Official Protocol Title:	A Phase 2a, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Efficacy, Safety and Tolerability of MK-7264 on Acute Cough in Participants with Induced Viral Upper Respiratory Tract Infection
NCT number:	NCT03569033
Document Date:	13-Oct-2017

Title Page

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Protocol Title: A Phase 2a, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Efficacy, Safety and Tolerability of MK-7264 on Acute Cough in Participants with Induced Viral Upper Respiratory Tract Infection

Protocol Number: 013-00

Compound Number: MK-7264

Sponsor Name and Legal Registered Address:

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

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Regulatory Agency Identifying Number(s):

IND NUMBER: 123007

EudraCT NUMBER: 2017-000472-28

Approval Date: 13-Oct-2017

Sponsor Signatory

Typed Name: Date
Title:

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

Investigator Signatory

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

Typed Name: Date
Title:

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1. Synopsis

Protocol Title:

A Phase 2a, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Efficacy, Safety and Tolerability of MK-7264 on Acute Cough in Participants with Induced Viral Upper Respiratory Tract Infection

Short Title:

MK-7264 on acute cough in participants with induced viral upper respiratory tract infection

Objectives/Hypotheses and Endpoints:

In this study, the objectives and endpoints will be evaluated in healthy adult participants with induced viral upper respiratory tract infection (URTI) as indicated in the following table. Since this is an exploratory study, hypotheses are not applicable.

Objective/Hypothesis	**Endpoint**
Primary	
Objective: To evaluate the efficacy of MK-7264 on cough frequency as measured while awake during a 24-hour period	Awake cough frequency (coughs per hour) on Day 3, as assessed by an objective cough-counting device
Secondary	
• Objective: To evaluate the efficacy of MK-7264 on the perception of cough severity	• Cough Severity visual analog scale (VAS) score measured as change from baseline on Day 3 • Cough Severity Diary (CSD) score measured as change from baseline on Day 3
• Objective: To evaluate the efficacy of MK-7264 on cough-specific quality of life	• Leicester Cough Questionnaire-acute (LCQ-acute) score measured as change from baseline on Day 3
• Objective: To evaluate the safety and tolerability of MK-7264	• Number of participants experiencing adverse events (AEs) • Number of participants discontinuing study treatment due to AEs

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.

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**	
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.

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

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**	
Chemistry	X			X						X			X	Days 1 and 7: premorning dose
Urine Pregnancy Test (Women of Child Bearing Potential [WOCBP] only)	X		X							X			X	
Serum β-Human Chorionic Gonadotropin (β-hCG; WOCBP only)	(this procedure will be performed ONLY if urine pregnancy test is positive)													
Adverse Event (AE)/Serious AE Review		X	X	X	X	X	X	X	X	X	X	X	X	
Taste-related AEs				X	X	X	X	X	X	X	X	X	X	Participants who report taste-related AEs will have additional questioning by the site staff.
Reminder to continue contraceptive use (WOCBP only)											X		X	For at least 14 days after last dose of study treatment (see Appendix 3)
Pharmacokinetics/ Biomarkers														
Blood for Genetic Analysis				X										Randomized participants only; see Sections 9.8. and 9.9

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**	
Pharmacokinetic (PK) Blood Samples				X	X		X			X				Day 1: premorning dose: and 1, 2, 4, 8, and 12 hours postmorning dose Day 2: premorning dose Day 4: premorning dose Day 7: premorning dose and 1, 2, 4, 8, and 12 hours postmorning dose See Section 9.6.1 for collection windows.

3. Introduction

Cough is one of the most common presenting symptoms for patients seeking care from primary care specialists, allergists, otolaryngologists, or pulmonologists worldwide. The importance of cough as a clinical problem globally has led to multiple societies publishing guidelines on the diagnosis and management of cough [Morice, A. H., et al 2004] [Chung, K. F., et al 2006] [Morice, A. H., et al 2006] [The committee for The Japanese Respiratory Society guidelines 2006] [Kardos, P., et al 2010]. In these clinical guidelines, cough is categorized based upon the duration of the cough; within each category (ie, acute, subacute, and chronic) are likely diagnostic possibilities [Irwin, R. S., et al 2006]. Acute cough is present for less than 3 weeks. Cough that has been present for longer than 3 weeks is considered either subacute (3 to 8 weeks) or chronic (>8 weeks).

This protocol will evaluate acute cough. Acute cough is a common condition, most often due to an acute viral upper respiratory tract infection (URTI). Viral URTIs can be diagnosed when patients present with an acute respiratory illness with accompanying symptoms and signs related to the nasal passages (eg, rhinorrhea, cough, sore throat, sneezing, nasal obstruction, and postnasal drip), with or without fever, lacrimation, and irritation of the throat. In the absence of any treatment, the prevalence of acute cough due to a URTI ranges from 83% within the first 48 hours of the cold to 26% on Day 14 [Curley, F. J., et al 1988].

Cough due to a viral URTI is usually transient and self-limited. If cough is significantly bothersome to the patient, symptomatic treatment is appropriate. Regrettably, there is a paucity of over-the-counter (OTC) treatments available that have established efficacy based on well-controlled clinical trials. In addition, many of these OTC agents (eg, diphenhydramine, dextromethorphan) have undesirable side effects. Codeine, a prescription narcotic, while widely used, has not been shown to be efficacious against acute cough due to a URTI in prospective, blinded, controlled trials [Freestone, C. 1997]. Therefore, a significant unmet need exists for an agent to demonstrate efficacy and a tolerable side effect profile in prospective, randomized, placebo-controlled clinical studies.

Mechanism of Cough

Each cough occurs through the stimulation of a complex reflex arc. Cough is initiated following activation of airway sensory nerves in the upper and lower respiratory tract. Airway sensory nerves are tailored to detect changes in the physical and chemical environment, and, if required, elicit protective reflex events such as cough. These reflexes are normally protective; however, in disease, airway reflexes can become hypersensitized, leading to an increase in symptoms and a pathologic cough.

Adenosine triphosphate (ATP) is released by damaged, stressed, and inflamed tissues. P2X3 and P2X2/3 receptors are ligand-gated ion channels that respond to ATP and are almost exclusively localized on C-fiber sensory neurons, which innervate the upper and lower airways and are the main nerve fibers responsible for cough. The action of ATP at sensory neurons in the periphery and spinal cord contributes to neural excitability and may cause hypersensitivity through binding to P2X3-containing receptors and stimulating of C-fiber neurons [North, R. A. 2004] [Khakh, B. S. 2006]. Antagonism of P2X3-containing receptors is predicted to normalize afferent sensitivity, based on data from P2X3 knock-out mice and

the effects of small interfering ribonucleic acid (siRNA) knock-down and pharmacological antagonists [Barclay, J., et al 2002] [Cockayne, D. A., et al 2000] [Souslova, V., et al 2000]. ATP and P2X3-containing receptors have been shown to be involved in airways sensitization and their involvement provides a rationale for P2X3 antagonism in the treatment of cough.

The current trial will evaluate MK-7264 in acute cough.

3.1 Study Rationale

The purpose of this trial is to evaluate the efficacy and safety of MK-7264 on acute cough symptoms in healthy participants 18 through 55 years of age who are infected with human rhinovirus type 16 (HRV-16). Evaluation of efficacy will be based on objective cough counting and symptoms of viral URTI over 7 days. Additionally, this trial will perform a cough challenge to evaluate the antitussive effect of MK-7264.

Current therapies for acute and subacute cough (ie, narcotic, non-narcotic, and OTC medications) have limited or unproven efficacy and an undesirable side effect profile. This trial aims to provide proof of concept for use of MK-7264 in the treatment of acute cough; positive results in this trial will support continued study of MK-7264 for the treatment of acute cough.

3.2 Background

Refer to the Investigator's Brochure (IB) for detailed background information on MK-7264 [IB Edition 16 2017].

3.2.1 Pharmaceutical and Therapeutic Background

MK-7264, a P2X3 receptor antagonist, has been evaluated in clinical studies for treatment of chronic cough, interstitial cystitis/bladder pain syndrome, osteoarthritis pain, and asthma. MK-7264 has also been evaluated in an extensive nonclinical program.

MK-7264 is an oral medication provided as a film-coated tablet. The MK-7264 tablets provided for this trial contain 45 mg of MK-7264. Based on results of an efficacy interim analysis (IA), a lower dose arm (15 mg of MK-7264) may be added to this study. The placebo tablets provided in this trial are indistinguishable from the MK-7264 high- and low-dose tablets in appearance, respectively. The placebo tablets contain no MK-7264, but contain the same inactive excipients as those included in the active tablets.

3.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

MK-7264 has been evaluated in an extensive nonclinical program. To date, there is little evidence from nonclinical studies that MK-7264 has any direct cellular or direct target organ toxicity.

The efficacy and safety of MK-7264 has been evaluated in 8 completed Phase 2 clinical studies for cough. In those studies, patients with chronic cough who took MK-7264 showed a reduction in awake cough frequency and improvement in patient-reported outcomes (PROs) [IB Edition 16 2017]. The current study (P013) will be the first study to evaluate MK-7264 in participants with acute cough; however, as noted in Section 3, based on the involvement of ATP and P2X3-containing receptors in airways sensitization, combined with the efficacy observed in the Phase 2 chronic cough studies, it is reasonable to expect that MK-7264 will also be effective in reducing acute cough. Additionally, in the completed and ongoing clinical studies (Phase 1 and Phase 2), no major safety concerns have been noted. Taste-related adverse experiences (eg, dysgeusia, ageusia, hypogeusia) were the most frequently reported adverse events (AEs) in the clinical studies, with doses up to 1800 mg twice daily (BID) for 14 days. Subjects also described oral paresthesias (tingling sensation in the mouth and/or throat). In many instances, subjects reported oral paresthesia or hypoesthesia concurrent with taste alterations dysgeusia/hypogeusia/ageusia). A rationale for taste modification exists with P2X2/3 antagonism because of the putative participation of ATP, acting via this receptor, in transducing taste signals from taste buds cells to gustatory afferents. Attenuation of taste acuity is considered more of a tolerability concern as opposed to a safety concern, and is anticipated to be fully and rapidly reversible after discontinuation of the study treatment and amenable to monitoring in clinical studies.

Overall, based on growing clinical evidence supporting efficacy and lack of significant safety findings in completed and ongoing nonclinical and clinical studies (see IB for details, Section 3.2), the benefit-risk balance of MK-7264 is assessed as positive.

The risks and side effects related to this trial are expected to be manageable. Because HRV-16 causes the common cold, participants can expect to have a combination of one or more of the following symptoms after inoculation with the virus: runny nose, itchy nose, congested nose, sneezing, itchy eyes, headache, low-grade fever, sore throat, and/or cough. During the course of treatment, participants will be medically monitored 24 hours a day at a clinic. During the ATP cough challenge, β-agonist will be available if participants experience bronchoconstriction; if this type of treatment is required, participants will not be exposed to further cough challenges on that day, but may participate in the cough challenges on subsequent days. Appropriate medical intervention will be provided throughout the trial, as needed.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents (Section 3.2).

4. Objectives/Hypotheses and Endpoints

In this study, the objectives and endpoints will be evaluated in healthy adult participants with induced viral URTI as indicated in the following table. Since this is an exploratory study, hypotheses are not applicable.

Objective(s)/Hypotheses	Endpoint(s)
Primary	
Objective: To evaluate the efficacy of MK-7264 on cough frequency as measured while awake over a 24-hour period	Awake cough frequency (coughs per hour) on Day 3, as assessed by an objective cough-counting device
Secondary	
• Objective: To evaluate the efficacy of MK-7264 on the perception of cough severity	• Cough Severity VAS score measured as change from baseline on Day 3 • CSD score measured as change from baseline on Day 3
• Objective: To evaluate the efficacy of MK-7264 on cough-specific quality of life	• LCQ-acute score measured as change from baseline on Day 3
• Objective: To evaluate the safety and tolerability of MK-7264	• Number of participants experiencing AEs • Number of participants discontinuing study treatment due to AEs
Exploratory	
• Objective: To evaluate the efficacy of MK-7264 on cough frequency as measured over a 24-hour period	• 24-hour cough frequency (coughs per hour) on Day 3, as assessed by an objective cough-counting device
• Objective: To evaluate the efficacy of MK-7264 on cough frequency as measured while awake over a 24-hour period	• Awake cough frequency (coughs per hour) on Days 1, 2, 4, 5, 6, and 7, as assessed by an objective cough-counting device
• Objective: To evaluate the impact of MK-7264 on quality of life during a URTI	• Wisconsin Upper Respiratory Symptom Survey (WURSS-24) score measured as change from baseline on Day 3

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.

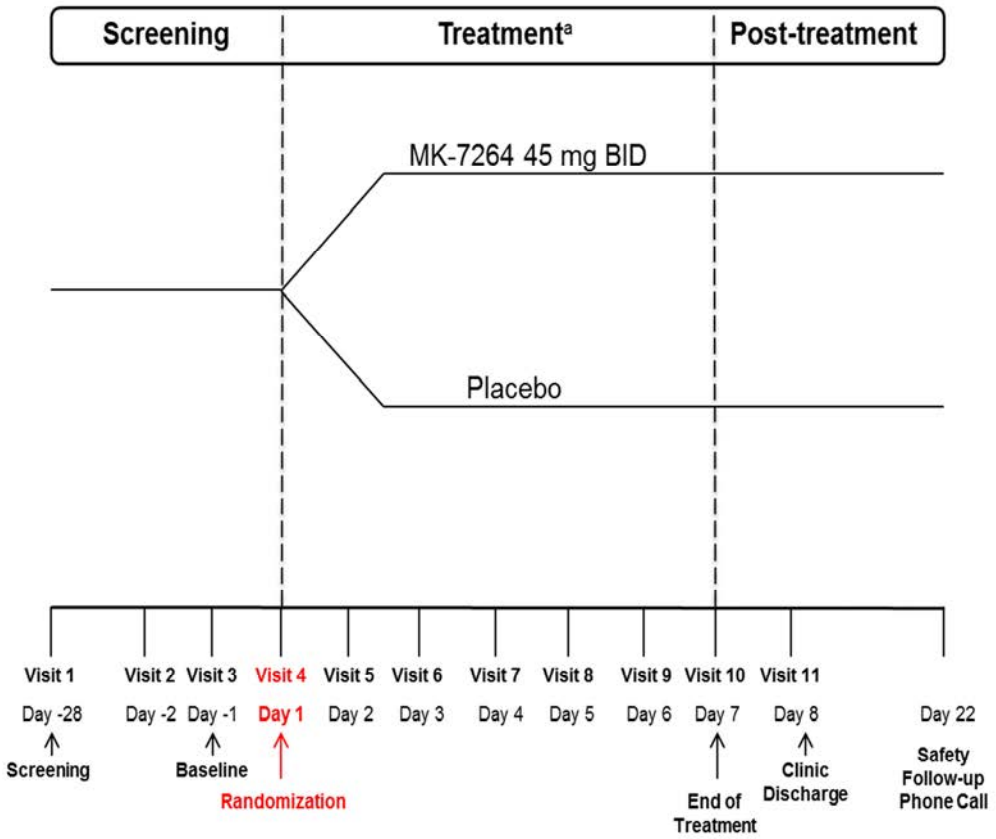
The results of the efficacy IA will be reviewed and the decision regarding trial modifications will be made by the standing internal Data Monitoring Committee (siDMC). The following actions are possible decisions from the siDMC, based on the results of the efficacy IA:

- 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.

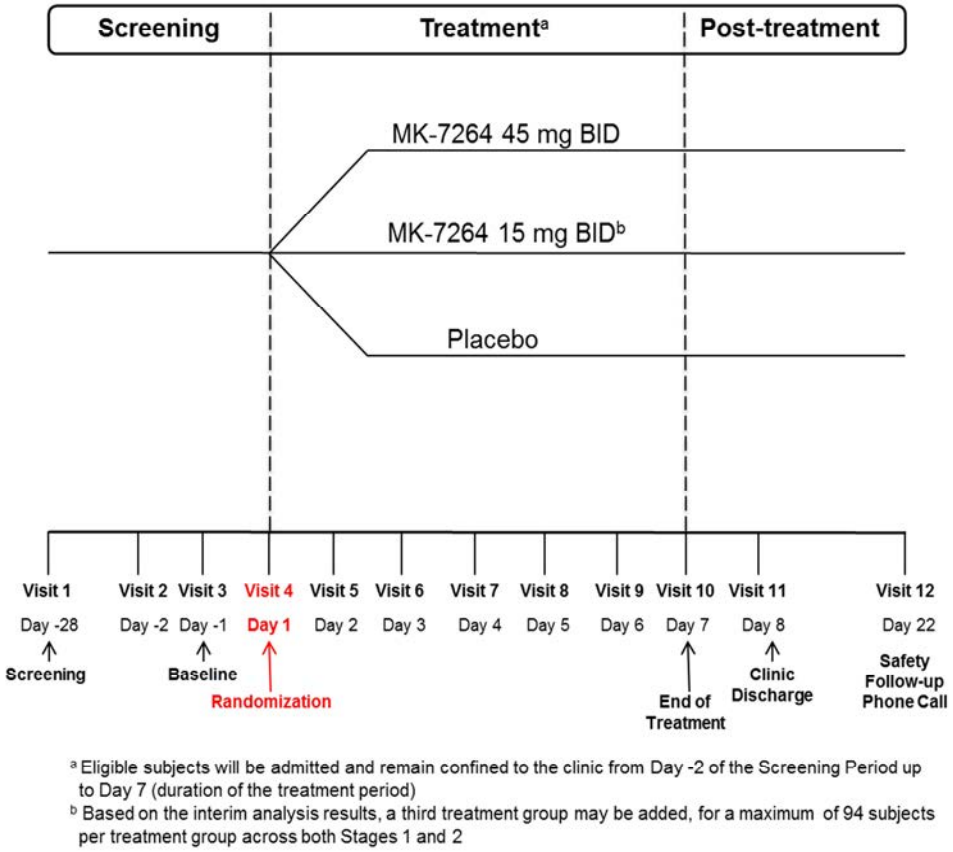
5.1.1 Study Diagram

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.



Abbreviations: BID = twice daily; IA = interim analysis

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



[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 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.

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.

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.

10. Had major surgery or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to Screening.
11. Has history of a cutaneous adverse drug reaction to sulfonamides or signs and symptoms suggestive of anaphylaxis to sulfonamides.
12. Has a history of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases that might expose the participant to risk by participating in the trial or investigational product administration or confound the results of the trial, or interfere with the participant's participation for the full duration of the trial, and, in the judgment of the investigator or Sponsor, would make the participant inappropriate for entry into this trial.
13. Is mentally or legally incapacitated, has significant emotional problems at the time of Screening, or is expected to during the conduct of the trial, or has a history of a clinically significant psychiatric disorder in the last 5 years. Participants who have had situational depression may be enrolled in the trial at the discretion of the investigator.
14. A WOCBP who has a positive urine pregnancy test within 72 hours before the first dose of study treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Prior/Concomitant Therapy

15. Has received medications to treat an acute viral URTI within 24 hours of study enrollment (defined as Day -1) (including dextromethorphan, diphenhydramine, and narcotic analgesics).
16. Has received medications within 14 days prior to randomization or needs to continue to receive any treatment (prescription or OTC) during the current trial, including antacids, high-dose multivitamins, nutritional supplements, and herbal preparations, beginning approximately 2 weeks (or 5 half-lives of the prior/concomitant medication) prior to administration of the initial dose of study treatment, throughout the trial, until the post-treatment visit (Day 8).

Prior/Concurrent Clinical Study Experience

17. Has previously received MK-7264.
18. Has participated in another investigational trial within 4 weeks (or 5 half-lives of the investigational product used in the other trial), whichever is greater, prior to the screening visit (the window will be derived from the date of the last visit in the previous trial) OR plans to take another investigational drug or biologic within 30 days of study completion of this current trial.

Diagnostic Assessments

19. Has significantly abnormal laboratory tests at Screening, including:
    a) Alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin >150% of the upper limit of normal (ULN);
    b) Hemoglobin <10 gm/dL, red blood cell (RBC) count < lower limit of normal (LLN) range, neutrophil count <LLN, platelet count <100 × 103/mm3
20. Has a clinically significant finding in a 12-lead ECG.

Other Exclusions

21. Current smoker, smoker within 5 years of Screening, or former smoker with a smoking history >20 pack-years.
22. Consumes >3 glasses of alcoholic beverages (ie, 1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Participant that consumes 4 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator.
23. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy-drinks, or other caffeinated beverages per day.
24. Is a regular user of cannabis or any illicit drugs, or has a history of drug (including alcohol) abuse within approximately 3 years of Screening. Participant must have a negative urine drug screen prior to randomization.
25. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this study.

6.3 Lifestyle Restrictions

6.3.1 Meals and Dietary Restrictions

There are no meal or dietary restrictions in this study.

6.3.2 Caffeine Alcohol, and Tobacco Restrictions

Participants will not be allowed to consume alcohol or nicotine-containing products while in the clinic unit. The consumption of caffeine or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) will be limited based on the standard policies of the study clinic at which they will remain 24 hours a day from Day -2 to Day 7.

6.3.3 Activity

Participants will be limited in exercise based on the standard policies of the study clinic at which they will remain 24 hours a day from Day -2 to Day 7.

On Day 1 to Day 7, participant's bathing activity will be limited to approximately 15 minutes per day as per the study clinic instructions. Bathing time is restricted in order to ensure that as close to 24 hours of recording time is obtained each day.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any adverse events or serious adverse events (SAE) meeting reporting requirements as outlined in the eCRF entry guidelines.

6.5 Participant Replacement Strategy

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

7. Treatments

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

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

7.1 Treatments Administered

The study treatments to be used in this study are outlined below in Table 1 and administered as shown in Table 2.

Table 1 Study Treatments

Study Treatment Name:	MK-7264 45 mg BID	MK-7264 15 mg BID	Placebo
Dosage Formulation:	Tablet	Tablet	Tablet
Unit Dose Strength(s):	45 mg	15 mg	Placebo to match each of MK-7264 45 mg and 15 mg[a]
Dosage Level(s):	45 mg BID	15 mg BID	Placebo to match MK-7264 45 mg BID and 15 mg BID[a]
Route of Administration:	Oral	Oral	Oral
Sourcing:	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor

Abbreviations: BID = twice daily

[a] As the images of MK-7264 45 mg and 15 mg are not identical, the placebo to match MK-7264 45 mg is different than the placebo to match MK-7264 15 mg.

Table 2 Treatment Administration

Period	**Trial Day**	**Double-Blinded Study Treatment Stage 1[a]**	**Double-Blinded Study Treatment[a] Stage 2[b]**
Treatment Period	1	MK-7264 45 mg BID or Placebo	MK-7264 45 mg BID or MK-7264 15 mg BID[c] or Placebo
	2		
	3		
	4		
	5		
	6		
	7		

Abbreviations: BID = twice daily; IA = interim analysis.

[a] Stage 1 - Prior to efficacy IA.

[b] Stage 2 - Post-efficacy IA.

[c] MK-7264 15 mg BID group applicable only if a decision is made to add a lower dose of MK-7264 based on results of the efficacy IA.

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

Refer to Section 9.1.8 for details regarding administration of the study treatment.

7.2 Dose Modification

Dose modifications are not allowed in this study.

7.3 Method of Treatment Assignment

Treatment randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are two treatment arms in Stage 1. Participants will be assigned randomly in a 1:1 ratio to either MK-7264 45 mg BID or placebo (approximately 50 total participants, 25 per arm) in Stage 1 (prior to the efficacy IA). The randomization schedule will be computer generated using a permuted block algorithm and will randomly allocate participants to randomization numbers/allocation numbers on Day 1.

In Stage 2 (post-efficacy IA), if a decision is made to include a lower dose of MK-7264 based on the efficacy IA results, there will be 3 treatment arms; participants will be randomized in a 1:2:1 ratio to MK-7264 45 mg BID, MK-7264 15 mg BID, or placebo, respectively. Otherwise, participants in Stage 2 will be randomized in a 1:1 ratio to either MK-7264 45 mg BID or placebo.

7.3.1 Stratification

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

- Gender (Male, Female)
- Site

The IVRS/IWRS will stratify participants by gender and at a site level. The study will endeavor to enroll a minimum of ~ 40% female participants in each stage. At the site level, the IVRS/IWRS will randomize participants to ensure there is a balance among treatment groups.

7.4 Blinding

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

See Section 9.1.10 for a description of the method of unblinding a participant during the study, should such action be warranted.

7.5 Preparation/Handling/Storage/Accountability

7.5.1 Dose Preparation

The rationale for dose interval to be used in this study is provided in Section 5.5.1. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant.

7.5.2 Handling, Storage and Accountability

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

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

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

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

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

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

7.6 Treatment Compliance

Randomized participants will remain in the clinic throughout the Treatment Period until Day 7 (or discontinuation). Administration of all study treatments will be witnessed by the investigator and/or study staff.

During the Treatment Period in Stage 1, all participants will receive 1 tablet of MK-7264 45 mg or placebo BID.

During the Treatment Period in Stage 2 (post-efficacy IA), if there are:

- Two treatment arms: all participants will receive 1 tablet of MK-7264 45 mg or placebo BID.

- Three treatment arms: all participants will receive 1 tablet of MK-7264 45 mg and 1 tablet of placebo for MK-7264 15 mg OR 1 tablet of MK-7264 15 mg and 1 tablet of placebo for MK-7264 45 mg OR 1 tablet of placebo for MK-7264 45 mg and 1 tablet of placebo for MK-7264 15 mg, BID.

Interruptions from the protocol specified treatment plan for >1 day require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

7.7 Concomitant Therapy

Concomitant medications are not permitted during the trial (see Section 6.2). If there is a clinical indication for any medication, discontinuation from study therapy may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

7.7.1 Rescue Medications and Supportive Care

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

7.8 Treatment After the End of the Study

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

7.9 Clinical Supplies Disclosure

The emergency unblinding call center will use the treatment/randomization schedule for the study to unblind participants and to unmask study treatment identity. In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic treatment allocation/randomization system (IRT) should be used in order to unblind participants and to unmask study treatment identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 9.1.10, for a description of the method of unblinding a participant during the study, should such action be warranted.

8. Discontinuation/Withdrawal Criteria

8.1 Discontinuation of Study Treatment

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

As certain data on clinical events beyond study treatment discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in the SoA (Section 2) and Section 9.10.3.

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 9.1.9.

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

- The participant or participant's legally acceptable representative requests to discontinue study treatment.
- The participant's treatment assignment has been unblinded by the investigator, Merck Sharp & Dohme. Inc. subsidiary, or through the emergency unblinding call center.
- The participant interrupts study treatment administration for more than 2 consecutive days.
- The participant has a medical condition (including urolithiasis or reduced eGFR by 30% or more from Screening value) or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the participant at unnecessary risk from continued administration of study treatment.
- Any drug-related SAE or any SAE which, in the opinion of the investigator and/or Sponsor, might affect the ability of the participant to safely continue to receive study treatment.
- Chronic failure to comply with the dosing, evaluations, or other requirements of the trial, despite documentation at the site of repeated efforts to reinforce compliance.
- The participant has evidence of a severe hypersensitivity reactions defined as progression of a treatment-related rash (eg, erythematous macules and papules), including increasing extent on body, rash accompanied by systemic findings (eg, fever, lymphadenopathy) or laboratory findings (eg, eosinophilia) or any signs or symptoms suggestive of drug-induced hypersensitivity syndrome (DIHS), also called drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome, or toxic epidermal necrolysis.
- The participant has a confirmed positive serum pregnancy test.
- The participant has a positive urine drug screen (UDS) at any time during the course of the trial.
- The participant has no confirmation of HRV-16 infection (based on HRV-16 shedding on nasal swab testing) within 72 hours of inoculation and will be discharged from the clinic.

For participants who are discontinued from study treatment but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

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

8.2 Withdrawal from the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study including the procedures to be performed if the study site is unable to contact the participant, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 9.1.9. The procedures to be performed if the study site is unable to contact the participant are outlined in Section 8.3.

8.3 Lost to Follow Up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, phone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the pre-specified statistical data handling and analysis guidelines.

9. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The Investigator is responsible for assuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- 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.

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

will be assigned only one screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 9.10.1.

9.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

9.1.8 Treatment Administration

Throughout the treatment period, administration of study treatment (all doses) will be witnessed by the investigator and/or study staff.

Study treatment will begin in the morning (before 11 am approximately) on the day of treatment randomization (Day 1). After randomization, the study participant will first have the VitaloJAK™ attached. The participant will then be inoculated with HRV-16 and then administered the first dose of study treatment. The VitaloJAK will then be immediately turned "on" after the first dose is administered. As dosing is BID, the next dose of study treatment on Day 1 should be taken orally in the evening, approximately 12 hours after the morning dose. Subsequent dosing through Day 7 will be performed in the same manner.

In Stage 1, all participants will be administered 1 tablet of study treatment BID (total daily dose: 2 tablets).

In Stage 2, if there are 2 treatment arms, all participants will be administered 1 tablet BID (total daily dose: 2 tablets). If there are 3 treatment arms (in order to maintain the blinding of the 2 different MK-7264 dose images), all participants will be administered 2 tablets of study treatment BID (totally daily dose: 4 tablets).

For more details about treatment compliance, see Section 7.6.

9.1.8.1 Timing of Dose Administration

Study treatments will be administered orally, BID (in the morning and in the evening), approximately 12 hours apart for 7 days and at approximately the same times each day.

9.1.9 Discontinuation and Withdrawal

Participants who discontinue study treatment prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.

When a participant withdraws from participation in the study, all applicable activities scheduled for the Early Discontinuation visit as described in the SoA (Section 2) should be performed (at the time of withdrawal). Any adverse events which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 9.3.

9.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for Future Biomedical Research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's consent for Future Biomedical Research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant’s personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

9.1.10 Participant Blinding/Unblinding

Participants whose treatment assignment has been unblinded by the investigator/delegate and/or non-study treating physician must be discontinued from study treatment, but should continue to be monitored in the study.

Additionally, the investigator must go into the IRT system and perform the unblind in the IRT system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding in the event that this is required for participant safety.

Study treatment identification information is to be unmasked ONLY if necessary for the welfare of the participant. Every effort should be made not to unblind the participant unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective participant’s code should be unblinded. Other study site personnel and Sponsor personnel directly associated with the conduct of the study should not be unblinded.

9.1.11 Domiciling

On Day -2 of the screening period, eligible participants will be admitted to the study clinic and remain confined to the clinic until completion of the treatment period on Day 7 (Section 5.1).

Note: Participants who fail screening between Day -2 and Day 1 (prior to randomization) will be discharged from the clinic and *excluded* from the trial.

Participants who lack confirmation of HRV-16 shedding by nasal swab testing within 72 hours of inoculation will be notified (once results are available), discontinued from study treatment, have discontinuation procedures performed (as specified in the SoA [Section 2]), and be discharged from the clinic; a safety follow-up telephone call will be performed 14 days after the last dose of study treatment.

9.1.12 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical study that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

Critical Equipment for this study includes:

- VitaloJAK™ cough monitor (study sourced): Calibration by the site is not necessary (See VitaloJAK™ Site Manual)
- Spirometer (site equipment): The spirometer should be calibrated according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines. Calibration checks should be performed (ie, with a 3-liter syringe) at a minimum of each day that a trial participant performs a spirometry assessment. The calibration check records should be printed and kept in a reviewable log. It is preferred that the calibration syringe used to check calibration of the spirometer also be subjected to a validated calibration according to the manufacturer's specifications.
- ECG machine (site equipment): Calibration should be performed according to the manufacturer's specifications.
- Equipment for Cough Challenge (locally sourced): Calibration should be performed according to the manufacturer's specifications.
- Equipment for HRV-16 administration (locally sourced): Calibration should be performed according to the manufacturer's specifications as necessary.

9.1.13 Other Study Procedures

9.1.13.1 Antibody Titers to Human Rhinovirus Type 16

Sample collection, storage, and shipment instructions to quantify antibody titers for HRV-16 at the Screening Visit are provided in the Central Laboratory Manual.

9.1.13.2 Ethanol Breath Test

The ethanol breath test, commonly known as alcohol breath test, will be performed at the site, as specified in the SoA (Section 2), to determine the level of ethanol in the blood. Alcohol in the mouth gives a rapid peak in ethanol concentration on the evidential test.

9.1.13.3 Urine Cotinine Test

Urine cotinine testing will be performed, as specified in the SoA (Section 2), to determine use of tobacco products by biochemical measurement of cotinine (nicotine metabolite) in a urine specimen.

9.1.13.4 Nasal Swabs for Human Rhinovirus Polymerase Chain Reaction

During the treatment period, experienced site staff will collect nasopharyngeal swabs from each participant every 12 hours for the 72-hour period immediately following inoculation with HRV-16, as specified in the SoA (Section 2). Instructions for collection, storage, and handling/shipment of nasal swab specimen and testing for HRV-16 by polymerase chain reaction (PCR) are provided in the Central Laboratory Manual.

9.2 Efficacy Assessments

Compliance with the efficacy and safety assessments (along with study treatment use) is essential, and any non-compliance noted by the investigator or designee should result in consultation with the participant on corrective measures needed to ensure compliance.

9.2.1 Cough Monitoring – VitaloJAK™ Recording Device

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

The VitaloJAK™ cough monitor recording device uses two input channels. The first channel records sounds from the lungs and trachea through a chest contact sensor, which is attached to the skin at the top of the sternum with adhesive. The second channel captures ambient sounds through a lapel air microphone. Sounds are stored on a high-capacity compact flash (CF) II card. The device will be carried in a cloth belt bag worn around the participant's waist, and it will record all sounds the participant makes during cough monitoring.

When the digital recording arrives at the central reading center, a human analyst uses standardized criteria to identify transitions between awake and asleep states. To reduce review time, the 24-hour recordings are processed through a computerized algorithm that

removes periods of silence and a high proportion of non-cough sounds. A cough analyst then evaluates the abbreviated recording by listening to both audio channels and inspecting the visual wave form of potential cough sounds. The analyst tags the explosive portion of each cough using 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.

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.

9.3 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.

9.5.2 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.

9.5.6 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

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.

9.10.1.2 Visit 2 (Day -2)

Eligible participants will be admitted to the clinic on Day -2 and will remain confined to the clinic until completion of the treatment period on Day 7 and discharged on Day 8 (or until discontinuation).

9.10.1.3 Visit 3 (Day -1; Baseline Visit)

Study clinic staff will instruct participants on how to properly complete study-related questionnaires (ie, Cough Severity VAS, CSD, LCQ-acute, and WURSS-24) and evaluate participant's capability to understand and complete the questionnaires for the duration of the trial. Note: Study clinic staff must never implement any updates on behalf of the participant or provide any interpretation of the questions.

On Day -1 of Stage 1, the ATP cough challenge will be administered to participants as described in Section 9.2.3. The number of coughs will be monitored manually at this visit. Details of the cough challenge procedures are provided in the Procedures Manual.

Note: ATP cough challenge is NOT performed during Stage 2 of the trial.

9.10.2 Treatment Period (Days 1 through 7)

Beginning at the randomization visit (Day 1), the cough monitor will be attached to the participant as described in Section 9.2.1. On Days 1 through 7, the CF card and battery pack must be removed from the cough monitor and replaced with a new CF card and new battery pack every 24 hours. Each CF card will then be sent for analysis, as described in the VitaloJAK™ Manual.

Note: The cough monitor can be removed for approximately 15 minutes each day, prior to taking a shower, with the assistance of site staff.

During Stage 1 of the trial, ATP cough challenge will be performed on all randomized participants 2 hours (± 30 minutes) postmorning dose as per the SoA (Section 2). The ATP cough challenge will NOT be performed during Stage 2 of the trial.

At the Discharge Visit (Day 8), a limited physical exam may be performed instead of a full physical exam, based on investigator judgment. Women of child bearing potential should be reminded to continue use of appropriate contraception (see Appendix 3) for at least 14 days after the last dose of study treatment.

9.10.3 Discontinued Participants Continuing to be Monitored in the Study

If a participant is discontinued from the study treatment, discontinuation procedures should be performed as specified in the SoA (Section 2). The participant will then be discharged from the study clinic and will be informed that they will receive a post-study telephone follow-up approximately 14 days (+ 3 days) after the last dose of study treatment.

Details about discontinuation of participants who do not show confirmation of HRV-16 shedding by nasal swab testing within 72 hours of inoculation are described in Section 9.1.11.

9.10.4 Post-study Telephone Follow-Up

Participants will be contacted for a safety follow-up phone call approximately 14 days (+ 3 days) after the last dose of study treatment. If the post-study telephone contact visit occurs less than 14 days after the last dose of study treatment, a subsequent follow-up phone call should be made at 14 days after the last dose of study treatment to determine if any AEs have occurred since the post-study telephone contact visit.

No other safety or efficacy assessments are required after discharge from the clinic; however, additional safety follow up may be performed, at the discretion of the investigator.

WOCBP potential must continue to use an acceptable birth control (defined in Appendix 3) for at least 14 days after the last dose of study treatment.

10. Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

10.1 Statistical Analysis Plan Summary

Key elements of the Statistical Analysis Plan (SAP) are summarized below. The comprehensive plan is provided in Sections 10.2 to 10.12.

Study Design Overview	A Phase 2a, double-blind, randomized, placebo-controlled, parallel-group trial to study efficacy, safety, and tolerability in male and female healthy participants with induced viral URTI.
Treatment Assignment	In Stage 1 (prior to the IA), participants will be randomized in a 1:1 randomization ratio to MK-7264 45 mg BID or placebo. In Stage 2 (post-IA), if a decision is made to include a lower dose of MK-7264 based on the IA results, participants will be randomized to MK-7264 45 mg BID, MK-7264 15 mg BID, or placebo in a 1:2:1 ratio, respectively. Otherwise, the 1:1 randomization ratio to MK-7264 45 mg BID or placebo will be used in Stage 2. Randomization will be stratified by gender and site.

Analysis Populations	Efficacy: The modified Full Analysis Set (mFAS) population, which 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; and Per Protocol (PP) Population, which excludes participants due to major deviations from the protocol from the mFAS population. Safety: All Participants as Treated (APaT) population, which consists of all randomized participants who received at least one dose of study treatment. PK: Population that includes all participants with at least one measurable PK sample.
Primary Endpoint	Awake coughs per hour on Day 3 of treatment.
Key Secondary Endpoints	• Cough Severity VAS score measured as change from baseline on Day 3 • CSD score measured as change from baseline on Day 3 • LCQ-acute score measured as change from baseline on Day 3
Statistical Methods for Key Efficacy Analyses	The primary efficacy endpoint will be analyzed using a longitudinal data analysis model (LDA). In this model, the response vector consists of daily awake coughs per hour at each postbaseline visit. 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.
Statistical Methods for Key Safety Analyses	The analysis of safety endpoints will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. Tier 1 safety endpoints will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals (CIs) provided for between-group comparisons. Tier 2 safety endpoints will be evaluated via point estimates and 95% CIs for between-group comparisons. Tier 3 safety endpoints will be evaluated via point estimates only.

Interim Analyses	One planned efficacy IA will be performed in this study. Results will be reviewed by an internal data monitoring committee (ie, siDMC). This IA is summarized below. • Timing: To be performed when approximately 50 participants have completed (or discontinued early from) Stage 1 of the trial • Purposes: o Conduct a futility analysis o Re-estimate sample size o Potentially add a lower dose (15 mg BID) of MK-7264 if a certain magnitude of efficacy of MK-7264 45 mg BID is detected compared with placebo o Evaluate safety and tolerability of MK-7264 Details are described in Section 10.7.1.
Multiplicity	No multiplicity adjustment is planned as there are no hypotheses for this study.
Sample Size and Power	The planned sample size is 100 participants, up to a maximum of 188 participants. [redacted]

10.2 Responsibility for Analyses/In-house Blinding

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

The study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol violators have been identified, and data have been declared final and complete.

Treatment assignment will be implemented by the external vendor of the study IVRS according to the adaptive allocation scheme provided in Section 7.3.

Unblinding for Efficacy and Safety Interim Analyses

Treatment-level results and/or participant-level data of the IA will be provided by an internal unblinded statistician to the siDMC.

The interim efficacy and safety analyses will be conducted by the unblinded statistician; the results will be reviewed and decision made by a siDMC that consists of Sponsor personnel. Limited additional Sponsor personnel may be unblinded to the treatment-level results of the IA, if required, in order to act on the recommendations of the siDMC. The details of the

siDMC monitoring guidelines, scope of work, the schedule of the interim safety monitoring, and stopping rules will be described in the Protocol-specific siDMC Charter. The extent to which individuals are unblinded with respect to results of IAs will be documented by the unblinded statistician. These individuals will not be involved in the day-to-day operations of the study.

The processes by which recommendations and decisions are reached and communicated are documented in the siDMC charter for the Sponsor. The protocol-specific siDMC charter will be referenced in the CSR. Prior to final study unblinding, individuals who have been unblinded at any level will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

10.3 Hypotheses/Estimation

There are no hypotheses for this study.

10.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

10.4.1 Efficacy Endpoints

Primary Efficacy Endpoint

Awake cough frequency (coughs per hour) on Day 3, as assessed by an objective cough-counting device

Secondary Efficacy Endpoints

- Cough Severity VAS score measured as change from baseline on Day 3
- CSD score measured as change from baseline on Day 3
- LCQ-acute score measured as change from baseline on Day 3

Exploratory Efficacy Endpoints

Exploratory efficacy endpoints are stated in Section 4.

10.4.2 Safety Endpoints

Safety endpoints are stated in Section 4.

10.4.3 Pharmacokinetic Endpoints

PK endpoints are stated in Section 4.

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.

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.

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 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.

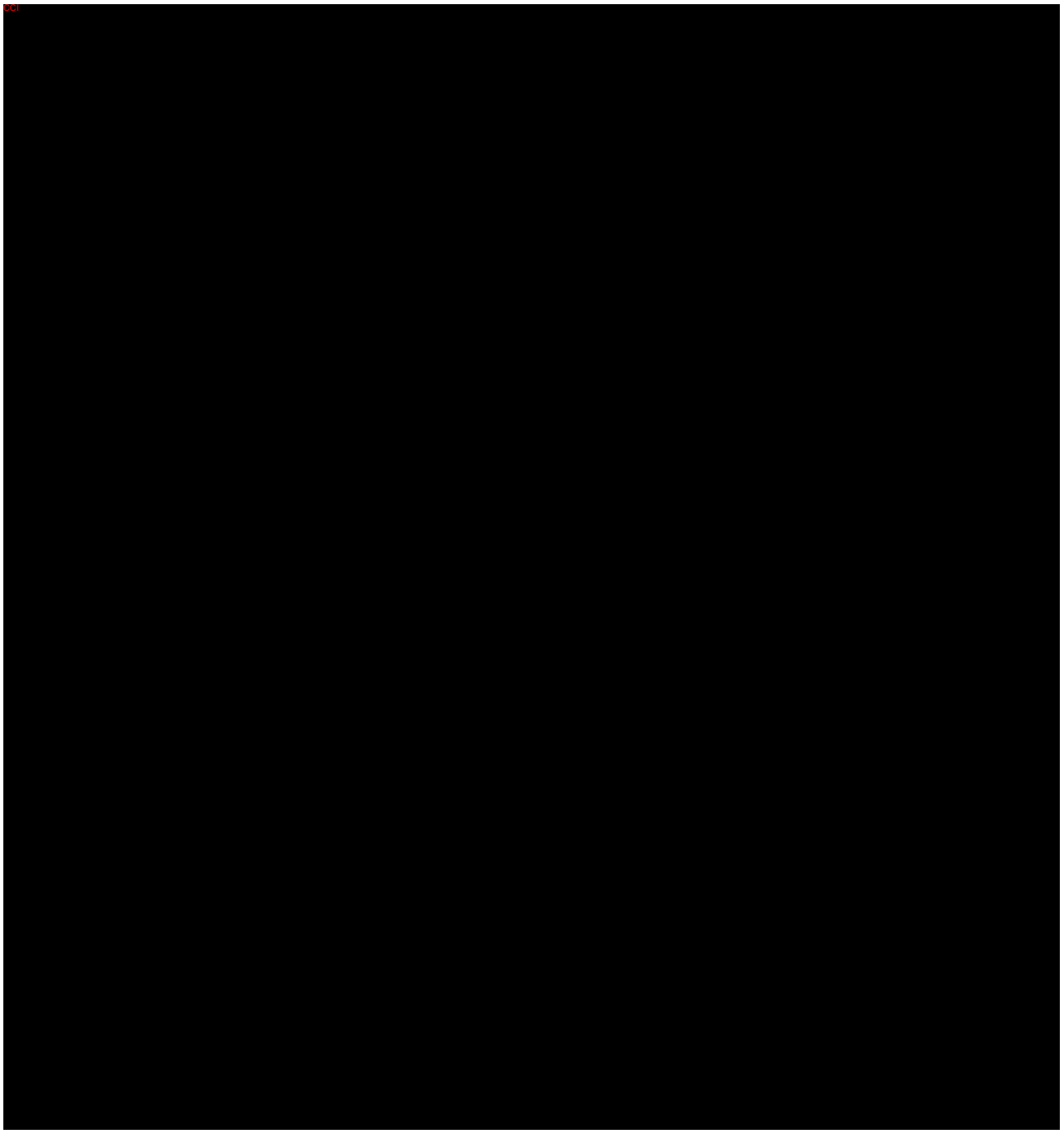
10.7 Interim Analyses

10.7.1 Efficacy Interim Analysis

One planned efficacy IA will be conducted once approximately 50 participants have completed (or discontinued early from) Stage 1 of the trial, and, although this trial is strictly exploratory/for estimation, the decision criteria will be based on the observed effect of the 45 mg BID dose group to help guide future studies. The efficacy IA is intended to:

- Conduct a futility analysis
- Re-estimate sample size
- Potentially add a lower dose (15 mg BID) of MK-7264 if a certain magnitude of efficacy of MK-7264 45 mg BID is detected compared with placebo

The criteria adopted for the IA decision rule will be based on the posterior probability and clinical relevance on the primary endpoint of awake coughs per hour on Day 3. [redacted]



The efficacy IA will be conducted by an internal unblinded statistician and programmer; the results will be reviewed and the decision will be made by siDMC. The details of the siDMC monitoring guidelines, scope of work, schedule of the interim safety monitoring, and decision rules will be described in the Protocol-specific siDMC Charter.

10.7.2 Safety Interim Analyses

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

10.8 Multiplicity

There are no hypotheses for this study. For Tier 1 safety endpoints, 95% CIs for between-group differences will be provided with nominal p-values as a descriptive measure without adjustment for multiplicity. There will be no formal method for assessing statistical significance.

10.9 Sample Size and Power Calculations

The final sample size of the trial depends on the outcome of the efficacy IA described in Section 10.7.1. If the trial design is unchanged based on the results of the efficacy IA, a total of 100 participants (50 per treatment group) will be randomized in a 1:1 ratio to either MK-7264 or placebo. Assuming a 20% attrition rate (including treatment discontinuation due to lack of viral shedding), this gives approximately 40 evaluable participants per treatment group.

[redacted]

An IA will be conducted once approximately 50 participants (25 per arm) have completed (or discontinued early from) Stage 1 of the trial. Depending on the decision from the IA, the total sample size of the trial will be up to a maximum of 188. Table 10 describes various scenarios of the sample sizes for the trial. The details of the IA decision rules will be described in the Protocol-specific siDMC Charter.

Table 10 Scenarios of Total Sample Size

Decision from the IA	Treatment Groups Included in Final Trial Design	Sample Size per Treatment Group	Total Sample Size
The trial will stop for futility	MK-7264 45 mg BID Placebo	25	50
Sample size will be increased	MK-7264 45 mg BID Placebo	>50 to 94	>100 to 188
Continue the trial as planned	MK-7264 45 mg BID Placebo	50	100
A lower dose of MK-7264 will be added	MK-7264 45 mg BID MK-7264 15 mg BID Placebo	50	150

Abbreviations: BID = twice daily; IA = interim analysis

10.10 Subgroup Analyses

Analysis for the primary efficacy endpoint will be provided for the following subgroups of baseline factors:

- Gender (Male, Female)
- Site
- Age group (18 to 36 years, 37 to 55 years)

The same LDA model as the primary efficacy endpoint will be performed.

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

10.11 Compliance (Medication Adherence)

Total number of doses and total number of days on study treatment will be summarized by treatment group. Compliance will also be summarized. Since the participants are inpatient participants, the compliance will only measure the compliance up to the end of study participation. That is, the compliance rate will not be impacted by premature discontinuation from the study.

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

10.12 Extent of Exposure

The duration of treatment for each participant will be evaluated by calculating the number of days on therapy. Exposure to study treatment will be summarized using descriptive statistics (ie, mean, SD, median, minimum, and maximum) for the APaT population.

11. References

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12. Appendices

12.1 Appendix 1: Study Governance Considerations

Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participant safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Participant Protection

A. IRB/IEC review

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

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Participants are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Participants are enrolled only after providing informed consent for participation. Participants may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

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

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

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

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

Financial Disclosure

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

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

Data Protection

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

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

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

Confidentiality of Data

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

Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of

verifying worksheet/case report form information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

Confidentiality of IRB/IEC Information

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

Committees Structure

To supplement the routine monitoring outlined in this protocol, a separate Standing Internal Data Monitoring Committee (siDMC) will monitor the interim data from this study. The siDMC comprises members of Sponsor Senior Management, none of whom are directly associated with the conduct of this study. The siDMC will monitor the study at an appropriate frequency (see Section 10.7 - Interim Analyses) for evidence of adverse effects of MK-7264; for re-estimation of the treatment effect and variability of the primary endpoint to ensure the study is sufficiently powered; and for investigating the possibility of adding a lower dose (15 mg BID) of MK-7264 if a certain magnitude of efficacy of MK-7264 45 mg BID is detected compared with placebo as described in the siDMC Charter]. The siDMC will determine whether the study should continue (or other modifications, pre-specified or otherwise, should be made) according to the protocol, considering the overall risk and benefit to study participants. The siDMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both participant safety and the continued ethical integrity of the study.

Specific details regarding responsibilities of the siDMC will be described in a separate charter that is reviewed and approved by the siDMC.

All personnel involved in the adjudication process will remain blinded to study treatment allocation throughout the study.

Publication Policy

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

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

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

Compliance with Study Registration and Results Posting Requirements

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

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

Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Merck Code of Conduct for Clinical Trials.

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

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

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

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in

conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

Data Quality Assurance

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

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

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

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

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

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

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

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

Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Site Closure

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

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

12.2 Appendix 2: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 9.9 will be used in various experiments to understand:

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

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

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

3. Summary of Procedures for Future Biomedical Research

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in the Future Biomedical Research sub-study.

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent

forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

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

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

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

4. Confidential Participant Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link participant' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the Future Biomedical Research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-study. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for Future Biomedical Research and ask that their biospecimens not be used for Future Biomedical Research. Participants may

withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for Future Biomedical Research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant’s personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized and are described in the Future Biomedical Research informed consent.

The Sponsor has developed strict security, policies and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute: https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; Available from: http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

12.3 Appendix 3: Contraceptive Guidance and Pregnancy Testing

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - Postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use one of the contraception methods described in consistently and correctly during the protocol-defined timeframe in Section 6.1 and Section 9.10.4.

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.

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.

12.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment. • NOTE: for purposes of AE definition, study treatment (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the sponsor for human use in this study.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. • For all reports of overdose (whether accidental or intentional) with an associated adverse event, the AE term should reflect the clinical symptoms or abnormal test result. An overdose of study treatment without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect." • Any new cancer or progression of existing cancer.

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

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.

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)?

- **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

another cause.

- No, there is not a reasonable possibility of Sponsor's product relationship: Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

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

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

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

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

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

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

AE, SAE, and Other Reportable Safety Event Reporting to Sponsor via Electronic Data Collection Tool

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference section 9.3.1 – Time Period and Frequency for Collecting AE and SAE and Other Reportable Safety Event Information for reporting time requirements

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the 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).

12.5 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.

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

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

Abbreviation	Term
WURSS-24	Wisconsin Upper Respiratory Syndrome Symptom Survey