Overall Design:

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

Number of Participants:

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

1.3 Schedule of Activities (SoA)

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

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

4 STUDY DESIGN

4.1 Overall Design

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

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

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

Individual participation is expected to be approximately 56 weeks from Screening through the Follow-up period.

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

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

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

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

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Safety Endpoints

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

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

4.2.1.2 Efficacy Endpoints

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

Secondary endpoint:

Leicester Cough Questionnaire (LCQ)

Exploratory endpoints:

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

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

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

The impact of chronic cough on HRQoL as assessed by the LCQ is included as the secondary endpoint. The LCQ is a 19-item cough-specific HRQoL questionnaire which contains three domains (physical, psychological and social), calculated as a mean score for each domain ranging from 1 to 7 and total score ranging from 3 to 21. Each item on the LCQ assesses symptoms or the impact of symptoms on HRQoL over the past two weeks using a 7-point Likert scale ranging from 1 to 7. Higher scores indicate better HRQoL. Data obtained from

the LCQ will provide information on the impact of chronic cough on patients' daily lives, beyond objective cough counts and severity, which is valuable information for assessing the full benefit of effective cough control.

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

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

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

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

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

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

4.2.1.3 Planned Exploratory Biomarker Research

4.2.1.3.1 Planned Genetic Analysis

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

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

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

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

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

Demographics

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

Female Participants

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

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

        OR

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

Informed Consent

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

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

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

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

1. Opioids (including codeine) for the treatment of cough are not allowed from 1 week prior to Visit 1 through Visit 2. Participants should not initiate therapy with opioids (including codeine) for the treatment of cough from Visit 2 through completion of the treatment period.

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

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

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

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

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

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

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

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

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

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

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

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

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

8.2.1.2 Cough Severity Diary (CSD)

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

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

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

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

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

8.2.1.4 Patient Global Impression of Change (PGIC)

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

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

8.3 Safety Assessments

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

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

8.3.1 Chest Radiography/Computed Tomography Thorax Scan

A chest radiograph or computer tomography scan of the thorax should be performed locally for participants, at Screening, if this has not been done within the last 5 years and after the onset of chronic cough. The chest radiograph or computer tomography scan of the thorax should not demonstrate any abnormality considered to be significantly contributing to the chronic cough or any other clinically significant lung disease in the opinion of the investigator (see inclusion criterion 1, Section 5.1).

8.3.2 Physical Examinations

A complete physical examination will include assessments of the following general appearance; skin and lymphatic; eyes, ears, nose, throat; cardiovascular system; respiratory system; abdomen/gastrointestinal system; urological system; musculoskeletal and neurological systems. Other body systems may be examined.

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

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

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

8.3.3 Vital Signs and Weight and Height Measurements

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

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

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

8.3.4 Electrocardiograms

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

8.3.5 Spirometry

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

Spirometry performed within the past year of Visit 1 and after the onset of chronic cough is acceptable if the investigator confirms that spirometry was done during a period where the participant was clinically stable (eg. not during an upper respiratory infection).

8.3.6 Clinical Safety Laboratory Assessments

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

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

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

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

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

8.3.7 Renal and Urological Safety Procedures

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

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

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

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

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

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

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

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

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

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

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

The investigator, who is a qualified physician, is responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE, as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

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

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

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

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

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

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

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

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

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

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-Specified Follow-up Period	Reporting Time Period: After the Protocol Specified Follow-up Period	Timeframe to Report Event and Follow-up Information to SPONSOR:
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report* - Potential DILI - Require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (Do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report* - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all*	Not required	Within 5 calendar days of learning of event

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

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECI), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

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

8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

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

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

8.5 Treatment of Overdose

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

No specific information is available on the treatment of overdose. Oral doses of up to 1800 mg BID for 14 days were explored in earlier clinical studies without any untoward clinical effects (see MK-7264 IB). Overdose should be treated according to the participant's clinical signs and symptoms.

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

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

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

- Blood for Genetic Analysis

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

9.5.2 Safety Analysis Population

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received at least one dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. Discontinued participants before Week 52 will be included in APaT population. For most participants this will be the treatment group to which they are randomized. Participants who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received.

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

9.6 Statistical Methods

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

9.6.1 Statistical Methods for Efficacy Analyses

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

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

9.6.2 Statistical Methods for Safety Analyses

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

All safety analyses will be based on APaT population.

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

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

10.3.1 Definition of AE

AE definition

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

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

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent, or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator.

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

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

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

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

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

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

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

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

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

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

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

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

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

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

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

Assessment of intensity

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

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

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

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

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

Assessment of causality

- Did the Sponsor's product cause the AE?

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

SAE reporting to the Sponsor via paper CRF

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

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

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

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

Female Participants

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

Table 5 Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception ○ Oral
● Progestogen only hormonal contraception ○ Oral
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Intrauterine hormone-releasing system (IUS) ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Notes: [a] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly).

10.5.3 Pregnancy Testing

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

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

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

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

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

3.6 Statistical Methods

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

3.6.1 Statistical Methods for Efficacy Analyses

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

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

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

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

<u>LCQ total score</u>

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

Intervention Groups and Duration:

Intervention Groups

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

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

Study Governance Committees:

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

Study Accepts Healthy Volunteers: No

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

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

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

DNA samples will be used for research related to the study intervention(s), the disease under study, and related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate).

DNA samples will be analyzed for variation across the entire genome. Analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

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

4.2.1.4 Future Biomedical Research

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

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

4.2.2 Rationale for the Use of Comparator/Placebo

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

4.3 Justification for Dose

4.3.1 Doses for This Study

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

The known mechanism of action of MK-7264 and related clinical study results support that the efficacy of MK-7264 in decreasing cough, and the prevalence of the most common AE, dysgeusia, are both dose related. In order to allow patients and prescribers appropriate flexibility based upon individual clinical needs, the MK-7264 development program has targeted two different doses to study in the Phase 3 program.

Study Participation

7. The participant is willing and able to comply with all aspects of the protocol including demonstrating an ability to follow study procedures (including completion of the patient report outcomes [PROs]) to the satisfaction of the investigator/qualified designee prior to randomization (see Section 8.1.2).

5.2 Exclusion Criteria

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

Medical Conditions

1. Current smoker.

2. Individuals who have given up smoking within 12 months of Visit 1.

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

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

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

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

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

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

9. Is, at the time of signing informed consent, a user of recreational or illicit drugs or has had a recent history (within the last year) of drug or alcohol abuse or dependence in the opinion of the principal investigator or the sub-investigator.

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

Table 2 Example of Concomitant Treatments Permitted in the Study

Condition	Treatment
GERD	Anti-reflux therapy (proton pump or H_2 blockers), and/or pro-kinetic agents
Asthma	Bronchodilators, inhaled corticosteroids, and/or other anti-inflammatory agents
SBS	14-membered ring macrolides (e.g. erythromycin)
Atopic cough	Antihistamine

5. Angiotensin converting enzyme inhibitors are not allowed from 3 months prior to signing informed consent through completion of the treatment period.

6.5.1 Rescue Medications and Supportive Care

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

6.6 Dose Modification

Dose modification is not allowed in this study.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

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

8.8.1 Planned Genetic Analysis Sample Collection

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

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

8.9 Future Biomedical Research Sample Collection

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

- Leftover DNA for future research

8.10 Visit Requirements

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

8.10.1 Pre-screening

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

8.10.2 Screening

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

8.10.3 Baseline

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

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

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

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

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Demographic and Baseline Characteristics

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

Demographic variables (including age, gender, weight, and height), baseline characteristics, primary and comorbid conditions, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables.

9.7 Interim Analyses

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

9.8 Multiplicity

No multiplicity adjustment is planned in this trial.

9.9 Sample Size and Power Calculations

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

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

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

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

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

f. **Other important medical events**

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

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

10.3.3 Additional Events Reported

Additional events that require reporting

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

- Is a cancer

- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

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

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

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

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

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

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

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

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

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

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

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

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

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

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

This appendix is not applicable for this study.

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

1. **Definitions**

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

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

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

d) DNA: Deoxyribonucleic acid.

e) RNA: Ribonucleic acid.

2. **Scope of Future Biomedical Research**

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

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

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

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

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

a) Participants for Enrollment

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

11 REFERENCES

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[Kanemitsu, Y., et al 2016]	Kanemitsu Y, Niimi A, Matsumoto H, Iwata T, Ito I, Oguma T, et al. Gastroesophageal dysmotility is associated with the impairment of cough-specific quality of life in patients with cough variant asthma. Allergol Int. 2016 Jul;65(3):320-6.	04SV2L

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

Mean weekly CSD total score

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

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

EQ5D-5L

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

EQ VAS

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

PGIC

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