- 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 (H3): 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 12	- Proportion of participants with a ≥30% reduction from baseline in 24-hour coughs per hour at Week 12
- 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 12 - Proportion of participants with a ≥2.7-point reduction from baseline in mean weekly CSD total score at Week 12 - Proportion of participants with a ≥30 mm reduction from baseline in Cough Severity Visual Analog Scale (VAS) score at Week 12
- Objective: To evaluate the ability of MK-7264 to provide a clinically significant improvement in cough specific quality of life	- Proportion of participants with a ≥1.3-point increase from baseline in Leicester Cough Questionnaire (LCQ) total score at Week 12

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

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.

Study Period	Screen-ing	Base-line	Main Study Period							Extension Study Period							Follow -up	Disc	Notes
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**		**Visit 5**		**Visit 6**		**Visit 7**	**Visit 8 (TC)**	**Visit 9**	**Visit 10 (TC)**	**Visit 11**	**Visit 12 (TC)**	**Visit 13**	**Visit 14 (TC)**		**V8, V10, V12, and Follow-up to be conducted by telephone**
Scheduled Day	**Day -14 to Day -7**	**Day 0**	**Day 1**	Day 27	**Day 28**	Day 55	**Day 56**	Day 83	**Day 84**	**Day 112**	**Day 140**	**Day 168**	**Day 217**	**Day 266**	**Day 315**	**Day 365**	**Day 379**		
Scheduling Window (Recommended)	**NA**	**NA**	**NA**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**±4 dys**	**±4 dys**	**±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**		
Study Intervention Distribution and/or Accountability			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 (MS/ ES)	
Efficacy Procedures																			
Attach Cough Monitor		X		X		X		X										X (MS)	See Section 8.2.1.
Collect Cough Monitor			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.
CSD	Daily	X	Daily							Daily				X		X			See Section 8.2.2.1.
Cough Severity VAS	Daily	X	Daily							Daily				X		X			See Section 8.2.2.2.
LCQ		X			X		X		X	X	X	X		X		X		X (MS/ ES)	See Sections 8.2.2 and 8.2.2.3.
SF-12		X							X			X						X (MS/ ES)	See Section 8.2.2.
WPAI		X							X			X						X (MS/ ES)	
EQ5D-5L		X							X			X						X (MS/ ES)	

Objectives	Endpoints
• 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 12 • Proportion of participants with a ≥2.7-point reduction from baseline in mean weekly CSD total score at Week 12 • Proportion of participants with a ≥30 mm reduction from baseline in Cough Severity Visual Analog Scale (VAS) score at Week 12
• Objective: To evaluate the ability of MK-7264 to provide a clinically significant improvement in cough specific quality of life	• Proportion of participants with a ≥1.3-point increase from baseline in Leicester Cough Questionnaire (LCQ) total score at Week 12
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

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 12. 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 12 in 24-hour coughs per hour in MK-7264 relative to placebo. Utilizing 24-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 12. 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.

CCI [redacted]

[redacted]

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

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

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

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,

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).

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 signing the informed consent.

Female Participants

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

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

        OR

    b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 from 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.

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 otherwise stated in this section. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

For participants who receive study intervention, any medication (including over-the-counter medications) or therapy administered to the participant during the course of the study will be recorded on the Prior and Concomitant Therapy case report form (CRF). Treatments for chronic cough received by the participant 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.

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 70 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

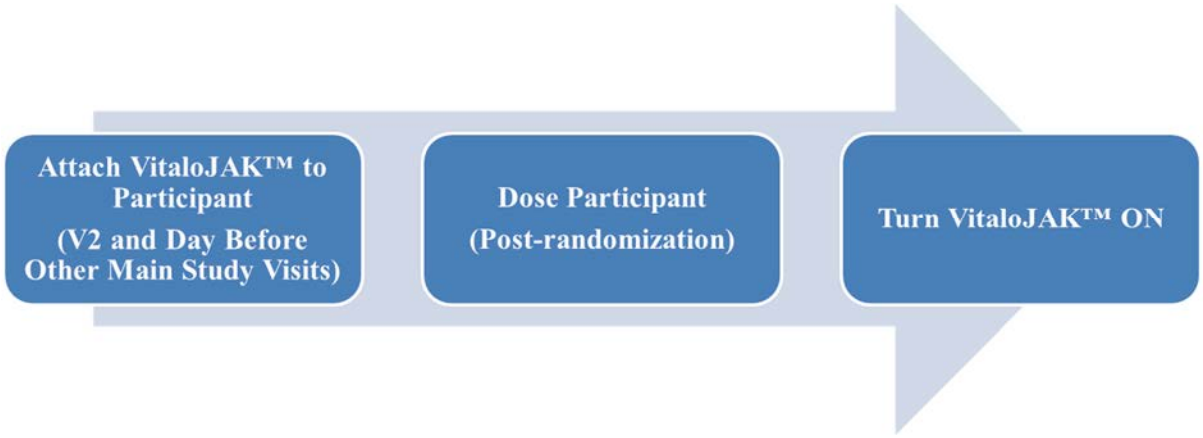
The investigator or medically qualified designee will explain the future biomedical research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the future biomedical research substudy. A copy of the informed consent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

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 4-6 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

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 PROs 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** (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 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

8.2.2.5 Work Productivity and Activity Impairment Questionnaire

The WPAI questionnaire yields 4 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), 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 below. 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 discontinue from the study intervention but continue to be monitored, only the AEs and other reportable safety events that are shown in Table 3 need to be reported. This specific approach for reporting starts from completion of the safety follow-up telephone call/visit following cessation of intervention until 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

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:
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all[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:

a. 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.

Secondary Efficacy Endpoints

- Awake coughs per hour at Week 12
- Proportion of participants with a ≥30% reduction from baseline in 24-hour coughs per hour at Week 12
- Proportion of participants with a ≥1.3 point reduction from baseline in mean weekly CSD total score at Week 12
- Proportion of participants with a ≥2.7 point reduction from baseline in mean weekly CSD total score at Week 12
- Proportion of participants with a ≥30 mm reduction from baseline in Cough Severity VAS score at Week 12
- Proportion of participants with a ≥1.3-point increase from baseline in LCQ total score at Week 12

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).

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, and >8 to ≤12 weeks in Main study period; and >12 to ≤24 weeks, >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".

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 intervention as instructed in Section 8. When a participant takes less than or more than the required 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.

Laboratory Assessments	Parameters
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.

Events NOT meeting the AE definition

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

10.3.2 Definition of SAE

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

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

1. **Results in death**
2. **Is life-threatening**
    - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
3. **Requires inpatient hospitalization or prolongation of existing hospitalization**
    - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.
4. **Results in persistent or significant disability/incapacity**
    - The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- 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:

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

Not applicable.

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.

Abbreviation	Expanded Term
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
WPAI	Work productivity and activity impairment
WBC	White blood cell (count)
WOCBP	Woman/Women of childbearing potential

Intervention Model	Parallel This is a multi-site study. This study includes a 12-week Main study period, followed by a 40-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 31 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 720 participants will be enrolled.

1.3 Schedule of Activities (SoA)

Study Period	Screen-ing	Base-line	Main Study Period							Extension Study Period							Follow -up	Disc	Notes
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**		**Visit 5**		**Visit 6**		**Visit 7**	**Visit 8 (TC)**	**Visit 9**	**Visit 10 (TC)**	**Visit 11**	**Visit 12 (TC)**	**Visit 13**	**Visit 14 (TC)**		**V8, V10, V12, and Follow-up to be conducted by telephone**
Scheduled Day	**Day -14 to Day -7**	**Day 0**	**Day 1**	Day 27	**Day 28**	Day 55	**Day 56**	Day 83	**Day 84**	**Day 112**	**Day 140**	**Day 168**	**Day 217**	**Day 266**	**Day 315**	**Day 365**	**Day 379**		
Scheduling Window (Recommended)	**NA**	**NA**	**NA**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**±4 dys**	**±4 dys**	**±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 in the use of Participant Comment Card			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 (MS/ ES)	
Informed Consent for Future Biomedical Research	X																		
Inclusion/ Exclusion Criteria	X	X																	
Demographics, Medical, & Medication History	X																		
Prior/ Concomitant Medications	X	X	X		X		X		X	X	X	X	X	X	X	X	X	X (MS/ ES)	

Study Period	Screen-ing	Base-line	Main Study Period							Extension Study Period							Follow -up	Disc	Notes
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**		**Visit 5**		**Visit 6**		**Visit 7**	**Visit 8 (TC)**	**Visit 9**	**Visit 10 (TC)**	**Visit 11**	**Visit 12 (TC)**	**Visit 13**	**Visit 14 (TC)**		**V8, V10, V12, and Follow-up to be conducted by telephone**
Scheduled Day	**Day -14 to Day -7**	**Day 0**	**Day 1**	Day 27	**Day 28**	Day 55	**Day 56**	Day 83	**Day 84**	**Day 112**	**Day 140**	**Day 168**	**Day 217**	**Day 266**	**Day 315**	**Day 365**	**Day 379**		
Scheduling Window (Recommended)	**NA**	**NA**	**NA**	**NA**	**±4 dys**	**NA**	**±4 dys**	**NA**	**±4 dys**	**±4 dys**	**±4 dys**	**±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**		
PGIC									X			X						X (MS/ ES)	
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 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 (MS/ ES)	
Height	X																		
Weight	X				X				X			X				X		X (MS/ ES)	
12-lead ECG	X																		
Spirometry	X																		Not required if done within past 1 year and during a clinically stable period.

4 STUDY DESIGN

4.1 Overall Design

Approximately 720 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 (12-week treatment period after Baseline): 84 days (see Section 8.10.3)
- Extension study period (40-week treatment period after the Main study period): 281 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, and the day before Visit 6 and Visit 6) 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.

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].

The impact of chronic cough on HRQoL as assessed by the LCQ is included as the third 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 12.

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).

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, 12 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:

a. 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.

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.

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 Treatment 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 postnasal 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.

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 Sections 5.1 and 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

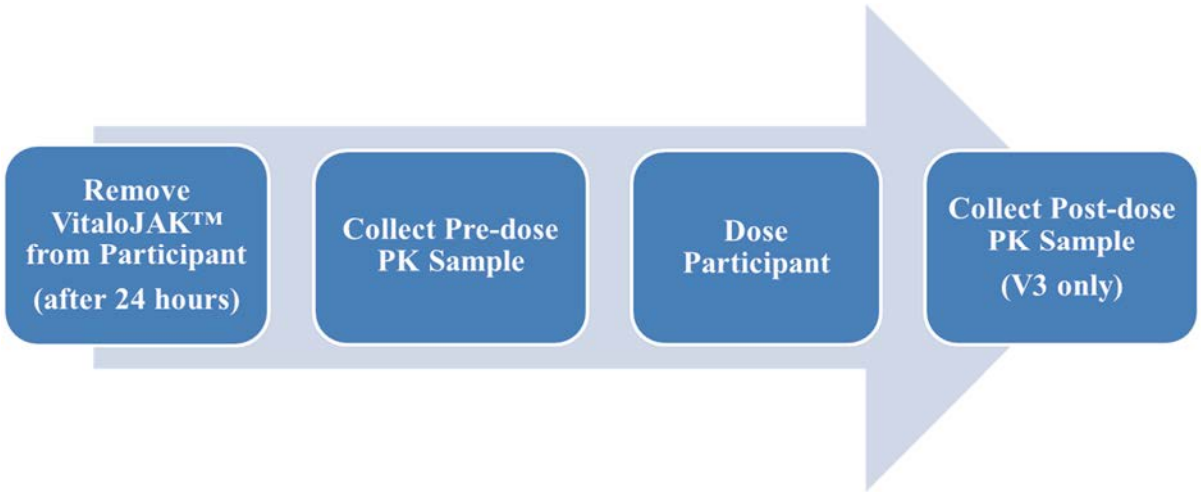
A medical history will be obtained by the investigator or qualified designee (refer to eCRF entry guidelines).

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 electronic case report form (eCRF) entry guidelines).

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.

text) during the Extension study period to remind them to complete the CSD during these weeks.

8.2.2.2 Cough Severity Visual Analogue 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.

8.2.2.3 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.

8.2.2.4 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.

8.8 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

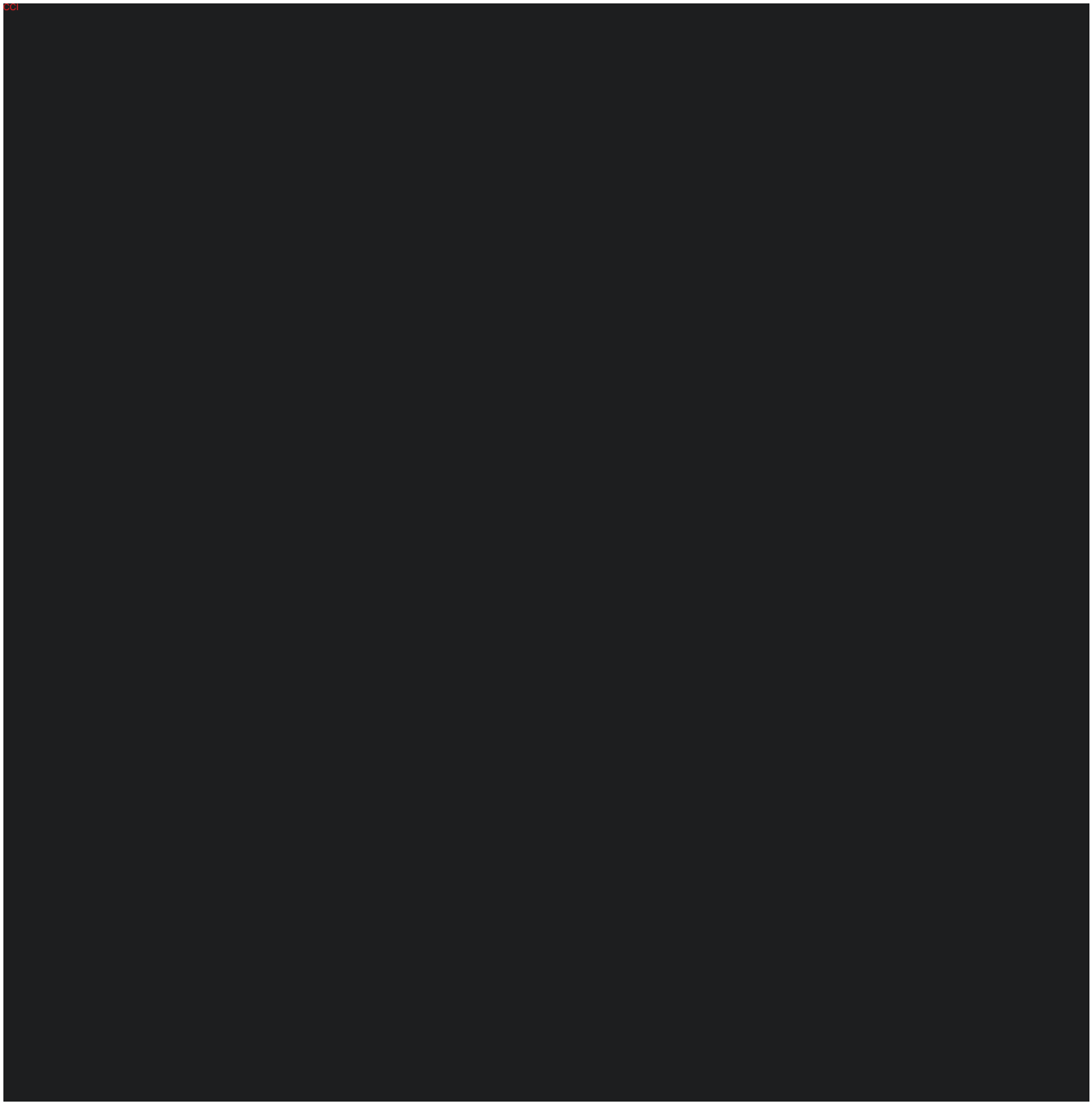
Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

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

Responders in 24-hour Coughs per Hour



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.

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 Endpoints[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 one 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.

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.

10.3 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.

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

5. Is a congenital anomaly/birth defect

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

6. Other important medical events

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

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

10.3.3 Additional Events Reported

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.

- **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?

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.

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.

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