environment, and if required, elicit protective reflex events such as cough. These reflexes are normally protective; however, in disease, airway reflexes can become hyper 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. Adenosine triphosphate 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]. Adenosine triphosphate 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. As described elsewhere in the protocol, the data from Protocol 012 support the role of P2X3 antagonism in the treatment of patients with refractory or unexplained chronic cough.

MK-7264 Development Program

MK-7264, a P2X3 receptor antagonist, is a clinical agent being developed for the treatment of cough.

The current MK-7264 cough development plan consists of two 12-month Phase 3 studies in participants with refractory or unexplained chronic cough: 1 study (Protocol 027) with a 12-week Main study period and a 40-week Extension study period, and a second study (Protocol 030) with a 24-week Main study period and a 28-week Extension study period.

2.1 Study Rationale

The purpose of this study is to evaluate the efficacy and safety of MK-7264, an orally available P2X3 antagonist, in participants, at least 18 years of age, who have either refractory or unexplained chronic cough.

Current therapies for acute and sub-acute 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 profile for MK-7264 in participants with refractory or unexplained chronic cough (see MK-7264 Investigator's Brochure [IB]). This Phase 3 study will evaluate the efficacy and safety of MK-7264 in participants with refractory or unexplained chronic cough.

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 tablets, 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 Phase 3 Studies in Adults

The Sponsor intends to conduct a second Phase 3 study of MK-7264 (Protocol 027) in adult participants with refractory or unexplained chronic cough. The design of Protocol 027 will, in most aspects, be similar to Protocol 030. The main difference between the 2 studies will be the length of the Main study period which will be a total of 12 weeks in Protocol 027 compared to 24 weeks in Protocol 030.

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 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 gustatory sensory 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 other sections of the protocol 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 Informed Consent Form (ICF) documents.

3 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

In this study, the objectives/hypotheses and endpoints below will be evaluated in adult participants with refractory or unexplained chronic cough as follows:

Objectives	Endpoints
Primary	
• Objective: To evaluate the efficacy of MK-7264 in reducing cough frequency as measured over a 24-hour period Hypothesis (H1): At least 1 MK-7264 dose is superior to placebo in reducing coughs per hour (over 24 hours) at Week 24	• 24-hour coughs per hour at Week 24
• Objective: To evaluate the safety and tolerability of MK-7264	• Number of participants experiencing an AE • Number of participants discontinuing study intervention due to an AE
Secondary	
• Objective: To evaluate the efficacy of MK-7264 in reducing cough frequency as measured while awake during a 24-hour period Hypothesis (H2): At least 1 MK-7264 dose is superior to placebo in reducing coughs per hour (while awake during a 24-hour period) at Week 24	• Awake coughs per hour at Week 24

Objectives	Endpoints
• Objective: To evaluate the ability of MK-7264 to provide a clinically significant improvement in cough specific quality of life Hypothesis (H3): At least 1 MK-7264 dose is superior to placebo with respect to the proportion of participants with a ≥1.3-point increase from baseline in Leicester Cough Questionnaire (LCQ) total score at Week 24	• Proportion of participants with a ≥1.3 point increase from baseline in LCQ total score at Week 24
• Objective: To evaluate the efficacy of MK-7264 based on the proportion of participants with a clinically significant reduction from baseline in 24-hour coughs per hour Hypothesis (H4): At least 1 MK-7264 dose is superior to placebo with respect to the proportion of participants with a ≥30% reduction from baseline in 24-hour coughs per hour at Week 24	• Proportion of participants with a ≥30% reduction from baseline in 24-hour coughs per hour at Week 24
• Objective: To evaluate the efficacy of MK-7264 in improving self-rated cough severity	• Proportion of participants with a ≥1.3 point reduction from baseline in mean weekly Cough Severity Diary (CSD) total score at Week 24 • Proportion of participants with a ≥2.7 point reduction from baseline in mean weekly CSD total score at Week 24 • Proportion of participants with a ≥30 mm reduction from baseline in Cough Severity Visual Analog Scale (VAS) score at Week 24

Objectives	Endpoints
Exploratory	
• Objective: To evaluate the efficacy of MK-7264 based on the proportion of participants with a clinically significant reduction from baseline in cough frequency	• Proportion of participants with ≥50% and ≥70% reduction from baseline in 24-hour coughs per hour • Proportion of participants with ≥30%, ≥50%, and ≥70% reduction from baseline in awake coughs per hour
• Objective: To evaluate the impact of MK-7264 on generic health-related quality of life, work productivity, and global rating of change	• 12-Item Short Form Survey (SF-12) • Work Productivity and Activity Impairment (WPAI) questionnaire • EuroQoL Five Dimension Questionnaire (EQ5D-5L) • Patient Global Impression Change (PGIC)
• Objective: 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 the study	• Germline genetic variation

4 STUDY DESIGN

4.1 Overall Design

Approximately 1290 participants who meet entry criteria will enter the study. The duration of intervention for each participant is as follows:

- Screening Period: a minimum of 7 days and up to approximately 14 days (see Section 8.10.1)
- Baseline: 1 day (including 24 hours of objective measurement of cough) (see Section 8.10.2)
- Main study period (24-week treatment period after Baseline): 168 days (see Section 8.10.3)

- Extension study period (28-week treatment period after the Main study period): 197 days (see Section 8.10.4)

- Follow-up period: 14 days (see Section 8.10.6)

During the Main study period, participants may be required to be seen by study site personnel for 2 consecutive days (eg, Visit 2 to Visit 3, the day before Visit 4 and Visit 4, the day before Visit 5 and Visit 5, the day before Visit 6 and Visit 6, the day before Visit 7 and Visit 7, the day before Visit 8 and Visit 8 and the day before Visit 9 and Visit 9) so that the cough monitor can be attached and removed (see Section 1.3). Study site staff or mobile research nurse services may be utilized (if locally available and approved for use), so participants have the opportunity to travel to the study site on 1 day instead of traveling to the study site for 2 consecutive 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.

This study will use an adaptive design based on pre-specified criteria, using an independent, external Data Monitoring Committee (DMC) to monitor safety and efficacy. There will be 1 planned interim efficacy analysis when approximately 40% of the total randomized participants have completed, or discontinued prior to completion of the Main study period. The study may be stopped for futility according to the results of the interim analysis.

Results of the interim analysis will be reviewed by the external DMC, which will make recommendations to the Executive Oversight Committee (EOC) of the Sponsor to continue, modify or stop the study according to the plan described in Section 9.

An initial database lock will occur after all participants have completed, or discontinued prior to completion of the Main study period, and a full analysis will be conducted.

The final database lock will be conducted when all participants have completed, or discontinued prior to the completion of, the Extension study period. Details of the blinding are in Section 9.2.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The primary efficacy endpoint is the 24-hour coughs per hour (ie, average hourly cough frequency based on 24-hour sound recordings) at Week 24. Cough counts will be measured using a digital recording device (VitaloJAK™, Vitalograph, Buckingham, United Kingdom;

hereafter referred to as cough monitor). Worn similar to a Holter monitor, with microphones affixed to the participant's chest wall and attached to the participant's clothing, the cough monitor provides high fidelity recordings and facilitates signal processing to accurately identify and quantify cough. Digital recordings will be processed in Vitalograph's centralized reading center, where recordings are condensed using a computer algorithm before human analysts identify and tag individual coughs. The output of this process is a count of coughs for each 24 hour recording period, as well as cough counts for portions of the day when the participant is awake and asleep.

The goal of this study is to demonstrate that MK-7264 is effective in the treatment of refractory or unexplained chronic cough, as evidenced by a change (reduction) from baseline at Week 24 in 24-hour coughs per hour in MK-7264 relative to placebo. Utilizing 2-hour coughs per hour as the primary endpoint is further supported with successful data from MK-7264 Protocol 012 (see MK-7264 IB). Results from MK-7264 Protocol 012 demonstrated statistically significant reduction, in change from baseline in 24-hour coughs per hour, with 50 mg MK-7264 BID compared to placebo at Week 12.

The first secondary endpoint of this study is awake coughs per hour at Week 24. As described above, the 24-hour period can be divided into periods of awake and asleep. In MK-7264 Protocol 012, awake baseline cough rates were numerically higher than 24-hour baseline cough rates and significantly higher than sleep cough rates. Based on these data, awake time may be a meaningful time period for participants with refractory or unexplained chronic cough. Therefore, awake coughs per hour will be evaluated as a secondary endpoint in this study.

The impact of chronic cough on health-related quality of life (HRQoL) as assessed by the LCQ is included as the second secondary endpoint. The goal is to demonstrate that a greater proportion of participants treated with MK-7264 relative to placebo achieve a clinically meaningful improvement from baseline in HRQoL defined as a ≥1.3-point increase in the LCQ total score at Week 24. The LCQ is a 19-item cough-specific HRQoL questionnaire which contains 3 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 2 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.

Two additional patient reported outcome (PRO) measures specific to cough, the CSD and Cough Severity VAS are included as secondary endpoints to assess cough frequency, intensity, disruption due to cough and cough severity.

The CSD is a 7-item, disease-specific PRO measure 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.

[redacted]

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

[redacted]
consistent with the provisional benchmarks outlined by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials which recommends that an improvement of approximately 30% on a 0 to 10 numeric rating scale can be considered clinically meaningful [Dworkin, R. H., et al 2009].

4.2.1.2 Safety Endpoints

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

In support of the safety objective to evaluate the safety and tolerability profile of MK-7264, the safety and tolerability endpoints will be assessed by clinical evaluation of AEs and inspection of other study parameters including vital signs, physical examination, and standard laboratory safety tests at timepoints specified in the SoA. Adverse events are graded and recorded according to Section 8.4 and Appendix 3.

4.2.1.3 Pharmacokinetic Endpoints

The relationship between MK-7264 plasma concentrations and cough frequencies/side effects will be explored. Population pharmacokinetic (PK) analyses will be conducted to understand the exposure-response relationships between MK-7264 and efficacy and safety data.

4.2.1.4 Pharmacodynamic Endpoints

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

4.2.1.5 Planned Exploratory Biomarker Research

4.2.1.5.1 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.

4.2.1.6 Future Biomedical Research

The Sponsor will conduct future biomedical research on DNA specimens for which consent was provided during this clinical study.

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

4.2.2 Rationale for the Use of Comparator/Placebo

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

4.3 Justification for Dose

4.3.1 Doses for This Study

The dose for this study will be either MK-7264 15 mg BID or MK-7264 45 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 2 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 365 days (see Section 6).

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 and 15 mg BID based on the safety and PK efficacy results observed to date.

Based on PK studies, MK-7264 is rapidly absorbed with a median time to reach maximum plasma concentration 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.

For this study, 24 weeks duration of intervention for the Main study period was selected based on regulatory guidance regarding duration of therapy for symptomatic treatment in chronic diseases.

The study includes an extension for a total duration of intervention of up to 1 year, in order to provide a more robust assessment of the longer-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

Early study termination will be the result of the following specified criterion:

During the interim analysis, based on the interim data, if the futility criteria are met, then the study may be stopped for futility.

5 STUDY POPULATION

This study will enroll male and female participants with chronic cough ≥1 year and a diagnosis of refractory chronic cough or unexplained chronic cough according to the American College of Chest Physician (ACCP) guidelines [Irwin, R. S., et al 2006]. 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 associated with chronic cough (eg, gastroesophageal reflux disease [GERD], asthma, or upper airway cough syndrome [UACS]), the participant has received appropriate diagnostic work-up and at least 2 months of therapy, prior to Screening, according to ACCP guidelines, and the participant continues to cough despite being on therapy. Also for the purposes of this study, unexplained chronic cough is defined as participants who have had a clinical evaluation of their cough per ACCP guidelines and this evaluation has not suggested a co-morbid condition that may be associated with chronic cough. Participants with refractory chronic cough or unexplained chronic cough and who are at least 18 years of age will be enrolled in this study.

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

5.1 Inclusion Criteria

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

1. Chest radiograph or computed tomography scan of the thorax (within 5 years of Screening/Visit 1 and after the onset of chronic cough) not demonstrating any abnormality considered to be significantly contributing to the chronic cough or any other clinically significant lung disease in the opinion of the principal investigator or the sub-investigator (note: sub-investigator must be a physician).

2. Have chronic cough for ≥1 year and a diagnosis of refractory chronic cough or unexplained chronic cough as specified in Section 5.

3. Have a score of ≥40 mm on the Cough Severity VAS at both the Screening and Baseline visits, as specified in Section 8.2.2.

Demographics

4. Participant is Male or Female at least 18 years of age at the time of 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 the time of signing the informed consent through at least 14 days after the last dose of study intervention.

Informed Consent

6. The participant (or legally acceptable representative if applicable) provides written informed consent for the study. The participant may also provide consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

Study Participation

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

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 Screening/Visit 1.

3. Former smokers with a pack/year history greater than 20 pack-years.

4. Forced expiratory volume in 1 second (FEV_1)/ forced vital capacity (FVC) ratio <60% (spirometry performed within the past year is acceptable if the investigator confirms that spirometry was done during a period where the participant was clinically stable, eg, not during an upper respiratory infection).

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

6. History of chronic bronchitis, defined as a cough that produces a clinically significant amount of sputum (greater than approximately 1 tablespoon of phlegm) that occurs every day for at least 3 months in a row, with those periods occurring at least 2 years in a row.

7. Individuals who are currently taking an angiotensin converting enzyme inhibitor or have taken an angiotensin converting enzyme inhibitor within 3 months of Screening/Visit 1.

8. Estimated glomerular filtration rate (eGFR) <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 Screening with unstable renal function (defined as a ≥50% increase of serum creatinine compared to a value obtained at least 6 months prior to Screening/Visit 1).

9. Has a history of malignancy ≤5 years prior to signing informed consent except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.

10. Is, at the time of signing informed consent, a user of recreational or illicit drugs or has had a recent history (within the last year) of drug or alcohol abuse or dependence.

11. Screening systolic blood pressure >160 mm Hg or a diastolic blood pressure >90 mm Hg.

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

13. Has a known allergy/sensitivity or contraindication to MK-7264 or its excipients (note: refer to the IB for details regarding excipients for MK-7264).

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

15. A WOCBP who has a positive urine pregnancy test at Visit 1. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Prior/Concomitant Therapy

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

Prior/Concurrent Clinical Study Experience

17. Has previously received MK-7264.

18. Is currently participating in or has participated in an interventional clinical study with an investigational compound or device within 30 days of participating in this current study

Diagnostic Assessments

19. Significantly abnormal laboratory tests at Screening (see Sections 8.3.6 and 8.3.7), including:

    a. alkaline phosphatase, alanine aminotransferase (ALT, SGPT), aspartate aminotransferase (AST, SGOT) >200% of the upper limit of normal, or bilirubin >150% of the upper limit of normal.

    b. hemoglobin <10 gm/dL, white blood cell count (WBC) <2500 mm^3 (<2.5 × 10^3/uL), neutrophil count <1500 mm^3 (<1.5 × 10^3/uL), platelet count <100 × $10^3/mm^3$ (<100 × 10^3/uL).

    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

20. Has a history or current evidence of any condition, therapy, lab abnormality, or other circumstance that may increase the risk associated with study participation or study intervention administration or may interfere with the interpretation of study results, and in the judgment of the investigator or Sponsor, would make the participant inappropriate for entry into this study.

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

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

No restrictions are required.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

Participants who currently smoke, who have given up smoking within the past 12 months, as well as participants who are former smokers with a pack/year history greater than 20 pack-years will not be permitted in the study. For the purposes of the study, smoking is intended to include cigars, e-cigarettes, cigarettes, vapes, etc. Smoking of any kind is not permitted during the course of the study.

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

On intermediate days, and at all other times, alcohol consumption per day is limited to no more than approximately 3 servings of alcoholic beverages or equivalent (1 serving is

approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]).

5.3.3 Activity Restrictions

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

Participants should also avoid allowing the cough monitor, microphone, or chest sensor to get wet. Thus, they must avoid bathing or showering for the duration of the 24-hour recording.

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

See the VitaloJAK™ site manual for further details.

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

5.5 Participant Replacement Strategy

Participants who discontinue from study intervention or withdraw 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 of MK-7264 and placebo will be packaged to support enrollment and replacement participants as required. 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 Admin.	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
MK-7264	Experimental	MK-7264	Drug	Tablet	45 mg	1 tablet BID	Oral	Main Study Period: 24 weeks Extension Study Period: 28 weeks	Experimental	IMP	Central
Placebo	Placebo Comparator	Placebo matched to MK-7264 45 mg	Other	Tablet	0 mg	1 tablet BID	Oral	Main Study Period: 24 weeks Extension Study Period: 28 weeks	Placebo	IMP	Central
MK-7264	Experimental	MK-7264	Drug	Tablet	15 mg	1 tablet BID	Oral	Main Study Period: 24 weeks Extension Study Period: 28 weeks	Experimental	IMP	Central
Placebo	Placebo Comparator	Placebo matched to MK-7264 15 mg	Other	Tablet	0 mg	1 tablet BID	Oral	Main Study Period: 24 weeks Extension Study Period: 28 weeks	Placebo	IMP	Central

Admin. = administration; BID = twice daily; IMP = investigational medicinal product; NIMP = non-investigational medicinal product.

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

Refer to Section 8.1.9 for details regarding administration of the study intervention.

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

6.1.1 Medical Devices

Not applicable.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Allocation or randomization to study intervention will occur centrally using an interactive response technology (IRT) system. There are 3 study intervention arms. Participants will be assigned randomly in a 1:1:1 ratio to MK-7264 45 mg BID, MK-7264 15 mg BID, or placebo. Study sites should contact the IRT system for the purposes of enrollment tracking and study intervention dispensation as outlined in Section 1.3. Participants will be assigned to treatments based on a randomization scheme. The details of the randomization scheme and identification for each participant will be included in the clinical study report (CSR). Randomization data will be kept strictly confidential, filed securely by an appropriate group in Merck or contract research organization, and accessible only to authorized persons per standard operating procedures until the time of unblinding.

6.3.2 Stratification

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

- Gender (Male, Female)
- Geographical Region (North America, Europe, Asia-Pacific, Others)

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. MK-7264 and placebo will be packaged identically, respectively, during the study. 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.

Details on the analysis and in-house blinding are provided in Section 9.2.

See Section 8.1.11 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 of <80% compliance between visits, based on the review with the participant, require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing study unless stated otherwise 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 will also be recorded. The investigator(s) will record any AE on the AEs CRF for which a concomitant medication/therapy was administered.

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

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

   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 Screening/Visit 1 and in the opinion of the investigator, is likely to remain on the stable treatment regimen through completion of the Main and Extension study periods.

2. Pregabalin, gabapentin, amitriptyline, or nortriptyline for the treatment of cough is not allowed from 2 weeks prior to Screening/Visit 1 through Randomization/Visit 3. Participants should not initiate therapy with pregabalin, gabapentin, amitriptyline, or nortriptyline for the treatment of cough from Randomization/Visit 3 through completion of the Main and Extension study periods.

Pregabalin, gabapentin, amitriptyline, or nortriptyline for indications other than chronic cough are permitted provided the participant is receiving a stable treatment regimen for at least 2 weeks prior to Screening/Visit 1 and in the opinion of the investigator, is likely to remain on the stable treatment regimen through completion of the Main and Extension study periods.

3. Dextromethorphan, guaifenesin, benzonatate and any other over the counter or prescription for the treatment of cough are not allowed from 2 weeks prior to Screening/Visit 1 through Randomization/Visit 3. Furthermore, participants should not initiate therapy with dextromethorphan, guaifenesin, benzonatate, or any over the counter or prescription treatments for cough from Randomization/Visit 3 through completion of the Main and Extension study periods. Lozenges/drops, teas/drinks, natural/herbal remedies, and other similar treatments which do not contain an active antitussive or expectorant are allowed, provided they have been used on a regular basis for at least 2 weeks prior to Screening/Visit 1. Lozenges/drops, teas/drinks, and natural/herbal remedies should not be initiated during the study. The Sponsor needs to be consulted for further information.

4. Treatments for conditions associated with chronic cough, such as GERD, asthma, UACS (formerly called post-nasal drip), or non-asthmatic eosinophilic bronchitis, are permitted provided that participants have been treated for at least 2 months for these co-morbid conditions associated with chronic cough and are receiving a stable treatment regimen for at least 2 weeks prior to Screening/Visit 1 and in the opinion of the investigator, are likely to remain on the stable treatment regimen through completion of the Main and Extension study periods. Possible treatments are provided in Table 2. Note, this list is not meant to be comprehensive. Sponsor to be consulted for further information.

Table 2 Examples of Concomitant Treatments Permitted in the Study

Condition	Treatment
GERD	Anti-reflux therapy (proton pump or H2 blockers), and/or pro-kinetic agents
Asthma	Bronchodilators, inhaled corticosteroids, and/or other anti-inflammatory agents
UACS (formerly post-nasal drip)	Antihistamine/decongestant therapy with a first-generation antihistamine
Non-asthmatic eosinophilic bronchitis	Inhaled/oral corticosteroids
GERD = gastroesophageal reflux disease; UACS = upper airway cough syndrome	

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

6. Angiotensin converting enzyme inhibitors are not allowed from 3 months prior to Screening/Visit 1 through completion of the Main and Extension study periods.

6.5.1 Rescue Medications and Supportive Care

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

6.6 Dose Modification

No dose modification is 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/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 8.1.11). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic intervention allocation/randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 8.1.11, 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 Sections 1.3 and 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 8.10.5.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant's treatment assignment has been unblinded by the investigator, Merck Sharp & Dohme Inc. subsidiary, or through the emergency unblinding call center.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study 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, all visits and procedures, as outlined in the SoA, should be completed. Also see Section 8.10.5.

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

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.10. 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 Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.

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

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

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

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required will be approximately 75 mL.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

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

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

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator who is a qualified physician to ensure that the participant qualifies for the study. Inclusion and exclusion criteria for this study are defined in Section 5.1 and Section 5.2, respectively.

For inclusion criterion 2, which states that eligible participants are to have chronic cough for ≥1 year and a diagnosis of refractory chronic cough of unexplained cough (Section 5.1), a combination of medical records and/or verbal history from participant/parent/legal guardian may be elicited at Screening/Visit 1 and can be used to fulfill this criterion if documented in the participant study file by the investigator.

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 Screening 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 the Screening Visit), 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 (refer to electronic case report form (eCRF) entry guidelines).

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use prior to Screening (see Section 6.5 and refer to eCRF entry guidelines).

8.1.5.2 Concomitant Medications

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

8.1.6 Participant Comment Card

Participants randomized into the study will be provided a separate participant comment card to capture any AEs that occur and any concomitant medications used between scheduled study site visits. The investigator or study site staff personnel will train the participant on the use of the participant comment card prior to dispensing study intervention to the participant at Visit 3.The participant comment card should be dispensed and collected/reviewed as outlined in Section 1.3.

Any AE data from the participant comment card will be entered into the eCRF with appropriate assessments made by the investigator. Any concomitant therapy data from the participant comment card will be entered as appropriate into the eCRF.

8.1.7 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 8.10.1.

8.1.8 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.

8.1.9 Study Intervention Administration

The distribution of study intervention will be witnessed by the investigator and/or study staff at the study site visits. Since MK-7264 45 mg and 15 mg will differ in appearance and have corresponding matching placebos, participants will receive 2 study intervention bottles (ie, either MK-7264 45 mg and placebo matched to MK-7264 15 mg OR MK-7264 15 mg and placebo matched to MK-7264 45 mg OR placebos matched to MK-7264 45 mg and 15 mg). Participants should be instructed to take 1 tablet from each bottle BID.

Study intervention should begin on the day of intervention allocation/randomization and will be administered at the study site at Visit 3. This first dose of study intervention at Visit 3 should be administered after the cough monitor is removed, after the pre-dose PK sample collection, and before approximately 11 AM. As dosing is BID, the next dose should be taken orally in the evening, approximately 12 hours later. Subsequent dosing will be performed by the participant (ie, unsupervised at his/her home) BID, approximately 12 hours apart at approximately the same time each day. However, on the day of a study site visit, the morning dose should *not* be taken at home and instead will be given as a witnessed dose at the study site, after the cough monitor is removed, after the pre-dose PK sample collection, and before approximately 11 AM (see Section 8.2.1 for further details).

On the day before Visits 4, 5, 6, 7, 8, and 9, the morning dose should *not* be taken at home and instead will be given as a witnessed dose at the study site. If the attachment of the cough monitor is to be managed by study site staff or a mobile nurse (where locally available and approved per regulations), the morning dose will be a witnessed dose with the study site staff or mobile nurse, at the participant's home. The cough monitor should be attached prior to dosing and TURNED ON immediately AFTER dosing, before approximately 11 AM (see Section 8.2.1 for further details).

Following the last Main study period visit (ie, Visit 9), participants will continue their assigned intervention in the Extension study period. The last dose of study intervention will be on the evening prior to Visit 13. Study intervention supplies will be collected at Visit 13 or Discontinuation.

8.1.9.1 Timing of Dose Administration

Study intervention will be administered orally, BID, approximately 12 hours apart for approximately 168 days (24 weeks) during the Main study period and then administered orally, BID, approximately 12 hours apart for approximately another 28 weeks during the Extension study period.

8.1.10 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the study 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/early withdrawal visit as described in Section 1.3 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.

8.1.10.1 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.

8.1.11 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 THE PARTICIPANT UNLESS NECESSARY.

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

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

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 or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention, but should continue to be monitored in the study.

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this study, the IRT

system should be used for emergency unblinding in the event that this is required for participant safety.

In the instance of identifying MK-7264 crystals in the urine, the participant will be discontinued from the study intervention (see Section 8.3.7 for further details). If a participant has confirmed MK-7264 crystals, it will be known that the participant was receiving MK-7264, but not which dose. In this circumstance, formal non-emergency unblinding should not be performed.

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained 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 and safety 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 Objective Cough Counts

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

The VitaloJAK™ cough monitor is a digital recording device that uses 2 input channels: biometric sensor and air microphone. The first records sounds from the lungs and trachea through a chest contact biometric sensor, which is attached to the skin at the top of the sternum. The second channel captures ambient sounds through a lapel air microphone. The device will be carried in a cloth belt bag worn around the participants' waist, and all sounds the participant makes during cough monitoring will be recorded on the compact flash (CF) card. The CF card contains the full, raw, sound recording data that is the output from the validated cough monitor and is the source for the recording data. The sound recordings on the CF cards are uploaded to the Vitalograph Web Portal for storage and analysis to generate cough data per Vitalograph standard operating procedures, and the Web Portal is the source for the cough counts data.

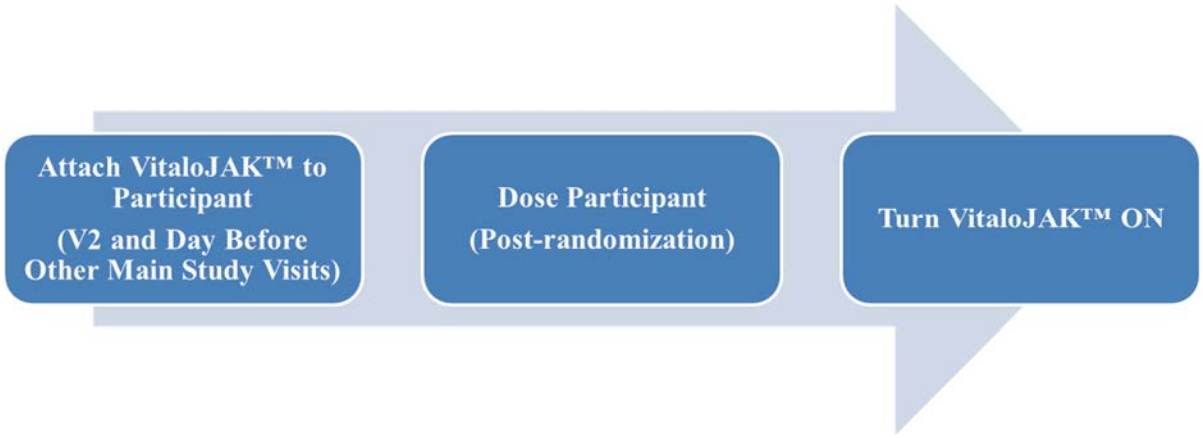
Sites will be uploading the CF card recordings to the Vitalograph Web Portal; however, if after troubleshooting the sites are unsuccessful, the site will securely ship the CF card to

Vitalograph for uploading. Long-term storage of the CF cards may be done by Vitalograph for those sites unable to provide long-term storage of the cards.

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

The cough monitor will be attached to the participant at Visit 2 **and the day before** for Visits 4-9 and Discontinuation, during the Main study period (see Section 1.3). Attachment should occur before approximately 11 AM and the cough monitor should be worn for 24 hours (see VitaloJAK™ site manual for further details). The participant should not remove the cough monitor during the 24-hour period; the monitor will be removed during the actual visit, at the clinic, by site staff the next day. The first dose of study intervention administered is at Visit 3 **after** the cough monitor is removed, **after** the pre-dose PK sample collection, and before approximately 11 AM.

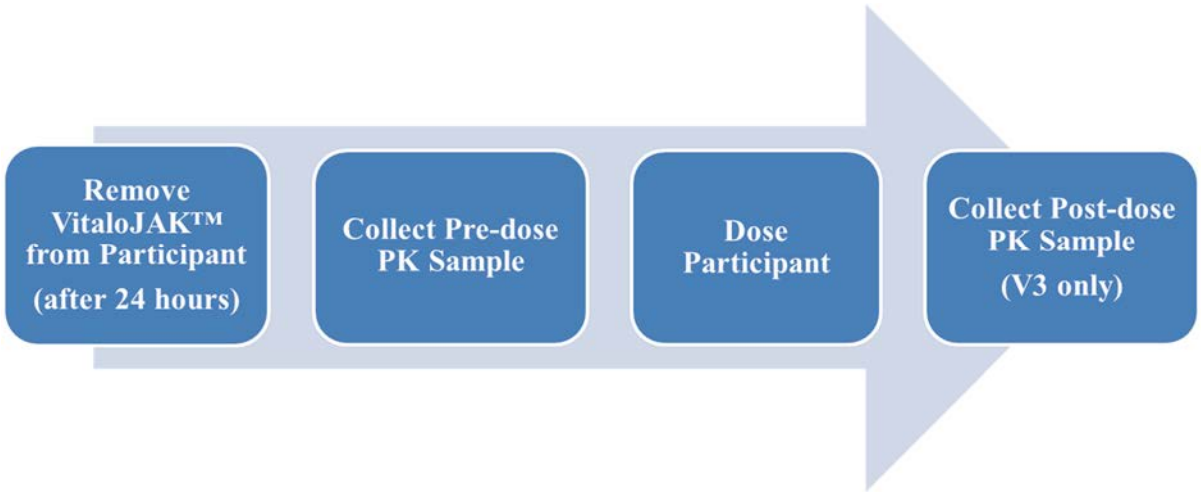
Attachment of the cough monitor may be managed by study site staff or mobile nurses if available and approved. On the day of a study site visit after Visit 3 (or mobile nurse visit where applicable) when the cough monitor will be attached, study intervention dosing should occur prior to the cough monitor being turned on. Therefore, the cough monitor should first be attached, the participant should then be dosed, and then the cough monitor should immediately be turned on (see Figure 2).



V = Visit.

Figure 2 Cough Monitoring: Attachment Procedure

Removal of the cough monitor will occur at the study site and be managed by study site staff. On the day of a study site visit when the cough monitor will be removed, the morning dose should not be taken at home and instead will be given as a witnessed dose at the study site. Therefore, dosing will occur after the cough monitor is removed (once 24-hour recording has completed), after the pre-dose PK sample collection, and before approximately 11 AM (see Figure 3).



PK = Pharmacokinetic; V = Visit.

Figure 3 Cough Monitoring: Removal Procedure

It is recommended that the monitor first be removed (once the 24-hour recording has completed) to avoid any interference. Pre-dose PK should then be collected, prior to study intervention dosing.

All visits, where the cough monitor will be attached/removed, should be scheduled prior to 11 AM to meet the attachment/removal timeframes as well as the PK sample collection(s), and study site dosing requirements.

If cough data is not usable and patient is required to return to the clinic to repeat, it should only be repeated upon Sponsor approval.

Participants who discontinue study intervention early will continue to be monitored in the study and should be encouraged to continue to complete the assessment of 24-hour coughs per hour for the remaining visits (as outlined in the SoA) through the end of the study.

8.2.2 Electronic Patient-reported Outcomes

At Screening (Visit 1), each participant will be properly trained and instructed on the use of an electronic diary (eDiary) for completing the ePRO measures. Participants should bring their eDiary device for all study visits, and should be contacted and reminded to do so (eg, by telephone or text) before each study site visit.

Compliance with daily completion of the eDiaries must be monitored by the investigator or designee. Each investigator site will contact individual participants who are non-compliant in order to retrain and/or remind them to complete their assessments as per Section 1.3 (SoA).

Participants will be instructed to complete daily ePRO measures (CSD and Cough Severity VAS) at approximately the same time in the evening as outlined in the SoA. If a participant fails to complete the CSD and/or Cough Severity VAS ePRO measure(s), the eDiary will allow the participant, based on recall, to complete measures at any time in the next 24 hours (also see vendor's site manual for further details).

Participants will also be asked to complete visit ePRO measures (Hull Airway Reflux Questionnaire [HARQ], LCQ, SF-12, EQ5D 5L, WPAI and/or PGIC) on the day of the visits as outlined in the SoA (also see vendor's site manual for further details). If a participant fails to complete the HARQ, LCQ, SF-12, EQ5D 5L, WPAI and/or PGIC ePRO measure(s), the eDiary will allow the participant, based on recall, to complete these measures at any time in the next 48 hours. If these visit ePROs are not completed, based on recall, within the 48 hours, participants may be asked to complete them at a later date. **All Visit 2 ePRO measures MUST be activated and completed prior to the first dose of study intervention/Randomization** (also see vendor's site manual for further details).

Electronic PRO measures must be activated as outlined in the SoA. Visit 8, Visit 11, Visit 13, and the Discontinuation Visit ePROs are "activated" by entering actual visit/event dates in the vendor portal (Engage). All other visit ePROs are activated at the clinic visit using the site menu on the device or remotely using a PIN if the participant forgets to bring the device to the clinic visit.

Participants who discontinue study intervention early will continue to be monitored in the study and should be encouraged to continue to complete the ePRO measures (along with the assessment of 24-hour coughs per hour) for the remaining visits (as outlined in the SoA) through the end of the study.

Data collection for all ePRO measures will be dependent on ePRO device and software availability.

8.2.2.1 Leicester Cough Questionnaire

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

8.2.2.2 Cough Severity Diary

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

Participants will complete the CSD at approximately the same time daily, beginning at Visit 1 until Visit 9 (with a minimum requirement of 7 days of completion prior to first dose of study intervention/Randomization).

During the Extension study period, completion of the CSD will be required daily, at approximately the same time for a 1 week period, beginning 1 week prior to Visit 11 and beginning 1 week prior to Visit 13. Participants should be contacted (eg, by telephone or text) during the Extension study period to remind them to complete the CSD during these weeks.

8.2.2.3 Cough Severity Visual Analog Scale

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

Participants will complete the Cough Severity VAS at approximately the same time daily, beginning at Visit 1 until Visit 9 (with a minimum requirement of 7 days of completion prior to first dose of study intervention/Randomization).

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

- Participant met the Screening Cough Severity VAS criteria from the measurement done on the day of Visit 1 (or from the next day, if the evening measure was missed).
- Participant met the Baseline Cough Severity VAS criteria from the measurement done on the day prior to Visit 2 prior to conducting any other Visit 2 procedures (or from the morning of Visit 2, prior to conducting any Visit 2 procedures, if the evening measure was missed).

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

During the Extension study period, completion of the Cough Severity VAS will be required daily, at approximately the same time for a 1 week period beginning 1 week prior to Visit 11 and beginning 1 week prior to Visit 13. Participants should be contacted (eg, by telephone or text) during the Extension study period to remind them to complete the Cough Severity VAS during these weeks.

8.2.2.4 12-item Short Form Survey

The SF-12 is a validated, 12-item questionnaire designed to assess general health-related quality of life. It is a widely used instrument that has been shown to be responsive to changes in disease severity following intervention. The SF-12 is scored such that a total score and 8 domain scores can be calculated with higher scores indicating better functioning: Physical Functioning, Role-Physical, Role-Emotional, Bodily Pain, General Health, Social

Functioning, Mental Health, and Vitality. Data obtained from the SF-12 will be used in health economic analyses.

8.2.2.5 Work Productivity and Activity Impairment Questionnaire

The WPAI questionnaire yields four types of scores as follows: (1) absenteeism (work time missed); (2) presenteeism (impairment at work / reduced on-the-job effectiveness); (3) work productivity loss (overall work impairment / absenteeism plus presenteeism); and (4) activity impairment. The WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, ie, worse outcomes.

Participants will be asked to indicate if they are currently employed and to respond to the following questions referring to "the past 7 days": work hours missed due to health problems, work hours missed for other reasons, hours actually worked, the degree to which their health has affected productivity while working, and the degree to which their health affected productivity in regular unpaid activities.

8.2.2.6 EuroQoL 5L Dimensions Questionnaire

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 a vertical VAS where the endpoints are labeled 'best imaginable health state' and "worst imaginable health state". This information can be used as a quantitative measure of health outcome as judged by the individual participant.

8.2.2.7 Patient Global Impression of Change Questionnaire

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".

8.2.2.8 Hull Airway Reflux Questionnaire

Unlike the other cough questionnaires used in this study (ie, LCQ, CSD, and Cough Severity VAS), the HARQ was designed as an aid to diagnosis rather than assess quality of life impacts or cough severity. The HARQ has demonstrated good psychometric properties and no redundant items. The HARQ consists of 14 questions with responses on a numeric scale from 0 to 5. A score of ''0'' means that no problems are caused by the cough symptom and ''5'' means severe/frequent problems. The HARQ will be used to more completely characterize the patient population.

8.3 Safety Assessments

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

Planned timepoints 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 principal investigator (or sub-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.

Any clinically significant abnormalities in physical examinations noted after Visit 1 will be recorded as AEs in the eCRF.

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

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

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, preferably by the same person.

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

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

8.3.4 Electrocardiograms

A 12-lead ECG will be performed at Screening using local standard procedures. Clinically significant abnormal findings should be recorded in the AE eCRF.

8.3.5 Spirometry

A spirometry assessment will be performed locally at Screening using a calibrated spirometer. Assessments will include FEV_1, FVC, and FEV_1/FVC ratio.

Spirometry should be performed in accordance with guidelines established by the ATS/ERS (Available from: http://www.thoracic.org/statements/). For safety reasons, spirometry should be performed with the participant sitting, using a chair with arms and without wheels; however, if necessary to undertake the testing with the participant standing or in another position, this should be noted in the participant's study file.

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

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

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the 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 7 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 Assessments

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 and hematuria through urinalysis (performed at the central laboratory). Dipstick and urinalyses (including microscopy) will be collected as outlined in the SoA.

If during screening, a participant has crystalluria and/or unexplained hematuria (defined as, for example, participants without a history of recent menses, urinary tract infection, or recent procedure/instrumentation that would explain the hematuria; Note: Any other explanation for hematuria finding must be reviewed with the Sponsor.), 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 per the central laboratory, an additional urine sample will need to be collected. One half of the sample will be sent to the central laboratory for reconfirmation of unexplained hematuria and/or urinary crystals. The other half of the sample will be collected via a specialized filter and 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 a 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 analyses performed until resolution of the MK-7264 urinary crystals. Once a participant has confirmed MK-7264 crystals, it will be known that the participant was receiving MK-7264 (formal unblinding should not be performed [see Section 8.1.11]).

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, surrogate, or the participant's legally authorized representative).

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

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

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

All AEs, SAEs, and other reportable safety events that occur after the 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 telephone call, all AEs, SAEs and other reportable safety events must be reported by the investigator; however, for those participants who discontinued from the study intervention but continuing to be monitored only the adverse events and other reportable safety events as shown in Table 3 need to be reported from completion of the safety follow-up telephone call/visit following cessation of intervention to the last study-related off-intervention telephone 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[a]	Previously reported – Follow to completion/termination ; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report[a] - 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[a] - 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

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:
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all[a]	Not required	Within 5 calendar days of learning of event

DILI = drug-induced liver injury; ECI = event of clinical interest

[a] Participants who discontinue study 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/lactations 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:

- 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 (Section 4.3.2). 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

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

8.6.1 Blood Collection for Plasma MK-7264

Blood samples will be collected at several visits during the study for determination of MK-7264 as outlined in the SoA. Samples will be collected pre-dose at the specified study site visits (ie, the morning dose of study intervention will be taken after the PK sample is collected). Only at Visit 3, there will be 2 PK sample collections: 1 at pre-dose and the other at 2 hours (±30 minutes) post-dose. Scheduled PK sample collections for all other visits, as outlined in the SoA, will be predose only. There will not be any dosing at Visit 13, but PK sample collection will be done.

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

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

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 randomized 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 Screening

Potential participants will be evaluated at Screening to determine if they fulfill the entry requirements as set forth in Sections 5.1 and 5.2. If any participant fails to meet the study entry criteria, screening procedures may be repeated once based on investigator judgment after initial screening, and after consultation with the Sponsor. However, participants will not be permitted to rescreen if inclusion criteria for the Cough Severity VAS was not met at Visit 1.

Participants who are consented and then are considered for washout of prohibited therapy (see Section 6.5), should complete the washout prior to completing other screening procedures. For these individuals, the screening period would begin after the completion of washout and when the participant returns to the clinic. Participants who washout of prohibited therapy should return to the clinic after washout to complete the remaining Visit 1 procedures.

Participants who are consented may, at the investigator's discretion, consider beginning the completion of daily ePROs (CSD and VAS) on the day of Visit 1 prior to completing other screening procedures (in order to first determine if the participant meets the Visit 1 VAS entry criterion). For participants who meet the Visit 1 VAS criterion, the screening period is noted as starting when the participant has provided consent. Participants who meet the Visit 1 VAS inclusion criterion should return to the clinic as soon as possible (within the recommended scheduling windows) after availability of the Visit 1 VAS score to complete the remaining Visit 1 procedures.

8.10.2 Baseline

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

Blood for PK assessments will be collected during Visit 2, and should be collected before attachment of the cough monitor (to avoid interference) as cough assessments will begin at Visit 2. The cough monitor should be attached before approximately 11 AM and worn for 24 hours.

8.10.3 Main Study Period

Participants will be required to be seen in the clinic at Visit 3 to have the cough monitor removed that was attached at Visit 2. Additionally, 1 day prior to Visits 4, 5, 6, 7, 8 9, and Discontinuation (from the Main study period) participants should return to the clinic to have the cough monitor attached. Attachment of the cough monitor at these visits, may be managed by study site staff or mobile nurses (if locally available and approved for use), who will attach the cough monitor at the home of the participant. Cough monitors will be removed at study site Visits 4, 5, 6, 7, 8, 9, and Discontinuation (from the Main study period). Refer to the vendor's site manual for additional details.

For all study site visits, participants are to be reminded to bring their eDiary device with them to the visit.

8.10.4 Extension Study Period

Participants will continue their assigned treatments during the 28-week Extension study period. Cough counts will not be collected during this period. Electronic PRO measures will continue to be completed as outlined in the SoA.

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 at the final study site visit.

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. Such contacts will allow collection of follow-up information, limited to AEs, concomitant medication use, objective cough counting and eDiary assessments as outlined in Section 1.3.

Concomitant therapies specifically prohibited (see Section 6.5) while the patient 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 the final visit date (at the end of Main study period if they discontinue intervention during the Main study or at the end of the Extension study period if they discontinue intervention during the Extension).

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

8.10.6 Poststudy

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

If the safety follow-up telephone contact occurs less than 14 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at approximately 14 days (+ 7 days) post the last dose of study intervention.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, there are changes made to the primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guidance for Industry E9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the CSR for the study. Post-hoc exploratory analyses will be clearly identified in the CSR. Separate analysis plans (ie, separate documents from the sSAP) will be developed to detail other planned analyses including those specific to the analysis of PK data and ePROs.

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 through 9.12.

Study Design Overview	A Phase 3, Randomized, Double-blind, Placebo-Controlled, 12-month Study to Evaluate the Efficacy and Safety of MK-7264 in Adult Participants with Chronic Cough (PN030)
Treatment Assignment	Participants will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups: MK-7264 45 mg BID, MK-7264 15 mg BID, or placebo.
Analysis Populations	Efficacy: Full Analysis Set (FAS) population which consists of all randomized participants who have taken at least 1 dose of study intervention and have at least 1 Baseline and at least 1 post-Baseline endpoint observation during the treatment period; and Per-protocol (PP) population which excludes participants due to important deviations from the protocol from the FAS population. Safety: All Participants as Treated (APaT) population, which consists of all randomized participants who received at least 1 dose of study intervention.
Primary Endpoint	24-hour coughs per hour at Week 24
Statistical Methods for Key Efficacy Analyses	The primary analysis will be based on the FAS population. The primary analysis approach will be conducted utilizing the longitudinal analysis of covariance (ANCOVA) model. In this model, the response vector consists of the change from baseline in log-transformed 24-hour coughs per hour at each post-Baseline visit. The model will include factors for treatment group, visit, the interaction of treatment group by visit, gender, and region; and the log-transformed baseline value and the interaction of log-transformed baseline value by visit as covariates. The model will use all available 24-hour coughs per hour data at Baseline and on Week 4, 8, 12, 16, 20 and 24. Contrasts will be constructed to compare each of the 2 MK-7264 treatment groups to the placebo group at each post-Baseline visit. The least squares mean change from baseline (in log scale) with the associated standard errors will be displayed for each treatment group. Estimated treatment differences (MK-7264 − placebo) along with corresponding 95% confidence intervals (CIs) will also be presented for each MK-7264 treatment group. In addition, the geometric mean of the 24-hour coughs per hour will be presented by treatment group and by visit. The percent difference in the change from baseline between MK-7264 and placebo will be estimated by $100*(^{ediff} - 1)$, where diff is the difference provided by the analysis of the log-transformed variable.

Statistical Methods for Key Safety Analyses	The analysis of safety endpoints will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. Tier 1 safety endpoints will be subject to inferential testing for statistical significance with p-values and 95% CIs provided for between-group comparisons. Tier 2 safety endpoints will be evaluated via point estimates and 95% CIs for between-group comparisons. Tier 3 safety endpoints will be evaluated via point estimates only.
Interim Analyses	One planned interim efficacy analysis will be performed in this study. Results will be reviewed by an external DMC. The interim analysis is summarized below. Details are provided in Section 9.7. a. Timing: To be performed when approximately 40% of participants have either completed, or discontinued prior to completion of the Main study period. b. Testing: Futility analysis based on the primary endpoint of 24-hour coughs per hour at Week 24 will be provided. [redacted] Additional interim safety reviews will also be conducted at regular intervals.
Multiplicity	The Type-I error rate over the multiple treatment group comparisons and multiple endpoints will be controlled by a step down testing procedure in a pre-specified order (details are described in Section 9.8).
Sample Size and Power Calculations	The planned sample size is 1290 participants. Table 6 in Section 9.9 provides power for the primary and key secondary efficacy endpoints. All calculations are based on 2-sided α=0.0499 significance level.

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 (both the Main study period and the Extension study period) will be conducted as a double-blind study under in-house blinding procedures. At the end of the Main study period, a copy of the database will be locked after medical/scientific review has been completed, and data have been declared final and complete. The study team will be unblinded in order to perform and review the full analysis of data from the Main study

period, as well as author a CSR for regulatory submission. A separate, blinded Sponsor team (ie, blinded to participant-level intervention assignment) will then be assigned to continue the conduct of the Extension study period. All personnel who are unblinded for the Main study period will be excluded from any future data review at the individual participant level.

At the end of the Extension study period, the CSR from the Main study period will be updated to include analyses of the additional data acquired from the completion of the Extension study period. The investigator site personnel and the participants will be blinded to intervention assignment until the entire study completion.

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

Unblinding for Interim Efficacy and Safety Analyses

Planned interim analyses are described in Section 9.7. Study enrollment is likely to be ongoing at the time of any interim analyses. Blinding to intervention assignment will be maintained at all investigational sites. The results of interim analyses will not be shared with the investigators prior to the completion of the study.

Results of the interim efficacy and safety analyses will be provided by the external unblinded statistician to the DMC. Limited additional Sponsor personnel may be unblinded to the treatment-level results of the interim analyses, if required, in order to act on the recommendations of the DMC. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the unblinded statistician.

The DMC will serve as the primary reviewer of the results of the interim efficacy and safety analyses and will make recommendations for discontinuation of the study or modification to an EOC of the Sponsor. If the DMC recommends modifications to the design of the protocol or discontinuation of the study, the EOC may be unblinded to the results at the treatment-level in order to act on these recommendations. Additional logistical details will be provided in the DMC Charter. Key aspects of the interim analyses are described in Section 9.7.

The external unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

9.3 Hypotheses/Estimation

The primary and secondary hypotheses for this study are stated in Section 3.

9.4 Analysis Endpoints

Efficacy and safety endpoints for evaluation are listed below, followed by the descriptions of the derivations of selected endpoints.

9.4.1 Efficacy Endpoints

Primary Efficacy Endpoint

- 24-hour coughs per hour at Week 24

Secondary Efficacy Endpoints

- Awake coughs per hour at Week 24
- Proportion of participants with a ≥1.3-point increase from baseline in LCQ total score at Week 24
- Proportion of participants with a ≥30% reduction from baseline in 24-hour coughs per hour at Week 24
- Proportion of participants with a ≥1.3-point reduction from baseline in mean weekly CSD total score at Week 24
- Proportion of participants with a ≥2.7-point reduction from baseline in mean weekly CSD total score at Week 24
- Proportion of participants with a ≥30 mm reduction from baseline in Cough Severity VAS score at Week 24

Exploratory Efficacy Endpoints

Exploratory efficacy endpoints are stated in Section 3.

9.4.2 Safety Endpoints

Safety endpoints are stated in Section 3.

9.4.3 Derivations of Efficacy Endpoints

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

Data Handling Rules for Cough Data

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

The cough data will contain all cough events occurring during that 24-hour monitoring period as well as the information about “sleep time” and “awake time”. Any session with a

duration of recording <20 hours will be considered as missing. If a session has a duration less than 24 hours but no less than 20 hours, the 24-hour coughs per hour will be based on the actual duration of the session.

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

24-hour Coughs per Hour

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

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

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

Change from baseline in log-transformed 24-hour coughs per hour
= Log (24-hour coughs per hour at post-Baseline visit) – Log (24-hour coughs per hour at Baseline)

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

Awake Coughs per Hour

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

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

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

Change from baseline in log-transformed awake coughs per hour
= Log (Awake coughs per hour at post-Baseline visit) – Log (Awake coughs per hour at Baseline)

Responders in 24-hour Coughs per Hour

The responder variable in 24-hour coughs per hour is defined based on the magnitude of the percent change from baseline in the original scale at each post-Baseline visit:

Participant is considered a responder if the percent change from baseline in 24-hour coughs per hour is ≤-30%; participant is a non-responder otherwise.

The percent change from baseline in 24-hour coughs per hour is defined as follows:

Percent change in 24-hour coughs per hour
= (Change from baseline in 24-hour coughs per hour/Baseline 24-hour coughs per hour)*100%

Responders for ePRO Endpoints

The responder variables in ePRO endpoints are defined based on the magnitude of the change from baseline at each post-Baseline visit:

- **LCQ total score**

  Participant is considered a responder if change from baseline in LCQ total score is ≥1.3 point; non-responder otherwise

- **Mean weekly CSD total score**

  1. Responder Endpoint 1: Participant is considered a responder if change from baseline in mean weekly CSD total score is ≤-1.3-point; non-responder otherwise

  2. Responder Endpoint 2: Participant is considered a responder if change from baseline in mean weekly CSD total score is ≤-2.7-point; non-responder otherwise

- **Cough Severity VAS score**

  Participant is considered a responder if change from baseline in Cough Severity VAS score is ≤-30 mm; non-responder otherwise

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

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 1 dose of study intervention and provided at least 1 Baseline and at least 1 post-Baseline endpoint observation during the treatment period.

The PP population excludes participants due to important deviations from the protocol that may substantially affect the results of the primary efficacy endpoint. Potential deviations that may result in the exclusion of a participant from the PP population will be specified in the sSAP. The final determination on important protocol deviations, and thereby the composition of the PP population, will be made prior to the first unblinding of the database and will be documented in a separate memo. A supportive analysis using the PP population may be performed for the primary efficacy endpoint if the proportion of the participants with important protocol deviations is >10%.

Participants will be included in the treatment group to which they are randomized for the analysis of efficacy data using both the FAS and PP populations. Details on the approach to handling missing data are provided in Section 9.6.

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 1 dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. For most participants this will be the treatment group to which they are randomized. Participants who take incorrect study intervention for the entire treatment period will be included in the treatment group corresponding to the study intervention actually received.

At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of study intervention is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a Baseline measurement is also required.

9.5.3 Pharmacokinetic Analysis Population

The evaluable PK population for PK data analysis is defined as all participants with 1 measurable PK sample.

9.6 Statistical Methods

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

Statistical testing and inference for efficacy and safety analyses are described in Sections 9.6.1 and 9.6.2, respectively. Controlling of family-wise Type I error rate is described in Section 9.8. Unless otherwise stated, all statistical tests will be conducted at α=0.0499 (2-sided) level.

9.6.1 Statistical Methods for Efficacy Analyses

The analysis of efficacy endpoints will be based on the FAS population. Unless otherwise specified, all efficacy data, regardless of participant exposure to study intervention, will be included in efficacy analyses.

Primary Efficacy Analysis

Cough monitoring is conducted for baseline and 24 hours after administration of the study intervention on Weeks 4, 8, 12, 16, 20, and 24. The primary efficacy endpoint of this study is 24-hour coughs per hour at Week 24. As the change from baseline in 24-hour coughs per hour may have a skewed and wide distribution, the data will be log-transformed prior to analysis for the primary approach. The primary analysis of the primary endpoint will be on the natural log scale of the cough rate data. The variable of change from baseline in log-transformed 24-hour coughs per hour will be used in the analysis of the primary endpoint. A negative result indicates a decrease in cough rate, while a positive result indicates an increase in cough rate.

The primary analysis approach will be conducted utilizing the longitudinal ANCOVA model. In this model, the response vector consists of the change from baseline in log-transformed 24-hour coughs per hour at each post-Baseline visit. The model will include factors for treatment group, visit, the interaction of treatment group by visit, gender, and region; and the log-transformed baseline value and the interaction of log-transformed baseline value by visit as covariates. The model will use all available 24-hour coughs per hour data at baseline on Weeks 4, 8, 12, 16, 20, and 24. Contrasts will be constructed to compare each of the 2 MK-7264 treatment groups to the placebo group at each post-Baseline visit. The least squares mean change from baseline (in log scale) with the associated standard errors will be displayed for each treatment group. Estimated treatment differences (MK-7264 − placebo) along with corresponding 95% CIs will also be presented for each MK-7264 treatment group. In addition, the geometric mean of the 24-hour coughs per hour will be presented by treatment group and by visit. The percent difference in the change from baseline between MK-7264 and placebo will be estimated by $100*(e^{diff} - 1)$, where diff is the difference provided by the analysis of the log transformed variable.

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

Further details of the model specification, assumptions, and SAS implementation codes will be provided in the sSAP.

Secondary Efficacy Analysis

The continuous secondary efficacy endpoints will be analyzed using a similar longitudinal ANCOVA model as used for the primary efficacy analysis.

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

Responder endpoints will be analyzed by the logistic regression model. The model will include terms for treatment group, visit, the interaction of treatment group by visit, gender, region, baseline, and the interaction of baseline by visit for the underlying continuous response. Log odds ratio will be back transformed into odds ratio for final reporting.

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

Table 4 Analysis Strategy for Primary and Key Secondary Efficacy Endpoints

Endpoint/Variable (At Week 24)	**Statistical Method**	**Missing Data Approach**
Primary		
24-hour coughs per hour	Longitudinal ANCOVA	Model-based[a]
Secondary		
Awake coughs per hour	Longitudinal ANCOVA	Model-based[a]
Proportion of participants with a ≥1.3 point increase from baseline in LCQ total score	Logistic Regression	Model-based[a]
Proportion of participants with a ≥30% reduction from baseline in 24-hour coughs per hour	Logistic Regression	Model-based[a]
Proportion of participants with a ≥1.3 point reduction from baseline in mean weekly CSD total score	Logistic Regression	Model-based[a]
Proportion of participants with a ≥2.7 point reduction from baseline in mean weekly CSD total score	Logistic Regression	Model-based[a]
Proportion of participants with a ≥30 mm reduction from baseline in Cough Severity VAS score	Logistic Regression	Model-based[a]

a Includes data collected after intervention discontinuation.
ANCOVA = analysis of covariance; CSD = Cough Severity Diary; LCQ = Leicester Cough Questionnaire; VAS = Visual Analogue Scales.

The strategy to address multiplicity issues with regard to multiple treatment comparisons, multiple efficacy endpoints, multiple timepoints, and interim analyses is described in Sections 9.7 and 9.8.

Handling of Missing Data

The missing data approach is specified in the above mentioned primary and secondary efficacy endpoints analysis sections. All other analyses will be conducted based on the observed data only. Additional sensitivity analyses with respect to the handling of missing data will be specified in the sSAP.

9.6.2 Statistical Methods for Safety Analyses

The safety endpoints will be analyzed based on the data collected in the Main study period, as well as based on the cumulative data collected across both the Main and Extension study periods.

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

The analysis of safety results will follow a tiered approach (Table 5). The tiers differ with respect to the analyses that will be performed. Tier 1 safety endpoints will be subject to inferential testing for statistical significance with p-values and 95% CIs provided for between-group comparisons. Tier 2 safety endpoints will be evaluated via point estimates and 95% CIs for between-group comparisons. Tier 3 safety endpoints will be evaluated via point estimates only.

Taste-related AEs (including dysgeusia, ageusia, and hypogeusia, as well as other related terms) will be classified as belonging to "Tier 1". The unadjusted p-values and point estimates with 95% CIs from the pairwise comparison between each of MK-7264 dose versus placebo will be provided. The definition of taste-related AEs will be finalized and documented before the database lock of the Main study period.

The frequency of taste-related AEs across pre-defined time intervals will be provided, where the time intervals will be defined as: >0 to ≤1 week, >1 to ≤4 weeks, >4 to ≤8 weeks, >8 to ≤12 weeks, >12 to 16 weeks, >16 to 20 weeks, and >20 to 24 weeks in the Main study period; and >24 to ≤38 weeks, and >38 to ≤52 weeks in Extension study period. In each time interval, the denominator for calculation of percentage will be the number of participants exposed at the beginning of the time interval and the numerator will be the number of participants with at least 1 taste related AE occurring in this time interval. Only the first event will be counted and all recurrent events will not be included.

The broad clinical and laboratory AE categories consisting of the percentage of participants with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, an oral paresthesia AE, an oral hypoesthesia AE, and who discontinued due to an AE will be classified as belonging to "Tier 2".

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory, and vital signs will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least

4 participants in any treatment group exhibit the event; all other adverse experiences and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.

The Tier 1 and Tier 2 safety endpoints will be analyzed using the Miettinen & Nurminen method [Miettinen, O. and Nurminen, M. 1985].

Continuous measures such as changes from baseline in laboratory and vital signs will be considered Tier 3 safety parameters.

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

Table 5 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint[a]	p-value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Any taste-related AE	X	X	X
Tier 2	Any oral paresthesia AE		X	X
	Any oral hypoesthesia AE		X	X
	Any AE		X	X
	Any Serious AE		X	X
	Any Drug-related AE		X	X
	Any Serious and Drug-related AE		X	X
	Discontinuation due to AE		X	X
	Specific AEs, SOCs, or PDLCs[b] (incidence ≥4 participants in 1 of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs, or PDLCs[b] (incidence <4 participants in all the treatment groups)			X
	Change from baseline results (Labs, Vital Signs)			X

a Adverse experience references refer to both clinical and laboratory AEs.
b Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier 2 endpoints.
AE = adverse event; CI = confidence interval; PDLC = Pre-defined Limit of Change; SOC = System Organ Class; X = results will be provided.

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, race, weight, and height), baseline characteristics, primary and co-morbid conditions, and prior and concomitant therapies will be summarized by treatment group either by descriptive statistics or categorical tables. The comparability of the treatment groups for each relevant characteristic will be assessed by the summary tables. No statistical hypothesis tests will be performed on these characteristics.

[redacted]

9.7.2 Interim Safety Analyses

Interim safety analyses will be performed periodically (determined either by calendar date or enrollment milestones, to be specified separately in the DMC charter). For these interim analyses, a general review of safety results will be performed based on review of AEs, laboratory safety parameters, and other safety endpoints.

9.8 Multiplicity

Primary and Key Secondary Endpoints

Due to the interim analysis for futility, an α-spending of 0.0001 will be applied to the 2-sided Type I error rate of 0.05 for the primary and secondary hypotheses based on the Haybittle Peto method [Haybittle, J. L. 1971] [Peto, R., et al 1976]. Multiplicity adjustment will be made for testing 2 doses on the primary and the key secondary endpoints for the analysis, ie, for testing a family of the following hypotheses:

- H11: MK-7264 45 mg BID is superior to placebo in reducing 24hour coughs per hour at Week 24
- H12: MK-7264 15 mg BID is superior to placebo in reducing 24-hour coughs per hour at Week 24
- H21: MK-7264 45 mg BID is superior to placebo in reducing awake coughs per hour at Week 24
- H22: MK-7264 15 mg BID is superior to placebo in reducing awake coughs per hour at Week 24
- H31: MK-7264 45 mg BID is superior to placebo on the proportion of participants with a ≥1.3-point increase from baseline in LCQ total score at Week 24
- H32: MK-7264 15 mg BID is superior to placebo on the proportion of participants with a ≥1.3-point increase from baseline in LCQ total score at Week 24
- H41: MK-7264 45 mg BID is superior to placebo with respect to the proportion of participants with a ≥30% reduction from baseline in 24-hour coughs per hour at Week 24
- H42: MK-7264 15 mg BID is superior to placebo with respect to the proportion of participants with a ≥30% reduction from baseline in 24-hour coughs per hour at Week 24

To strongly control the Type I error rate for this family, a step down testing procedure will be applied in the order specified above. Each hypothesis will be formally tested only if the preceding one is significant at α=0.0499 level.

, Table 6 provides power for the primary and key secondary efficacy endpoints with a total of 1290 participants (430 participants per treatment group). All calculations are based on 2-sided α=0.0499 significance level. The dropout rate is expected to be 20% at Week 24.

Table 6 Power for the Primary and Key Secondary Efficacy Endpoints

Endpoints (At Week 24)	Power in MK-7264 45 mg BID Group	Power in MK-7264 15 mg BID Group
24-hour coughs per hour	>99%	98%
Awake coughs per hour	98%	97%
Proportion of participants with ≥1.3-point increase from baseline in LCQ total score	81%	56%
Proportion of participants with ≥30% reduction from baseline in 24-hour coughs per hour	55%	50%

BID = twice daily; LCQ = Leicester Cough Questionnaire

[redacted]

Note: details of the concomitant medications will be provided in a separate sSAP.

A similar longitudinal ANCOVA model as the primary efficacy endpoint will be performed.

For each subgroup, summary statistics including mean, SD, and 95% CIs will be provided for each treatment group.

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 study intervention as instructed in Section 8. When a participant takes less than or more than the required study intervention 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 intervention day to the last scheduled intervention 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 intervention day to the last dose day.

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

9.12 Extent of Exposure

The duration of intervention for each participant will be evaluated by calculating the number of days on therapy. Exposure to study intervention 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 (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF 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 Committees Structure

10.1.4.1 Scientific Advisory Committee

This study was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide input with respect to study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.4.2 Executive Oversight Committee

The Executive Oversight Committee (EOC) is comprised of members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the DMC regarding the study.

10.1.4.3 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the 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.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International 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.

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

Records and documents, including 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.

10.1.9 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.

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 8 will be performed at the study site or by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 8 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry	Electrolytes	Sodium Potassium Chloride Bicarbonate Calcium Phosphorous	
	Liver function tests	AST/ SGOT ALT/ 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 (BUN) Creatinine eGFR calculation: eGFR will be calculated with each serum creatinine measurement (using the Chronic Kidney Disease Epidemiology Collaboration [CKD EPI] formula [http://mdrd.com/])	
	Other	Glucose (non-fasting) Albumin Total Protein	
Urine Dipstick/ Routine Urinalysis	• Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (crystals will be characterized) Note: Dipstick performed at the site for ALL participants. Urine samples are also collected and sent to central laboratory for ALL participants.		
Other Screening Tests	• Serum or urine β-human chorionic gonadotropin (β-hCG) pregnancy test (as needed for women of childbearing potential) a. Urine pregnancy test will be performed at site in women of child bearing potential. Refer to Section 1.3.		

ALT/SGPT = alanine aminotransferase (SGPT); AST/SGOT = aspartate aminotransferase (SGOT); eGFR = estimated glomerular filtration rate; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell.

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

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

10.3.1 Definition of AE

AE definition

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

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

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, 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, considered clinically significant in the medical and scientific judgment of the investigator.

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

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

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

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

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

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

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

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

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

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

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

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

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

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

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

f. **Other important medical events**

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

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

10.3.3 Additional Events Reported

Additional events that require reporting

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

- Is a cancer
- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

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

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

Assessment of intensity

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

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

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

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

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

Assessment of causality

- Did the Sponsor's product cause the AE?

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

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

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

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

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

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

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

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

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

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

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

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

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

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

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

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

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

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

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

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

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

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

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

Follow-up of AE and SAE

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

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

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

10.3.5 Reporting of 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

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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 one of the contraception methods described in Table 9 consistently and correctly during the protocol-defined time frame in Section 5.1.

Table 9 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[b] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen only hormonal contraception[b] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant[b] ● Intrauterine hormone-releasing system (IUS)[b] ● 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: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [a] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [b] If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation. WOCBP = women of childbearing potential

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 Visit 1 whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected. Testing can also be performed as necessary based on local requirements.

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.[1]

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 8.9 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.

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10.7 Appendix 7: Country-specific Requirements

The information in this appendix is added to the main protocol to describe the Off-treatment Durability Study Period that will be conducted only at certain study sites in the United Kingdom, United States of America, Ukraine, Germany and Poland.

1.1 Synopsis

Study Type: The Off-treatment Durability Study Period is observational.

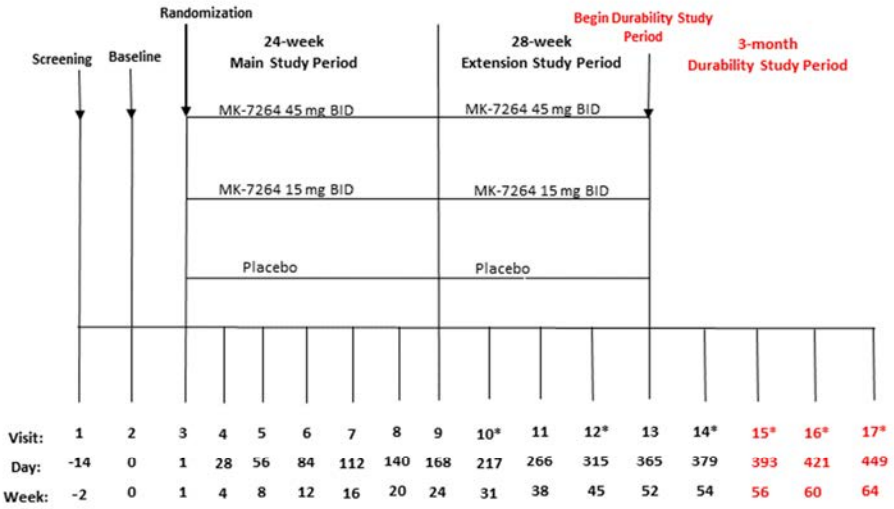
Intervention Model: At selected sites and countries, participants from any treatment group (ie, MK-7264 45 mg BID, MK-7264 15 mg BID, or placebo) who provide written informed consent, may also participate in a 3-month, Off-treatment Durability Study Period.

Estimated Duration of Study: The Sponsor estimates that the Off-treatment Durability Study Period will require approximately 16 months from the time the first participant starts the Off-treatment Durability Study Period until the last participant's last study-related telephone call of the Off-treatment Durability Study Period.

Number of Participants: Approximately 150 total participants who complete the Main and Extension Study Periods (up to Week 52) of this study and another ongoing, Phase 3 study being conducted by the Sponsor (P027) will be enrolled in the Off-treatment Durability Period of the study in which they are participating. The number of participants enrolled from each study may vary.

Duration of Participation: Participants in the Off-treatment Durability Study Period will be in the study for approximately 3 more months after their Week 52 visit.

1.2 Schema



**Note: Visits 10, 12, 14, 15, 16, and 17 will be conducted by telephone. Visit 14 is a safety follow-up after the last dose of study intervention.*

BID = twice daily

1.3 Schedule of Activities (SoA)

Study Period	**Extension/Off-treatment Durability Study Period**		**Off-treatment Durability Study Period**				**Notes**
		Follow-up				**Disc Durability Period**	**"Off-treatment Durability Study Period" is also referred to as "Durability Period"**
Visit Number	**Visit 13 (Last visit of Extension Study Period and start Durability Study Period)**	**Visit 14 (TC)**	**Visit 15 (TC) Month 1**	**Visit 16 (TC) Month 2**	**Visit 17 (TC) Month 3**		**Sections noted below may be referenced in the main body of the protocol (for general information and information about the Main and Extension Study Periods) and in Appendix 7 (information specific to the Durability Period).**
Scheduled Day	**Day 365**	**Day 379**	**Day 393**	**Day 421**	**Day 449**		
Scheduling Window (Recommended)	**±4 days**	**+7 days**	**±7 days**	**±7 days**	**±7 days**		
Scheduled Week	**Week 52**	**Week 54**	**Week 56**	**Week 60**	**Week 64**		
Written Informed Consent for Durability Study Period	X						Consent may be obtained at Visit 9 or later, but prior to performing any procedures related to the Durability Period. If obtained prior to Visit 13, consent should be reviewed with the participant at Visit 13.
Inclusion/Exclusion Criteria for Durability Period	X						
Collect/Review Participant Comment Card	X	X	X	X	X	X	During the Durability Period, review of comment card will be conducted during each TC. See Section 8.1.6 below.
Issue/Instruct in use of new Participant Comment Cards for Durability Period	X						
Review Concomitant Medications	X	X					
Review Treatments Used for Cough and any use of ACEI			X	X	X	X	
Study Intervention Accountability	X						
Contact IRT System	X						

Study Period	**Extension/Off-treatment Durability Study Period**		**Off-treatment Durability Study Period**				**Notes**
		Follow-up				**Disc Durability Period**	**"Off-treatment Durability Study Period" is also referred to as "Durability Period"**
Visit Number	**Visit 13 (Last visit of Extension Study Period and start Durability Study Period)**	**Visit 14 (TC)**	**Visit 15 (TC) Month 1**	**Visit 16 (TC) Month 2**	**Visit 17 (TC) Month 3**		**Sections noted below may be referenced in the main body of the protocol (for general information and information about the Main and Extension Study Periods) and in Appendix 7 (information specific to the Durability Period).**
Scheduled Day	**Day 365**	**Day 379**	**Day 393**	**Day 421**	**Day 449**		
Scheduling Window (Recommended)	**±4 days**	**+7 days**	**±7 days**	**±7 days**	**±7 days**		
Scheduled Week	**Week 52**	**Week 54**	**Week 56**	**Week 60**	**Week 64**		
Efficacy Procedures							
Activate ePROs	X		X	X	X	X	See Section 8.2.2 below.
CSD	Daily						
Cough Severity VAS	Daily						
LCQ	X		X	X	X	X	
EQ5D-5L	X		X	X	X	X	
PGIC					X	X	
Safety Procedures							
Physical Examination	X						Directed physical exam
Vital Signs	X						
Weight	X						
Hematology & Chemistry	X						
Urinalysis (w/Microscopy)	X						Dipstick performed for ALL participants. Samples are also collected and sent to central laboratory for ALL participants. See Table 8 (Section 10.2 – Appendix 2).
Specialized Urine Collection for Crystal Assay	X						Only if central laboratory urinalysis is positive for crystals and/or unexplained hematuria. See Section 8.3.7 (main body of protocol).
Adverse Event Monitoring	X	X					Spontaneous reports of certain AEs will be collected after V14. See Section 8.4.1 below for AE reporting requirements after V14.

Study Period	Extension/Off-treatment Durability Study Period		Off-treatment Durability Study Period				Notes
		Follow-up				Disc Durability Period	"Off-treatment Durability Study Period" is also referred to as "Durability Period"
Visit Number	Visit 13 (Last visit of Extension Study Period and start Durability Study Period)	Visit 14 (TC)	Visit 15 (TC) Month 1	Visit 16 (TC) Month 2	Visit 17 (TC) Month 3		Sections noted below may be referenced in the main body of the protocol (for general information and information about the Main and Extension Study Periods) and in Appendix 7 (information specific to the Durability Period).
Scheduled Day	Day 365	Day 379	Day 393	Day 421	Day 449		
Scheduling Window (Recommended)	±4 days	+7 days	±7 days	±7 days	±7 days		
Scheduled Week	Week 52	Week 54	Week 56	Week 60	Week 64		
Pharmacodynamics/Biomarkers							
Pharmacokinetic Sample (blood)	X						

AE = adverse event; ACEI = angiotensin converting enzyme inhibitor; CSD = Cough Severity Diary; Disc = discontinuation; ePRO = electronic patient-reported outcome; EQ5D-5L = EuroQoL 5 Version 5L dimensions questionnaire; IRT = interactive response technology; LCQ = Leicester Cough Questionnaire; PGIC = Patient Global Impression of Change; TC = telephone contact; V = visit; VAS = Visual Analog Scale

2.1 Study Rationale

The MK-7264 Phase 3 program is designed primarily to define the efficacy, safety and tolerability of MK-7264, an orally available P2X3 antagonist, for the treatment of refractory or unexplained chronic cough (RCC, UCC). The Phase 3 studies are designed as randomized, parallel treatment for 1 year with either placebo or 1 of 2 MK-7264 dose levels (15 mg BID, 45 mg BID). However, it is currently unknown how participants will respond to cessation of treatment with MK-7264 after 1 year of therapy. Though limited, short-term data from Protocol 012 (the phase 2b dose ranging study with MK-7264) suggests that participants treated with MK-7264 for 12 weeks and observed 14 days after discontinuation of treatment showed a mean cough frequency off-treatment that did not increase compared to baseline (Week 0), suggesting no evidence of immediate rebound cough.

The addition of the Off-treatment Durability Study Period via the proposed amendment is intended to explore the impact of withdrawing MK-7264 therapy in RCC/UCC patients who have been treated for 1 year.

3 Hypothesis, Objectives, and Endpoints

Objectives	Endpoints
Exploratory	
• Objective: To evaluate the off-treatment durability after 1 year of treatment with MK-7264, over the course of 3 months off treatment	• Cough Severity VAS • LCQ • CSD • PGIC • EQ5D-5L
• Objective: To evaluate the time to "loss of response" in on-treatment responders over the course of 3 months off treatment	• Time to loss of response based on VAS • Time to loss of response based on CSD • Time to first use of a medication for cough

4.1 Overall Design

Approximately 150 total participants, in either this study or P027 at selected sites and countries, will enter an Off-treatment Durability Study Period at their last visit of the Extension Study Period (V13). The duration of this period will be approximately 3 months.

Individual participation in the entire study is expected to be approximately 66 weeks from Screening (Visit 1) through the end of the Off-treatment Durability Study Period (Visit 17).

Specific procedures to be performed during the Off-treatment Durability Period of the study, as well as associated visit windows, are outlined in the SoA above. General information about each procedure is in Section 8 of the main body of the protocol. Information specific to

the Off-treatment Durability Study Period is in various sections of this appendix (eg, Section 6.5 Concomitant Therapy).

The final database lock for this protocol will be conducted after participants have completed, or discontinued prior to the completion of the Extension Study Period. The final database lock will occur independent of enrollment in the Off-treatment Durability Study.

The data from the Off-treatment Durability Study Period will be summarized in a separate report from the Main and Extension Study Period data.

5.1 Inclusion Criteria

Participants are eligible to be included in the Off-treatment Durability Study Period only if all of the following additional criteria apply:

1. Participant completed the Main and Extension Study Periods, on study intervention, through the evening prior to Visit 13.

2. Participant completed the baseline, (Visit 2, Day 0) ePRO diaries (ie, LCQ and EQ5D-5L).

3. Participant completed the Visit 13 LCQ.

4. Participant was at least 80% compliant with completion of the Cough Severity VAS throughout all study periods.

5. Participant was at least 80% compliant with taking the study intervention throughout the Main and Extension Study Periods.

Informed Consent

6. Participant (or legally acceptable representative if applicable) provides written informed consent for the Off-treatment Durability Study Period.

5.2 Exclusion Criteria

Participants are excluded from participation in the Off-treatment Durability Study Period if the following criteria apply:

1. Participant is expected to need to take an angiotensin converting enzyme inhibitor during the Off-treatment Durability Study Period.

2. Participant experienced a serious or clinically significant adverse experience which is still present at the time of providing informed consent for the Off-treatment Durability Study Period.

3. Participant has had clinically significant changes in his/her general medical condition since enrolling in P030.

6.5 Concomitant Therapy

Between Visit 13 and Visit 14:

Participants must adhere to the guidance parameters (Section 6.5 of main protocol) and exclusion criteria (Section 5.2 of main protocol) regarding use of concomitant therapy until the Visit 14 telephone contact (ie, for approximately the first 2 weeks of the Off-treatment Durability Study Period).

After Visit 14:

- Participants may take medications and use other treatment as needed, with one exception:
    - Participants should continue to refrain from use of angiotensin converting enzyme inhibitors through completion of the Off-treatment Durability Study Period.

8.1.5.2 Concomitant Medications

During the Off-treatment Durability Study Period, only the following treatments will be recorded in the eCRF:

- Treatments used for cough, (prescription and over-the-counter) including natural/herbal remedies, lozenges, or drinks that may include an active anti-tussive or expectorant.
- Angiotensin converting enzyme inhibitors

8.1.6 Participant Comment Card

Participants will be provided new participant comment cards for use during the Off-treatment Durability Study Period to capture treatments used between scheduled telephone contacts. The participant comment card should be discussed at each telephone contact as outlined in the SoA. Participants will be encouraged to return comment cards to the study site. Instructions will be provided.

Concomitant therapy described above (Section 8.1.5.2) will be entered into the eCRF.

8.1.8 Assignment of Treatment/Randomization Number

Participants in the Off-treatment Durability Study Period will continue with the same treatment/randomization number assigned at study start.

8.2.2 Electronic Patient-reported Outcomes

Participants in the Off-treatment Durability Study Period will continue to complete the following ePRO measures as specified in the Off-treatment Durability Study Period SoA above: CSD, Cough Severity VAS, LCQ, PGIC, and EQ5D-5L.

Participants will be instructed to complete the daily ePRO measures (CSD and Cough Severity VAS) at approximately the same time each day, from the evening of Visit 13 (ie, the last visit of the Extension Period) until the evening before Visit 17 (ie, last visit of the Off-treatment Durability Study Period) or Discontinuation Visit. If a participant fails to complete the CSD and/or Cough Severity VAS ePRO measure(s), the eDiary will allow the participant, based on recall, to complete the measures at any time in the next 24 hours.

Participants will also be asked to complete the visit ePRO measures (LCQ, EQ5D 5L, and/or PGIC) on the day of the telephone visits as outlined in the SoA. If a participant fails to complete any of the visit ePRO measure(s), the eDiary will allow the participant, based on recall, to complete these measures at any time in the next 48 hours. If these visit ePROs are not completed, site personnel may be asked to reactivate visit questionnaires for the participant and the participant may be asked to complete them at a later date.

Electronic PRO measures must be activated as outlined in the SoA. Visit 13, Visit 15, Visit 16, Visit 17 and the Discontinuation visit ePROs are “activated” by entering actual visit/event dates in the vendor portal (Engage).

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

Between Visit 13 and Visit 14:

For all study participants, including those entering the Off-treatment Durability Study Period, see Section 8.4.1 of the main protocol for information regarding collection of AEs, SAEs, and Other Reportable Safety Event Information through the 14-day safety follow-up contact (Visit 14).

After Visit 14:

For participants in the Off-treatment Durability Study Period, after Visit 14, the following must be reported to the Sponsor within 24 hours of learning of the event:

- Any drug-related SAEs or SAEs considered to be study participation related and brought to the attention of the investigator
- Any drug-related NSAEs brought to the attention of the investigator during the time the participant is active in the Off-treatment Durability Study Period
- Any pregnancy that is brought to the attention of the investigator during the time the participant is active in the Off-treatment Durability Study Period. The pregnancy must be followed to completion/termination. If the pregnancy continues to term, the outcome (health of the infant) must also be reported.

If the investigator elects to submit AEs for non-Merck products, they should be reported to the Marketing Authorization Holder (MAH) for that product or to the health authority according to the institution's policy or local laws and regulations.

8.10 Visit Requirements

Off-treatment Durability Study Period

- Participants must provide written informed consent to participate in the Off-treatment Durability Study Period. (See Sections 8.1.1 and 8.1.1.1 of the main body of the protocol.)
    - Consent may be obtained at Visit 9 or later, but prior to performing any procedures related to the Off-treatment Durability Study Period. If obtained prior to Visit 13, the consent should be reviewed with the participant at Visit 13.
- Participants will begin the 3-month Off-treatment Durability Study Period on the same day as their final clinic visit (Visit 13) of the Extension Study Period.
- Participants will not take study intervention during the Off-treatment Durability Study Period.
- Participants will continue to complete ePROs as outlined in the SoA.
- No additional clinic visits will be required after the final visit of the Extension Study Period (Visit 13).
    - Telephone contacts will occur as specified on the SoA

Participants will be provided with instructions to return their eDiary device to the study site at the end of the Off-treatment Durability Study Period.

9 Statistical Analysis Plan

9.2 Responsibility for Analyses/In-house Blinding

The Main Period of the phase 3 study will be completed while the Extension Study Period and Off-treatment Durability Study Period are ongoing. Selected members of the Sponsor study team may be unblinded to review the data from the Main Study Period and author a CSR for facilitating regulatory submission.

A final database lock will occur after all participants have completed the Extension Study Period. This database lock will occur independent of enrollment into the Off-treatment Durability Study Period. The data from the Off-treatment Durability Study Period will be summarized in a separate report from the Main and Extension Study Period data.

The investigator site personnel and the participants will be blinded to intervention assignment until the entire study is completed.

9.3 Hypotheses/Estimation

No hypothesis will be tested for the Off-treatment Durability Study Period. Point estimates and 95% confidence intervals (as appropriate) will be provided for the efficacy and safety endpoints.

9.4 Analysis Endpoints

The main analyses will be performed in all subjects who enter the Off-treatment Durability Study Period. It is acknowledged that this population will include participants with varying measures of cough impact and severity as assessed by the ePROs both at the end of the 1-year treatment (ie, Week 52), as well as compared to prestudy baseline (ie, Week 0).

The primary metric of treatment durability will compare the ePRO measurement after 12 weeks off-treatment, to the measurement at Week 52 (ie, immediately prior to treatment discontinuation), and will specifically seek to describe the proportion of participants who either fail to maintain their treatment response, or who maintain treatment response.

One way to describe “failure to maintain the response” for a given ePRO, as an example, is that either the 12 weeks off-treatment measurement is decreased by at least X% of the Week 52 response, or the participant needs treatment for cough. The actual threshold would be based on considerations about clinically important differences and real-world data experiences. The definition will be specific to each ePRO.

In addition, the data will be explored to examine the impact of on-treatment response to MK-7264 on the outcome measures described above. Specifically, the on-treatment measurement (defined as the difference in the Week 52 measurement compared to Week 0) will be categorized using different threshold definitions of "response", and the subsequent off-treatment ePRO measurement in the Off-treatment Durability Study Period will be explored as a function of the on-treatment response.

One way to describe the "on-treatment response" for VAS, as an example, is that a participant has a Week 52 measurement at least X-mm lower than the Week 0 measurement. The definition will be specific to each ePRO.

The final details about the analysis endpoints, as well as other aspects of the analyses, will be documented in an Off-treatment Durability Study Period memo, separate from the treatment period supplemental SAP, to be finalized before the completion of the Off-treatment Durability Study Period.

9.5 Analysis Populations

Analyses will generally be based on All Subjects Enrolled.

9.6.1 Statistical Methods for Efficacy Analyses

For each ePRO separately, the proportion of participants who maintain treatment response during the 12-week off-treatment period will be estimated and the associated 95% CI will be calculated using the Clopper-Pearson method.

Time-to-event endpoints will be summarized using Kaplan-Meier estimates.

9.6.2 Statistical Methods for Safety Analyses

In the beginning of the Off-treatment Durability Study Period, up to 14 days after the last dose of study intervention, AE collection will follow the same process as in the Main and Extension Study Periods and will be analyzed with the AEs from the Main and Extension Study Periods in the CSR.

For the Off-treatment Durability Study Period, post 14 days after the last dose of study intervention, only drug-related SAEs, SAEs considered to be study participation related, drug-related NSAEs, and any pregnancy that is brought to the attention of the investigator will be collected. While such events will not be considered treatment emergent, they will be summarized in a separate report.

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The number and percentage of participants who discontinue from the Off-treatment Durability Study Period and the primary reasons for discontinuation will be displayed.

Demographic variables (including age, gender, race, weight and height), baseline characteristics, and primary and co-morbid conditions will be summarized at Week 0 either by descriptive statistics or categorical tables.

9.7 Interim Analyses

No interim analysis is planned during the Off-treatment Durability Study Period.

9.8 Multiplicity

Multiplicity is not applicable since this study has no inferential testing.

9.9 Sample Size and Power Calculations

The intended sample size for the Off-treatment Durability Study Period is approximately 150 participants across both P027 and P030.

9.10 Subgroup Analyses

No subgroup analysis is planned.

9.11 Compliance (Medication Adherence)

Not applicable since no study intervention will be taken by the participants during the Off-treatment Durability Study Period.

9.12 Extent of Exposure

Not applicable since no study intervention will be taken by the participants during the Off-treatment Durability Study Period.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
ACCP	American College of Chest Physician
AE	Adverse event
ALT (SGPT)	Alanine aminotransferase (serum glutamic pyruvic transaminase)
ANCOVA	Analysis of covariance
APaT	All participants as treated
ATP	Adenosine triphosphate
AST (SGOT)	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
ATS	American Thoracic Society
BID	Twice daily
CF	Compact flash
CFR	Code of Federal Regulations
CI	Confidence interval
CKD EPI	Chronic Kidney Disease Epidemiology Collaboration
CP	Conditional power
CRF	Case report form
CSD	Cough Severity Diary
CSR	Clinical study report
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECI	Event of clinical interest
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOC	Executive Oversight Committee
ePRO	Electronic patient-reported outcome
EQ5D-5L	EuroQoL 5 Dimensions Questionnaire
ERS	European Respiratory Society
FAS	Full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GERD	Gastroesophageal reflux disease
HARQ	Hull Airway Reflux Questionnaire
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive response technology
LCQ	Leicester Cough Questionnaire
NSAE	Non-serious adverse event
PGIC	Patient Global Impression of Change
PK	Pharmacokinetic
PP	Per-protocol
PRO	Patient-reported outcome
RBC	Red blood cell (count)

Abbreviation	Expanded Term
RNA	Ribonucleic acid
SAE	Serious adverse event
SD	Standard deviation
SF-12	12-item short form survey
SoA	Schedule of Activities
SOP	Standard operating procedure
sSAP	Supplemental Statistical Analysis Plan
UACS	Upper airway cough syndrome
VAS	Visual analog scale
WBC	White blood cell (count)
WOCBP	Woman/women of childbearing potential
WPAI	Work productivity and activity impairment

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