Official Protocol Title:	A Phase 3b Randomized, Double-blind, Placebo Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Gefapixant in Adult Participants with Recent Onset Chronic Cough
NCT number:	NCT04193202
Document Date:	25-Nov-2020

Title Page

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Protocol Title: A Phase 3b Randomized, Double-blind, Placebo Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Gefapixant in Adult Participants with Recent Onset Chronic Cough

Protocol Number: 043-03

Compound Number: MK-7264

Sponsor Name:

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	123007
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Approval Date: 25 November 2020

Sponsor Signatory

Typed Name:
Title:

Date

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

Investigator Signatory

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

Typed Name:
Title:

Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Protocol Amendment 03	25-NOV-2020	Removal of procedures/assessments for specialized urine crystal analysis added in Protocol Amendment 02 and other clarifications.
Protocol Amendment 02	20-FEB-2020	Addition of procedures/assessments required for specialized urine crystal analysis.
Protocol Amendment 01	04-OCT-2019	Correction to entry criteria and other clarifications
Original Protocol	10-SEP-2019	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

Overall Rationale for the Amendments:

Removal of procedures/assessments for specialized urine crystal analysis.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Section 1.3 – Schedule of Activities (SoA)	Added note to Urine Pregnancy Test: *Performed locally at study site.*	To clarify that the urine pregnancy test is performed locally at the study site.
Section 1.3 – Schedule of Activities (SoA)	Deleted text: ~~*Urine Collection and Preparation for Specialized Urine Crystal Analysis*~~ ~~*Urine sample collected (at Visit 4/Discontinuation) is immediately prepared per central laboratory manual and stored at site; if central laboratory urinalysis positive for crystals and/or unexplained hematuria, sample shipped to Sponsor or designee for Specialized Urine Crystal Analysis.*~~ ~~*See Section 8.3.7.*~~	Urine collection for specialized urine crystal analysis is removed from the list of assessments performed during the study.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 – Schedule of Activities (SoA)	Added footnote "d" for Pharmacokinetic Blood Collection: *A pharmacokinetic blood sample should be collected within approximately 96 hours of the final dose of study medication. If the discontinuation or final visit is scheduled to occur greater than 96 hours following the final dose of study medication, please contact the Sponsor for guidance.*	To clarify the timing for pharmacokinetic samples.
Section 5.2 – Exclusion Criteria	Added note to number 18: *Note: Participants with a known history or current evidence of SARS-CoV-2 (COVID-19) infection are ineligible to enroll in the study.*	To clarify that participants with a known history or current evidence of SARS-CoV-2 (COVID-19) infection are ineligible to enroll in the study.

Section # and Name	Description of Change	Brief Rationale
Section 7.1 – Discontinuation of Study Intervention	Updated text (deleted strikethrough text): • *The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention ~~(including recommendation to discontinue participant from study intervention as part of monitoring for crystalluria/urolithiasis, see Section 8.3.7)~~.*	To remove the recommendation for participants to be discontinued from the study intervention if gefapixant crystalluria is detected.
Section 8.1.10 – Participant Blinding/Unblinding	Deleted text: ~~*In the instance of identifying gefapixant crystals in the urine (see Section 8.3.7 for further details), the participant will be discontinued from the study intervention (see Section 7.1 for further details). If a participant has confirmed gefapixant crystals, it will be known that the participant was receiving gefapixant. In this circumstance, formal non-emergency unblinding should not be performed.*~~	To remove that participants should be discontinued from the study intervention if gefapixant crystalluria is detected.

Section # and Name	Description of Change	Brief Rationale
Section 8.2.1 Patient-reported Outcomes	Updated text (new text in bold font, deleted text with strikethrough): *the e-Diary will allow the participant, based on recall, to complete these missed measures ~~at any time~~ in the next ~~24 hours~~ **day** (also see vendor's site manual for further details)*	To clarify when missed measures can be completed.
Section 8.2.1 Patient-reported Outcomes	Updated text (new text in bold font, deleted text with strikethrough): *At the clinic visits, participants will be asked to complete ePRO measures (in the following order: ~~LCQ~~, Cough Severity VAS, **LCQ**, PGIC, and WPAI), as outlined in the SoA (also see vendor's site manual for further details).*	To correct order of ePRO outcome measures.
8.3.7 – Renal and Urological Safety Assessments	Updated text (new text in bold font, deleted text with strikethrough): *8.3.7.2 Visit 4/Discontinuation* *At Visit 4 or Discontinuation Visit, a urine sample will be collected from all participants, as outlined in the SoA. ~~All urine samples will be collected and prepared as detailed in the central laboratory manual:~~*	To remove procedures/assessments for specialized urine crystal analysis.

Section # and Name	Description of Change	Brief Rationale
	• ~~*Part of the collected sample will be shipped to the central laboratory for urinalysis (that includes, but is not limited to, testing for blood and urinary crystals).*~~ • ~~*The second part of the collected sample will be immediately prepared using a specialized filter for gefapixant urinary crystal analysis. The filtered sample will be stored at the study site until the urinalysis results from the central laboratory are received.*~~ ~~*On receipt of the urinalysis results from the central laboratory,*~~ ***If*** ~~*results indicate a participant has*~~ *unexplained hematuria and/or urinary crystals* ***are identified and deemed to be clinically significant by the investigator, the participant should be considered for further evaluation.***~~*the filtered sample stored at the site will be immediately shipped to the Sponsor or designee and assessed for the presence of gefapixant urinary crystals via Raman spectroscopy. Raman spectroscopy is sensitive to the chemical structure of the*~~	

Section # and Name	Description of Change	Brief Rationale
	~~*molecule and gefapixant has a unique chemical structure compared with common urinary crystals. If there is an explanation for hematuria (for example, recent menses, urinary tract infection, or a recent procedure/instrumentation that would explain the hematuria) the sample will not be sent to the Sponsor or designee. See central laboratory manual for further procedural details.*~~ ~~*If a participant has confirmed gefapixant urinary crystals, the Sponsor will inform the investigator and recommend follow-up with the participant at approximately 2-week intervals; additional specialized urine crystal analyses should be performed until resolution of the gefapixant urinary crystals. Once a participant has confirmed gefapixant crystals, it will be known that the participant was receiving gefapixant (formal unblinding should not be performed [see Section 8.1.10]).*~~ *If an investigator deems it necessary to perform an unscheduled urinalysis at any time during the study (after randomization), the same procedures for collection/preparation of the urine sample and evaluation of hematuria (as explained*	

Section # and Name	Description of Change	Brief Rationale
	or unexplained) described for Visit 4 or Discontinuation Visit should be performed. ~~The sample will be analyzed for the presence of gefapixant urinary crystals as appropriate.~~	
8.6.1 Blood Collection for Plasma Gefapixant	Added text: *A pharmacokinetic blood sample should be collected within approximately 96 hours of the final dose of study medication. If the discontinuation or final visit is scheduled to occur greater than 96 hours following the final dose of study medication, please contact the Sponsor for guidance.*	To clarify the timing for pharmacokinetic samples.

Section # and Name	Description of Change	Brief Rationale
8.10 3 Discontinued Participants Continuing to be Monitored in the Study	Updated text (new text in bold font): *If a participant is discontinued from the study intervention early:* • *the Discontinuation Visit should be performed as soon as possible;* ***Procedures, including e-Diary assessments, should be performed as outlined for the Discontinuation Visit in the SoA (Section 1.3).*** ***Note: If a participant discontinues at a regularly scheduled study visit, the procedures outlined for the Discontinuation Visit in the SoA should be followed in place of the procedures for the regularly scheduled study visit.***	To clarify the procedures that should be performed if a participant discontinues.

Section # and Name	Description of Change	Brief Rationale
8.10.3 Discontinued Participants Continuing to be Monitored in the Study	Updated text (new text in bold font): • *Study site visits should continue to be performed at timepoints that correspond to each remaining study visit. These visits will allow collection of follow-up information, limited to:* o *AEs;* o *Concomitant medication use; and* o *e-Diary assessments, as outlined in the SoA (Section 1.3)**.*** ***Note: If the participant discontinues study intervention at a regularly scheduled study visit but remains in the study, the Discontinuation Visit should be performed, and the regularly scheduled study visits should resume thereafter. For example: If a participant discontinues study intervention at the time of Visit 3, procedures for the Discontinuation Visit should be performed at that time. The next expected study visit would be Visit 4.***	To clarify the procedures that should be performed if a participant discontinues study intervention but remains in the study.

Section # and Name	Description of Change	Brief Rationale
Section 9.1 Statistical Analysis Plan Summary	Updated text (new text in bold font, deleted text with strikethrough): *Interim Analyses* *Timing: To be performed when approximately 40% of participants (approximately the first 166 ~~enrolled~~ **randomized** participants) have either completed the study or discontinued the study intervention early.*	Revised enrolled participants to randomized participants.
Section 9.7.1 Interim Efficacy Analysis	Updated text (new text in bold font, deleted text with strikethrough): *One planned efficacy IA will be conducted when approximately 40% of target participants (approximately the first 166 ~~enrolled~~ **randomized** participants) have either completed the study (approximately 141 ~~enrolled~~ **randomized** participants) or discontinued study intervention early.*	Revised enrolled participants to randomized participants.

Section # and Name	Description of Change	Brief Rationale
Section 9.7.2 Interim Safety Analysis	Updated text (new text in bold font, deleted text with strikethrough): *Interim safety will also be assessed at the time of prespecified IA for futility, ie, when approximately 40% of target participants (approximately the first 166 ~~enrolled~~* ***randomized*** *participants) have either completed the study or discontinued the study intervention early.*	Revised enrolled participants to randomized participants.
Throughout the document	Editorial and formatting changes.	Consistency.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3b Randomized, Double-blind, Placebo Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Gefapixant in Adult Participants with Recent Onset Chronic Cough

Short Title: Gefapixant Phase 3b Study in Adult Participants with Recent Onset Chronic Cough

Acronym: None

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

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

Primary Objectives	Primary Endpoints
- Objective: To evaluate the efficacy of gefapixant in improving cough specific quality of life, measured as change from baseline in the Leicester Cough Questionnaire total score at Week 12 Hypothesis: Gefapixant is superior to placebo in increasing Leicester Cough Questionnaire total score change from baseline at Week 12	- Leicester Cough Questionnaire total score
Secondary Objectives	Secondary Endpoints
- Objective: To evaluate the efficacy of gefapixant in improving self-rated cough severity, measured as change from baseline in the Cough Severity Visual Analog Scale score at Week 12	- Cough Severity Visual Analog Scale score
- Objective: To evaluate the safety and tolerability of gefapixant compared to placebo in percent of participants with adverse events	- Adverse events - Study intervention discontinuations due to an adverse event

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Treatment of Chronic Cough
Population	Participants who are at least 18 years of age with recent onset refractory or unexplained chronic cough
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo
Study Blinding	Double-blind with in-house blinding
Masking	Participant or Subject Investigator
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 18 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 414 participants will be randomized, with approximately 207 participants in each intervention group.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Admin-istration</th><th>Regimen/ Treatment Period</th><th>Use</th></tr>
<tr><td>Gefapixant</td><td>Gefapixant</td><td>45 mg</td><td>1 tablet BID</td><td>Oral</td><td>12 weeks</td><td>Experi-mental</td></tr>
<tr><td>Placebo</td><td>Placebo</td><td>0 mg matched to gefapixant 45 mg</td><td>1 tablet BID</td><td>Oral</td><td>12 weeks</td><td>Placebo</td></tr>
<tr><td colspan="7">Abbreviations: BID = twice daily</td></tr>
</table>
</td></tr>
<tr><td>Total Number</td><td>2 intervention groups</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study for approximately 16 weeks from the time the participant provides documented informed consent through the final contact. After a screening phase of approximately 2 weeks, each participant will receive assigned intervention for approximately 12 weeks. Each participant will have a safety follow-up telephone call 14 days (with an allowed variance of up to +7 days) after completion, discontinuation, or withdrawal of the study intervention.</td></tr>
</table>

Study Governance Committees:

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

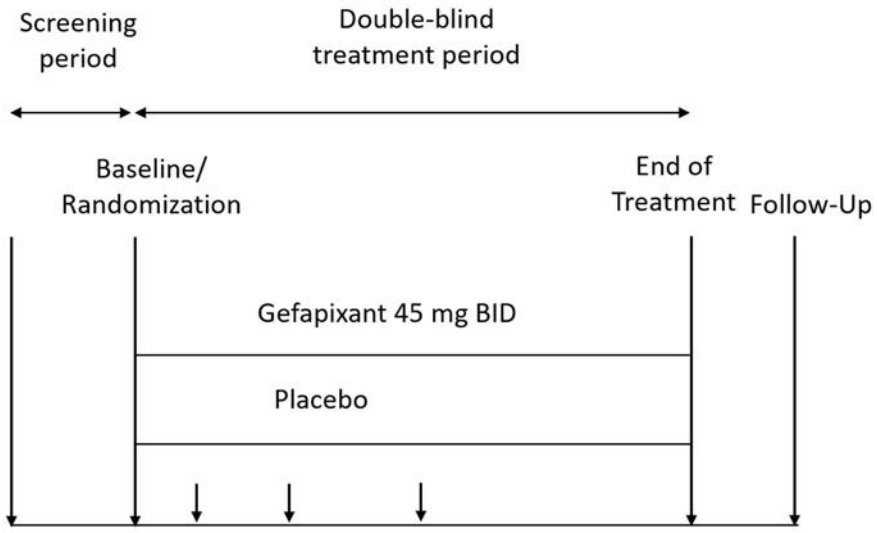
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 10.8.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema



Visit:	1	2	-	-	3	4	-
Day:	-14	1	7	21	42	84	98
Week:	-2	-	1	3	6	12	14

BID = twice daily, e-Diary = electronic diary.

At study entry, participants will be randomized in a 1:1 ratio to 1 of 2 intervention groups: gefapixant 45 mg BID or placebo. Participants will remain on their assigned intervention at Randomization throughout the study.

Telephone contact will be made on Day 7 (+3 days) and Day 21 (±3 days) to review any adverse events, concomitant medications, study drug administration compliance, and e-Diary completion.

A safety follow-up telephone call will be conducted a minimum of 14 days (with an allowed variance of up to +7 days) after Visit 4 or after the last dose of study intervention (for participants who discontinue from intervention).

1.3 Schedule of Activities (SoA)

Study Period	Screening	Baseline / Randomization	Intervention				Follow-up TC[a]	Disc[c]	Notes
Visit	1	2	TC	TC	3	4	-	NA	
Scheduled Day	-14 to -1	1	7	21	42	84	98	NA	
Scheduling Window (recommended)	NA	NA	+3 days	±3 days	±4 days	±4 days	+7 days	NA	
Scheduled Week	-2 to -1	-	1	3	6	12	14	NA	
Administrative Procedures									
Informed Consent	X								
Informed Consent for FBR	X								FBR is optional for the participant.
Participant Identification Card	X	X							Update with allocation number once randomized.
Inclusion/Exclusion Criteria	X	X							
Demographics, Medical History	X								
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	
Randomization		X							
Gefapixant/Placebo Administration/Dispensing		X			X				
Study Intervention Accountability					X	X		X	
Contact IRT System	X	X			X	X		X	
Efficacy Procedures									
Activate ePROs	X	X			X	X		X	See ePRO vendor manual.
Issue/instruct on use of e-Diary	X								
Review e-Diary compliance and instructions for use		X	X	X	X	X		X	Disc: Only when participant discontinues from study intervention (not discontinues from study).
Deactivate/collect e-Diary						X		X	Disc: Only when participant discontinues from study (not just discontinues study intervention).

Study Period	Screening	Baseline / Randomization	Intervention				Follow-up TC[a]	Disc[c]	Notes
Visit	1	2	TC	TC	3	4	-	NA	
Scheduled Day	-14 to -1	1	7	21	42	84	98	NA	
Scheduling Window (recommended)	NA	NA	+3 days	±3 days	±4 days	±4 days	+7 days	NA	
Scheduled Week	-2 to -1	-	1	3	6	12	14	NA	
LCQ		X			X	X		X	Complete at clinic visit: - Visit 2: After confirming eligibility for randomization and before first dose of study intervention. - Visits 3 & 4/Disc: Before all other procedures.
CSD	Complete daily (in evening)								Remind participant of need to complete daily.
Cough Severity VAS	Complete at Visit 1 clinic visit and daily (in evening)								Visits 2 & 3: Remind participant of need to complete daily.
PGIC						X		X	Complete at clinic visit.
WPAI		X				X		X	Visit 2: Complete at clinic visit before first dose of study intervention.
Safety Procedures									
Chest Radiograph or CT Thorax	X								Not required if done in the past 1 year and after onset of chronic cough.
Physical examination	X					X		X	Visit 1 (Screening): full examination. Visit 4 and Disc: directed examination.
Height	X								
Weight	X					X		X	
Vital Signs	X	X			X	X		X	
12-lead ECG	X								
Spirometry	X								
Urine Pregnancy Test	X								Performed locally at study site.
Serum Pregnancy Test	X								Only if urine pregnancy test is positive.
Hematology & Chemistry	X					X		X	
Urinalysis (with microscopy)	X					X		X	
Adverse Event Monitoring	X	X	X	X	X	X	X	X	

Study Period	Screening	Baseline / Randomization	Intervention				Follow-up TC[a]	Disc[c]	Notes
Visit	1	2	TC	TC	3	4	-	NA	
Scheduled Day	-14 to -1	1	7	21	42	84	98	NA	
Scheduling Window (recommended)	NA	NA	+3 days	±3 days	±4 days	±4 days	+7 days	NA	
Scheduled Week	-2 to -1	-	1	3	6	12	14	NA	
Pharmacokinetics / Biomarkers									
Pharmacokinetic blood collection[d]						X		X	Only 1 sample will be collected, either at Visit 4 or Disc Visit, whichever is the first visit following the last dose of study intervention.
Blood for Genetic Analysis[b]	X								

CSD = Cough Severity Diary; CT = computed tomography; Disc = Discontinuation; ECG = electrocardiogram; e-Diary = electronic diary; ePRO = electronic patient-reported outcomes; FBR = Future Biomedical Research; IRT = interactive response technology; LCQ = Leicester Cough Questionnaire; NA = not applicable; PGIC = Patient Global Impression of Change; TC = telephone call; VAS = Visual Analog Scale; WPAI = Work Productivity and Activity Impairment.

a. A safety follow-up telephone call will be conducted a minimum of 14 days (with an allowed variance of up to +7 days) after the last dose of study intervention (for participants who complete the study, discontinue from intervention, or discontinue from the study).

b. This sample should be drawn for planned analysis of the association between genetic variants in deoxyribonucleic acid and drug response. This sample will not be collected at a site if there is either a local law or regulation prohibiting collection, or if the Institutional Review Board / Independent Ethics Committee 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 (or their legally acceptable representative) provides documented informed consent for future biomedical research. If the planned genetic analyses are not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research.

c. For participants who discontinue from study intervention early, study visits/assessments should continue to be performed at timepoints that correspond to each remaining study visit, but procedures will be limited to collection of adverse events, concomitant medications, and e-Diary assessments.

d. A pharmacokinetic blood sample should be collected within approximately 96 hours of the final dose of study medication. If the discontinuation or final visit is scheduled to occur greater than 96 hours following the final dose of study medication, please contact the Sponsor for guidance.

2 INTRODUCTION

Cough is one of the most common presenting symptoms for patients seeking care from primary care specialists, allergists, pulmonologists, or otolaryngologists worldwide. Although cough is an important mechanism to protect the airway from potentially harmful stimuli, excessive or inappropriate cough can be associated with significant morbidity including physical, psychological and social consequences [French, C. L., et al 1998] [Young, E. C. 2010] [Chamberlain, S. A., et al 2015] [Dicpinigaitis, P. V., et al 2006] [Kuzniar, T. J., et al 2007] [French, C. L., et al 2017] [Everett, C. F., et al 2007]. 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] [Irwin, R. S. 2006] [Chung, K. F., et al 2006] [Raj, A. A., et al 2009] [Irwin, R. S., et al 2014]. In these clinical guidelines, cough is categorized based upon the duration of the cough. Acute cough is present for less than 3 weeks and most often due to acute viral upper respiratory tract infection. A cough that has been present longer than 3 weeks is either subacute (3 to 8 weeks) or chronic (>8 weeks) [The committee for The Japanese Respiratory Society guidelines 2006]. There are multiple diagnostic possibilities for each category, acute, subacute, and chronic, that are presented in clinical guidelines [Gibson, P., et al 2016].

The overall prevalence of chronic cough is approximately 10% [Song, W. J., et al 2015]. For approximately two-thirds of these patients, a potential co-morbid condition can be identified, and the cough effectively managed by optimizing therapy for the condition. Patients who have been diagnosed with conditions that are suspected to cause chronic cough (ie, asthma, GERD, UACS, or non-eosinophilic bronchitis [Irwin, R. S., et al 2018]) but whose cough does not resolve with the appropriate treatment of those conditions are considered to have refractory chronic cough [McCrory, D. C., et al 2013]. Patients with chronic cough in whom an underlying etiology cannot be identified despite a thorough diagnostic work-up are considered to have unexplained chronic cough [McCrory, D. C., et al 2013].

Professional guidelines describe systematic approaches to the evaluation and management of chronic cough. These guidelines are based largely on consensus opinion and observational data from the medical literature. There are currently no treatments approved by the United States FDA or EMA for the treatment of chronic cough [Smith, J. A. 2016]. Given the prolonged nature, significant morbidity, and lack of effective treatment, unexplained or refractory chronic cough is a major unmet medical need.

Mechanism of Cough

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

P2X3 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. Adenosine triphosphate is released by damaged, stressed, and inflamed tissues. The action of ATP at sensory neurons in the periphery and spinal cord contributes to neural excitability and may cause hyperresponsiveness through binding to P2X3 containing receptors and stimulation of C-fiber neurons [North, R. A. 2004] [Khakh, B. S. 2006]. Antagonism of P2X3-containing receptors is predicted to normalize sensory neuron sensitivity, based on data from P2X3 knock-out mice and the effects of small interfering RNA knock-down and pharmacological antagonists [Barclay, J., et al 2002] [Cockayne, D. A., et al 2000] [Souslova, V., et al 2000]. Adenosine triphosphate and P2X3-containing receptors have been shown to be involved in airways sensitization and their involvement provides a rationale for P2X3 antagonism in the treatment of cough [Cockayne, D. A., et al 2000].

Recently, the term cough hypersensitivity syndrome has been proposed to describe a group of patients with chronic cough and similar clinical characteristics. These similar clinical characteristics include irritation in the throat or upper chest, cough triggered by stimuli that do not normally cause cough, increased cough sensitivity to inhaled stimuli, and cough paroxysms. A potential biologic explanation for cough hypersensitivity syndrome suggests an underlying sensory neuropathy characterized by sensory nerve hypersensitization. Prior Phase 2 data support the role of P2X3 antagonism in the treatment of patients with refractory or unexplained chronic cough.

2.1 Study Rationale

Current therapies for acute and subacute cough (narcotic, non-narcotic, and over-the-counter medications) have limited and/or unproven efficacy and an undesirable side effect profile. There are currently no approved therapies for chronic cough.

Previous Phase 2 studies have demonstrated dose-related efficacy and an acceptable safety and tolerability profile for gefapixant in participants with refractory or unexplained chronic cough. Gefapixant, at a dose of 50 mg BID for 12 weeks, demonstrated a significant reduction in the objective measure of awake cough frequency compared to placebo (see gefapixant IB).

The ongoing Phase 3 program is enrolling participants with chronic cough ≥12 months and a diagnosis of refractory chronic cough or unexplained chronic cough according to the current ACCP guidelines. However, there may be value in treating unexplained or refractory chronic cough earlier in its course, in order to improve quality of life.

The purpose of this Phase 3b study is to evaluate the efficacy of gefapixant in participants with chronic cough (duration > 8 weeks after onset of cough symptoms) for <12 months and a diagnosis of refractory or unexplained chronic cough. The data from this study will supplement the ongoing pivotal Phase 3 program by directly informing the potential benefit of treating refractory or unexplained chronic cough within 14 months of the onset of cough symptoms (per participant report and/or medical history).

2.2 Background

Refer to the IB for detailed background information on gefapixant.

2.2.1 Pharmaceutical and Therapeutic Background

Gefapixant is an oral P2X3 antagonist. Gefapixant has been evaluated in clinical studies for the treatment of chronic cough, interstitial cystitis/bladder pain syndrome, osteoarthritis pain, and asthma, and is currently being evaluated in endometriosis-related pain. Based on data generated from clinical studies to date, the gefapixant development program is focused on cough. Gefapixant has also been evaluated in an extensive nonclinical program.

Gefapixant is provided as a film-coated tablet. The gefapixant tablets provided for this study contain gefapixant 45 mg. The placebo tablets provided in this study are indistinguishable from the gefapixant tablets in appearance. The placebo tablets contain no gefapixant but contain the same inactive excipients as those included in the active tablets.

2.2.2 Preclinical and Clinical Studies

Refer to the IB for detailed information on preclinical and clinical studies.

2.2.3 Ongoing Clinical Studies

Gefapixant Development Program

The current gefapixant cough development plan consists of three 12-month Phase 3 studies, still ongoing, in participants with refractory or unexplained chronic cough (protocols 027, 030, and 038). Protocols 027 and 030 are being conducted in approximately 720 and 1290 participants, respectively, in the US, Europe, and other regions. In both studies, participants are randomized in a 1:1:1 ratio to either gefapixant 45 mg BID, gefapixant 15 mg BID, or placebo. Protocol 038 is being conducted in approximately 160 participants in Japan; participants are randomized in a 1:1 ratio to either gefapixant 45 mg BID or gefapixant 15 mg BID.

2.3 Benefit/Risk Assessment

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

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

The efficacy and safety of gefapixant has been evaluated in multiple completed clinical studies for cough. In those studies, participants with chronic cough who took gefapixant showed a reduction in cough frequency while awake and improvement in PROs (see IB for further details).

In the completed and ongoing clinical studies, no major safety concerns have been noted. Taste-related adverse experiences (eg, dysgeusia [change in taste], hypogeusia [diminished taste], ageusia [loss of taste]) were the most frequently reported AEs in clinical studies with doses up to 1800 mg BID for 14 days. The percentage of participants receiving doses ≤50 mg BID reported less taste-related AEs than those receiving doses >50 mg BID. Some participants also described oral paresthesias (tingling sensation in the mouth and/or throat). In many instances, participants reported oral paresthesia or hypoesthesia (numbness) concurrent with taste disturbances.

There is a rationale for taste disturbance with P2X2/3 antagonism because of the putative participation of ATP, acting via this receptor, in transducing taste signals from taste bud cells to sensory neurons. Attenuation of taste acuity, considered a tolerability concern as opposed to a safety concern, is fully reversible after discontinuation of study intervention and amenable to monitoring in clinical studies.

Overall, based on growing clinical evidence supporting the efficacy of gefapixant in participants with refractory or unexplained chronic cough and the lack of significant safety findings in completed and ongoing nonclinical and clinical studies, the benefit-risk balance of gefapixant is assessed as positive.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

Objectives	Endpoints
Primary	
• Objective: To evaluate the efficacy of gefapixant in improving cough-specific quality of life, measured as change from baseline in the Leicester Cough Questionnaire total score at Week 12 Hypothesis: Gefapixant is superior to placebo in increasing Leicester Cough Questionnaire total score change from baseline at Week 12	• Leicester Cough Questionnaire total score

Objectives	Endpoints
Secondary	
• Objective: To evaluate the efficacy of gefapixant in improving self-rated cough severity, measured as change from baseline in the Cough Severity Visual Analog Scale score at Week 12	• Cough Severity Visual Analog Scale score
• Objective: To evaluate the safety and tolerability of gefapixant compared to placebo in percent of participants with adverse events	• Adverse events • Study intervention discontinuations due to an adverse event
Tertiary/Exploratory	
• Objective: To evaluate the efficacy of gefapixant in improving self-rated cough frequency, intensity, and disruption, measured as change from baseline in the Cough Severity Diary total score at Week 12	• Cough Severity Diary total score
• Objective: To evaluate the impact of gefapixant on work productivity (measured as change from baseline in the Work Productivity and Activity Impairment score) and global rating of change (measured by the Patient Global Impression of Change score) at Week 12	• Work Productivity and Activity Impairment score • Patient Global Impression of Change score
• Objective: To explore the relationship between genetic variation and response to the treatment administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study.	• Germline genetic variation

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, double-blind, placebo-controlled, parallel-group, multi-site study of gefapixant in participants with unexplained or refractory chronic cough. Approximately 414 participants will be randomized in a 1:1 ratio to 1 of 2 intervention groups: gefapixant 45 mg BID or placebo. Participants will remain on their assigned intervention at Randomization throughout the study. The duration of intervention for each participant is as follows:

- Screening Period: approximately 14 days (see Section 8.10.1)
- Study intervention period, including Randomization (12-week intervention period): approximately 84 days (see Section 8.10.2)
- Follow-up period: approximately 14 days (see Section 8.10.4)

Individual participation is expected to be approximately 16 weeks from Screening through the Follow-up period.

The study will comprise of 4 study visits and 3 scheduled telephone calls: Visit 1 (Screening, from -2 weeks to -1 week), Visit 2 (Baseline/Randomization, Day 1), Telephone Call (Day 7), Telephone Call (Day 21), Visit 3 (Week 6), Visit 4 (Week 12), and a Telephone Safety Follow-up, Week 14.

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

This study will use an external DMC to monitor efficacy and safety. There will be one planned IA when approximately 40% of the total randomized participants have either completed the study or discontinued study intervention early (all available follow-up data will be included in the analysis).

Results of the IA will be reviewed by the DMC, which will make recommendations to the EOC of the Sponsor to continue or stop the study according to the statistical analysis plan described in Section 9. The study may be stopped for futility or strong benefit (efficacy) according to the results of the IA.

Final database lock will occur after all participants have completed the study, or discontinued study intervention early, and a full analysis will be conducted. Details of the blinding are in Section 9.2.

4.2 Scientific Rationale for Study Design

The ongoing Phase 3 studies (Protocols 27 and 30) are evaluating the efficacy of gefapixant in reducing objective cough frequency and improving quality of life in participants with

≥ 12 months of chronic cough and a diagnosis of refractory or unexplained chronic cough. This study, which will enroll participants with more recent onset chronic cough (< 12 months), will focus on an assessment of cough from the participant's perspective, which is important for evaluating the response to therapy.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

***Primary endpoint**:*

- Leicester Cough Questionnaire (LCQ) total score

The primary goal of the study is to demonstrate that gefapixant is superior to placebo in improving cough-related quality of life, evidenced by a change from baseline in the LCQ total score with gefapixant relative to placebo assessed at Week 12 (2-week recall period).

The LCQ is a validated, 19-item, cough-specific HRQoL questionnaire which contains three domains (physical, psychological, and social). Each domain score is calculated as the mean score of the items within the domain, with a range from 1 to 7. The LCQ total score is the sum of the 3 domains, with a range from 3 to 21. Each item on the LCQ assesses symptoms or the impact of symptoms on HRQoL over the past 2 weeks using a 7-point Likert scale ranging from 1 to 7. Higher scores indicate better HRQoL. Data obtained from the LCQ will provide information on the impact of chronic cough on participants' daily lives.

***Secondary endpoint**:*

- Cough Severity VAS score.

The secondary objective of the study is to evaluate the efficacy of gefapixant in improving self-rated cough severity as assessed by the Cough Severity VAS change from baseline at Week 12.

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

***Exploratory endpoints**:*

This study will evaluate the impact of gefapixant on cough severity as assessed by the CSD. It will also evaluate the impact of gefapixant on global rating of change using the PGIC questionnaire and impact on work productivity using the WPAI.

- **Cough Severity Diary (CSD):** The CSD is a validated, 7-item, disease-specific PRO measure with a recall period of "today." The measure evaluates frequency of cough (3 items), intensity of cough (2 items), and disruption 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 (frequency, intensity, disruption) can be calculated. Domain scores are calculated as the average of the items within the domain and range from 1 to 7. The total score is the sum of the domain scores with a range of 3 to 21.

- **Patient Global Impression of Change (PGIC) questionnaire**: The PGIC is a 2-part measure asking the participant to rate the change in their cough symptoms compared to the start of the study, with response options ranging from "very much improved" to "very much worse" (7-point scale). Based on the response to the initial question, the participant is asked a follow-up question to evaluate the meaningfulness of the improvement or worsening, with response options of 'yes' or 'no' indicating whether the improvement or worsening was important or not.

- **Work Productivity and Activity Impairment (WPAI) questionnaire:** The WPAI questionnaire yields 4 types of scores as follows: (1) absenteeism (work time missed); (2) presenteeism (impairment at work/reduced on-the-job effectiveness); (3) work productivity loss (overall work impairment/absenteeism plus presenteeism); and (4) activity impairment. The WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, ie, worse outcomes [Reilly, M. C., et al 1993].

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

4.2.1.2 Safety Endpoints

The safety data for gefapixant to date has been described in detail in the gefapixant IB.

In support of the safety objective to evaluate the safety and tolerability profile of gefapixant, the safety and tolerability endpoints will be assessed by clinical evaluation of AEs and discontinuation due to AEs. Inspection of other study parameters including vital signs, physical examination, and standard laboratory safety tests will be assessed at timepoints specified in the SoA (Section 1.3). Adverse events are graded and recorded according to Section 8.4 and Appendix 3.

4.2.1.3 Pharmacokinetic Endpoints

To determine exposure to gefapixant, a blood sample will be collected as specified in the SoA (Section 1.3) to estimate the C_{trough}.

4.2.1.4 Pharmacodynamic Endpoints

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

4.2.1.5 Planned Exploratory Biomarker Research

4.2.1.5.1 Planned Genetic Analysis

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

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome. Analysis may be conducted if it is hypothesized that this may help further understand the clinical data.

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

4.2.1.6 Future Biomedical Research

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

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

4.2.2 Rationale for the Use of Comparator/Placebo

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

4.3 Justification for Dose

In this study, gefapixant will be orally administered as gefapixant 45 mg BID based on the safety and efficacy results observed to date. Although the Phase 2 studies demonstrated efficacy of gefapixant at a dose of 50 mg BID, based on modeling and simulation work, a dosing regimen of 45 mg BID is proposed to provide maximum efficacy with a more acceptable tolerability profile than the 50 mg BID dose.

The known mechanism of action of gefapixant and related clinical study results support that the efficacy of gefapixant in decreasing cough, and the prevalence of the most common AE, dysgeusia, are both dose-related. Gefapixant 15 mg and 45 mg BID are being evaluated in the main Phase 3 program for chronic cough. The 45 mg BID dose is anticipated to provide meaningful efficacy in the reduction of cough symptoms with a manageable incidence of dysgeusia.

Based on PK studies, gefapixant is rapidly absorbed with a median time to reach maximum plasma concentration of 1.0 to 2.0 hours. In addition, the half-life of gefapixant is approximately 7 to 10 hours and consistent with a BID dosing schedule.

For this study, 12 weeks of intervention was selected for consistency with prior studies of gefapixant in chronic cough which have shown meaningful efficacy in cough reduction.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

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

- During the IA, based on the interim data:
    a. If the futility criteria are met, then the study may be stopped for futility and all participants would be discontinued from the study.
    b. If the efficacy criteria are met, then the study may be stopped for efficacy and all participants would be discontinued from the study.

5 STUDY POPULATION

Male and female participants of at least 18 years of age, with chronic cough for <12 months and a diagnosis of refractory chronic cough or unexplained chronic cough according to the current ACCP guidelines.

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

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. Has a chest radiograph or CT thorax (within 1 year of Screening/Visit 1 and after the onset of chronic cough) not demonstrating any abnormality considered to be significantly contributing to the chronic cough or any other clinically significant lung disease, in the opinion of the principal investigator or the subinvestigator (subinvestigator must be a physician). Note: If not available, can be performed at Screening/Visit 1. Chest radiograph or CT scan of the thorax performed after the onset of cough symptoms but before the diagnosis of chronic cough require consultation with the Sponsor to determine if acceptable for inclusion in the study.

2. Has chronic cough (defined as duration of >8 weeks after onset of cough symptoms) for <12 months prior to the screening visit (ie, <14 months after onset of cough symptoms), per participant report and/or medical history.

3. Has a diagnosis of refractory chronic cough or unexplained chronic cough. Note: For the purposes of this study

    a) A participant is defined as having refractory chronic cough when:

        1. the participant has had a clinical evaluation that suggests a co-morbid condition that may be associated with chronic cough (eg, GERD, asthma, or UACS), AND

        2. the participant has received appropriate diagnostic work-up and at least 2 months of therapy for the co-morbid condition, prior to Screening, according to the current ACCP guidelines, AND

        3. the participant continues to cough despite being on therapy for the co-morbid condition.

    b) A participant is defined as having unexplained chronic cough when:

        1. the participant has had a clinical evaluation of their chronic cough per current ACCP guidelines, AND

        2. the evaluation does not suggest a co-morbid condition that may be associated with chronic cough.

4. Has a score of ≥40 mm on the Cough Severity VAS at Screening/Visit 1 and Randomization/Visit 2.

Demographics

5. Is male or female, at least 18 years of age, at the time of signing the informed consent.

Female Participants

Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

6. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

    - Is not a woman of childbearing potential (WOCBP)

      OR

    - Is a WOCBP and using an acceptable contraceptive method, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 during the intervention period and for at least 2 weeks (14 days) after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

Informed Consent

7. Provides documented informed consent/assent for the study (or legally acceptable representative). The participant may also provide consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

Study Participation

8. Is willing and able to comply with all aspects of the protocol, including agreeing not to smoke during the study and demonstrating an ability to follow study procedures (including completion of the LCQ, CSD, and Cough Severity VAS) to the satisfaction of the investigator/qualified designee prior to randomization.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Is a current smoker.

2. Has given up smoking within 12 months of Screening/Visit 1.

3. Is a former smoker with a smoking history greater than 20 pack-years (eg, 1 pack [20 cigarettes] per day for 20 years).

4. Has a FEV_1/ FVC ratio <60%.

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

6. Has a history of chronic bronchitis, defined as a cough that produces a clinically significant amount of sputum (greater than approximately 1 tablespoon of phlegm) that occurs every day for at least 3 months in a row.

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

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

9. Is, at the time of Screening/Visit 1, a user of recreational or illicit drugs or has a recent history (within the last year) of drug or alcohol abuse or dependence.

10. Has a history of anaphylaxis or cutaneous adverse drug reaction (with or without systemic symptoms) to sulfonamide antibiotics or other sulfonamide-containing drugs.

11. Has a known allergy/sensitivity or contraindication to gefapixant or its excipients (Note: Refer to the IB for details regarding excipients for gefapixant).

12. Has donated or lost ≥1 unit of blood (approximately 300 mL) within 8 weeks prior to the first dose of gefapixant.

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

Prior/Concomitant Therapy

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

Prior/Concurrent Clinical Study Experience

15. Has previously received gefapixant or other P2X3 antagonists.

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

Diagnostic Assessments

17. Has significantly abnormal laboratory tests at Screening/Visit 1, including:

    a. alkaline phosphatase, ALT, AST >200% of the upper limit of normal, or bilirubin >150% of the upper limit of normal.

    b. hemoglobin <10 g/dL, WBC count <2500 mm3 (<2.5 × 103/µL), neutrophil count <1500 mm3 (<1.5 × 103/µL), platelet count <100 × 103/mm3 (<100 × 103/uL).

    For any of the above listed laboratory assessments, 1 repeat measurement will be allowed at the investigator's discretion, before being considered a screen failure.

Other Exclusions

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

    Note: Participants with a known history or current evidence of SARS-CoV-2 (COVID-19) infection are ineligible to enroll in the study.

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

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

There are no meal or dietary restrictions.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

Participants will be advised that smoking (including cigarettes, cigars, vapes/e-cigarettes, etc) is not permitted during the course of the study, and alcohol consumption should not increase during the study.

5.3.3 Activity Restrictions

There are no exercise restrictions.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the

Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

Participants identified as screen failures can be rescreened once. If the Cough Severity VAS inclusion criterion is not met at Screening/Visit 1, the participant will not be allowed to be rescreened. If the Cough Severity VAS inclusion criterion is not met at Randomization/Visit 2, the participant may be rescreened only with Sponsor consultation.

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

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws from the study will not be replaced.

6 STUDY INTERVENTION

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

Clinical supplies of gefapixant will be packaged to support enrollment where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc.). Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 1.

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin-istration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
Gefapixant	Experimental	Gefapixant	Drug	Tablet	45 mg	1 tablet BID	Oral	12 weeks	Experimental	IMP	Central
Placebo	Placebo Comparator	Placebo to match Gefapixant 45mg	Other	Tablet	0 mg	1 tablet BID	Oral	12 weeks	Placebo	IMP	Central

BID = twice daily, IMP = Investigational Medicinal Product, NIMP = Non-Investigational Medicinal Product.

Note: Definition of IMP and NIMP is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in Table 1 will be provided per the "Sourcing" column depending upon local country operational requirements.

Refer to Section 8.1.8 for details regarding administration of the study intervention.

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an interactive response technology (IRT) system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to gefapixant and placebo, respectively.

6.3.2 Stratification

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

1. Gender (Male, Female)

2. Geographical region (North America, Europe, Asia-Pacific, Other). Details of the regions will be provided in the separate supplemental document for randomization.

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. Gefapixant will be packaged identically relative to its matching placebo so that the blind is maintained throughout the duration of the study. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

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

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

6.4 Study Intervention Compliance

Interruptions from the protocol-specified intervention plan (compliance <80% between study visits, based on review with the participant) require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

Records of intervention compliance for each participant will be kept during the study. The clinical research associates will review intervention compliance during investigational site visits and at the completion of the study. Compliance should be based on participant reporting (and supplemented by tablet count, where possible). Issues with compliance should be discussed with the participant and addressed as deemed appropriate by the investigator.

6.5 Concomitant Therapy

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing study unless otherwise stated in this section. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study intervention

may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

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

Listed below are specific restrictions for concomitant therapy:

1. Opioids (including codeine) for the treatment of cough are not allowed from 1 week prior to Visit 2 through completion of the study. Opioids (including codeine) for indications other than chronic cough are permitted provided the participant is receiving a stable treatment regimen for at least 1 week prior to Visit 2 and, in the opinion of the investigator, is likely to remain on the stable treatment regimen through completion of the study.

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

3. Dextromethorphan, guaifenesin, benzonatate and any other over the counter or prescription medication for the treatment of cough are not allowed from 2 weeks prior to Visit 2 through completion in the study.

4. Lozenges/drops, teas/drinks, natural/herbal remedies, and other similar treatments which do not contain an active antitussive or expectorant are allowed, provided they have been used on a regular basis for at least 2 weeks prior to Visit 2. Lozenges/drops, teas/drinks, and natural/herbal remedies should not be initiated during the study. The Sponsor needs to be consulted for further information.

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

Table 2 Examples of Concomitant Treatment Permitted in the Study

Condition	Treatment
GERD	Anti-reflux therapy (proton pump or H_2-blockers) and/or pro-kinetic agents
Asthma	Bronchodilators, inhaled corticosteroids, and/or other anti-inflammatory agents
UACS (formerly postnasal drip)	Antihistamine/decongestant therapy with a first-generation antihistamine
Non-asthmatic eosinophilic bronchitis	Inhaled/oral corticosteroids

GERD = gastroesophageal reflux disease; UACS = upper airway cough syndrome.

Note: the treatments included in this table are not exhaustive, but examples of treatment class. The guidelines in bullet #5 above the table should be referred to when determining appropriate concomitant treatment use during the study.

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

7. Angiotensin converting enzyme inhibitors are not allowed from 3 months prior to Screening/Visit 1 through completion of the study.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

6.6 Dose Modification (Escalation/Titration/Other)

No dose modification is allowed in this study.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity . The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic intervention allocation/randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant's treatment assignment has been unblinded by the investigator, MSD subsidiary, or through the emergency unblinding call center.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- In case of clinically significant and potentially drug-related rash or signs and/or symptoms consistent with allergic drug reaction or anaphylaxis to study intervention.
- Chronic failure to comply with the dosing, evaluations, or other requirements of the study, despite documentation at the site of repeated efforts to reinforce compliance.

For participants who discontinue study intervention early, refer to Section 8.10.3.

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

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

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

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

- Procedures conducted as part of the participant's routine clinical management (eg, chest x-ray) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA. The Sponsor may provide protocol-specific guidance and/or guidance for special circumstances.

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

The maximum amount of blood collected from each participant over the duration of the study will not exceed 40 mL (Appendix 2).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples; blood volumes for these repeat or unscheduled samples are not included in the above calculation of maximum amount of blood collected. Some local regulations require blood samples to be drawn for additional serology testing; blood volumes for these samples are also not included in the maximum amount of blood collected.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the trial protocol number, trial protocol title, dated signature, and /agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised 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 or the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent form.

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

For Inclusion Criteria 2 and 3 (see Section 5.1 for details), a combination of medical records and/or verbal history from the participant can be used to fulfill these criteria if documented in the participant study file by the investigator.

Source documentation for all eligibility criteria needs to be maintained at the site.

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

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified

designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention (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 healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use at Screening/Visit 1 (see Section 6.5 and refer to eCRF entry guidelines).

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

8.1.7 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.

8.1.8 Study Intervention Administration

The distribution of study intervention will be performed by the investigator and/or study staff at the study site visits.

At Randomization/Visit 2, study intervention will be dispensed by the study site.

Then, according to when the clinic visit is during the day, the participant will take the first dose of study intervention either in the morning or in the evening. Subsequent dosing should be performed by the participant BID approximately 12 hours apart and approximately at the same time each day for the duration of the study.

The last dose of study intervention will be on the evening prior to Visit 4. Study intervention supplies will be collected at Visit 3 and Visit 4.

8.1.8.1 Timing of Dose Administration

Study intervention will be administered orally, BID, approximately 12 hours apart for approximately 12 weeks (84 days) during the study.

A missed dose may be taken if it is <4 hours after the expected dosing time. If it is ≥4 hours after the expected dosing time, then the dose can be skipped, and the regular schedule resumed.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the intervention period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA (Section 1.3 and Section 8.10.3).

When a participant withdraws from participation in the study, all applicable activities scheduled for the Discontinuation Visit should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.3.

8.1.9.1 Withdrawal From Future Biomedical Research

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

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between

the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.10 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

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

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

Once an emergency unblinding has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention, but should continue to be monitored in the study.

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

8.1.11 Calibration of Equipment

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

8.2 Efficacy/Immunogenicity Assessments

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

8.2.1 Patient-Reported Outcomes

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

Between clinic visits, participants will be instructed to complete the ePRO measures (in the following order: CSD and Cough Severity VAS) at approximately the same time each evening, as outlined in the SoA (Section 1.3). If a participant fails to complete the evening CSD and/or Cough Severity VAS ePRO measure(s), the e-Diary will allow the participant, based on recall, to complete these missed measures in the next day (also see vendor's site manual for further details). Participants will be prompted within the e-Diary to complete the missed measures first, prior to the measures for the current day.

At the clinic visits, participants will be asked to complete ePRO measures (in the following order: Cough Severity VAS, LCQ, PGIC, and WPAI), as outlined in the SoA (also see vendor's site manual for further details). All Visit 2 ePRO measures MUST be activated and completed prior to the first dose of study intervention/randomization (see vendor's site manual for further details). For subsequent clinic visits, the e-Diary must be activated by the site to enable the collection of the ePROs at the clinic visit.

Electronic PRO measures must be activated, as outlined in the SoA (Section 1.3). More details on PRO measures are given in Section 4.2.1.1.

Participants who discontinue study intervention early will continue to be monitored in the study and should be encouraged to continue to complete the ePRO measures for the remaining visits (as outlined in the SoA, Section 1.3) through the end of the study.

Compliance with daily completion of the eDiaries must be monitored by the investigator or designee. Each investigator site will contact individual participants who are non-compliant in order to retrain and/or remind them to complete their assessments as per the SoA (Section 1.3). Discussion with the participant and retraining will be performed if any question on any e-Diary is missing and/or if any e-Diary scheduled for completion per the SoA is missing, in error.

Once a participant has completed the study (or discontinued from the study), the participant should return the e-Diary to the study site, and all ePRO measures should be deactivated.

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

8.2.1.1 Leicester Cough Questionnaire

Participants will be asked to complete the 19-item LCQ to assess the impact of their cough severity on physical, social and psychological functioning, as detailed in SoA (Section 1.3).

Leicester Cough Questionnaire will be completed at Randomization/Visit 2, after eligibility for randomization has been confirmed, and at Visits 3 and 4 before all other assessments.

8.2.1.2 Cough Severity Diary

Participants will complete the CSD at approximately the same time each evening before going to bed beginning at Visit 1 and continuing through Visit 4, as outlined in the SoA (Section 1.3).

8.2.1.3 Cough Severity Visual Analog Scale

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

At Screening/Visit 1, participants will complete a single Cough Severity VAS questionnaire at the study visit in order to assess the eligibility criterion. For the remainder of the study, beginning with the evening of Screening/Visit 1, participants will complete the Cough Severity VAS at approximately the same time each evening before going to bed, as outlined in the SoA (Section 1.3). The Cough Severity VAS assessment completed the evening before Randomization/Visit 2 will be used as the baseline value and to assess the Randomization/Visit 2 Cough Severity VAS eligibility criterion. If the assessment was not completed the evening before randomization, then a measurement done on the day of randomization, prior to any non-PRO Randomization/Visit 2 procedures, can be used as the baseline value and to assess the Randomization/Visit 2 Cough Severity VAS eligibility criterion.

In order to confirm participant eligibility, study site staff will be required to review/confirm the participant met the Cough Severity VAS eligibility criteria from the measurement done at Screening/Visit 1 at the clinic and the measurement done the evening before Randomization/Visit 2 (or from the morning of Randomization/Visit 2, prior to conducting any Visit 2 procedures, if the evening measurement was missed). A score of ≥40 mm on the Cough Severity VAS, for both Screening/Visit 1 and Randomization/Visit 2 is required for randomization into the study.

8.2.1.4 Patient Global Impression of Change Questionnaire

Participants are required to complete the PGIC at the last clinic visit, as outlined in the SoA (Section 1.3).

8.2.1.5 Work Productivity and Activity Impairment Questionnaire

The WPAI questionnaire will be used to assess impairment and productivity at work. Participants will be asked to indicate if they are currently employed and to respond to a series of work-related questions referring to "the past 7 days" (Section 4.2.1.1).

Participants are required to complete the WPAI at Visits 2 and 4, as outlined in the SoA (Section 1.3).

8.3 Safety Assessments

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

The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found at the beginning of Section 8.

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

8.3.1 Chest Radiography/Computed Tomography Thorax Scan

A chest radiograph or CT scan of the thorax should be performed locally for participants, at Screening/Visit 1, if this has not been done within the last 1 year and after the onset of chronic cough. The chest radiograph or CT scan of the thorax should not demonstrate any abnormality considered to be significantly contributing to the chronic cough or any other clinically significant lung disease, in the opinion of the principal investigator (or subinvestigator; Inclusion Criterion 1, Section 5.1). Chest radiograph or CT scan of the thorax performed after the onset of cough symptoms but before the diagnosis of chronic cough requires consultation with the Sponsor to determine if acceptable for inclusion in the study.

8.3.2 Physical Examinations

A complete physical examination will be conducted as described in the SoA (Section 1.3) and will include assessments of the following: general appearance; skin and lymphatic; eyes, ears, nose, throat; cardiovascular system; respiratory system; abdomen/gastrointestinal system; urological system; musculoskeletal and neurological systems. Other body systems may be examined at the discretion of the investigator.

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

A brief directed physical examination should be performed at Visit 4 or the Discontinuation Visit.

A brief directed physical examination may be performed at any study visit that does not already include a physical examination if deemed necessary by the investigator due to

signs/symptoms. A physical examination (complete or directed) can be performed at any unscheduled visit if deemed necessary by the investigator.

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

8.3.3 Vital Signs

Vital sign measurements, including systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), heart rate (beats per minute), respiratory rate (breaths per minute), and body temperature will be collected, as outlined in the SoA (Section 1.3). All blood pressure measurements should be performed on the same arm, preferably by the same person. Height and weight will also be collected as per the SoA (Section 1.3).

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

8.3.4 Electrocardiograms

A 12-lead ECG will be performed at Screening/Visit 1 using local standard procedures. Clinically significant abnormal findings should be recorded in the AE eCRF.

8.3.5 Spirometry

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

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

8.3.6 Clinical Safety Laboratory Assessments

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

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

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

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

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.7 Renal and Urological Safety Assessments

Safety assessments will be performed in all participants in order to monitor renal and urological safety during the course of the study. Participants will be monitored for hematuria and urinary crystals through urinalysis (performed at the central laboratory). Urinalyses (including microscopy) will be collected as outlined in the SoA (Section 1.3).

8.3.7.1 Screening

If, during Screening/Visit 1, a participant has crystalluria and/or unexplained hematuria (defined as, for example, participants without a history of recent menses, urinary tract infection, or recent procedure/instrumentation that would explain the hematuria), the investigator should perform the below steps. (Note: Any other explanation for hematuria finding must be reviewed with the Sponsor).

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

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

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

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

8.3.7.2 Visit 4/Discontinuation

At Visit 4 or Discontinuation Visit, a urine sample will be collected from all participants, as outlined in the SoA. If, unexplained hematuria and/or urinary crystals are identified, and deemed to be clinically significant by the investigator, the participant should be considered

for further evaluation. If an investigator deems it necessary to perform an unscheduled urinalysis at any time during the study (after randomization), the same procedures for collection/preparation of the urine sample and evaluation of hematuria (as explained or unexplained) described for Visit 4 or Discontinuation Visit should be performed.

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

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

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

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

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

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

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent but before intervention 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 intervention randomization through 14 days following cessation of treatment, all AEs, SAEs, and other reportable safety events must be reported by the investigator. However, for those participants who discontinue from the study intervention but continue to be monitored, only the AEs and other reportable safety events that are shown in Table 3 need to be reported. This specific approach for reporting starts from completion of the safety follow-up telephone call following cessation of intervention until the last study-related off-intervention telephone call.

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 related to study intervention.

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

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

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

Type of Event	**Reporting Time Period:** Consent to Randomization/ Allocation	**Reporting Time Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting Time Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
Nonserious 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[a]	Report if: - due to intervention - causes exclusion	Report all[a]	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report[a] - Potential 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[a] - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all[a]	Not required	Within 5 calendar days of learning of event

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

a Participants who discontinue study intervention and are continuing to be monitored in the study do not require the reporting of ECIs, pregnancy/lactation exposure, and overdose. Previously reported pregnancies/lactations exposure need to be followed for completion/termination; report outcome.

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

Reporting time periods and time frames are fully detailed in Table 3.

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

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

8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

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

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

Reporting time periods and time frames are fully detailed in Table 3.

8.5 Treatment of Overdose

In this study, an overdose is any dose >1 tablet BID (Section 4.3). Study intervention should be taken once in the morning and once in the evening. If more than the protocol-specified intervention is taken within a 1-day period (ie, >2 tablets/day) this is regarded as an overdose.

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

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

8.6 Pharmacokinetics

8.6.1 Blood Collection for Plasma Gefapixant

Blood samples will be collected, as outlined in the SoA in Section 1.3. A pharmacokinetic blood sample should be collected within approximately 96 hours of the final dose of study medication. If the discontinuation or final visit is scheduled to occur greater than 96 hours following the final dose of study medication, please contact the Sponsor for guidance.

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

Gefapixant plasma concentrations will be determined using a validated LC-MS/MS assay. Sample collection, storage and shipment instructions for plasma samples will be provided in the operations/laboratory manual for the study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants as specified in the SoA (Section 1.3):

- Blood for Genetic Analysis

8.8.1 Planned Genetic Analysis Sample Collection

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

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

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for future biomedical research, the following specimens will be obtained as part of future biomedical research:

- Leftover DNA for future research

8.10 Visit Requirements

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

8.10.1 Screening

Approximately 2 weeks prior to intervention randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Screening/Visit 1 procedures may be repeated after consultation with the Sponsor. However, participants will not be permitted to rescreen if the inclusion criterion for the Cough Severity VAS is not met at Screening/Visit 1.

Participants who are consented will complete the Cough Severity VAS on the day of Screening/Visit 1 in the clinic, prior to completing other screening procedures (in order to first determine if the participant meets the Screening/Visit 1 Cough Severity VAS entry criterion).

Washout of concomitant medication (Section 6.5) is permitted after signing informed consent and participants must remain off these medications throughout the study. The investigator should evaluate medical history and overall condition when making the decision as to whether individuals can withdraw from medications in order to participate in the study. The screening period would begin after the completion of washout. These individuals should return to the clinic after washout for Screening/Visit 1 procedures. Participants are to be reminded to bring their e-Diary device with them to the next visit.

8.10.2 Treatment Period

The Randomization/Visit 2 must be scheduled between 7 days and approximately 14 days after Screening/Visit 1.

The CSD and Cough Severity VAS will be collected daily in the evening between Screening/Visit 1 and Randomization/Visit 2. Participants must meet the Cough Severity VAS inclusion criterion at both Screening/Visit 1 and Randomization/Visit 2 (Section 5.1) in order to be eligible for study participation. Study intervention will be dispensed at Randomization/Visit 2. Once randomized, participants will receive either gefapixant 45 mg or placebo BID for 12 weeks. Both the participants and study personnel will be blinded to the study intervention.

Participants will be contacted by telephone on Day 7 (+3 days; following Randomization/Visit 2) and Day 21 (±3 days; following Randomization/Visit 2) to review

any AEs that may have occurred and concomitant medications taken, instructions on/compliance with study drug administration, and e-Diary completion (as necessary), and any questions the participant may have about the study.

For all study site visits, participants are to be reminded to bring their e-Diary device with them to the next visit.

Randomization/Visit 2 will be assigned as Day 1, and subsequent visit scheduling will be calculated from Day 1 (and not from the previous study visit).

8.10.3 Discontinued Participants Continuing to be Monitored in the Study

It is intended that all participants should be followed throughout the study, regardless of premature discontinuation of intervention, unless the participant withdraws consent. Thus, participants who discontinue from study intervention prior to completion of the study should continue to be monitored to obtain relevant information through the end of the study.

If a participant is discontinued from the study intervention early:

- the Discontinuation Visit should be performed as soon as possible; Procedures, including the e-Diary assessments, should be performed as outlined for the Discontinuation Visit in the SoA (Section 1.3).

  Note: If a participant discontinues at a regularly scheduled study visit, the procedures outlined for the Discontinuation Visit in the SoA should be followed in place of the procedures for the regularly scheduled study visit.

- a safety follow-up telephone call should be conducted a minimum of 14 days (with an allowed variance of up to +7 days) after the last dose of study intervention; and

- Study site visits should continue to be performed at timepoints that correspond to each remaining study visit. These visits will allow collection of follow-up information, limited to:

  - AEs;

  - Concomitant medication use; and

  - e-Diary assessments, as outlined in the SoA (Section 1.3).

  Note: If the participant discontinues study intervention at a regularly scheduled study visit but remains in the study, the Discontinuation Visit should be performed, and the regularly scheduled study visits should resume thereafter. For example: If a participant discontinues study intervention at the time of Visit 3, procedures for the Discontinuation Visit should be performed at that time. The next expected study visit would be Visit 4.

Concomitant therapies specifically prohibited (Section 6.5) while the participant was on study intervention are no longer prohibited after discontinuation of study intervention.

- For these participants who have discontinued study intervention early, sites will be instructed to exert diligent efforts to continue to contact them. To enable sites to reach participants, the participants should provide primary and secondary contact information (eg, home telephone, work telephone, mobile telephone). Sites must document the outcome of the telephone contact(s), to demonstrate diligent efforts have been made.

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

8.10.4 Poststudy

All participants that complete the treatment period will be required to complete the safety follow-up telephone call approximately 2 weeks (14 days, with an allowed variance of up to +7 days) after the last dose of study intervention to determine if any AEs have occurred since discontinuing study intervention.

Note: Participants that discontinue intervention and/or discontinue from the study should also complete the safety follow-up telephone call 14 days (+7 days) after the last dose of intervention.

If the safety follow-up telephone contact occurs less than 14 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at approximately 2 weeks (14 days, with an allowed variance of up to +7 days) post the last dose of study intervention.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guidance E9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a sSAP and referenced in the CSR for the study. Post-hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below. The comprehensive plan is provided in Sections 9.2 through 9.12.

Study Design Overview	A Phase 3b, Randomized, Double-blind, Placebo Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Gefapixant in Adult Participants with Recent Onset Chronic Cough (P043)
Treatment Assignment	Participants will be randomized in a 1:1 ratio to 1 of 2 treatment groups: Gefapixant 45 mg BID or Placebo.
Analysis Populations	Efficacy: FAS population, which consists of all randomized participants who have taken at least 1 dose of study intervention. Safety: APaT population, which consists of all randomized participants who received at least 1 dose of study intervention.
Primary Endpoint	LCQ total score
Statistical Methods for Key Efficacy Analyses	The primary analysis will be based on the FAS population. The primary analysis approach will be conducted utilizing the longitudinal ANCOVA model. In this model, the response vector consists of LCQ change from baseline in total score at each post-Baseline visit. The model will include factors for intervention group, visit, the interaction between intervention group and visit, gender, and baseline LCQ total score. The model will use all available LCQ change from baseline in total score data at Weeks 6 and 12. Contrasts will be constructed to compare the Gefapixant group to the Placebo group at each post-Baseline visit. The least squares mean change from baseline with the associated standard errors will be displayed for each intervention group. Estimated treatment differences (Gefapixant − Placebo) along with corresponding p-values and CIs will also be presented.
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 and Tier 2 safety endpoints will be evaluated via point estimates and 95% CIs for between-group comparisons, with p-values provided for the Tier 1 safety endpoints. Tier 3 safety endpoints will be evaluated via point estimates only.

Interim Analyses	One planned IA will be performed in this study to examine the futility and efficacy. Results will be reviewed by the DMC. The IA is summarized below. Details are provided in Section 9.7. • Timing: To be performed when approximately 40% of participants (approximately the first 166 randomized participants) have either completed the study or discontinued the study intervention early. • Testing: Futility and Strong Benefit (Efficacy) analysis based on the primary endpoint of LCQ change from baseline in total score at Week 12 will be provided.
Multiplicity	Since there is only one hypothesis (for the primary endpoint), no multiplicity adjustment is planned other than the IA alpha adjustment to the primary efficacy endpoint.
Sample Size and Power Calculations	The planned sample size is 414 participants (207 per treatment group) for comparing the primary endpoint of LCQ change from baseline in total score at Week 12, assuming a pooled SD of 3.5 points. This sample size will detect a treatment difference of 1.1 points or more with at least 80% power at an overall one-sided 0.025 alpha level, adjusted for the IA (α=0.001) for strong benefit and the final analysis (α=0.024). This sample size accounts for a 15% dropout rate, targeting for 352 evaluable participants at Week 12. The details are described in Section 9.9.

9.2 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.

This 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 deviations have been identified, and data have been declared final and complete. The investigator site personnel and the participants will be blinded to intervention assignment until the entire study completion.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study intervention assignment. Treatment assignment will be implemented in an IRT system by a study vendor according to the adaptive allocation scheme provided in Section 6.3.1.

Blinding issues related to the planned IA are described in Section 9.7.

9.3 Hypotheses/Estimation

The primary hypothesis for this study is stated in Section 3.

9.4 Analysis Endpoints

Efficacy and safety endpoints for evaluation are listed below.

9.4.1 Efficacy Endpoints

9.4.1.1 Primary Efficacy Endpoint

- LCQ total score measured as change from baseline at Week 12

9.4.1.2 Secondary Efficacy Endpoints

- Cough Severity VAS score measured as change from baseline at Week 12

9.4.1.3 Exploratory Efficacy Endpoints

- CSD total score measured as change from baseline at Week 12
- PGIC measured at Week 12
- WPAI measured as change from baseline at Week 12

9.4.2 Safety Endpoints

- Adverse events
- Study intervention discontinuations due to an AE

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The FAS population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all randomized participants who have taken at least 1 dose of study intervention.

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

9.5.2 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received at least 1 dose of study

intervention. Participants will be included in the intervention group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. For most participants, this will be the intervention group to which they are randomized. Participants who take incorrect study intervention for the entire intervention period will be included in the intervention group corresponding to the study intervention actually received. Participants who take incorrect study intervention during only a part of the treatment period and took at least 1 dose of active study intervention will be included in the active treatment group.

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

9.6 Statistical Methods

This section describes the statistical methods that address the primary objective. Methods related to exploratory objectives and supportive analyses will be described in the sSAP. Statistical testing and inference for efficacy and safety analyses are described in Sections 9.6.1 and 9.6.2, respectively. The statistical test of the primary efficacy endpoint will be conducted at the overall significance level of 0.05 (2-sided).

9.6.1 Statistical Methods for Efficacy Analyses

The analysis of efficacy endpoints will be based on the FAS population. Unless otherwise specified, all efficacy data from participants who have taken at least 1 dose of study intervention will be included in efficacy analyses.

Primary Efficacy Analysis

The LCQ is collected at baseline and after administration of the study intervention at Weeks 6 and 12. The primary efficacy endpoint of this study is the LCQ change from baseline in total score. The primary analysis approach will be conducted utilizing the longitudinal ANCOVA model. In this model, the response vector consists of the LCQ change from baseline in total score at each post-Baseline visit. The model will include factors for intervention group, visit, interaction of treatment by visit, gender, and the baseline LCQ score. The model will use all available LCQ change from baseline in total score at Weeks 6 and 12. Contrasts will be constructed to compare the Gefapixant intervention group to the Placebo group at Week 6 and Week 12. The least squares mean change from baseline with the associated standard errors will be displayed for each intervention group. Overall estimated treatment differences (Gefapixant − Placebo) along with corresponding p-values and 95% CIs will also be presented, with the exception of the primary efficacy endpoint, in which the CI width will be adjusted for an IA (Section 9.6). Further details of the model specification, assumptions, and SAS implementation codes will be provided in the sSAP.

Secondary Efficacy Analysis

The continuous secondary efficacy endpoints will be analyzed using a similar longitudinal ANCOVA model as used for the primary efficacy analysis. The model will include terms for intervention group, visit, interaction of treatment by visit, gender, and baseline score.

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

Table 4 Analysis Strategy for Primary and Secondary Efficacy Endpoints

Endpoint/Variable (at Week 12)	**Statistical Method**	**Missing Data Approach**
Primary		
Change from baseline in LCQ total score	Longitudinal ANCOVA	Model-based[a]
Secondary		
Change from baseline in Cough Severity VAS score	Longitudinal ANCOVA	Model-based[a]

ANCOVA=analysis of covariance; LCQ=Leicester Cough Questionnaire; VAS=Visual Analog Scale
[a] Includes data collected after early intervention discontinuation.

The strategy for the IA is described in Section 9.7.

Exploratory Efficacy Analyses

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

Handling of Missing Data

A participant will be considered for inclusion in the assessment of an efficacy endpoint if the CSD and Cough Severity VAS are completed on at least 4 days during the 7-day period prior to a post-Baseline visit (other ePROs are completed at the clinic visit only). All efficacy analyses will be conducted based on the observed data only. No imputation is planned for the missing diaries or missing questionnaire items. The pattern of missing is assumed to be MAR. The missing pattern will be inspected to determine if the MAR assumption is met.

Sensitivity analyses will be implemented to explore the impact of departures from the assumption made in missing diaries. Additional sensitivity analyses with respect to the handling of missing data will be specified in the sSAP.

9.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 5). The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as system organ class terms) and events that meet predefined limits of change in laboratory and vital signs are either prespecified as “Tier 1” endpoints, or will be classified as belonging to "Tier 2" or "Tier 3" based on the observed proportions of participants with an event.

Tier 1 Events

Safety parameters or adverse events of interest that are identified *a priori* constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% CIs to be provided for between-treatment differences in the proportion of participants with events; these analyses will be performed using the Miettinen and Nurminen (M&N) method (1985) [Miettinen, O. and Nurminen, M. 1985], an unconditional, asymptotic method. For this protocol, taste-related AEs (including dysgeusia, ageusia, and hypogeusia, as well as other related terms) are considered Tier 1 events. The definition of taste-related AEs will be finalized and documented before the database lock of the study.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates and 95% CIs provided for differences in the proportion of participants with events.

Membership in Tier 2 requires that at least 4 participants in any treatment group exhibit the event. The threshold of at least 4 events was chosen because the 95% confidence interval 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% confidence intervals for Tier 2 events may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse events and safety parameters that meet predefined limits of change.

In addition to individual events that occur in 4 or more participants in any treatment group, any oral paresthesia AE, any oral hypoesthesia AE, and the broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, and discontinuation due to an AE will be considered Tier 2 events.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Continuous Safety Measures

For continuous measures such as changes from baseline in laboratory and vital signs, summary statistics for baseline, on-treatment, and change from baseline values will be provided by intervention group in table format.

Table 5 Analysis Strategy for Safety Parameters

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

AE =adverse event; CI=confidence interval; PDLC=predefined limit of change; SOC=system organ class; X =results will be provided.
a Adverse experience references refer to both clinical and laboratory AEs.
b Includes only those endpoints not prespecified as Tier 1 or not already prespecified as Tier 2 endpoints.

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

9.6.3.1 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (eg, age, gender, race, weight, and height), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

There is one planned IA for this study. Study enrollment is likely to be ongoing at the time of any IA. Blinding to treatment assignment will be maintained at all investigational sites. The results of IA will not be shared with the investigators prior to the completion of the study. Participant-level unblinding will be restricted to an external unblinded statistician and scientific programmer performing the IA, who will have no other responsibilities associated with the study.

If the study is stopped early, the CSR will include all available data up to and including the close-out visits.

Unblinding for Interim Analyses

After approximately 40% of the enrolled participants (approximately the first 166 enrolled participants) have completed the study or discontinued the study intervention early, a copy of the database will be locked for the IA, and an independent statistician and scientific programmer will be unblinded to perform the IA.

An external DMC will serve as the primary reviewer of the results of the IA of the study and will make recommendations for discontinuation of the study or protocol modifications to the EOC of the Sponsor. If the DMC recommends modifications to the design of the protocol or discontinuation of the study, this executive committee may be unblinded to results at the treatment level in order to act on these recommendations. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the unblinded statistician. Additional logistical details will be provided in the DMC charter (Section 10.1.4.3). Key aspects of the interim analyses are described in Sections 9.7.1 and 9.7.2.

Treatment-level results from the interim analysis will be provided to the DMC by the unblinded statistician. Prior to final study unblinding, the unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

9.7.1 Interim Efficacy Analysis

One planned efficacy IA will be conducted when approximately 40% of target participants (approximately the first 166 randomized participants) have either completed the study (approximately 141 randomized participants) or discontinued study intervention early. All available data will be included in the analysis, including follow-up data and partial data from participants enrolled after the participants triggering the IA.

The purpose of the IA is to allow early stop for strong benefit (efficacy) or for futility. The efficacy IA will be based on the primary endpoint of the LCQ change from baseline in total score at Week 12.

[redacted]

The decision criteria are prespecified as follows:

[redacted]

9.7.2 Interim Safety Analysis

Interim safety will also be assessed at the time of prespecified IA for futility, ie, when approximately 40% of target participants (approximately the first 166 randomized participants) have either completed the study or discontinued the study intervention early. A general review of safety results will be performed based on review of AEs, laboratory safety parameters, and other safety endpoints.

9.8 Multiplicity

Other than an adjustment to the alpha level for the IA for efficacy, no multiplicity adjustment is planned.

9.9 Sample Size and Power Calculations

The sample size calculations are powered to test the primary efficacy endpoint, with the following assumptions based on the results from a phase 2 chronic cough study.

[redacted]

[redacted]

Based on the assumptions above, a total of 414 participants (207 participants per intervention group) will provide at least 80% power. The calculation is based on an overall one-sided α=0.025 significance level, adjusted for one IA for efficacy (α=0.001), and one final efficacy analysis (α=0.024). A dropout rate of 15% at Week 12 is accounted for the sample size calculation to ensure 352 evaluable participants complete the Week 12 evaluation.

With assumptions on the AE rates in the placebo group based on the Protocol 012 results, the minimum detectable AE rate differences are 8.4%, 9.0%, and 7.7% in overall taste-related AEs, oral paresthesia AEs, and oral hypoesthesia AEs, respectively.

9.10 Subgroup Analyses

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

- Gender (male, female)
- Region (North America, Europe, Asia-Pacific, Other)
- Age group (<60 years, ≥60 years old)
- Baseline Cough Severity VAS (<60 mm, ≥60 mm)
- Potential co-morbid conditions associated with cough (ie, GERD, asthma, UACS) Note: Details of the conditions will be provided in a separate sSAP.
- Concomitant medications (ie, antitussives and treatments for potential co-morbid conditions, proton pump inhibitors, inhaled corticosteroids first-generation anti-histamines). Note: Details of the concomitant medications will be provided in a separate sSAP.

A similar longitudinal ANCOVA model as that used for the primary efficacy endpoint will be utilized. For each subgroup, summary statistics including means and their 95% CIs will be provided for each intervention group at Week 12. For the subgroups with 15% or more of the FAS population across both intervention groups, the mean treatment differences (gefapixant - placebo) and their 95% CIs will also be provided at Week 12.

9.11 Compliance (Medication Adherence)

For each participant, percent compliance will be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days Expected on Therapy}} \times 100\%$$

A day within the study will be considered an "on-therapy" day if the participant takes all required intervention as instructed in Section 8. When a participant takes less than or more than the required intervention on a day, that day is not considered an on-therapy day.

For participants who are followed for the entire study period, the "Number of Days Should be on Therapy" is the total number of days from the first scheduled intervention day to the last scheduled intervention day. For participants who discontinue from the study permanently, the "Number of Days Should Be on Therapy" is the total number of days from the first scheduled intervention day to the last dose day.

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

9.12 Extent of Exposure

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

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations, and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud,

scientific/research misconduct or serious GCP-non-compliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

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

10.1.4.2 Scientific Advisory Committee (SAC)

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

10.1.4.3 External Data Monitoring Committee

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

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

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

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov,

www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

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

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor’s studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator’s knowledge, threatened.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator

or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

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

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

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

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

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

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). 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/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

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

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 6 will be performed at the study site or by the central laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 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.

Pregnancy testing:

- Pregnancy testing requirements for study inclusion are described in Section 5.1.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Table 6 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry	Electrolytes	Sodium Potassium Chloride Bicarbonate Calcium Phosphorous
	Liver function tests	AST/ SGOT ALT/ SGPT Alkaline phosphatase Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Renal function tests	Blood Urea Nitrogen Creatinine eGFR calculation eGFR will be calculated with each serum creatinine measurement (using the Chronic Kidney Disease Epidemiology Collaboration [CKD EPI] formula [http://mdrd.com/])
	Other	Glucose (nonfasting) Albumin Total Protein
Routine Urinalysis	• Routine urinalysis will be performed at a central laboratory for all participants and include: specific gravity, pH, glucose, protein, and blood. Microscopic examination will also be performed (crystals will be analyzed).	
Other Screening Tests	Serum or urine β-hCG pregnancy test (as needed for women of childbearing potential) 1. Urine pregnancy test will be performed at site in women of child bearing potential. Refer to Section 1.3.	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = β-human chorionic gonadotropin; eGFR = estimated glomerular filtration rate; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell.

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

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

10.3.1 Definition of AE

AE definition

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

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

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

Events meeting the AE definition

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

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

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

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

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

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

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

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

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

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

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

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

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

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

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

f. **Other important medical events**

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

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

10.3.3 Additional Events Reported

Additional events that require reporting

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

- Is a cancer
- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant

number, will be blinded on the copies of the medical records before submission to the Sponsor.

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

Assessment of intensity

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

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

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

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

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

Assessment of causality

- Did the Sponsor's product cause the AE?

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

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

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary,

etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

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

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

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

  - If yes, did the AE resolve or improve?
  - If yes, this is a positive dechallenge.
  - If no, this is a negative dechallenge.

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

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

  - If yes, did the AE recur or worsen?
  - If yes, this is a positive rechallenge.
  - If no, this is a negative rechallenge.

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

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

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

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

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

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

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

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

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

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

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

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

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

Follow-up of AE and SAE

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

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

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

10.3.5 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

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

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Male Participants

Male participants are not required to use a form of contraception.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use one of the contraception methods described in Table 7 consistently and correctly during the protocol-defined time frame in Section 5.1.

Table 7 Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen- containing) hormonal contraception[b] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
• Progestogen only hormonal contraception[b] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant[b] • Intrauterine hormone-releasing system[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 intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Notes:
Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.

- Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly).
- If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

WOCBP = women of childbearing potential

10.5.3 Pregnancy Testing

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

Pregnancy testing will be performed at Screening/Visit 1 (in WOCBP) and after Screening/Visit 1 whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected. Testing can also be performed, as necessary, based on local requirements.

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

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

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

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

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

3. Summary of Procedures for Future Biomedical Research.

a. Participants for Enrollment

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

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

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

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

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

4. Confidential Participant Information for Future Biomedical Research

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participant' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and intervention 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 future biomedical research protocol and consent. 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 investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Participants

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

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

10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research

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

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

12. Questions

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

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10.7 Appendix 7: Country-specific Requirements

Not applicable

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
ACCP	American College of Chest Physicians
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APaT	All participants as treated
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BID	Twice daily
CHS	Cough hypersensitivity syndrome
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus infectious disease 2019
CP	Conditional power
CRF	Case report form
CSD	Cough Severity Diary
CSR	Clinical study report
CT	Computed tomography
C_{trough}	Concentration of study drug at the end of the dosage interval
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECIs	Events of clinical interest
eCRF	Electronic case report form
EDC	Electronic data collection
e-Diary	Electronic diary
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOC	Executive Oversight Committee
ePRO	Electronic patient-reported outcomes
FAS	Full analysis set
FDA	United States Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
GERD	Gastroesophageal reflux disease
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
HRQoL	Health-related quality of life
IA	Interim analysis/analyses
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive response technology

Abbreviation	Expanded Term
LCQ	Leicester Cough Questionnaire
MAR	Missing at random
PGIC	Patient Global Impression of Change
PK	Pharmacokinetic
PRO	Patient-reported outcomes
RNA	Ribonucleic acid
SAC	Scientific Advisory Committee
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SoA	Schedule of activities
sSAP	Supplemental statistical analysis plan
SAS	Statistical analysis software
SUSAR	Suspected unexpected serious adverse reactions
UACS	Upper airway cough syndrome
VAS	Visual analog scale
WBC	White blood cell
WOCBP	Woman/women of childbearing potential
WPAI	Work Productivity and Activity Impairment Questionnaire

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TITLE PAGE

Protocol Title: A Phase 3b Randomized, Double-blind, Placebo Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Gefapixant in Adult Participants with Recent Onset Chronic Cough (P043)

TABLE OF CONTENTS

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Supplemental Statistical Analysis Plan (sSAP)

1. INTRODUCTION

This supplemental SAP (sSAP) is a companion document to the protocol. In addition to the information presented in the protocol SAP which provides the principal features of confirmatory analyses for this trial, this supplemental SAP provides additional statistical analysis details/data derivations and documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

2. SUMMARY OF CHANGES

Date	Page	Changes
13JAN2021	9	Updated the week duration for calculating baseline value for mean weekly VAS score and CSD total score.
13JAN2021	15, 16	Added a list of terms for taste-related AEs (including dysgeusia, ageusia, hypogeusia, hypergeusia, and taste disorder).
13JAN2021	16	Added two Tier 3 safety endpoints in Table 2. • Time to Onset from the First Dosing Date and Duration of Event for Taste-Related AEs • Frequency of taste-related AEs for time intervals
14JAN2021	19	Removed subgroup analyses for potential co-morbid conditions and concomitant medications.
02DEC2021	9	Fixed the typos for WPAI measured change from baseline at Week 12 and VAS score using 100 mm visual analogue scale.
02DEC2021	10	Added important protocol violation criteria
02DEC2021	11	Added language to be aligned with phase 3 studies.
02DEC2021	11	Updated the text for the secondary efficacy endpoint.
02DEC2021	12	Updated the text of responses to the PGIC questionnaire and modified the analysis method using stratified M&N. Added description to include PGIM.
02DEC2021	12	Updated the model structure by removing the interaction of treatment by visit since there is only one post-baseline time point for WPAI.
02DEC2021	14	Updated the tipping point analyses to be performed in two-dimensional where missing data in both active and control arms are assumed to have a worse response by a constant c.

3. ANALYTICAL AND METHODOLOGICAL DETAILS

3.1 STATISTICAL ANALYSIS PLAN SUMMARY

Key elements of the statistical analysis plan are summarized below. The comprehensive plan is provided in following Sections 3.2 – Responsibility for Analyses/In-House Blinding to 3.12 – Extent of Exposure.

Study Design Overview	A Phase 3b, Randomized, Double-blind, Placebo Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Gefapixant in Adult Participants with Recent Onset Chronic Cough (P043)
Treatment Assignment	Participants will be randomized in a 1:1 ratio to 1 of 2 treatment groups: Gefapixant 45 mg BID or Placebo.
Analysis Populations	Efficacy: Full Analysis Set (FAS) population, which consists of all randomized participants who have taken at least one dose of study intervention. For endpoints that are measures of change from baseline, participants need to have baseline and at least one post-baseline measurement for inclusion in the analysis of each specific endpoint; and Per-Protocol (PP) population which excludes participants due to important protocol violations from the FAS population. Safety: All Participants as Treated (APaT) population, which consists of all randomized participants who received at least one dose of study intervention. In this population, participants will be included in the treatment group corresponding to the study intervention they actually received. If a participant is found to have taken partial (one or more) incorrect doses of study medication from which he/she was randomized to, then the participant will be counted in the active treatment intervention group.
Primary Endpoint	LCQ total score
Statistical Methods for Key Efficacy Analyses	The primary analysis will be based on the FAS population. The primary analysis approach will be conducted utilizing the longitudinal ANCOVA model. In this model, the response vector consists of LCQ change from baseline in total score at each post-Baseline visit. The model will include factors for intervention group, visit, the interaction between intervention group and visit, gender, and baseline LCQ total score. The model will use all available LCQ change from baseline in total score data at Weeks 6 and 12. Contrasts will be constructed to compare the Gefapixant group to the Placebo group at each post-Baseline visit. The least squares mean change from baseline with the associated standard errors will be displayed for each intervention group. Estimated treatment differences (Gefapixant − Placebo) along with corresponding p-values and CIs will also be presented.
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 and Tier 2 safety endpoints will be evaluated via point estimates and 95% CIs for between-group comparisons, with p-values provided for the Tier 1 safety endpoints. Tier 3 safety endpoints will be evaluated via point estimates only.

Interim Analyses	One planned IA will be performed in this study to examine the futility and efficacy. Results will be reviewed by the DMC. The IA is summarized below. Details are provided in Section 3.7 – Interim Analyses. • Timing: To be performed when approximately 40% of participants (approximately the first 166 enrolled participants) have either completed the study or discontinued the study intervention early. • Testing: Futility and Strong Benefit (Efficacy) analysis based on the primary endpoint of LCQ change from baseline in total score at Week 12 will be provided.
Multiplicity	Since there is only one hypothesis (for the primary endpoint), no multiplicity adjustment is planned other than the IA alpha adjustment to the primary efficacy endpoint.
Sample Size and Power	The planned sample size is 414 participants (207 per treatment group) for comparing the primary endpoint of LCQ change from baseline in total score at Week 12, assuming a pooled SD [redacted] This sample size accounts for a 15% dropout rate, targeting for 352 evaluable participants at Week 12. The details are described in Section 3.9 – Sample Size and Power Calculations.

3.2 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.

This 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 deviations have been identified, and data have been declared final and complete. The investigator site personnel and the participants will be blinded to intervention assignment until the entire study is completed.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study intervention assignment. Treatment assignment will be implemented in an IRT system by a study vendor according to the adaptive allocation scheme provided in Section 6.3.1 – Intervention Assignment of the protocol.

Unblinding for Interim Efficacy and Safety Analyses

Planned interim analyses are described in Section 3.7 – Interim Analyses. Study enrollment is likely to be ongoing at the time of any interim analyses. Blinding to treatment assignment will be maintained at all investigational sites. The results of interim analyses will not be shared with the investigators prior to the completion of the study.

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

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

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

3.3 HYPOTHESES/ESTIMATION

The primary and secondary hypotheses for this study are stated in Section 3 – Objectives/ Hypotheses and Endpoints of the protocol.

3.4 ANALYSIS ENDPOINTS

Efficacy and safety endpoints for evaluation are listed below.

3.4.1 Efficacy Endpoints

3.4.1.1 Primary Efficacy Endpoint

- LCQ total score measured as change from baseline at Week 12

3.4.1.2 Secondary Efficacy Endpoint

- Cough Severity VAS score measured as change from baseline at Week 12

3.4.1.3 Exploratory Efficacy Endpoints

- CSD total score measured as change from baseline at Week 12
- PGIC measured at Week 12
- WPAI measured as change from baseline at Week 12

3.4.2 Safety Endpoints

- Adverse events
- Study intervention discontinuations due to an adverse event

3.4.3 Derivations of Efficacy Endpoints

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

Data Handling Rules for Efficacy Endpoints

- **LCQ Total Score**

There are three domains in the LCQ instrument: Physical (items 1, 2, 3, 9, 10, 11, 14 and 15), Psychological (items 4, 5, 6, 12, 13, 16, and 17), and Social (items 7, 8, 18, and 19). For each domain, the domain score (range 1-7) is the sum of individual item score within the domain divided by the number of items in the domain. The LCQ total score (range 3-21) is the sum of the three domain scores.

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

- **Cough Severity VAS score**

Cough severity VAS is scored from 0 to 100 using a 100 mm visual analogue scale. Mean weekly VAS score will be derived as the average of the VAS scores collected during the week prior to each visit. Baseline is defined as the average of VAS scores collected during the week prior to Day 1 (Day -7 to Day -1).

The mean weekly VAS score will be considered as missing if there are more than 3 missing days during the week prior to each visit. If there are less than 7 but at least 4 non-missing days during the week prior to a visit, the mean weekly score will be based on the actual non-missing days of the week prior to the visit.

- **CSD Total Score**

The daily CSD instrument has a total of 7 items, each with scores ranging from 0 (best) to 10 (worst). The total daily CSD score is the sum of these seven item scores. Mean total daily score (the sum of 7 item scores divided by 7) and three subscales (cough frequency, intensity, and disruption) will be derived for each day. Mean weekly total score is defined as the average of the mean total daily scores collected during the week prior to each visit. Mean weekly subscales will be derived in a similar fashion. Baseline is defined as the average CSD scores collected during the week prior to Day 1 (Day -7 to Day -1).

The mean weekly total score will be considered as missing if there are more than 3 missing days during the week prior to each visit. If there are less than 7 but at least 4 non-missing days during the week prior to a visit, the mean weekly total score will be based on the actual non-missing days of the week prior to the visit. Mean weekly subscales will be derived in a similar fashion.

3.5 ANALYSIS POPULATIONS

3.5.1 Efficacy Analysis Populations

The FAS population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all randomized participants who have taken at least 1 dose of study intervention. For endpoints that are measures of change from baseline, participants need to have baseline and at least one post-baseline measurement for inclusion in the analysis of each specific endpoint. Per-Protocol (PP) population excludes participants due to important violations from the protocol that may substantially affect the results of the primary efficacy endpoint. Potential violations that may result in the exclusion of a participant from the PP population will be specified in this document approaching database lock. The final determination on important protocol violations, and thereby the composition of the PP population, will be made prior to the first unblinding of the database and will be documented in a separate memo. A supportive analysis using the PP population may be performed for the primary efficacy endpoint if the proportion of the participants with important protocol deviations is >10%.

The list below shows important protocol violation criteria that may be considered as affecting the results of the efficacy endpoints:

[redacted]

Participants will be included in the intervention group to which they are randomized for the analysis of efficacy data using the FAS population. Details on the approach to handling missing data are provided in Section 3.6 – Statistical Methods.

3.5.2 Safety Analysis Population

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

actually received. Participants who take incorrect study intervention during only a part of the treatment period and took at least 1 dose of active study intervention will be included in the active treatment group.

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

3.6 STATISTICAL METHODS

Statistical testing and inference for efficacy and safety analyses are described in Sections 3.6.1 – Statistical Methods for Efficacy Analyses and 3.6.2 – Statistical Methods for Safety Analyses, respectively. Unless otherwise stated, all statistical tests will be conducted at an overall significant level of 0.05 (2-sided).

3.6.1 Statistical Methods for Efficacy Analyses

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

Primary Efficacy Analysis

The LCQ is collected at baseline and after administration of the study intervention at Weeks 6 and 12. The primary efficacy endpoint of this study is the LCQ change from baseline in total score. The primary analysis approach will be conducted utilizing the longitudinal ANCOVA model. In this model, the response vector consists of the LCQ change from baseline in total score at each post-Baseline visit. The model will include factors for intervention group, visit, interaction of treatment by visit, gender, and the baseline LCQ score. The model will use all available LCQ change from baseline in total score at Weeks 6 and 12. Contrasts will be constructed to compare the Gefapixant intervention group to the Placebo group at Week 6 and Week 12. The least squares mean change from baseline with the associated standard errors will be displayed for each intervention group. Overall estimated treatment differences (Gefapixant − Placebo) along with corresponding p-values and 95% CIs will also be presented, with the exception of the primary efficacy endpoint, in which the CI width will be adjusted for an IA.

Secondary Efficacy Analysis

The secondary efficacy endpoint will be analyzed using a similar longitudinal ANCOVA model as used for the primary efficacy analysis. The model will include terms for intervention group, visit, interaction of treatment by visit, gender, and baseline score.

Table 1 summarizes the analysis strategy of the primary and secondary efficacy endpoints.

Table 1 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (at Week 12)	Statistical Method	Missing Data Approach
Primary		
Change from baseline in LCQ total score	Longitudinal ANCOVA	Model-based[a]
Secondary		
Change from baseline in Cough Severity VAS score	Longitudinal ANCOVA	Model-based[a]

ANCOVA = analysis of covariance; LCQ = Leicester Cough Questionnaire; VAS = Visual Analogue Scale

[a] Includes data collected after early intervention discontinuation.

Exploratory Efficacy Analysis

- **CSD Total Score**

Change from baseline of the weekly average total daily CSD score and three subscales will be analyzed using a similar longitudinal ANCOVA model as used for the primary efficacy analysis in the original scale.

- **PGIC and PGIM Questionnaire**

The self-report measure PGIC reflects a participant's belief about the efficacy of treatment. PGIC is a 7-point scale depicting a participant's rating of overall improvement. Participants rate their change as “much better”, “better”, “a little better”, “the same”, “a little worse”, “worse”, or “much worse”. PGIM is a subsequent question that asks participants to indicate whether the level of change they report on the PGIC is a meaningful change, with yes/no response.

The numbers and proportions of participants with each response to the PGIC questionnaire will be provided at Week 12 by treatment group. Participants with improvements (“much better”, “better”, or “a little better” on the PGIC scale) and participants with a response of yes in the PGIM questionnaire to indicate important change for the improvement will be summarized. Proportion of participants with improvements will be analyzed by the stratified (region and gender) Miettinen and Nurminen (M&N) method.

- **WPAI Questionnaire**

The WPAI questionnaire consists of 6 questions and yields four types of scores over the past 7 days as follows: (1) absenteeism (work time missed); (2) presenteeism (impairment at work / reduced on-the-job effectiveness); (3) work productivity loss (overall work impairment/absenteeism plus presenteeism); and (4) activity impairment. The WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, ie, worse outcomes. The 4 scores of the questionnaire are

expressed as impairment percentages: the percent work time missed due to problem (Q2/(Q2+Q4)), the percent impairment while working due to problem (Q5/10), the percent activity impairment due to problem (Q6/10), and overall percent work impairment score due to problem Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4)))x(Q5/10)].

Change from baseline in each of the 4 scores will be analyzed using an ANCOVA model. The response vector consists of the change from baseline in WPAI at Week 12. The model will include factors for intervention group, visit, gender, and the baseline WPAI score.

Handling of Missing Data and Sensitivity Analyses

A participant will be considered for inclusion in the assessment of an efficacy endpoint if the CSD and Cough Severity VAS are completed on at least 4 days during the 7-day period prior to a post-Baseline visit (other ePROs are completed at the clinic visit only). All efficacy analyses will be conducted based on the observed data only. No imputation is planned for the missing diaries or missing questionnaire items. The pattern of missing is assumed to be missing at random (MAR). The missing pattern will be inspected to determine if the MAR assumption is met. Sensitivity analyses will be implemented to explore the impact of departures from the assumption made in missing diaries.

The longitudinal ANCOVA model (aka. LDA method) assumes that data are missing at random. In this study, it is expected that missing at random and missing completely at random (MAR/MCAR) mechanisms will underlie most of the missingness, and the proportion of data missing not at random (MNAR), driven solely by unobserved values of the study endpoints, will be small.

In addition to the analysis approach specified in the above mentioned primary efficacy endpoint analysis section, the following sensitivity analyses will be used to assess the robustness of the primary analysis approach.

Tipping-point Multiple-imputation Analysis

The Variant 3 of the tipping point as described in paper [Ratitch et al. 2013] will be used. In that approach, missing data are first imputed for all visits under the MAR assumption, and then the worsening/shift is applied. This is repeated with increasing the delta-shift (worsening) until the result is no longer statistically significant. Specifically, for a given constant, *c*, the tipping point analysis is conducted in a fashion similar to that used in standard multiple imputation, whereby *m (=100)* complete datasets are randomly generated using the original observed dataset. These *m* complete datasets are subsequently analyzed using the primary model, and the results of those analyses are then combined. The construction and analysis of these *m* (=100) datasets requires four primary steps:

1) Using a Markov Chain Monte Carlo method, make the observed dataset monotone-missing. This will be accomplished for each treatment group using “proc mi” within SAS 9.3 or higher by utilizing the options “mcmc chain=multiple impute=monotone;”, in conjunction with all of the covariates (excluding treatment)

included in the primary analysis model. The random seed will be set equal to 72644243. This step will generate *m* monotone-missing datasets.

2) Applying parametric regression to the monotone-missing datasets, impute all the missing values. This will be accomplished for each treatment group using "proc mi" within SAS 9.3 or higher utilizing the option "monotone reg", in conjunction with all of the covariates (excluding treatment) included in the primary analysis model. The random seed will be set equal to 72644243. This step will generate *m* complete datasets.

3) To implement the tipping-point aspect of the procedure, subtract a constant *c* from each of the imputed values of the active arms (to the detriment of active).

4) Analyze each of the post-imputation complete datasets using the primary model, obtaining point estimates for the mean of interest (e.g. change-from-baseline treatment difference at 12 weeks) and the associated variance.

Using "proc mianalyze" within SAS 9.3 or higher, the m=100 means and variances from the m analyses will be combined to obtain the final test statistic and p-value (Rubin, 1987). The final test statistic $\bar{Q} / (T^{-(1/2)})$ is approximately distributed as t_v, where $\bar{Q}$ is the sample mean of the m treatment difference estimates, $T=\bar{U} + (m+1)(B/m)$, $\bar{U}$ is the sample mean of the m variance estimates, and B is the sample variance of the m treatment difference estimates. The degrees of freedom, ν, will be computed as follows [Barnard and Rubin, 1999]: $\nu = [(\nu_1)^{-1} + (\nu_2)^{-1}]^{-1}$, where $\nu_1 = (m-1)[1 + (\bar{U}/(1+m^{-1})B)]^2$ and $\nu_2 = (1-\gamma)\nu_0(\nu_0+1)/(\nu_0+3)$, with $\gamma = (1+m^{-1})B/T$ and where ν_0 represents the complete-data degrees of freedom .

This procedure will be repeated (using the same m imputed datasets) until the smallest c is found such that the significant result turns non-significant (i.e., $p > 0.05$). This tipping point value c provides a measure of robustness of the primary result. A relatively large value of c implies better robustness of the primary analysis against the impact of missing data in the study. It is noted that when c=0 the tipping point analysis described above corresponds to an analysis conducted under the assumption that the missing data are MAR. For values of c larger than 0, the tipping point analyses do not assume that the missing values follow a MAR mechanism. In fact, the analysis is based on a special MNAR mechanism in which all missing data across the arms are assumed to have a worse response by a constant amount of c than the values would have had under MAR.

Jump-to-reference (J2R) Multiple-imputation Analysis

J2R imputation falls under the category of pattern mixture models known as reference-based imputation (RBI). The RBI approach uses different imputation models for missing data in different treatment groups. In J2R, missing data in the control group are imputed under the MAR assumption, while missing data in the treatment groups are imputed under a MNAR assumption using the control group profile for time points after withdrawal.

The following steps will be used to implement the J2R multiple-imputation analysis.

1) A parameter-estimation model is fitted using PROC MCMC. All the covariates included in the primary analysis will be used for the parameter-estimation model. For the MCMC procedure, an initial random seed=72644243 will be used. N=500 sets of pseudo-independent samples of the model parameters will be drawn from the joint posterior distribution.
2) The imputation model is built, where, for each pattern of withdrawal, a predicted value model is created using the parameters estimated in Step 1. The random seed for the imputations is 72644243. For subjects in the control (reference) group, the predicted means are calculated under MAR assumption; for subjects in the other treatment arms, the predicted means are calculated under MNAR using the jump-to-reference approach, that is, the mean profile is based on the same treatment arm before withdrawal and 'jumps' to the mean profile based on the reference arm after withdrawal. A complete dataset will be generated using the imputation model for each set of the N=500 parameters obtained in Step 1.
3) For each of the imputed complete datasets, an ANCOVA model will be used for the change from baseline values at last time point. The model will include the same covariates as in the primary analysis model. The treatment difference across the 500 datasets will then be combined using PROC MIANALYZE, i.e., using Rubin's rule for multiple imputation (Rubin, 1987) to provide the final results.

The J2R sensitivity analysis was implemented using macros developed by the DIA (Drug Information Association) Missing Data Working Group, which were available on page of www.missingdata.org.uk.

To get correct variance for the jump-to-reference imputation method, a pattern mixture model approximation will also be used. Based on the definition, the jump-to-reference imputation will have 0 mean treatment difference between treatment and control for those who dropped out in the treatment arm. Therefore, the overall mean treatment difference for jump-to-reference becomes

$$\theta^{J2R} = (\pi_t\, \mu_t^d + (1-\pi_t)\mu_t^p) - \mu_t^p = \pi_t(\mu_t^d - \mu_t^p)$$

where π_t is the proportion of completers in the drug group, *t* is the last time point, and μ_t^d and μ_t^p are the mean effects for drug and control, respectively. It can be estimated from the primary analysis model as $\widehat{\theta}^{J2R} = \hat{\pi}_t(\hat{\mu}_t^d - \hat{\mu}_t^p)$. The variance can be approximated by,

$$\mathrm{var}\left(\hat{\theta}^{J2R}\right) = \hat{\pi}_t^2\mathrm{var}(\hat{\mu}_t^d - \hat{\mu}_t^p) + \left(\hat{\mu}_t^d - \hat{\mu}_t^p\right)^2\hat{\pi}_t(1-\hat{\pi}_t)/n$$

where n is sample size in the drug treatment arm. The first term can be estimated from the primary analysis model.

3.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 2). The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as system organ class terms) and events that meet predefined limits of change in laboratory and vital signs are either prespecified as “Tier 1” endpoints, or will be classified as belonging to "Tier 2" or "Tier 3" based on the observed proportions of participants with an event.

Tier 1 Events

Safety parameters or adverse events of interest that are identified a priori constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% CIs to be provided for between-treatment differences in the proportion of participants with events; these analyses will be performed using the Miettinen and Nurminen (M&N) method (1985) [Miettinen, O. and Nurminen, M. 1985], an unconditional, asymptotic method. For this protocol, taste-related AEs (including dysgeusia, ageusia, hypogeusia, hypergeusia, and taste disorder) are considered Tier 1 events.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates and 95% CIs provided for differences in the proportion of participants with events.

Membership in Tier 2 requires that at least 4 participants in any treatment group exhibit the event. The threshold of at least 4 events was chosen because the 95% confidence interval 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% confidence intervals for Tier 2 events may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse events and safety parameters that meet predefined limits of change.

In addition to individual events that occur in 4 or more participants in any treatment group, any oral paresthesia AE, any oral hypoesthesia AE, and the broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, and discontinuation due to an AE will be considered Tier 2 events.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Continuous Safety Measures

For continuous measures such as changes from baseline in laboratory and vital signs, summary statistics for baseline, on-treatment, and change from baseline values will be provided by intervention group in table format.

The frequency of taste-related AEs across pre-defined time intervals will be provided, where the time intervals will be defined as: >0 to ≤1 week, >1 to ≤4 weeks, >4 to ≤8 weeks, and>8 to ≤12 weeks. In each time interval, the denominator for calculation of percentage will be the number of participants treated during the time interval and the numerator will be the number of participants with at least one taste-related AE occurring in this time interval.

Table 2 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint[a]	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Any taste-related AE (including dysgeusia, ageusia, hypogeusia, hypergeusia, and taste disorder)	X	X	X
Tier 2	Any oral paresthesia AE		X	X
	Any oral hypoesthesia AE		X	X
	Any AE		X	X
	Any Serious AE		X	X
	Any Drug-related AE		X	X
	Any Serious and Drug-related AE		X	X
	Discontinuation due to AE		X	X
	Specific AEs, SOCs, or PDLCs[b] (incidence ≥4 participants in one of the treatment groups)		X X	X X
Tier 3	Time to Onset from the First Dosing Date and Duration of Event for Taste-Related AEs			X
	Frequency of Taste-Related AEs for Time Intervals: >0 to ≤1 Week, >1 to ≤4 Weeks, >4 to ≤8 Weeks, and >8 to ≤12 Weeks			X
	Specific AEs, SOCs or PDLCs[b] (incidence <4 participants in all of the treatment groups)			X
	Change from Baseline Results (Labs, Vital Signs)			X

AE = adverse event; CI = confidence interval; PDLC = predefined limit of change; SOC = system organ class; X = results will be provided.

[a] Adverse experience references refer to both clinical and laboratory AEs.

[b] Includes only those endpoints not prespecified as Tier 1 or not already prespecified as Tier 2 endpoints.

Table 3 Predefined Limit of Change from Baseline

Laboratory Test	Criteria
hematocrit	↓ ≥20% and <LLN ↑ ≥20% and >ULN
WBC	↓ ≥20% and <LLN ↑ ≥20% and >ULN
Platelet	↓ ≥25% and <LLN ↑ ≥50% and >ULN
Bilirubin	↑ ≥100% and >ULN ↑ ≥50% and >1.5x ULN ↑ ≥50% and >2x ULN >3x ULN >5x ULN
AST	↑ ≥100% and >ULN ↑ ≥50% and >1.5x ULN ↑ ≥50% and >2x ULN >3x ULN >5x ULN
ALT	↑ ≥100% and >ULN ↑ ≥50% and >1.5x ULN ↑ ≥50% and >2x ULN >3x ULN >5x ULN
Neutrophil	↓ ≥20% and <LLN ↑ ≥20% and >ULN
BUN	↑ ≥50% ↑ ≥20% and BLN >ULN
Serum creatinine	↑ ≥50% ↑ ≥20% and BLN >ULN
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BLN = baseline; BUN = blood urea nitrogen; LLN = Lower limit of normal range; ULN = Upper limit of normal range; WBC = white blood cell.	

3.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

3.6.3.1 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (eg, age, gender, race, weight, and height), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

3.7 INTERIM ANALYSES

Results of all interim analyses will be reviewed by an external DMC, which will make recommendations to the EOC of the Sponsor to continue, modify or stop the study.

3.7.1 Interim Efficacy Analysis

One planned efficacy IA will be conducted when approximately 40% of target participants (approximately the first 166 enrolled participants) have either completed the study

(approximately 141 enrolled participants) or discontinued study intervention early. All available data will be included in the analysis, including follow-up data and partial data from participants enrolled after the participants triggering the IA.

The purpose of the IA is to allow early stop for strong benefit (efficacy) or for futility. The efficacy IA will be based on the primary endpoint of the LCQ change from baseline in total score at Week 12.

[redacted]

3.7.2 Interim Safety Analyses

Interim safety will also be assessed at the time of prespecified IA for futility, ie, when approximately 40% of target participants (approximately the first 166 enrolled participants) have either completed the study or discontinued the study intervention early. A general review of safety results will be performed based on review of AEs, laboratory safety parameters, and other safety endpoints.

3.8 MULTIPLICITY

Other than an adjustment to the alpha level for the IA for efficacy, no multiplicity adjustment is planned.

3.9 SAMPLE SIZE AND POWER CALCULATIONS

The sample size calculations are powered to test the primary efficacy endpoint, with the following assumptions based on the results from a phase 2 chronic cough study. In MK-7264 Protocol 012, the change from baseline in LCQ total score at Week 12 was 1.1 and 1.7 for 20 mg and 50 mg compared to placebo. In this study, given the population is targeted for participants with recent onset chronic cough (< 12 months) which is different from participants with chronic cough (≥ 12 months) in Protocol 012, conservative assumptions were used for sample size calculation:

- Treatment difference in change from baseline in LCQ total score at Week 12 is 1.1 point
- Common SD of change from baseline in LCQ total score is 3.5

Based on the assumptions above, a total of 414 participants (207 participants per intervention group) will provide at least 80% power. The calculation is based on an overall one-sided α=0.025 significance level, adjusted for one IA for efficacy (α=0.001), and one final efficacy analysis (α=0.024). A dropout rate of 15% at Week 12 is accounted for the sample size calculation to ensure 352 evaluable participants complete the Week 12 evaluation.

With assumptions on the AE rates in the placebo group based on the Protocol 012 results, the minimum detectable AE rate differences are 8.4%, 9.0%, and 7.7% in overall taste-related AEs, oral paresthesia AEs, and oral hypoesthesia AEs, respectively.

3.10 SUBGROUP ANALYSES

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

- Gender (male, female)
- Region (North America, Europe, Asia-Pacific, Other)
- Age group (<60 years, ⩾60 years old)
- Baseline Cough Severity VAS (<60 mm, ⩾60 mm)

A similar longitudinal ANCOVA model as that used for the primary efficacy endpoint will be utilized. For each subgroup, summary statistics including means and their 95% CIs will be provided for each intervention group at Week 12. For the subgroups with 15% or more of the FAS population across both intervention groups, the mean treatment differences (gefapixant - placebo) and their 95% CIs will also be provided at Week 12.

3.11 COMPLIANCE (MEDICATION ADHERENCE)

For each participant, percent compliance will be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days Expected on Therapy}} \times 100\%$$

A day within the study will be considered an "on-therapy" day if the participant takes all required intervention as instructed in Section 8. When a participant takes less than or more than the required intervention on a day, that day is not considered an on-therapy day.

For participants who are followed for the entire study period, the "Number of Days Should be on Therapy" is the total number of days from the first scheduled intervention day to the last scheduled intervention day. For participants who discontinue from the study permanently, the "Number of Days Should Be on Therapy" is the total number of days from the first scheduled intervention day to the last dose day.

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

3.12 EXTENT OF EXPOSURE

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

4. APPENDICES

4.1 Model Specification, Assumptions, and Sample SAS Implementation Codes for the Primary Efficacy Analysis

Model

Let Y_{ijt} denote the measurement for subject *i,* with treatment assignment *j*, at time *t*. Here $j = 0, 1$ represent Placebo and MK-7264 45 mg BID, respectively. Also, $t = 0,1,2$ represent Baseline, visits at Week 6 and 12, respectively.

The longitudinal ANCOVA model, that is, a mixed linear model will treat percent change from baseline in measurement, $(Y_{ijt} - Y_{ij0})/Y_{ij0}$, as the dependent variable, and adjust for the following independent variables:

- baseline measurement Y_{ij0}
- treatment (categorical variable with 2 levels, Placebo and MK-7264 45 mg BID)
- week (categorical variable with 2 levels, 6, 12)
- Gender (males and females)
- the interaction of treatment by week

Observations across subjects are assumed to be independent. Post-baseline measurements within the same subject are assumed to follow multivariate normal distribution with mean vector as specified above and an unstructured covariance matrix.

This longitudinal model provides valid statistical inference in the presence of possible missing data if the missing data mechanism is ignorable (or more specifically, MAR or MCAR). This missing data mechanism requires that the probability of a data point being missing does not depend on the missing data after adjusting for the observed data.

Reasons for discontinuation from the trial may include lack of efficacy, clinical or laboratory adverse experiences, relocation, withdrawal of consent, protocol deviations, and/or data processing issues. Missing data caused by relocation and data processing issues, are likely to be MCAR. On the other hand, missing data caused by discontinuation due to lack of efficacy may belong to MAR because the discontinuation may depend on the observed efficacy outcomes. The MAR or MNAR mechanisms might each underlie the other reasons to some extent. If treatment in large part determines the loss of data for these other reasons (such as clinical or laboratory adverse experiences), the mechanism may be close to MAR since treatment assignment is an observed variable and included in the analysis model. Based on the prior trial results, missing data due to other reasons is relatively infrequent.

Model Convergence

If the unstructured covariance matrix fails to converge with the default algorithm, then the AR(1) structure can be used to provide initial values of the covariance parameters.

Example SAS Codes

```
proc mixed data=adeff;
    where avisitn > 0;
    class subjid trt01p avisitn sex;
    model chg = base trt01p avisitn sex trt01p*avisitn/ solution notest;
    repeated avisitn / subject = subjid type=un;
    lsmestimate trt01p*avisitn 'MK at Week 12'   [1, 1 2];
    lsmestimate trt01p*avisitn ' Placebo at Week 12'   [1, 2 2];
    lsmestimate trt01p*avisitn 'Treatment Differences at Week 12' [1, 1 2]  [-1, 2 2];
run;
```

4.2 Model Specification for the Safety Analysis

Miettinen and Nurminen method

Denote the sample size and response rate as n_0, p_0, n_1, p_1 for the two treatment groups. The $100(1-\alpha)\%$ confidence interval is provided by solving the equation for δ,

$$\frac{(\hat{p}_1^* - \hat{p}_0^* - \delta)^2}{\sum_{i=1}^{I}\left(\frac{w_i}{\sum_k w_k}\right)^2 \tilde{v}_i} = \chi^2_{1,\alpha}$$

Here $i = 1, \ldots, I$ is the index for strata and

$\hat{p}_1^* = \sum_{i=1}^{I}\left(\frac{w_i}{\sum_k w_k}\right)\hat{p}_{1i}$, where $\hat{p}_{1i}$is the observed response rate for group 1 in stratum i;

$\hat{p}_0^* = \sum_{i=1}^{I}\left(\frac{w_i}{\sum_k w_k}\right)\hat{p}_{0i}$, where $\hat{p}_{1i}$is the observed response rate for group 0 in stratum i;

$w_i = \frac{n_{1i}n_{0i}}{n_{1i}+n_{0i}}$, which corresponds to the Cochran Mantel-Haenszel's weights;

$\tilde{v}_i = \left[\frac{\tilde{p}_{1i}(1-\tilde{p}_{1i})}{n_{1i}} + \frac{\tilde{p}_{0i}(1-\tilde{p}_{0i})}{n_{0i}}\right]\frac{n_{1i}+n_{0i}}{n_{1i}+n_{0i}-1}$;

$\tilde{p}_{0i}$ is the maximum likelihood estimate for p_{0i} under the restriction that $p_{1i} - p_{0i} = \delta$;

$\tilde{p}_{1i} = \tilde{p}_{0i} + \delta$.

The point estimate for the treatment difference is provided by $\hat{p}_1^* - \hat{p}_0^*$ with corresponding variance $\sum_{i=1}^{I}\left(\frac{w_i}{\sum_k w_k}\right)^2 \tilde{v}_i$.

5. REFERENCES

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