Overall Design:

Study Phase	Phase 2a
Clinical Indication	Treatment of acute cough
Population	Healthy adult participants with induced viral URTI
Study Type	Interventional
Type of Design	Parallel study design
Type of Control	Placebo
Study Blinding	Double-blind
Estimated Duration of Study	The Sponsor estimates that the study will require approximately ~ 45 weeks from the time the first participant signs the informed consent until the last participant's last study-related phone call or visit.

Number of Participants:

Approximately 188 participants will be enrolled.

Treatment Groups and Duration:

Treatment Groups	Stage 1 - Prior to Interim Analysis (efficacy IA): • MK-7264 45 mg twice daily (BID) • Placebo Stage 2 - Post-efficacy IA: • MK-7264 45 mg BID • MK-7264 15 mg BID* • Placebo * The MK-7264 15 mg BID treatment group during Stage 2 is applicable only if a decision is made to add a MK-7264 lower dose group based on results of the efficacy IA.
Duration of Participation	Each participant will participate in the study for approximately 50 days from the time the participant signs the informed consent form through the final contact. After a screening period of up to 28 days, each eligible participant will receive assigned treatment for 7 days. At the end of the treatment period, each participant will be discharged from the clinical research unit and have a safety follow-up phone call 14 days after completion or discontinuation or withdrawal of the study treatment.

Study governance considerations are outlined in Appendix 1. A list of abbreviations used in this document can be found in Appendix 6.

Study Period	Screening			Treatment							Dis-charge	Telephone Follow-Up (14 days post last dose)	Early Discon-tinuation	Notes
			Base-line	Random-ization										
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**			
Scheduled Day and Window:	**Day -28 to Day -3**	**Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 22** (+ 3 days)	**Between Days 1 and 7**	
Urine Cotinine Test	X		X											Performed at site locally
Urine Drug Screen (UDS)	X													Performed at site locally. Additional UDS can be performed for cause during the study, at the investigator's discretion .
Nasal Swabs for HRV 16 polymerase chain reaction (PCR)				X	X	X								After inoculation of HRV-16, nasal swabs are collected every 12 hours for 72 hours (Day 1 to Day 3)
Efficacy Procedures														
Attach Cough Monitor				X										Just prior to inoculation with HRV-16
Remove Cough Monitor											X			
Cough Monitoring				X	X	X	X	X	X	X				Cough monitoring using cough monitor device (VitaloJAK™) begins after first dose of study treatment on Day 1 through Day 7 or early discontinuation.
Adenosine Triphosphate (ATP) Cough Challenge			X	X			X			X				Manual cough monitoring is performed during ATP cough challenge at designated visits only during Stage 1 On Days 1, 4, and 7, it is performed 2 hours (± 30 min) post-morning dose.

Objective(s)/Hypotheses	Endpoint(s)
• Objective: To evaluate the efficacy of MK-7264 on cough reflex sensitivity to ATP	• C2 and C5 (ie, concentration of cough challenge agent inducing 2 or more coughs, and 5 or more coughs, respectively) during Stage 1 on Days 1, 4, and 7
• Objective: To assess the plasma pharmacokinetics (PK) of MK-7264	• PK parameters (mean maximum observed concentration [C_{max}], mean minimum observed concentration [$C_{min,}$], time to reach C_{max} [T_{max}], and area under the concentration time-curve [$AUC_{0-\tau}$] on Days 1, 2, 4, and 7
• 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 this trial.	• Germline genetic variation

5. Study Design

5.1 Overall Design

This is a double-blind, randomized, placebo-controlled, parallel-group trial of MK-7264 for acute cough in healthy male and female adult participants with induced viral URTI. The total trial duration for each participant is approximately 50 days, including a screening period of up to 28 days, a 7-day treatment period, 1 day for discharge from the clinic, and a 14-day safety follow-up period after the last dose of trial treatment. An efficacy IA is planned for the trial after approximately 50 randomized participants complete (or discontinue early from) the treatment period (Day 1 to Day 7). Details of the efficacy IA are described in Section 10.7.1.

Screening Period

The Screening Period (~ Day -28 to Day -2) should be only as long as it is needed to complete all screening activities.

On Day -2, eligible participants will be admitted to the clinic. Participants will remain confined to the clinic until completion of the treatment period on Day 7. Between Day -2 (Visit 2) and Day -1 (Visit 3), participants will be under observation to ensure that they are healthy (ie, do not show any signs/symptoms of a community-acquired URTI or any other

type of infection). During this time, safety labs will be evaluated to ensure lab values do not meet criteria for exclusion and are not clinically significant.

Treatment Period

On Day 1 (Visit 4), participants who continue to meet eligibility criteria will be randomized according to the Sponsor's computer-generated allocation schedule via an interactive voice response system/integrated web response system (IVRS/IWRS). During Stage 1 of the trial (ie, all enrollment prior to the efficacy IA), approximately 50 eligible participants will be randomized in a 1:1 ratio to either MK-7264 45 mg BID or placebo. An efficacy IA will be performed when approximately 50 randomized participants in Stage 1 complete (or discontinue early from) the Treatment Period (Day 1 to Day 7). Enrollment (ie, screening and randomization) will be paused once Stage 1 enrollment is complete, pending the results of the efficacy IA. In Stage 2 (ie, all enrollment post- efficacy IA), if a decision is made to include a lower dose of MK-7264 based on the efficacy IA results, participants will be randomized to MK-7264 45 mg BID, MK-7264 15 mg BID, or placebo in a ratio (1:2:1, respectively) that will provide approximately 50 participants per group at the end of the trial.

If the MK-7264 15 mg BID treatment group is not included in Stage 2, depending on the re-estimated sample size during the efficacy IA as described in Section 10.7.1, a total of 100 to 188 participants (50 to 94 per treatment group for Stages 1 and 2 combined) will be randomized in a 1:1 ratio to either MK-7264 45 mg BID or placebo.

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

This trial will use an adaptive design based on pre-specified criteria. There is one planned efficacy IA when approximately 50 randomized participants have completed (or discontinued early from) Stage 1 of the trial.

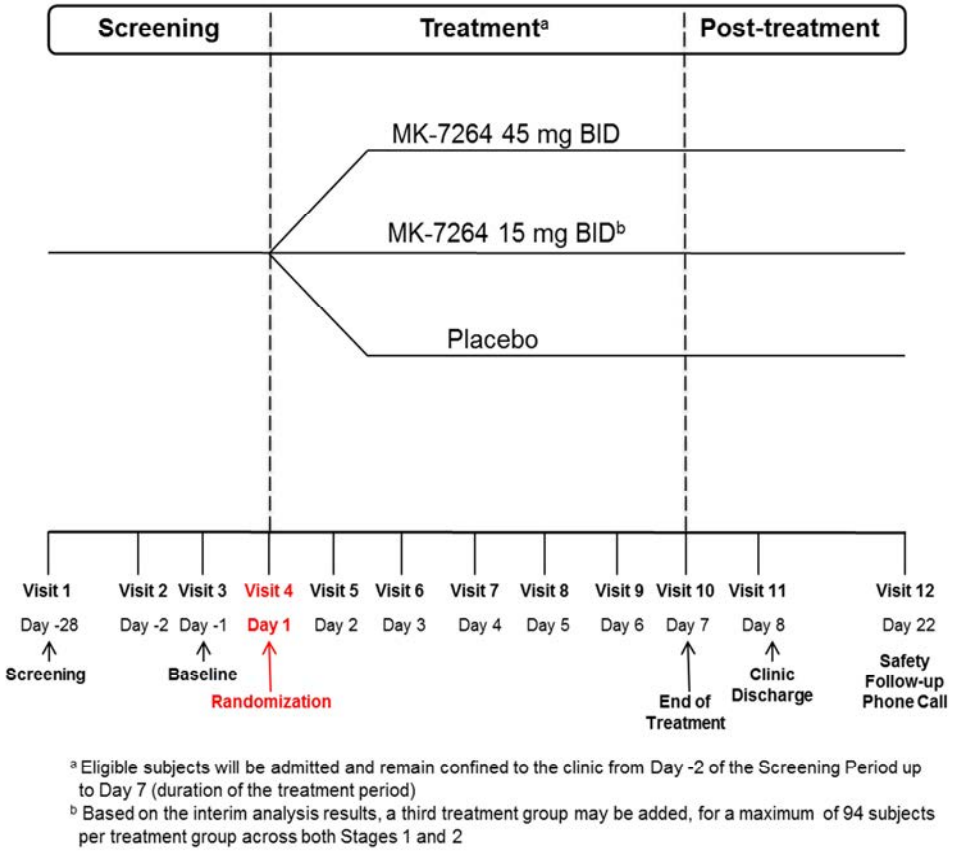
The results of the efficacy IA will be reviewed and the decision regarding trial modifications will be made by the standing internal Data Monitoring Committee (siDMC). The following actions are possible decisions from the siDMC, based on the results of the efficacy IA:

- The trial may be stopped for futility
- The sample size may be re-estimated
- Continue the trial as planned
- A lower dose of MK-7264 (15 mg BID) may be added

Details are described in Section 10.7.1.

5.1.1 Study Diagram

The study design prior to the efficacy IA (Stage 1) is depicted in Figure 1. Based on the results of the efficacy IA, in Stage 2 of the trial (post-efficacy IA), a third treatment group may be added in which participants would receive a lower dose of MK-7264 (15 mg BID). The study design for Stage 2 (post-efficacy IA), if an additional treatment arm is added, is presented in Figure 2.



[a] Eligible subjects will be admitted and remain confined to the clinic from Day -2 of the Screening Period up to Day 7 (duration of the treatment period)
[b] Based on the interim analysis results, a third treatment group may be added, for a maximum of 94 subjects per treatment group across both Stages 1 and 2

Abbreviations: BID = twice daily; IA = interim analysis

Figure 2 Study Design for Stage 2 (Post-Efficacy IA) with Additional Treatment Arm

5.2 Number of Participants

Approximately 100 to 188 participants will be randomized in this study.

5.3 Beginning and End of Study Definition

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

5.3.1 Clinical Criteria for Early Study Termination

Early study termination will be the result of the criteria specified below:

- Based on the efficacy IA, if the siDMC recommends termination of the trial per the stopping rules as stated in the siDMC Charter.

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for Study Design

Conducting studies that evaluate treatment in participants with naturally occurring URTIs is challenging because it is difficult to identify and enroll participants during the early stage of the illness. URTIs are short-lived and self-limited. In addition, with naturally occurring URTIs, it is not possible to know when infection begins or to determine with certainty the duration of the illness at the time that the patient presents for enrollment [Gwaltney, J. M. Jr., et al 2003]. Due to these limitations, the induced rhinovirus URTI model will be used to evaluate MK-7264 in this trial. In this rhinovirus infection model, the virus is inoculated into the nose of susceptible volunteers to produce an induced URTI. Therefore, the incubation period of the infection and the duration of illness are known. Comparisons between naturally occurring infections and induced infections have demonstrated that there may be differences in the severity of symptoms or types of symptoms, but in general the illnesses associated with the two types of infection were more similar than they were different; this may be due to selection bias of the natural cold patients [Rao, S. S., et al 1995]. Overall, the induced rhinovirus model is still the preferred model for evaluating treatments for the common cold. This model has the advantage of replicating the actual pathology of an acute URTI caused by rhinovirus and incorporates knowledge of the timing and evolution of the URTI into the study design.

Further, in this protocol, all participants will be required to demonstrate viral shedding within 72 hours of inoculation of HRV-16 in order to continue in the trial and be included in the analyses; thus, this model will provide a controlled environment for evaluation of URTI in participants with the same virus and with a similar duration of illness (infection). It is anticipated that approximately 15% to 20% of participants will not demonstrate viral shedding within the 72 hour timeframe; these participants will be discontinued from study treatment and discharged from the clinic (See Section 9.1.11).

The natural history of URTI, as well as the onset and duration of cough, have not been well described. Data published in 1988 by Curley et al suggests that 80% of patients infected with the common cold will develop cough [Curley, F. J., et al 1988]. Consultation with cough experts and centers experienced with induced rhinovirus studies suggests that the proportion of patients infected with rhinovirus who develop cough is between 60% to 80%. Data published by Gwaltney et al in 2003 suggest that the mean total symptom severity scores for participants with experimental rhinovirus colds peak 48 hours after viral inoculation [Gwaltney, J. M. Jr., et al 2003]. These symptoms are dramatically reduced by Day 5, and likely disappear around Day 7. These findings further support the use of the induced infection model (to ensure treatment and evaluation as early as possible in the course of the illness) and evaluation of participants over the course of 7 days of treatment.

5.4.2 Rationale for Cough Challenge in a Subset of Participants

Inhalation cough challenges allow for quantification of cough and the assessment of antitussive effects of specific therapies. Cough challenges rely on the delivery of tussive agents, such as capsaicin, citric acid, or ATP, as aerosols administered from jet or ultrasonic nebulizers.

There are 2 main methods used for cough challenges: single-dose and dose-response. Single-dose inhalation challenges involve the administration of one concentration of the tussive agent. This method has been used for the screening of a large population of participants to detect those with reproducible cough. The second method is the dose-response cough challenge and involves the inhalation of incremental concentrations of tussive agent interspersed with inhalations containing placebo to increase challenge blindness. This trial will perform a modified dose-response cough challenge; details will be provided in the Procedures Manual.

A large number of tussive agents have been tested in cough challenges, with capsaicin and citric acid demonstrating the best reproducibility. Recent studies have suggested a role for ATP-activated P2X3 receptors in the pathophysiology of chronic cough. In a small trial evaluating hypersensitivity to ATP in chronic cough patients, chronic cough patients had increased sensitivity to ATP compared with healthy volunteers. There were no reports of bronchospasm in that trial [Fowles, H. E. 2015].

In P013, an ATP cough challenge will be conducted during Stage 1. All participants in Stage 1 will undergo the ATP cough challenge during the screening and treatment periods. It is expected that ~ 5 to 10% of participants may not respond to cough challenge during the screening period. ATP has been selected as the tussive agent for the cough challenge based on the hypothesis that patients infected with rhinovirus have increased sensitivity to ATP cough challenge. In summary, the ATP cough challenge is included in this trial as it may allow a better evaluation of the antitussive effect of MK-7264.

5.4.3 Rationale for Endpoints

5.4.3.1 Efficacy Endpoints

The primary efficacy endpoint is awake coughs per hour (based on 24-hour sound recordings using an objective cough-counting device) on Day 3 of the treatment period (defined in Section 10.4.1). Cough counting will begin on Day 1 (ie, after randomization, inoculation with the rhinovirus, and first dose of study treatment) and continue over the course of 7 days of treatment. Cough count will be measured using a digital recording device (VitaloJAK™ cough monitor, Vitalograph, Buckingham, United Kingdom). Worn similar to a Holter monitor with a sensor affixed to the participant's chest wall with adhesive and a microphone attached to the participant's clothing, the device provides high fidelity recordings and facilitates signal processing to accurately identify and quantify cough. Digital recordings will be processed in Vitalograph's centralized reading center, where recordings are condensed using a computer algorithm before human analysts identify and tag individual coughs. The output of this process is a count of coughs for each 24-hour recording period, as well as cough counts for portions of the day when the participant is awake and when they are asleep.

As approximately 83% of participants with a URTI are expected to cough within the first 48 hours of infection [Curley, F. J., et al 1988], the goal of the trial is to demonstrate that MK-7264 is effective in the treatment of acute cough, as evidenced by a decreased frequency of awake coughs on Day 3 in participants who are infected with rhinovirus. In unexplained or treatment refractory chronic cough, cough frequency is much higher during the day. This pattern is expected to be similar with acute cough, but to assess concretely; P013 will include 24-hour cough counts as an exploratory endpoint.

An assessment of cough from the participant's perspective is also important for evaluating the response to a given therapy. PROs associated with cough can be measured in terms of cough frequency, intensity, and severity; disruptions due to cough; and cough-specific quality of life. The following secondary efficacy endpoints will be measured as change from baseline on Day 3 of the treatment period in this trial:

- Cough Severity visual analog scale (VAS)
- Cough Severity Diary (CSD)
- Leicester Cough Questionnaire (LCQ)-acute

The Cough Severity VAS is a single-item questionnaire 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 in chronic pain, the Cough Severity VAS provides a quick and easily interpreted subjective assessment to monitor improvement of acute cough during treatment.

The CSD is a 7-item, disease-specific PRO measure with a recall period of "today". The measure evaluates three domains: frequency of cough (3 items), intensity of cough (2 items), and disruption due to cough (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 (ie, frequency, intensity, disruption) can be calculated.

The LCQ-acute is a 19-item health-related quality-of-life (HRQoL) questionnaire specific for acute cough which contains three domains (ie, 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-acute assesses symptoms or the impact of symptoms on HRQoL in the last 24 hours using a 7-point Likert scale ranging from 1 to 7. Higher scores indicate better HRQoL.

The following exploratory efficacy endpoints will also be measured:

1. 24-hour cough count (based on 24-hour sound recordings) on Day 3
2. Awake cough count on Days 1, 2, 4, 5, 6, 7
3. Wisconsin Upper Respiratory Syndrome Symptom Survey (WURSS-24) as change from baseline on Day 3
4. Cough reflex sensitivity (C2 and C5 on Days 1, 4, and 7) measured by standardized methodology incorporating an ATP cough challenge (Stage 1 only)

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

5.4.3.5 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-study are presented in Appendix 2 – Collection and Management of Specimens for Future Biomedical Research.

5.4.4 Rationale for the Use of Placebo

The placebo arm is included in this trial to maintain the study blinding, allowing for an unbiased assessment of efficacy and safety. Additionally, in the event that a lower MK-7264 dose group is added to the trial in Stage 2 (after the efficacy IA), the placebo arm will help ascertain whether the two active doses are equally effective or equally ineffective. No rescue medication will be permitted in the trial. Participants will be medically monitored during the trial and provided appropriate treatment, if warranted. Participants may discontinue the trial at any time if they find the treatment intolerable or for any other reason.

5.5 Justification for Dose

5.5.1 Rationale for Dose Interval and Study Design

In this trial, MK-7264 45 mg (and potentially MK-7264 15 mg if an additional treatment arm is added in Stage 2) will be orally administered in tablet form BID based on the safety and PK efficacy results observed to date.

Based on PK studies conducted to date, MK-7264 is rapidly absorbed with a median T_{max} of 1 to 2 hours and a half-life of approximately 7 to 10 hours, and is consistent with a BID dosing schedule.

In the clinical development program, oral doses of MK-7264 up to 1800 mg BID for 14 days were evaluated in Phase 1 studies and oral doses of up to 600 mg BID have been evaluated in Phase 2 studies. Overall, MK-7264 has been generally safe and well tolerated. Across studies, taste-related AEs (eg, dysgeusia, ageusia, hypogeusia) and tingling sensation in the mouth and/or throat were the most frequently reported events. These AEs have been reversible and are amenable to monitoring.

In participants with chronic cough, improved tolerability (relative to higher doses of MK-7264) and efficacy have been observed at doses of MK-7264 ≤50 mg BID. Doses from 7.5 mg to 200 mg BID were studied in participants with chronic cough (in P010 Cohort 1)

and 50 mg BID was as effective as higher doses; however, doses higher than 50 mg BID were associated with less tolerability.

The mechanism of action of MK-7264 and related clinical study results demonstrate 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 provide patients and prescribers the flexibility to balance efficacy and tolerability based on individual clinical situations, the MK-7264 development program has targeted two doses (15 mg BID and 45 mg BID) to study.

The 45 mg BID dose has been selected for Stage 1 of this trial to evaluate whether this dose will effectively reduce acute cough with a side effect profile that is tolerable to patients. During Stage 2 of the trial (after the efficacy IA), a third treatment group with a lower dose of MK-7264 (15 mg BID) may be added, based on the results of the IA and PK modeling, taking both efficacy and safety/tolerability into consideration.

For additional details on MK-7264, refer to the IB (Section 3.2).

6. Study Population

Healthy male and female participants between the ages of 18 and 55 years (inclusive) will be enrolled in this study.

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

6.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. In good general health with no clinically relevant abnormalities based on the medical history, physical examination, vital sign measurements, clinical laboratory evaluations (ie, hematology, clinical chemistry, and urinalysis), and 12-lead ECG.
2. Susceptible to HRV-16, as evidenced by a serum-neutralizing antibody titer of 1:4 or less, or the definition used by the individual clinic.

Demographics

3. Between 18 and 55 years of age (inclusive) at the Screening Visit, of either gender, and of any race.
4. A female participant is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:
    a) Not a woman of childbearing potential (WOCBP) as defined in Appendix 3

    OR

    b) A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 14 days after the last dose of study treatment.

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

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed approximately 85 mL.

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

9.1 Administrative and General Procedures

9.1.1 Informed Consent

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

9.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature 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 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.

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 the Vitalograph Web Portal for analysis and annotation of sound recordings. Cough counts are then tallied automatically from the annotated audio file.

During the Treatment Period, the cough monitor will be attached to all randomized participants and set up prior to first dose of study treatment (see Section 9.10.2 and the VitaloJAK™ Site Manual for further details). The monitor will be set to begin recording immediately after the first morning dose. The device will be worn 24 hours a day for the 7-day treatment period with approximately 15 minutes/day "off-time" permitted for showering. Participants will continue to wear the cough monitor during the cough challenge procedures on Days 1, 4, and 7, as the cough counting data from the cough monitor will be used to support the primary analysis.

9.2.2 Intranasal Administration of Rhinovirus

All randomized participants will be administered HRV-16 intranasally on Day 1. A detailed description of the preparation and administration of HRV-16 is provided in the Procedures Manual.

If there is no confirmation of viral infection within 72 hours post-inoculation with HRV-16 by PCR assay, the participant will be discontinued from treatment.

The trial site will be responsible for recording the lot number, manufacturer, and expiry date of applicable supplies related to HRV-16 administration.

Note: Participants will receive the first dose of study treatment immediately after administration of HRV-16. There is no requirement for participants to display symptoms of infection prior to administration of first dose of trial treatment.

9.2.3 ATP Cough Challenge (Stage 1 Only)

Cough reflex sensitivity is measured by standard clinical methodology incorporating ATP cough challenge in accordance with the Procedures Manual. The ATP cough challenge will be administered ONLY during Stage 1 of the trial.

The standard endpoints measured in cough challenge testing are reflex sensitivity to ATP measured by C2 and C5 (ie, concentration of cough challenge agent [ATP] inducing at least 2 or 5 coughs, respectively) during Stage 1 on Days -1, 1, 4, and 7.

The number of coughs during the ATP cough challenge will be assessed manually by site staff during all ATP cough challenges.

Participants will continue to wear the cough monitor during the cough challenge procedures on Days 1, 3, and 7, as the cough counting data from the cough monitor will be used to support the primary analysis. All analyses related to the ATP cough challenge will be performed using manual cough counting data, including the exploratory analysis related to cough reflex sensitivity.

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

The definitions of an adverse event (AE) or serious adverse event (SAE), as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE and other reportable safety event reports can be found in Appendix 4.

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

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs and other reportable safety events for outcome according to Section 9.3.3.

Adverse events will not be collected for participants during the pre-screening period (for determination of archival tissue status) as long as that participant has not undergone any protocol-specified procedure or intervention. If the participant requires a blood draw, fresh tumor biopsy etc., the participant is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

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

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

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

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

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

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

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

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-Specified Follow-up Period	Reporting Time Period: After the Protocol Specified Follow-up Period	Timeframe to Report Event and Follow-up Information to SPONSOR:
Non-Serious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential drug-induced liver injury (DILI) - Require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (Do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

Type of Event		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	Not required		Within 5 calendar days of learning of event

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE and other reportable safety events including pregnancy and exposure during breastfeeding, ECI, Cancer and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). In addition, the investigator will make every attempt to follow all non-serious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 4.

9.3.4 Regulatory Reporting Requirements for SAE

- Prompt notification (within 24 hours) by the investigator to the sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

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

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

9.3.6 Pregnancy and Exposure During Breastfeeding

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

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

9.3.7 Events of Clinical Interest (ECI)

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

Events of clinical interest for this study include:

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

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

9.4 Treatment of Overdose

In this study, an overdose is any dose >1 tablet BID in Stage 1 and Stage 2 (if only 2 treatment arms are included). If a 3rd treatment arm is added in Stage 2 based on the results of the efficacy IA, an overdose will be defined as >2 tablets BID (Section 7.1).

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 [IB Edition 16 2017]. Overdoses 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.

9.5 Safety

Details regarding specific safety procedures/assessments to be performed in this study are provided below.

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

9.5.1 Physical Examinations

All participants will undergo a full physical examination (except for rectal and genital examination) at the visits specified in the SoA (Section 2).

The full examination will be conducted as per institutional standard on the following body systems: general appearance, head (ie, oral inspection, ears, eyes, nose, and throat), respiratory (ie, auscultation/stethoscope examination of the lungs), heart (ie, auscultation/stethoscope examination of the heart), abdomen, musculoskeletal, neurological, lymph nodes, and skin. Participants with evidence of current, clinically significant, intercurrent illness (eg, significant cold or flu) may be rescheduled for rescreening upon resolution of their illness (See Section 9.10.1.1).

Based on investigator judgment, questioning regarding symptoms may be sufficient for the following body systems: abdomen, urogenital, musculoskeletal, and neurological. If deemed necessary by the investigator, a physical examination of these body systems will be performed.

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

A physical exam (full or limited) may be performed at any clinic visit that does not already include a physical exam or at any unscheduled visit if deemed necessary by the investigator due to signs/symptoms.

Clinically significant changes from baseline will be recorded as AEs. Baseline for physical examination is defined as the examination performed during the Screening Visit.

9.5.6 Clinical Safety Laboratory Assessments

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

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 5, must be conducted in accordance with the Central Laboratory Manual and the SoA (Section 2).
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study treatment, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

9.5.6.1 Urine Pregnancy Test – if applicable

Urine pregnancy test will be performed at the site on female participants of childbearing potential as specified in the SoA (Section 2). A positive urine pregnancy test should be followed up with a serum pregnancy test performed by the central laboratory. Collection, storage, and shipment of serum for pregnancy testing should be performed as described in the Central Laboratory Manual.

9.6 Pharmacokinetics

The decision as to which plasma samples collected will be assayed for evaluation of PK will be collaboratively determined by the Department of Quantitative Pharmacology and Pharmacometrics (QP2) for assay in an exploratory manner for metabolites and/or additional PK markers.

9.6.1 Blood Collection for Plasma MK-7264

PK samples will be collected at the time points specified in Table 4 and in the SoA (Section 2). Blood collection, storage, and shipment instructions for plasma samples are provided in the Central Laboratory Manual.

Table 4 Pharmacokinetic Samples Collection

Period	Trial Day	PK Sample	Time of Collection of PK Sample
Treatment Period (Stages 1 and 2)	1	X	Predose, 1, 2, 4, 8, and 12 hours postmorning dose
	2	X	Premorning dose
	3		NA
	4	X	Premorning dose
	5		NA
	6		NA
	7	X	Premorning dose, 1, 2, 4, 8, and 12 hours postmorning dose
Abbreviations: NA = not applicable; PK = pharmacokinetic			

A variance in procedure collection times as specified in Table 5 will be permitted.

Table 5 Pharmacokinetic (Blood) Collection Windows

PK Collection Time	PK Collection Window
Pre-dose	Within 15 minutes before dose
1 hr post-dose	± 5 minutes
2 hrs post-dose	± 10 minutes
4 hrs post-dose	± 10 minutes
8 hrs post-dose	± 15 minutes
12 hrs post-dose	± 15 minutes
Abbreviations: PK = pharmacokinetic	

9.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

9.8 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA (Section 2):

- Blood for genetic analysis

10.4.4 Derivations of Efficacy Endpoints

The primary efficacy endpoint of this study is the awake coughs per hour on Day 3 of the treatment period. It is calculated as:

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

Awake is time between waking up and sleep during the 24-hour monitoring period.

10.5 Analysis Populations

10.5.1 Efficacy Analysis Populations

The modified Full Analysis Set (mFAS) population will serve as the primary population for the analysis of efficacy data in this study. The mFAS population consists of all randomized participants who receive at least one dose of study treatment and have confirmation of viral shedding within 72 hours of administration of HRV-16.

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

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

10.5.2 Safety Analysis Populations

The All Participants as Treated (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.

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.

Details on the approach to handling missing data for safety analyses are provided in Section 10.6.

10.5.3 Pharmacokinetic Analysis Population

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

10.6 Statistical Methods

Statistical testing and inference for efficacy and safety analyses are described in Section 10.6.1 and Section 10.6.2, respectively.

10.6.1 Statistical Methods for Efficacy/Immunologic Analyses

Primary Efficacy Analysis

The primary analysis will be conducted on the mFAS population.

The primary efficacy endpoint for the study is the awake coughs per hour on Day 3 of treatment. It will be analyzed using a longitudinal data analysis (LDA) model. In this model, the response vector consists of daily awake coughs per hour at each post-baseline visit; and covariates will include treatment, visit, the interaction of treatment by visit, gender, and site. The unstructured approach will be used to model the covariance of the repeated cough measurements over time within participants. Additional covariance structures, such as Toeplitz covariance, may be considered if convergence issues are encountered with the analysis model.

Point estimates and two-sided 95% confidence interval (CI) of the treatment difference in adjusted means will be presented.

Secondary Efficacy Analysis

The secondary efficacy endpoints will be analyzed based on the mFAS population using a longitudinal analysis of covariance (ANCOVA) model. In this model, the response vector consists of the change from baseline value at each post-baseline visit. The model will adjust for treatment, visit, the interaction of treatment by visit, gender, site, and baseline value as a covariate. Further details of the model specification, assumptions, and SAS implementation codes will be provided in the sSAP. Table 6 summarizes the key analyses.

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 AEs and predefined limits of change.

Continuous measures such as changes from baseline in laboratory, vital sign, and ECG parameters 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.

For this protocol, a composite endpoint of taste-related AEs (including dysgeusia, ageusia, and hypogeusia, as well as other related terms) is considered a Tier 1 event. In addition, the broad clinical and laboratory AE categories consisting of the percentage of participants with any AE, a drug-related AE, an SAE, an AE which is both drug-related and serious, any oral paresthesia AE, any oral hypoesthesia AE, and discontinuations due to an AE will be considered Tier 2 endpoints. P-values (Tier 1 only) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of participants with events; these analyses will be performed using the Miettinen and Nurminen method (1985), an unconditional, asymptotic method [Miettinen, O. and Nurminen, M. 1985].

Table 11 Contraceptive Methods

Acceptable 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, c] ● Intrauterine hormone-releasing system[b] ● Intrauterine device ● Bilateral tubal occlusion
● Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
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 hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 14 days after the last dose of study treatment. [c] If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

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

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening ● The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization ● Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the patient's medical history.
d. Results in persistent or significant disability/incapacity ● The term disability means a substantial disruption of a person's ability to conduct normal life functions. ● This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Assessment of Intensity

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

Assessment of Causality

- Did the Sponsor's product cause the adverse event?
  - The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the adverse event based upon the available information
  - **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:
    - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
    - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Trial File Binder (or equivalent).

SAE Reporting to the Sponsor via Paper CRF

- If the electronic data collection tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

12.6 Appendix 6: Abbreviations and Trademarks

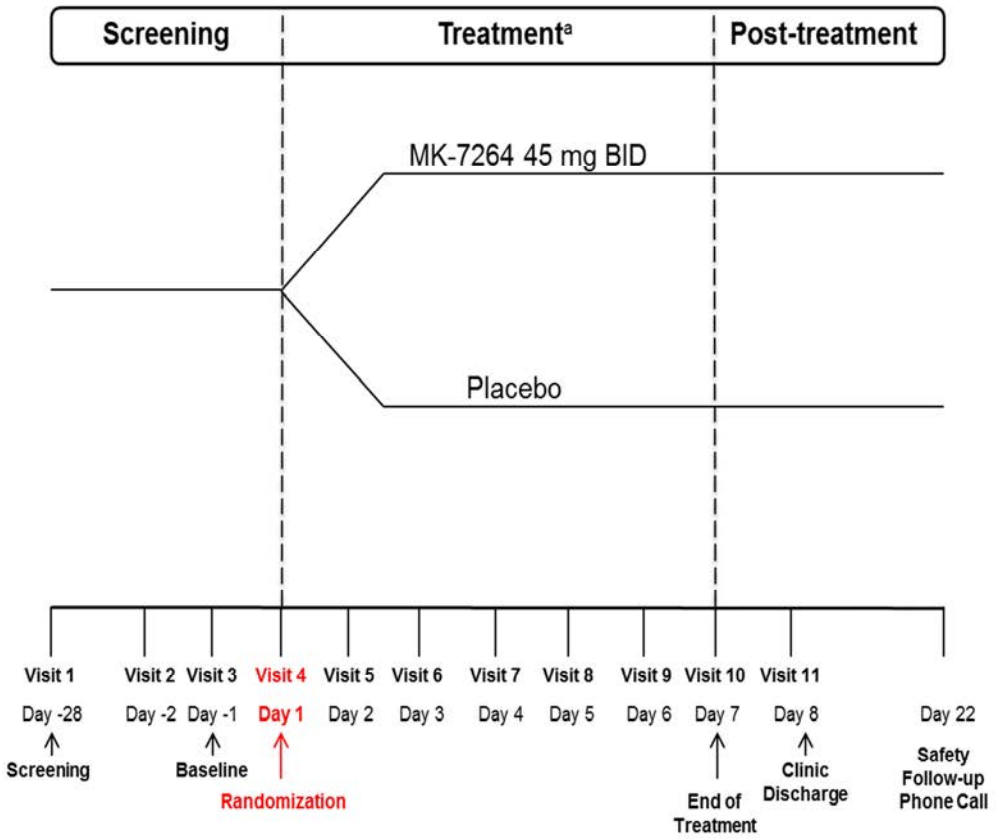
Abbreviation	Term
β-hCG	β-human chorionic gonadotropin
AE	adverse event
ALT	alanine aminotransferase
AMA	American Medical Association
ANCOVA	analysis of covariance
APaT	all participants as treated
AST	aspartate aminotransferase
ATP	adenosine triphosphate
ATS	American Thoracic Society
AUC	area under the concentration time-curve
BID	twice daily
BMI	body mass index
Bpm	beats per minute
BUN	blood urea nitrogen
C2	concentration of cough challenge agent [ATP] inducing at least 2 coughs
C5	concentration of cough challenge agent [ATP] inducing at least 5 coughs
CBC	complete blood count
CF	compact flash
CFR	Code of Federal Regulations
CI	confidence interval
CKD EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	mean maximum observed concentration
C_{min}	mean minimum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CSD	Cough Severity Diary
CSR	clinical study report
CTFG	Clinical Trial Facility Group
DBP	diastolic blood pressure
DIHS	drug-induced hypersensitivity syndrome

Abbreviation	Term
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DRESS	drug reaction with eosinophilia and systemic symptoms
ECG	electrocardiogram
ECI	event of clinical interest
EDC	electronic data collection
ERS	European Respiratory Society
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle stimulating hormone
GERD	gastroesophageal reflux disease
GCP	Good Clinical Practice(s)
HIV	human immunodeficiency virus
HRQoL	health-related quality-of-life
HRT	hormonal replacement therapy
HRV-16	human rhinovirus type 16
IA	interim analysis
IB	Investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IVRS	interactive voice response system
IWRS	interactive web response system
LCQ-acute	Leicester Cough Questionnaire-acute
LDA	longitudinal data analysis

2. Schedule of Activities (SoA)

Study Period	Screening			Treatment							Dis-charge	Telephone Follow-Up (14 days post last dose)	Early Discon-tinuation	Notes
			Base-line	Random-ization										
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**			
Scheduled Day and Window:	**Day -28 to Day -3**	**Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 22** (+ 3 days)	**Between Days 1 and 7**	
Administrative and General Procedures														
Written Informed Consent	X													
Informed Consent for Future Biomedical Research	X													
Participant Identification Card	X													
In-Patient Period		X	X	X	X	X	X	X	X	X				
Inclusion/Exclusion Criteria	X	X	X	X										Day 1: Prior to morning dose
Administer Intranasal human Rhinovirus Type 16 (HRV-16)				X										Immediately prior to morning dose (first dose of study treatment)
Demographics	X													
Medical History (includes substance usage)	X													Substances: drugs, alcohol, tobacco, and caffeine
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	
Treatment Randomization				X										
Treatment (MK-7264/Placebo) Administration				X	X	X	X	X	X	X				
Monitor Compliance with Study Treatment					X	X	X	X	X	X			X	
Antibody Titers to HRV-16	X													
Ethanol Breath Test	X		X											Performed at site locally

Study Period	**Screening**			**Treatment**								**Dis-charge**	**Telephone Follow-Up** (14 days post last dose)	**Early Discon-tinuation**	**Notes**
			Base-line	**Random-ization**											
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**			
Scheduled Day and Window:	**Day -28 to Day -3**	**Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 22** (+ 3 days)	**Between Days 1 and 7**	
Collect Previous Cough Monitor Data					X	X	X	X	X	X	X		X	Collect compact flash (CF) memory card from cough monitor and insert new CF card and new battery pack every ~ 24 hours
Cough Severity Visual Analog Scale (VAS)			X	X	X	X	X	X	X	X				Completed in the evening
Cough Severity Diary (CSD)			X	X	X	X	X	X	X	X				Completed in the evening
Leicester Cough Questionnaire-Acute (LCQ-acute)			X	X	X	X	X	X	X	X				Completed in the evening
Wisconsin Upper Respiratory Syndrome Symptom Survey (WURSS-24)			X	X	X	X	X	X	X	X				Completed in the evening
Safety Procedures														
Full Physical Examination	X										X		X	Refer to Section 9.5.1 for details
Height & Weight	X		X								X		X	Day -1, Day 8, and Early DiscontinuationVisit: weight only
Vital Signs (heart rate, blood pressure, respiratory rate, and temperature)	X	X	X	X	X	X	X	X	X	X	X		X	All visits during Treatment Period: predose
12-lead Electrocardiogram (ECG)	X		X								X		X	Performed with site equipment
Spirometry	X													Performed with site equipment
Hematology	X			X						X			X	Days 1 and 7: premorning dose
Urinalysis	X			X						X			X	Days 1 and 7: premorning dose



Abbreviations: BID = twice daily; IA = interim analysis

Figure 1 Study Design for Stage 1 (Prior to Efficacy IA)

The WURSS-24 is a 24-item HRQoL questionnaire specific for acute upper respiratory infection, including influenza-like symptoms. The WURSS-24 assesses symptoms or the impact of symptoms on HRQoL 'over the last 24 hours' using an 8-point Likert scale ranging from 0 to 7. Higher scores indicate worse HRQoL.

MK-7264 has been shown to reduce cough reflex sensitivity, as measured by ATP cough challenges, in healthy participants as well as participants with chronic cough [IB Edition 16 2017]. Stage 1 of P013 will evaluate whether similar effects also occur in participants with acute cough.

The secondary and exploratory efficacy endpoints will add supportive information to the primary efficacy endpoint of awake coughs per hour on Day 3 of treatment.

5.4.3.2 Safety Endpoints

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 trial parameters including vital signs, physical examination, electrocardiogram (ECG), and standard laboratory safety tests at time points specified in the SoA (Section 2). Adverse events are graded and recorded according to Appendix 4. Additional safety monitoring may be performed at the discretion of the investigator.

5.4.3.3 Pharmacokinetic Endpoints

The pharmacokinetics (PK) of MK-7264 will be evaluated by measuring mean maximum observed concentration [C_{max}], mean minimum observed concentration [C_{min},], time to reach C_{max} [T_{max}], and area under the concentration time-curve [$AUC_{0-\tau}$] on Days 1, 2, 4, and 7 in healthy adult participants infected with rhinovirus. Blood samples will be collected on Days 1, 2, 4, and 7, as outlined in Section 9.6.1. The relationship between MK-7264 plasma concentrations and cough frequencies/side effects will be explored.

5.4.3.4 Planned Exploratory Biomarker Research

5.4.3.4.1 Planned Genetic Analysis

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

DNA samples will be used for research related to the study treatment(s), the disease under study and related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases and study treatment(s). Genetic research may consist of the analysis of one 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.

Informed Consent

5. 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 study without participating in Future Biomedical Research.

Study Procedures

6. Demonstrates an ability to follow study procedures (including use of the digital cough recording device [VitaloJAK™] and completing the PROs [Cough Severity VAS, CSD, LCQ-acute, and WURSS-24]) to the satisfaction of the investigator/qualified designee prior to randomization.
7. Has clinical laboratory tests (complete blood count [CBC], blood chemistries, including urine pregnancy for female participants of childbearing potential [ie, who have started menstruating], and urinalysis) conducted during Screening documented to be clinically acceptable to the investigator before beginning the Treatment Period. A female participant of childbearing potential (ie, who has started menstruating) must have a negative urine pregnancy test (or a negative serum pregnancy test, if required) at both the Screening Visit and Baseline Visit (Day -1) to be considered eligible for the trial.

6.2 Exclusion Criteria

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

Medical Conditions

1. Donated blood within 56 days or donated plasma within 7 days prior to dosing.
2. Has forced expiratory volume in one second (FEV1) <70% of predicted and/or FEV1/forced vital capacity (FVC) ratio <80%.
3. Has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (ie, systemic allergic reaction) to prescription or nonprescription drugs or food.
4. Has recent history of an upper or lower respiratory tract infection or recent significant change in pulmonary status within 4 weeks of the Baseline Visit (Day -1).
5. Has estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m2 (using the Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) formula [http://mdrd.com/]) at Screening.
6. Has a history of cancer (malignancy).
7. Has any condition possibly affecting drug absorption (eg, gastrectomy, gastroplasty, any type of bariatric surgery, or vagotomy).
8. Has screening systolic blood pressure (SBP) >160 mm Hg or a diastolic blood pressure >90 mm Hg.
9. Has a body mass index <18 kg/m2 or ≥40 kg/m2.

9.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

9.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee at the Screening Visit and on Days -2, -1, and 1 to ensure that the participant qualifies for the study. Inclusion and exclusion criteria for this study are defined in Sections 6.1 and 6.2, respectively.

9.1.3 Participant Identification Card

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

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

9.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. It will include a history of medical conditions within 30 days prior to the Screening Visit.

9.1.5 Prior and Concomitant Medications Review

9.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 30 days (or longer if appropriate) prior to the Screening Visit (See Section 6.2).

9.1.5.2 Concomitant Medications

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

9.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization. Each participant

The challenge should be discontinued for the day if a participant experiences severe side effects or coughs excessively and makes a clear request to stop taking the challenge test (see Procedures Manual).

β-agonist should be available for participants who experience bronchoconstriction; other appropriate medical interventions should be provided as necessary. Those who need to discontinue the cough challenge may still participate in the cough challenges on subsequent days.

9.2.4 Patient-reported Outcomes

At Baseline (Day -1), each participant will be properly trained and instructed on the completion of all PRO assessments/questionnaires: CSD, Cough Severity VAS, LCQ-acute, and WURSS-24. These assessments/questionnaires should be provided to the participant and conducted in the same order each day at approximately the same time in the evening, as specified in the SoA (Section 2.0). Data must be reviewed by the investigator or designee each time a participant completes an assessment/questionnaire. Overall completeness and accuracy of all recorded entries should be reviewed. Deficiencies should be immediately discussed with the participant to improve the quality of future assessment/ questionnaire entries. The investigator and qualified designee should ensure that any relevant comments that refer to possible AEs are discussed or clarified with the participant, and any AEs are collected in the AE electronic case report form (eCRF).

9.2.4.1 Cough Severity Diary

Participants are instructed to record their cough frequency, intensity, and associated disruptions 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 of cough.

9.2.4.2 Cough Severity Visual Analog Scale

Participants are instructed to rate the severity of their cough "today" using a 100 mm VAS single-item questionnaire with the response ranging from 0 ("no cough") to 100 ("extremely severe cough").

9.2.4.3 Leicester Cough Questionnaire-Acute

Participants are instructed to complete the 19-item LCQ-acute to assess the impact of their cough severity in the last 24 hours on physical, social, and psychological functioning, using a 7-point Likert scale ranging from 1 to 7; higher scores indicate better HRQoL.

9.2.4.4 Wisconsin Upper Respiratory Symptom Survey-24

Participants are instructed to complete the WURSS-24 questionnaire, an illness-specific quality of life instrument designed to assess the negative impact of acute URTI, using an 8-point Likert scale ranging from 0 to 7; higher scores indicate worse HRQoL. Influenza-like illness symptoms of headache, body aches, and fever are included on the WURSS-24.

9.5.2 Vital Signs and Weight and Height Measurements

Vital signs (including oral body temperature (centigrade), blood pressure (mm Hg), pulse rate (beats per minute), and respiratory rate (breaths per minute)), height (cm), and weight (kg) will be assessed at the visits specified in the SoA (Section 2). All vital signs will be measured after each participant has been sitting/resting for at least 5 minutes. Blood pressure measurements should be performed on the same arm, preferably by the same person. At the Screening Visit, vital signs will be measured just before the spirometry measurement.

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

9.5.3 Electrocardiograms

A single 12-lead ECG will be obtained as outlined in the SoA (Section 2) using local standard procedures. Clinically significant abnormal findings should be recorded in the AE eCRF.

9.5.4 Spirometry

A spirometry assessment will be performed at the Screening Visit using a local calibrated spirometer.

Spirometry should be performed in accordance with guidelines established by 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 on the spirometry report.

9.5.5 Taste-Related Adverse Events

The tolerance to taste-related AEs will be evaluated during the study if a taste-related AE(s) is reported. At the time the taste-related AE is reported and every day until the AE is reported as resolved, the site staff will obtain information on the timing, duration, intensity, etc., of the taste-related AE.

The information will be entered into the appropriate eCRFs based on the eCRF entry guidelines, which will be provided to the sites by the Sponsor.

9.8.1 Planned Genetic Analysis Sample Collection

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

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the Central Laboratory Manual.

9.9 Future Biomedical Research Sample Collection

If the participant signs the Future Biomedical Research consent, the following specimens will be obtained as part of Future Biomedical Research:

- DNA for future research

9.10 Visit Requirements

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

All study procedures will be performed as specified in the SoA (Section 2).

The PROs (CSD, Cough Severity VAS, LCQ-acute, and WURSS-24) should be performed in the same order each evening, as listed in the SoA (Section 2.0).

Additional details of certain procedures at specific visits are described in this section.

9.10.1 Screening Period

9.10.1.1 Visit 1

During the Screening Period, between Days -28 to -3, potential participants will be evaluated to determine their eligibility as described in Sections 6.1 and 6.2. Screening procedures may be repeated after consultation with the Sponsor.

Participants may be rescreened once within 30 days of not meeting entry criteria during the screening period. Rescreening should include all screening procedures listed in the SoA (Section 2), including consent review. A consultation or Sponsor Consultation Form is not required for rescreening a participant. Note: Participants who were previously randomized and discontinued due to lack of viral shedding within 72 hours of inoculation (or discontinued for any other reason) may not be rescreened for this trial.

Table 6 Analysis Strategy for Key Efficacy Endpoints

Endpoint	Statistical Method	Missing Data Approach
Primary Efficacy Endpoint		
Awake coughs per hour on Day 3	LDA	Model-based
Secondary Efficacy Endpoints		
Change from Baseline in daily Cough Severity VAS on Day 3	Longitudinal ANCOVA	Model-based
Change from Baseline in daily CSD on Day 3	Longitudinal ANCOVA	
Change from Baseline in daily LCQ-acute total score on Day 3	Longitudinal ANCOVA	

Abbreviations: LDA = longitudinal data analysis; ANCOVA = analysis of covariance; VAS = Visual Analogue Scale; CSD = Cough Severity Diary; LCQ = Leicester Cough Questionnaire; mFAS = modified Full Analysis Set

Note: Efficacy analysis will be based on the mFAS.

Exploratory Efficacy Analysis

Details of the exploratory efficacy analysis methods will be provided in the sSAP.

Handling of Missing Data

No missing data will be imputed. All analyses will be conducted based on the observed data only.

10.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 7). 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.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory, vital sign, and ECG parameters 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 AEs and predefined limits of change will belong to Tier 3.

Table 7 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint†	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 SAE		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‡ (incidence ≥4 participants in one of the treatment groups)		X X	X X
Tier 3	Specific AEs, SOCs or PDLCs‡ (incidence <4 participants in all of the treatment groups)			X
	Change from Baseline Results (Labs, ECGs, Vital Signs)			X

Abbreviations: AE = adverse event; CI = confidence interval; ECG = electrocardiogram; PDLC = pre-defined limit of change; SAE = serious adverse event; SOC = system organ class; X = results will be provided

† Adverse Experience references refer to both Clinical and Laboratory AEs.

‡ Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier-2 endpoints.

10.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Demographic and Baseline Characteristics

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

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

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine test. If the urine pregnancy test is positive, a serum pregnancy test should be performed and if the test result is negative, the participant may be enrolled in the trial.

Pregnancy testing will be performed as specified in the SoA (Section 2) and whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

e. Is a congenital anomaly/birth defect

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

f. Other important medical events:

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

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

Additional Events Reported

Additional Events which require reporting

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

Recording AE and SAE

AE and SAE Recording

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

- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
  - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
  - If no, this is a negative dechallenge.

  (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study); or (4) Sponsor's product(s) is/are only used one time).
- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?
  - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
  - If no, this is a negative rechallenge.

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

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

- **Consistency with Study treatment Profile**: Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship: There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by

12.5 Appendix 5: Clinical Laboratory Tests

- The tests detailed in Table 12 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the eCRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 12 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Platelet count	White blood cell (WBC) count with differential: – Neutrophils – Lymphocytes – Monocytes – Eosinophils – Basophils
	Red blood cell (RBC) count	
	Hemoglobin	
	Hematocrit	
Chemistry	Albumin	estimated glomerular filtration rate (eGFR) calculation
	Alkaline phosphatase	Glucose (nonfasting)
	Alanine aminotransferase (ALT)	Phosphorous
	Aspartate aminotransferase (AST)	Potassium
	Bicarbonate	Sodium
	Blood urea nitrogen (BUN)	Total protein
	Calcium	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Chloride	
	Creatinine	
Routine Urinalysis	• Specific gravity, pH, glucose, protein, and blood; microscopic examination will be performed if abnormal results are observed	
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum β-human chorionic gonadotropin (β-hCG) pregnancy test (as needed for women of childbearing potential) if urine pregnancy test is positive. Refer to SoA (Section 2)	
Notes: eGFR will be calculated with serum creatinine measurement (using the Chronic Kidney Disease Epidemiology Collaboration formula [http://mdrd.com/])		

Investigators must document their review of each laboratory safety report.

Abbreviation	Term
LLN	lower limit of normal
mFAS	modified full analysis set
NA	not applicable
NSAE	non-serious adverse event
OTC	over-the-counter
PCR	polymerase chain reaction
PDLC	Pre-defined Limit of Change
PK	pharmacokinetic
PP	per protocol
PROs	patient-reported outcomes
QP2	Quantitative Pharmacology and Pharmacometrics
QTc	corrected QT
RBC	red blood cell (count)
RR	relative reduction
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
siDMC	Standing Internal Data Monitoring Committee
siRNA	small interfering ribonucleic acid
SLAB	supplemental laboratory tests
SoA	schedule of activities
SOC	System Organ Class
sSAP	supplemental statistical analysis plan
SUSAR	suspected unexpected serious adverse reactions
T_{max}	time to reach C_{max}
ULN	upper limit of normal
URTI	upper respiratory tract infection
US	United States
VAS	visual analog scale
WBC	white blood cell (count)
WOCBP	women of childbearing potential