Center for Drug Evaluation and Research

Pulmonary-Allergy Drugs Advisory Committee Briefing Document

Gefapixant

Oral Treatment for Refractory or Unexplained Chronic Cough

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ADVISORY COMMITTEE BRIEFING MATERIALS:

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following terms may be used interchangeably within the document:

- Participant, patient, and subject
- Study and trial
- Intervention, treatment, and medication
- Sex and gender

This list serves as first appearance in text.

Abbreviation	Definition
ACCP, also known as CHEST	American College of Chest Physicians
ACE	Angiotensin-converting enzyme
AE	Adverse event
AHI	Apnea-Hypopnea Index
ANCOVA	Analysis of covariance
APaT	All-participants-as-treated
ATP	Adenosine triphosphate
AUC	Area under the curve
BCRP	Breast cancer resistance protein
BID	Twice daily
BMI	Body mass index
CHMP	Committee for Medicinal Products for Human Use
CHS	Cough hypersensitivity syndrome
CI	Confidence interval
C_{max}	Maximum concentration
CNS	Central nervous system
CRL	Complete Response Letter
CSD	Cough Severity Diary
CSR	Clinical study report
C-SUI	Cough-induced stress urinary incontinence
DDI	Drug-drug interaction
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOP2	End-of-Phase 2
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration

Abbreviation	Definition
GERD	Gastroesophageal reflux disease
GMR	Geometric mean ratio
HRQoL	Health-related quality of life
IQR	Interquartile range
IRR	Inter-rater reliability
LCQ	Leicester Cough Questionnaire
LS mean	Least-squares mean
MAD	Maximum allowable difference
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
NDA	New drug application
OSA	Obstructive sleep apnea
PAP	Positive airway pressure
PD	Pharmacodynamic
PGIC	Patient Global Impression of Change
PK	Pharmacokinetic
PPI	Proton pump inhibitor
PRO	Patient-reported outcome
PSG	Polysomnography
PT	Preferred Term describes an adverse event and other medical term in the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA is a standardized medical terminology, published by the International Council for Harmonisation.
QD	Once daily
QHS	Daily at bedtime
QoL	Quality of Life
RCC	Refractory chronic cough
RI	Renal impairment
SAE	Serious adverse event
SaO_2	Oxygen saturation
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
TDD	Total daily dose
UCC	Unexplained chronic cough
US	United States of America
VAS	Visual analog scale
WPAI	Work Productivity and Activity Impairment questionnaire

1 EXECUTIVE SUMMARY

This document summarizes the results of the development program conducted to support gefapixant (MK-7264) for the treatment of adults with refractory chronic cough (RCC) or unexplained chronic cough (UCC). Within this document, this condition is referred to as RCC/UCC.

As a subset of chronic cough, defined as a cough lasting more than 8 weeks, RCC is a chronic cough that persists despite comprehensive evaluation and treatment of any comorbid conditions (eg, asthma, GERD), and UCC is a cough for which no underlying etiology has been determined despite extensive and appropriate evaluation. RCC/UCC is a result of dysregulation of the cough reflex and the cough is thought to occur following ATP release from airway mucosal cells as a result of airway stress or inflammation. This extracellular ATP binds to purinergic P2X3 receptors that are expressed selectively on a subpopulation of peripheral sensory nerves (C-fibers) that are activated in the airway to trigger cough [1] [2]. Chronic cough has a prevalence of about 5% of the US adult population [3]; the CHEST cough guidelines estimate that 5% to 10% of patients seeking medical care for chronic cough have RCC/UCC [4].

RCC/UCC can last for many years and is associated with substantial physical, social, and psychological consequences. No therapies are approved to treat RCC/UCC in the US, though opioids or centrally acting neuromodulators (eg, gabapentin) are used off-label and carry risks, such as addiction or other significant side effects.

Gefapixant is a non-narcotic, peripherally active, orally administered, small molecule that is a P2X3-receptor antagonist. Gefapixant blocks extracellular ATP signaling through P2X3 receptors expressed selectively on C-fibers, reducing the excess activation of airway C-fibers and thereby reducing excessive coughing.

The efficacy of gefapixant was demonstrated in 2 double-blind, randomized, placebo-controlled pivotal Phase 3 clinical studies of 2 doses of gefapixant [Studies P027 (N=730) and P030 (N=1314)] in adults with RCC/UCC. The primary endpoint in both studies was reduction in 24-hour cough frequency, as measured by the VitaloJAK™ (Vitalograph, Ltd) cough counting system. This system includes: a wearable sound recorder that has FDA designation as a 510(k) cleared device; a compression algorithm that removes periods of silence and noncough sounds from the 24-hour recordings to make cough counting operationally feasible; and review of the recordings by a trained analyst who counts the coughs. In the original, protocol-prespecified analyses (longitudinal ANCOVA applied to the original dataset), both studies met the success criteria for the primary endpoint; patients treated with gefapixant 45 mg BID had a significant reduction, relative to placebo, in 24-hour cough frequency at Week 12 in Study P027 (-18.45%, p=0.041) and at Week 24 in Study P030 (-14.64%, p=0.031). The gefapixant 15 mg BID arm did not differentiate from placebo; based on this result, the proposed dosing regimen is gefapixant 45 mg BID (and the results presented in this document largely focus on this regimen).

The observed reduction in cough frequency is clinically meaningful to patients, as measured by a number of patient-reported outcomes (PROs). Specifically, the Leicester Cough Questionnaire (LCQ), a validated measure of cough-specific health-related quality of life (HRQoL), was assessed as a key secondary endpoint (multiplicity controlled) in Study P030; results demonstrated that a significantly greater proportion of patients treated with gefapixant 45 mg BID, compared with placebo, achieved a ≥1.3-point increase (a threshold considered clinically meaningful [5]) in the LCQ total score at Week 24 (odds ratio vs. placebo: 1.41, p=0.040). Study P027 was not powered for this endpoint, but results trended in a positive direction. Results of Studies P027 and P030 were published in The Lancet, as the "COUGH-1" and "COUGH-2" studies, respectively [6].

The safety of gefapixant was characterized in Studies P027 and P030. Taste-related AEs were the most frequently reported AEs in patients who received gefapixant 45 mg BID; most (96.2%) were mild or moderate in intensity and all were nonserious. No clinically meaningful sequelae associated with taste-related AEs, such as loss of appetite, weight loss, or dehydration, were observed. Overall, 96.0% of the patients in the gefapixant 45 mg group with taste-related AE resolved all taste-related AEs by database lock. Follow-up done after database lock showed continued resolution of taste-related AEs with 98.4% of patients reporting resolution of taste-related AEs. The incidence of SAEs was low and similar across treatment groups.

The original marketing application for gefapixant for the treatment of RCC/UCC in adults was submitted to FDA on 21-DEC-2020. This package included nonclinical and clinical assessments. FDA issued a Complete Response Letter (CRL) on 20-JAN-2022 expressing concerns about validation of the cough counting system; specifically, the compression algorithms applied to the Phase 3 raw cough recordings and the inter-rater reliability (IRR) for counting coughs. FDA also requested further evidence of content validity of the LCQ to better understand the clinical relevance of cough reduction in patients treated with gefapixant.

To address the CRL, Merck conducted 3 additional studies as described below:

1. A new validation study of the compression algorithm.
    - Results of the validation study demonstrated no systematic bias with use of the algorithm.

2. A new IRR study to assess the inter-rater reliability of cough analysts' (raters) cough counting on compressed and uncompressed recordings.
    - Results of the IRR study demonstrated no relevant cough analyst impact on cough counts.

Together, the results of the compression algorithm validation and IRR studies support that the VitaloJAK™ cough counting system is reliable and appropriate to assess the efficacy of gefapixant for the treatment of RCC/UCC.

3. A 2-part qualitative interview study (concept elicitation and cognitive debriefing) of the LCQ.
    - In this study, participants (n=20) with RCC/UCC, consistent with the target Phase 3 study population, confirmed that the LCQ is appropriate and relevant for use in this population.

In response to a prior FDA request (ie, not part of the CRL), Merck performed posthoc analyses of the Phase 3 LCQ data using higher thresholds than that prespecified for defining clinically meaningful change in the LCQ total score. Results from these analyses are consistent with the prespecified analyses.

Following agreement with FDA, the new validation study and the new IRR study were completed, most of the original cough recordings from the pivotal studies were compressed with the single-channel compression algorithm, and then the coughs were recounted and reanalyzed. Following the recount and posthoc analyses, the recount dataset from the pivotal Studies P030 and P027 demonstrated reductions in 24-hour cough frequency were consistent with the prespecified analysis. Although one of the pivotal studies, P030, remained statistically significant (p=0.030), the second study, P027, just missed statistical significance (p=0.057). A consistent treatment effect was observed across different analyses and datasets, and patients reported improvement in their condition across multiple Phase 3 and Phase 3b studies. Taken together with PRO results, these data confirm the conclusion that gefapixant provides clinically meaningful treatment benefit.

All of these data and supporting documents to address the CRL were provided to FDA in a resubmission on 27-JUN-2023.

In addition to the pivotal studies of gefapixant in the treatment of RCC/UCC, 2 Phase 3b studies were performed that add to the confirmatory body of evidence supporting the efficacy and safety of gefapixant. The first (Study P043) was a study in adults with RCC/UCC of <12 months duration, which extends the understanding of gefapixant's benefit in patients with a more recent diagnosis of RCC/UCC. The second (Study P042) was a study in women with RCC/UCC and with cough-induced stress urinary incontinence (C-SUI), an important and burdensome clinical complication of RCC/UCC, a condition for which there is no approved therapy. While cough counts were not the primary efficacy endpoint, clinical meaningfulness was measured using the PROs utilized in the pivotal Studies P027 and P030. Both Phase 3b studies met the success criteria for their primary endpoints and add to the substantial evidence of effectiveness for gefapixant, as well as provide additional safety data, which was generally consistent with Studies P027 and P030.

The clinical development program provides evidence of efficacy and characterizes the safety in patients with RCC/UCC. The totality of the data generated in the gefapixant development program, both in the original marketing application and more recently in the response to the CRL, supports the positive benefit-risk of gefapixant 45 mg BID in adults with RCC/UCC. Approval of gefapixant would provide patients with RCC/UCC, a debilitating condition with

no approved therapies, an effective and safe treatment, and would allow clinicians and patients to make a shared decision whether treatment with gefapixant is right for them.

2 PRODUCT DEVELOPMENT RATIONALE

2.1 Unmet Medical Need

Cough in adults can be classified, based on duration, as acute (<3 weeks), subacute (3 to 8 weeks), or chronic (>8 weeks). Clinical treatment guidelines recommend that treatable causes of chronic cough, including malignancy, infection, use of certain drugs (eg, ACE inhibitors), and smoking, be identified and treated [7] [8] [4] [9]. Patients with chronic cough are mostly female; the mean age in a recent publication was 55 years [10]. The most recent estimates suggest that 5% of the US population may suffer from chronic cough [3].

Patients who have been diagnosed with conditions that are suspected to be associated with chronic cough (eg, asthma, nonasthmatic eosinophilic bronchitis, upper airway cough syndrome, GERD), but whose cough does not resolve with the appropriate treatment of those conditions, are considered to have RCC. Patients with chronic cough in whom conditions associated with cough cannot be identified despite a thorough diagnostic workup are considered to have UCC. There is a paucity of literature to accurately characterize the epidemiology of RCC/UCC in the US; much of the epidemiology has been collected in small studies with variability in their methodology. The most recent estimates suggest that 5% of the US population may suffer from chronic cough [3]. RCC/UCC is reported to occur in a subset of 5% to 10% of patients seeking medical attention for chronic cough [11].

Currently in the US, there are no therapies approved for RCC/UCC. Off-label use of opioids and neuromodulators have undesirable side effect profiles and/or addictive potential. Patients with chronic cough may experience substantial physical, social, and psychological consequences because of excessive coughing.

Patients with chronic cough may experience substantial physical, social, and psychological consequences because of excessive coughing. Physical consequences include C-SUI, sleep disturbance, breathlessness, and in some cases, more severe effects such as cough-induced rib fracture or syncope. In addition to frequent cough, patients often experience an irritation or “tickling” in the larynx and chest; this can sometimes be accompanied by chest tightness, dysphonia, or muscular pain. Cough has been shown to have a significant impact on the HRQoL of patients, with clinical sequelae including cardiovascular, constitutional, gastrointestinal, genitourinary, musculoskeletal, neurologic, ophthalmologic, psychosocial, and skin complications [12]. Many patients experience symptoms that persist for years and require numerous physician visits, exacerbating the burden on both patients and their families.

As coughing can persist for years, chronic cough can cause considerable social distress and social isolation for patients. Chronic cough can lead to social isolation due to fear of

coughing in public places and appearing to have a transmissible infection, difficulties at work (such as embarrassment at meetings), and tensions in relationships.

Chronic cough patients report higher levels of depression, anxiety, fatigue, and somatic symptoms compared with noncoughers [13]. In addition, chronic cough patients report embarrassment, fear of a serious illness, and frustration as factors that impact their psychological well-being. In a prospective study of 100 patients with chronic cough, more than 50% of patients with chronic cough have significant symptoms of depression [14] that may be due to the disruptive and externally visible nature of chronic cough. Cough can affect patients every hour of every day and affect a wide range of basic activities such as eating, answering the telephone, work productivity, and activities of daily living [15] [3]. Furthermore, patients with chronic cough lack the support and sympathy associated with other conditions [15].

Chronic cough represents a significant unmet medical need associated with a considerable economic burden arising from high rates of health care utilization, the use of off-label medications with undesirable effects, and high indirect costs associated with loss of productivity [16] [17]. In general, the assessment and treatment of cough is a substantial burden to the health care system and patients [3]. A survey administered to adults with chronic cough indicated that 72% of respondents had seen a physician at least 3 times for their cough, yet only 53% had received a suggested diagnosis for their cough [18].

2.2 Pathobiology of RCC/UCC

The cough in patients with RCC/UCC is potentially related to airway sensory nerve activation via binding of extracellular ATP to P2X3 receptors expressed on sensory C-fibers.

- P2X3 receptors are ATP-gated ion channels found on sensory C-fibers of the vagus nerve in the airways (but not on other airway sensory fibers; eg, Aδ-fibers, which are activated by mechanical stimulation). C-fibers are nociceptive fibers that can be activated in response to inflammation or chemical irritants (ie, C-fibers serve a chemosensory function). C-fiber activation in the airway can initiate a cough reflex [19].
- ATP is released from airway mucosal cells under conditions of airway stress or inflammation. Binding of extracellular ATP to P2X3 receptors is sensed by C-fibers as a damage signal; this ATP signaling can lead to activation of these sensory fibers in the airway to trigger cough [2].
- Studies conducted in animal models indicate that antagonism of P2X3 (or the closely related P2X2/3 receptor subtype) reduces ATP-stimulated activation of C-fibers. P2X receptors are also known to mediate chemosensory function in a different sensing organ, the tongue: P2X receptors are found on the gustatory C-fibers in the taste buds, where ATP is the signaling molecule for taste sensation [20].

Gefapixant is a first-in-class, non-narcotic, peripherally active, orally administered, selective antagonist of the P2X3 receptor.

2.3 Overview of Clinical Development Program

Gefapixant has been extensively evaluated in nonclinical and clinical studies. The nonclinical program includes a comprehensive assessment of the pharmacology, metabolism, pharmacokinetics, and safety of gefapixant. Clinical pharmacology studies characterize the human PK of gefapixant, including the effects of intrinsic factors (specific populations) and extrinsic factors (drug-drug interactions) on gefapixant PK.

Cumulatively, 3169 patients have been exposed to gefapixant across the clinical development program, including Phase 1, Phase 2, and Phase 3 studies.

Across Phase 1 studies, patients received gefapixant 10 mg to 1800 mg as single oral doses or 7.5 mg BID to 1800 mg BID for up to 14 days. These studies were conducted to characterize the clinical pharmacology profile.

In the Phase 2 program, multiple indications were explored based on the mechanism of action. The effect of gefapixant was assessed in the following cough populations: acute cough in patients with viral-induced upper respiratory tract infection (P013), cough reflex sensitivity (P014 and P015), and idiopathic pulmonary fibrosis (P016 and P019) [Table 1]. Given the biological role of P2X3 antagonism in cough, the efficacy observed for gefapixant in Phase 2 studies, and the safety profile observed across the program, the Phase 3 clinical development program was directed toward addressing the substantial unmet medical need in patients with RCC/UCC.

Dose selection for Phase 3 cough studies was based on extensive modeling and simulation using data from Phase 1 and 2 studies. Initial efficacy data for gefapixant in patients with RCC/UCC were generated in 3 Phase 2 studies: Study P006 (proof of concept), Study P010 (dose escalation), and Study P012 (dose ranging). The PK and PD of gefapixant, evaluated in Studies P010 and P012, were used for population-PK and exploratory E-R analyses which predicted that gefapixant 15 mg BID would provide a clinically meaningful reduction in cough frequency with minimal incidence of specific AEs and that gefapixant 45 mg BID would provide maximal reduction in cough frequency with an acceptable incidence of specific AEs. Given that the efficacy and the AEs related to gefapixant are exposure-related in that dose range, these 2 doses with acceptable benefit-risk profile were brought forward in the Phase 3 program to maximize treatment flexibility for physicians and patients.

The 2 pivotal Phase 3 studies for gefapixant were double-blind, randomized, placebo-controlled studies (P027 and P030), each with a total treatment duration of 1 year. These studies evaluated the efficacy and safety of gefapixant 15 mg and 45 mg BID in adult patients with RCC/UCC. The studies had identical entry criteria and dosing regimens; they collected the same endpoints and were therefore planned to be pooled for the safety and efficacy evaluation of gefapixant. The duration of the main study period (ie, when the primary efficacy endpoint was evaluated) for Study P027 was 12 weeks, followed by a 40-week blinded extension period. The duration of the main study period for Study P030 was

increased to 24 weeks (followed by a 28-week blinded extension period) based on guidance received from FDA and EMA at end-of-Phase 2 discussions.

The Phase 3b program included the following studies: a study in patients with RCC/UCC of recent onset (Study P043) and a study in patients with RCC/UCC and with C-SUI (Study P042).

In all of these studies, RCC was defined as cough in a patient whose clinical evaluation suggested a comorbid condition that may be associated with chronic cough (eg, GERD, asthma, upper airway cough syndrome, or nonasthmatic eosinophilic bronchitis) for which the patient received, according to CHEST guidelines, appropriate diagnostic workup and also received at least 2 months of stable treatment for the comorbid condition(s) prior to screening, yet continued coughing despite treatment. UCC was defined as cough in patients whose clinical evaluation per CHEST guidelines did not suggest a comorbid condition associated with chronic cough. To further ensure that patients in Studies P027 and P030 had clinically relevant RCC/UCC, patients had to rate their cough severity at screening and baseline as ≥40 mm on the Cough Severity VAS (0 to 100 mm scale). Smokers (current, recent within 1 year, or >20 pack-year history) and patients receiving ACE inhibitors were excluded. Concomitant use of over-the-counter or prescription medications to treat cough, such as opioids, anticonvulsants, tricycle antidepressants, codeine, dextromethorphan, guaifenesin, and benzonatate, was prohibited.

The pivotal studies, P027 and P030, included objective outcome measures and PROs. For the objective measurement of cough frequency (evaluated during the main study period of each study), a cough counting system collected cough sounds using a wearable digital sound recorder that is a 510(k) cleared device. For the PRO endpoints, validated cough-specific measures (LCQ, CSD, Cough Severity VAS), and a cough-specific PGIC were administered to assess the physical, social, and psychological aspects of cough-specific HRQoL; cough frequency, intensity, and disruption due to cough; cough severity; and patient self-ratings of change in cough. The endpoints derived from these validated and reliable cough-specific PROs provide additional information on the clinical meaningfulness of the objective endpoints by assessing the impact of cough and of reduced cough frequency from the patient perspective.

Study P043 in patients with RCC/UCC of recent onset and Study P042 in patients with RCC/UCC and with C-SUI were designed to provide confirmatory evidence of the clinical meaningfulness of treatment with gefapixant. The cough-specific PROs were the same as those used in the pivotal studies, with the exception that the LCQ was not used in P042.

- The primary efficacy endpoint of Study P043 was the change from baseline in LCQ total score at Week 12, and the secondary efficacy endpoint was change from baseline in Cough Severity VAS score at Week 12. Exploratory endpoints evaluated the impact of gefapixant on cough severity as assessed by the CSD, the impact of gefapixant on global rating of change using the PGIC questionnaire, and the impact on work productivity using the WPAI.
- The primary efficacy endpoint of Study P042 was episodes of C-SUI (as determined by a patient incontinence diary), measured as percent change from baseline in daily episodes of C-SUI at Week 12. There were no secondary efficacy endpoints. Exploratory endpoints evaluated the impact of gefapixant on improving urinary incontinence-related QoL as assessed by the Incontinence QoL questionnaire, and on cough severity as assessed by the CSD and Cough Severity VAS. Other exploratory endpoints evaluated the impact of gefapixant on overall incontinence episodes, global rating of change using the PGIC questionnaire, and the impact on work productivity using the WPAI.

As of the authoring of this briefing document, all clinical studies have completed. An overview of the Phase 2 and Phase 3 clinical development program in chronic cough is provided in [Table 1].

Table 1
Summary of Phase 2 and Phase 3 Clinical Studies in Patients With Chronic Cough in the Gefapixant Development Program

Study Number **Number of Countries**	**Design** **Population**	**Number of Patients** **by Intervention Group**	**Study Population** **Treated (N)**
Phase 2 Studies[1]			
MK-7264-006 (referred to as P006, for proof of concept) 1 country (UK)	Single-center, randomized, double-blind, placebo-controlled, 2-period, crossover study Duration of treatment: 4 weeks Population: chronic cough	MK-7264 600 mg BID or placebo: 24 randomized/24 treated/18 completed	N=24 18 female and 6 male patients Age range: 24 to 70 years
MK-7264-010 (referred to as P010, for dose escalation) 1 country (US)	Multicenter, randomized, double-blind, placebo-controlled, crossover study Duration of treatment: Cohort 1: two 16-day treatment periods (MK-7264 or placebo) with a 3- to 7-day washout period Cohort 2: two 16-day treatment periods (MK-7264 or placebo) with a 14- to 21-day washout period Population: RCC	Cohort 1: MK-7264/Placebo: 29 randomized/28 treated/26 completed Dose titration range: 50 to 200 mg BID Cohort 2: MK-7264/Placebo: 30 randomized/30 treated/29 completed Dose titration range: 7.5 to 50 mg BID	Cohort 1: N=28 24 female and 4 male patients Age range: 40 to 76 years Cohort 2: N=30* 24 female and 6 male patients Age range: 23 to 73 years * 18 patients from Cohort 1 participated in Cohort 2
MK-7264-012 (referred to as P012, for dose ranging) 2 countries (US, UK)	Multicenter, randomized, double-blind, placebo-controlled study Duration of treatment: 12 weeks Population: RCC/UCC	MK-7264 7.5 mg BID: 64 randomized/63 treated/56 completed MK-7264 20 mg BID: 63 randomized/63 treated/58 completed MK-7264 50 mg BID: 63 randomized/63 treated/50 completed Placebo: 63 randomized/63 treated/58 completed	N=252 192 female and 60 male patients Age range: 22 to 79 years

Study Number Number of Countries	Design Population	Number of Patients by Intervention Group	Study Population Treated (N)
MK-7264-021 (referred to as P021 for dose escalation) 1 country (US)	Multicenter, randomized, parallel-group, double-blind, placebo-controlled study Study P021 was an extension to Study P010; all patients in Study P021 were previously enrolled in Study P010. Duration of treatment: 8 weeks Population: RCC	MK-7264 15 mg BID: 8 randomized/8 treated/7 completed MK-7264 30 mg BID: 6 randomized/5 treated/5 completed MK-7264 50 mg BID: 6 randomized/6 treated/5 completed Placebo: 4 randomized/4 treated/4 completed	N=23 20 female and 3 male patients Age range: 41 to 73 years
MK-7264-033 (referred to as P033) 1 country (Japan)	Multicenter, parallel-group, randomized, double-blind, placebo-controlled study Duration of treatment: 4 weeks Population: RCC/UCC	MK-7264 45 mg BID: 11 randomized/11 treated/10 completed Placebo: 12 randomized/12 treated/12 completed	N=23 17 female and 6 male patients Age range: 29 to 77 years
Phase 3 Studies			
MK-7264-027 (referred to as P027, also published as COUGH-1) 17 countries	Multicenter, randomized, double-blind, placebo-controlled study Duration of treatment: 52 weeks The 52-week treatment period consisted of a 12-week Main Study period and a 40-week blinded Extension Study period. Population: RCC/UCC	MK-7264 15 mg BID: 244 randomized/244 treated/187 completed MK-7264 45 mg BID: 244 randomized/243 treated/147 completed Placebo: 244 randomized/243 treated/183 completed	N=730 542 female and 188 male patients Age range: 19 to 89 years
MK-7264-030 (referred to as P030, also published as COUGH-2) 20 countries	Multicenter, randomized, double-blind, placebo-controlled study Duration of treatment: 52 weeks The 52-week treatment period consisted of a 24-week Main Study period and a 28-week blinded Extension Study period. Population: RCC/UCC	MK-7264 15 mg BID: 442 randomized/440 treated/327 completed MK-7264 45 mg BID: 439 randomized/439 treated/283 completed Placebo: 436 randomized/435 treated/350 completed	N=1314 984 female and 330 male patients Age range: 19 to 88 years

Study Number Number of Countries	Design Population	Number of Patients by Intervention Group	Study Population Treated (N)
MK-7264-042 (referred to as P042, for RCC/UCC and with C-SUI) 12 countries	Multicenter, randomized, double-blind, placebo-controlled study Duration of treatment: 12 weeks Population: RCC/UCC and with C-SUI	MK-7264 45 mg BID: 186 randomized/185 treated/176 completed Placebo: 190 randomized/190 treated/184 completed	N = 375 375 female patients Age range: 22 to 83 years
MK-7264-043 (referred to as P043, for recent-onset chronic cough) 12 countries	Multicenter, randomized, double-blind, placebo-controlled, parallel-group study Duration of treatment: 12 weeks Population: Recent onset (<12 months) RCC/UCC	MK-7264 45 mg BID: 208 randomized/206 treated/192 completed Placebo: 211 randomized/209 treated/201 completed	N=415 268 female and 147 male patients Age range: 18 to 83 years

BID=twice daily; C-SUI=cough-induced stress urinary incontinence; MK-7264=gefapixant; RCC=refractory chronic cough; UCC=unexplained chronic cough.

[1] In the Phase 2 program, the effect of gefapixant was also assessed in the following cough populations: acute cough in patients with viral-induced upper respiratory tract infection (P013), cough reflex sensitivity (P014 and P015), and idiopathic pulmonary fibrosis (P016 and P019).

2.4 Regulatory Guidance and Advice

Prospective regulatory guidance over the course of the clinical development program supporting the proposed indication was obtained from regulatory agencies including FDA. Gefapixant has been approved for the treatment of RCC/UCC in the following countries:

Country	Approval Date
Japan	20-JAN-2022
Switzerland	24-MAY-2022
European Union	18-SEP-2023

2.4.1 End-of-Phase 2 (EOP2) Discussion

At the EOP2 meeting (19-JUN-2017), FDA provided guidance on the Phase 3 study designs (including efficacy and safety endpoints, duration of the main study period to evaluate efficacy, and pooling of data for integrated summaries of efficacy and safety). Specifically, FDA agreed with Merck's proposal to use change from baseline in the 24-hour cough frequency as the primary endpoint in both studies, as measured using the VitaloJAK™ recording device, which is 510(k) cleared by FDA. At the EOP2 (and a follow-up meeting), FDA also agreed this primary endpoint could be supported by PROs and additional measures as secondary/exploratory endpoints. Results from a validation study of the compression algorithm and an evaluation of the IRR of cough analysts were submitted as part of the EOP2 briefing document.

The study design initially proposed for Study P030 and reviewed by FDA was similar to that of Study P027; however, based on guidance received during discussions with FDA, the duration of the main study period for Study P030 was increased from 12 to 24 weeks to assess the durability of the treatment effect with the primary endpoint at 24 weeks. After discussion with EMA, the LCQ was moved up to become a key secondary endpoint (in the multiplicity testing hierarchy) to support the clinical relevance of the reduction in cough frequency, and the sample size in Study P030 was increased to provide sufficient power for the LCQ responder endpoint analysis. The original Phase 3 protocols (P027 and P030), including the SAPs, were submitted to FDA on 01-NOV-2017 and 02-NOV-2017, respectively.

2.4.2 Pre-NDA Meeting

On 01-JUL-2020, FDA provided written feedback on the proposed submission dossier for gefapixant. The FDA noted that the clinical development program appeared adequate to support filing of an NDA for the 45 mg dose of gefapixant for the proposed indication "treatment of refractory or unexplained chronic cough"; however, recommended inclusion of data from the entire 52 weeks' study period. These data were included in the submission filed on 21-DEC-2021.

2.4.3 Complete Response Letter

On 20-JAN-2022, FDA issued a CRL to the submitted NDA. The deficiencies listed in the CRL included: 1) the validation of the compression algorithm used to remove noncough data from cough recordings; and 2) the inter-rater reliability of the trained cough analysts. Specifically, FDA noted "While the 45 mg dose in both of your Phase 3 studies met the primary endpoint of cough frequency reduction compared with placebo, there are insufficient validation data to support that the VitaloJAK™ cough counting system accurately and reliably assesses cough frequency." FDA also expressed concerns regarding the content validity of the LCQ patient-reported outcome measure because it could not be confirmed that patients with RCC/UCC were involved in the original development of the measure.

2.4.4 Post-CRL Correspondence

Subsequent discussions were held between FDA and Merck to reach alignment on addressing the deficiency outlined by FDA in the CRL.

On 07-MAR-2022, a meeting was held between the FDA and Merck following the CRL to discuss the proposed designs of the new validation study and the new IRR study. The agency recommended that the Phase 3 recordings should be recompressed and recounted using the methods to be validated in the new validation and IRR studies. Regarding the LCQ, FDA requested detailed information on the patient population included in the original development of the measure and the relevance of the items to patients with RCC/UCC; FDA indicated that without this information, it would be difficult to fully evaluate the content validity of this instrument.

In response to FDA's comments at the initial meeting, Merck requested a follow-up meeting, which was held on 12-JUL-2022. At this meeting, Merck discussed its revised proposals for the validation study and IRR study, as well as FDA's recommendation to perform recompression, recounting and posthoc analyses for the Phase 3 cough frequency data that had not originally been compressed with the method assessed in the new validation study. Plans for further assessing the content validity of the LCQ (by conducting qualitative interviews with patients who have RCC/UCC) were also discussed. Overall, FDA provided input and general agreement to Merck's proposals.

3 CLINICAL PHARMACOLOGY

A comprehensive clinical pharmacology program was completed to characterize the initial safety, tolerability, and PK of gefapixant. The clinical pharmacology program consisted of 18 studies, a population-PK analysis that integrated data from Phase 1, 2, and 3, and exposure-response analyses of efficacy and safety. Gefapixant was generally well tolerated in healthy participants, has low potential to be a victim or perpetrator of drug-drug interactions, and exhibits PK that supports BID dosing without regard to food. Gefapixant is primarily cleared through renal elimination, and renal function was identified as a predictor of

gefapixant PK. Otherwise, no clinically meaningful changes in gefapixant PK based upon intrinsic factors (ie, weight, age, gender, race) have been observed.

3.1 Human Pharmacokinetics

In Phase 1 trials, single oral doses ranging from 10 mg to 1800 mg and multiple oral doses ranging from 15 mg to 3600 mg daily (1800 mg BID for up to 2 weeks) were evaluated, corresponding to a plasma $AUC_{0\text{-}12,ss}$ up to 18-fold greater than the mean predicted exposure for the 45-mg BID dose.

Absorption

Following oral administration, absorption of gefapixant is relatively rapid with median peak plasma concentrations achieved at 1.0 to 4.0 hours. Food or coadministration with PPIs does not have a meaningful effect on gefapixant PK; therefore, gefapixant may be administered without regard to meals or concomitant use of acid-reducing agents.

Distribution

Gefapixant is widely distributed, with a volume of distribution of 137.8 L following oral administration. In vitro, the unbound fraction of gefapixant in human plasma is 0.45, and the protein-bound fraction is mainly bound to serum albumin. Gefapixant is a substrate of P-glycoprotein and BCRP transporters; therefore, gefapixant is expected to have very low CNS penetration in humans.

Metabolism

Metabolism is a minor pathway of gefapixant elimination, with approximately 12% and 2% of the dose recovered as metabolites in urine and feces, respectively [21].

Excretion

Gefapixant is primarily eliminated via renal excretion of intact gefapixant. Following a single oral [^{14}C]gefapixant dose, approximately 76% (64% as parent and 12% as metabolites) of the administered oral dose was recovered in urine. In feces, 20% and 2% of the dose were recovered as parent and metabolites, respectively [21]. Renal elimination involves active tubular secretion in addition to filtration. Gefapixant is an in vitro substrate of MATE1 and MATE2K, P-glycoprotein, and BCRP transporters. Active renal secretion of gefapixant is estimated to account for no more than 50% of the total plasma clearance. The mean terminal $t_{1/2}$ for gefapixant is 6 to 10 hours.

Linearity/Dose-Proportionality

In healthy participants, gefapixant exposure increased in a dose-proportional manner after single oral doses up to 450 mg and multiple oral doses up to 300 mg BID. The systemic PK

of gefapixant following multiple-dose administration were consistent with those following single-dose administration, indicating time-independent PK. Steady state is achieved within approximately 2 to 3 days of BID dosing, with an accumulation ratio of approximately 1.4- to 1.5-fold in the clinical dose range of 7.5 to 50 mg BID.

3.2 Intrinsic Factors and Special Populations

The gefapixant clinical dose of 45 mg BID can be used in patients from a broad demographic background. The integrated population-PK analysis assessed potential covariate effects on PK variability and specifically, to determine any relevant effects of age, gender, weight, race, or renal impairment on exposure [22]. The magnitude of the effect of age, gender, weight, and race on gefapixant PK were less than 20% and not clinically relevant. Based on these data, the dose of 45 mg BID may be used in patients with RCC/UCC from a broad demographic background with respect to these intrinsic factors.

Although an increase in gefapixant exposure is expected in patients with mild and moderate renal impairment, these are anticipated to be within 1.5-fold relative to patients with normal renal function and therefore would not require a dose adjustment. By comparison, the corresponding AUC increase in patients with severe RI, relative to patients with normal renal function, is predicted to be 1.89-fold [22]. An adjustment in the dosage regimen is recommended to achieve exposures within those observed in the Phase 3 trials and to limit unnecessary taste-related AEs: Following 45 mg QD dosing, the steady state C_{max} and AUC in patients with severe RI are comparable to those following 45 mg BID dosing in patients with normal renal function.

3.3 Extrinsic Factors: Drug-Drug Interactions

In vitro and clinical data indicate that there is low potential for gefapixant to be a victim or perpetrator of DDIs. Based on in vitro data, 2 DDI trials were conducted to test the potential of gefapixant as a victim or a perpetrator of drug interactions.

In a DDI trial conducted with pyrimethamine, an inhibitor of the MATE1 and MATE2K transporters, coadministration resulted in an approximately 1.24-fold increase in AUC, 30% decrease in gefapixant renal clearance, and no change in C_{max} of gefapixant [23]. The 24% increase in AUC is not considered clinically relevant, and no dose adjustment is required when gefapixant is coadministered with MATE1/2K inhibitors.

In a DDI trial conducted with pitavastatin, a probe substrate of the OATP1B1 transporter, coadministration did not significantly alter pitavastatin exposure, and no dose adjustment is required when gefapixant is coadministered with OATP1B substrates [24].

4 CLINICAL DEVELOPMENT PROGRAM

4.1 Overview of Efficacy

Initial efficacy data for gefapixant in patients with RCC/UCC were generated in 3 Phase 2 studies: Study P006 (proof of concept), Study P010 (dose escalation), and Study P012 (dose ranging). Results across these studies consistently showed dose-related reductions in objective cough frequency in the gefapixant groups, compared with the placebo groups.

Results from the individual Phase 3 studies (P027 and P030) and from the dataset that pooled both studies (hereafter, P027/P030 Pool) are summarized in this briefing document to support the evaluation of efficacy of gefapixant in adult patients with RCC/UCC at a dose of 45 mg BID. Phase 3 results consistently showed reductions in cough in the gefapixant 45 mg BID group, compared with placebo, as measured by objective cough frequencies. In addition, improvements in objective cough frequencies were clinically relevant, as supported by associated improvements in cough-specific PRO endpoints. Taken together, the Phase 3 data support that gefapixant is consistently effective in reducing cough frequency, patient-reported cough severity, and the impact of cough on important aspects of HRQoL (physical, social, and psychological function).

In addition, 2 Phase 3b studies (P043 and P042) have now been completed that add to the body of efficacy data of gefapixant. The endpoints for these studies were PROs and did not include cough frequency. Study P043 assessed gefapixant in adults with RCC/UCC of less than 12 months duration (considered “recent onset chronic cough” relative to Studies P027 and P030). Study P042 assessed gefapixant in women with RCC/UCC and with C-SUI. Both studies met the success criteria for their primary endpoints and provide supportive evidence of efficacy.

4.1.1 Methods and Validation

4.1.1.1 Objective Endpoints

In Phase 2 and Phase 3 studies, the primary (and secondary) endpoints were based on objective measurements of cough frequency using the VitaloJAK™ cough counting system.

4.1.1.1.1 Description of the Cough Counting System

The VitaloJAK™ cough counting system is the most commonly used cough counting system in academic and clinical studies. Merck used this system as a research tool in the clinical studies; this system is not being used (or developed) to diagnose, cure, mitigate, treat, or prevent disease. Characterizing chronic cough has traditionally been difficult; the VitaloJAK™ system provides an objective tool to measure cough frequencies [25].

The VitaloJAK™ cough counting system includes 3 steps: 1) Record the patient’s cough sounds, as a 24-hour digital audio recording; 2) Compress the recording, which shortens the

duration of the 24-hour recording by removing periods of silence and noncough sounds; 3) Count the coughs: a human analyst reviews the compressed recording and counts the coughs. These steps are explained in more detail below and summarized in [Table 2].

Step 1: The cough counting process begins with the VitaloJAK™ device, a wearable digital audio recorder that is FDA 510(k) cleared to record (cough) sounds. Sound is recorded via 2 audio input channels: a sensor is adhered to the patient's chest wall (onto the sternum) and a microphone is attached to clothing on the front of the patient's chest (eg, onto a lapel). The device records sound for a 24-hour period.

Step 2: After the recording is uploaded to a web portal, the quality of the recording is evaluated to assess if it is suitable for compression. For example, a recording with too much background noise may not be of sufficient quality to be compressed. If the raw recording is deemed suitable, a compression algorithm is used to remove periods of silence and noncough sounds from the recording. This reduces the duration of the recording that must be assessed by the human analyst. [Figure 1] shows an example of areas that are compressed (removed) from a recording. Compressing the 24-hour recordings makes cough counting operationally feasible; ie, enabling analysis of thousands of individual 24-hour recordings.

There are 2 methods of compression [Table 2]: "dual-channel" compression, where the algorithm is applied to the audio input from both the chest wall sensor and the lapel microphone; and "single-channel" compression, where the algorithm is applied to the audio input from the chest wall sensor only. However, if the recording overall is not of sufficient quality to be compressed, then cough analysts must assess the full uncompressed 24-hour recording.

Step 3: To count the coughs in the compressed recording (or the raw recording if quality was insufficient for compression), a blinded cough analyst (also referred to as a rater), who is trained and qualified to count coughs, marks the cough while listening to the cough sounds and viewing the sound waveforms on a computer screen. The marked coughs are then tallied to obtain the total number of coughs in the recording.

Figure 1
Sound Waveform From a Recording and Example of What Compression Removes

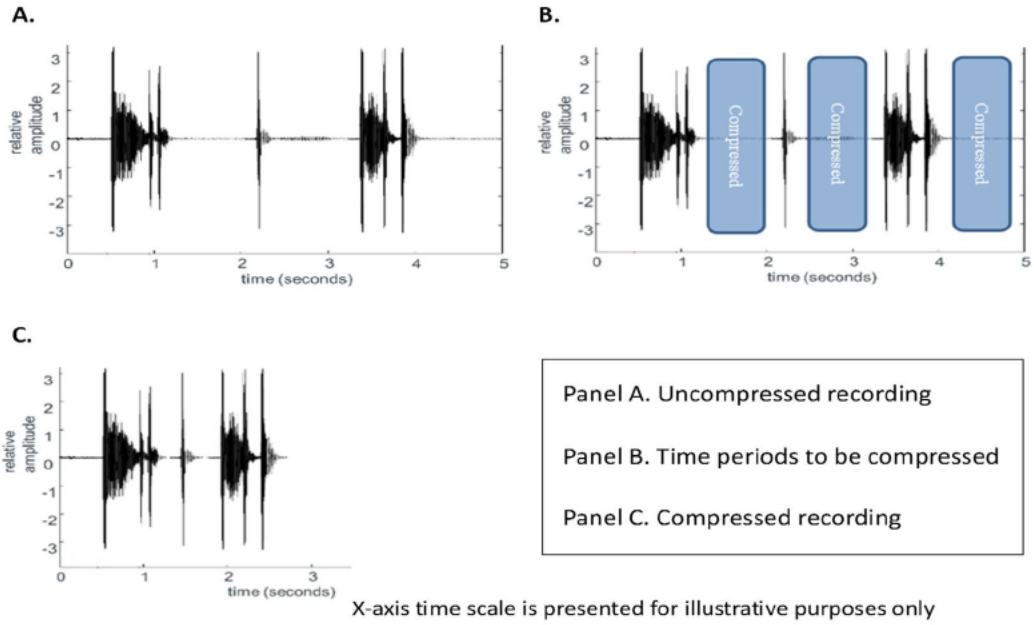


Table 2
Summary of Steps Used to Count Coughs

	Step 1: Record	Step 2: Compress	Step 3: Count
Dual-channel Compression			
Audio Input	Chest wall and lapel	Chest wall and lapel (ie, dual-channel)	Chest wall and lapel
Action	Device records audio file and waveforms from both inputs.	These algorithms[1,2] use both inputs for removing periods of silence and noncough sounds[3].	Analysts review the audio and waveforms from both inputs to count the coughs.
Single-channel Compression			
Audio Input	Chest wall and lapel	Chest wall only (ie, single-channel)	Chest wall and lapel
Action	Device records audio file and waveforms from both inputs.	The algorithm[2] uses input from the chest wall sensor only, for removing periods of silence and noncough sounds[3]. After compression, audio inputs are recombined keeping only the compressed time periods.	Analysts review the audio and waveforms from both inputs to count the coughs.

[1] WH03 version 2.0 – This algorithm version was written to use dual-channel inputs.
[2] WH03 version 3.0 – This later algorithm version enabled the use of dual- or single-channel inputs.
[3] If the raw recording was not of sufficient quality to be compressed, the cough analysts assessed the full, uncompressed, 24-hour recording.

4.1.1.1.2 Evaluation of the Cough Counting System – Validation and Results

4.1.1.1.2.1 Prior to Finalizing the Phase 3 Protocols

As the FDA 510(k) clearance of the VitaloJAK™ cough counting system covered only the recording device and web portal, studies were performed to assess the performance of the compression algorithm and to assess the reliability of having multiple cough analysts. As part of the briefing document for the EOP2 meeting, results from a compression validation study and an IRR study of cough analysts were provided to the FDA [Sec. 2.4.1].

- Validation study: The WH03 version 2.0 algorithm was tested (using dual-channel compression) to assess its sensitivity, defined as the proportion of cough sounds in the uncompressed recording that were retained after compression (only uncompressed recordings were counted). For the 24-hour recordings that were assessed from 60 chronic cough patients, median sensitivity was 99.7% (IQR 99.04% to 100%).
- IRR study: The reliability of cough analysts was assessed separately for compressed and uncompressed recordings. The intraclass correlation coefficients for both intra- and inter-rater reliability exceeded 0.99, indicating excellent agreement both within cough analysts over time and between cough analysts [26].

4.1.1.1.2.2 After the Original NDA Submission

Validation Studies and Results to Address CRL

The FDA issued a CRL that expressed concerns regarding the existing validation and IRR studies; therefore, additional analyses (new validation and IRR studies) were conducted, using cough recordings from patients in Studies P027 and P030, to assess: the validity of the compression (using single-channel compression applied to all compressed recordings) and the reliability of cough counts from multiple cough analysts. Details of the designs of these studies are:

- New validation study: The WH03 version 3.0 algorithm was evaluated (using single-channel compression). Through an end-to-end evaluation of the cough counting process (ie, different analysts counted coughs on compressed and uncompressed formats of 66 recordings selected randomly from the P027 and P030 trials), the study demonstrated that compression does not introduce a systematic bias when comparing cough frequencies before versus after compression. The mean of the differences between compressed and uncompressed cough frequencies was small (<0.2 coughs/hour, noting that mean cough frequency of uncompressed recordings in the validation study sample was 28.5 coughs/hour).
    - When a difference was noted, this was observed at low cough frequencies and usually due to minor variations in how the coughs were counted by the analysts, not due to the compression process.

- New IRR study: Using a complete block design with a 4-week washout period, cough analysts were randomly assigned the same recordings in compressed or uncompressed format. Results of the study showed that the participation of multiple cough analysts (n=5) to count coughs, on compressed or uncompressed recordings (n=20), does not impact the reliability of cough frequencies. The p-value for the likelihood ratio test was 0.7966, indicating that the variation among cough analysts was not statistically different from 0. The level of variation among the cough analysts met the study's prespecified criterion of success, indicating that the analysts' cough counts are reliable.

4.1.1.2 Patient-reported Outcomes

4.1.1.2.1 Description of Patient-reported Outcome Measures

Cough-specific PRO measures provide clinical information not assessed by measures of objective cough frequency [15]. The Phase 3 studies therefore included PRO measures to assess the impact of cough and reduced cough frequency from the patient's perspective, to support the primary endpoint and the overall assessment of efficacy. Cough assessment tools can complement one another by measuring distinct yet related aspects of the impact of cough.

- The LCQ is a validated PRO that measures the impact of cough on patients' daily lives by assessing physical, social, and psychological domains of cough-specific HRQoL [5].
- The CSD is a validated PRO measures cough severity in domains of self-rated cough frequency, cough intensity, and cough-related disruption to sleep and activities [27].
- The Cough Severity VAS is a validated, single-item PRO that measures self-rated cough severity [28].
- The PGIC is a commonly used PRO that provides an easily interpretable self-rating of the overall change in cough.
- The incontinence diary captures episodes of urinary incontinence occurring throughout each day of data collection.

Leicester Cough Questionnaire

The LCQ is a 19-item cough-specific questionnaire that has been validated to assess the most important impacts of chronic cough across 3 relevant domains of HRQoL (physical, social, and psychological). Each item of the LCQ assesses symptoms or the impact of symptoms on patients over the 2 weeks prior to assessment using a 7-point Likert scale. Mean individual domain scores, ranging from 1 to 7, are used to calculate the LCQ total score, ranging from 3 to 21. The LCQ total score was intended to be the primary metric to reflect the most relevant and important impacts of cough on patients, with higher scores reflecting less impact. Based on published data from the LCQ instrument developer, an increase of ≥1.3 points in the LCQ total score is considered a clinically meaningful improvement for defining LCQ responders [5].

In the Phase 3 program, Study P030 was designed and powered to assess the efficacy of gefapixant to reduce the impact of RCC/UCC on relevant aspects of cough-specific HRQoL, as measured by the LCQ total score. The proportion of patients defined as an LCQ responder at Week 24 was positioned as a key secondary endpoint in the step-down procedure for multiplicity adjustment in Study P030.

During review of the original submission, FDA expressed concerns about the LCQ because it could not be confirmed that patients with RCC/UCC were involved in the original development of the measure. After the CRL, Merck conducted a qualitative concept-elicitation and cognitive-debriefing study in patients with RCC/UCC as defined in the Phase 3 studies. Results of these interviews confirmed: the most important impacts of RCC/UCC are captured within the physical, social, and psychological domains; no major concepts are missing from the LCQ; and the response options are appropriate and relevant. Based on these data, Merck considers the LCQ to be a content-valid, fit-for-purpose instrument to assess the impact of RCC/UCC on the physical, social, and psychological domains of HRQoL as assessed by the LCQ total score.

Cough Severity Diary

CSD is a validated 7-item, disease-specific PRO instrument completed daily and intended to assess the frequency (3 items), intensity (2 items), and disruptiveness (2 items) of cough; each item is rated on an 11-point numeric rating scale (0 to 10 points), with higher scores indicating greater severity. Mean total daily scores (the sum of 7 item scores divided by 7) were derived for each day; the mean weekly CSD total score is defined as the average of the mean total daily scores for each successive week of the study. Changes of ≥1.3-points (on the 0 to 10-point scale) [27] and ≥2.7-points (an additional threshold requested by the FDA), were used to define clinically meaningful reductions from baseline in mean weekly CSD total scores. Therefore, both thresholds were prespecified in the CSD responder analyses.

Cough Severity VAS

Cough Severity VAS is a single-item PRO instrument completed each evening, asking the patient 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. The mean weekly VAS score is defined as the average of the daily scores for each successive week of the study. Psychometric analyses (using data from Study P012) yielded an estimate for a meaningful change in the Cough Severity VAS as a reduction from baseline of ≥30 mm [28].

Patient Global Impression of Change (PGIC)

The PGIC is a single-item PRO measure asking patients to rate the change in their chronic cough compared with the start of the study. The measure included a 7-point rating scale with response options ranging from “very much improved” to “very much worse”.

Incontinence Diary

For Study P042, an event-driven diary was used to capture episodes of urinary incontinence ("urine leak") occurring throughout each day of data collection. Patients recorded all episodes of incontinence in an electronic diary for 7 days prior to each study visit. For each incontinence episode, the patient recorded the main cause of the episode: "Coughing", "Another stress reason", or "Other cause". Incontinence episodes reported with the main cause as "Coughing" were counted as cough-induced incontinence episodes; these were the episodes counted for the analyses of the primary endpoint of the study, reduction in episodes per day of C-SUI (as percent change from baseline).

4.1.1.2.2 After the Original NDA Submission

LCQ Qualitative Study Results

To answer questions raised by FDA as part of the CRL regarding content validity of the LCQ, Merck conducted a qualitative interview study, with 2 parts (concept elicitation and cognitive debriefing), of the LCQ in the RCC/UCC population. Patients (20 adults) with a clinical diagnosis of RCC/UCC were recruited from 2 clinical sites in the US.

Results of the 2-part qualitative study with 20 adult patients confirmed that the LCQ is valid for use in the RCC/UCC population.

- Concept elicitation: Individual virtual interviews were conducted with the patients. Experienced researchers used semistructured interview guides that included open-ended questions to elicit a comprehensive set of impacts associated with RCC/UCC. Data collected in this phase were highly consistent, and saturation, defined as the point at which no new information is gleaned from qualitative interviews, was reached.

  Results from this part of the study indicate that the most bothersome/important aspects of cough that were reported by the patients are assessed by the various items in the LCQ, and these aspects span all 3 domains (physical, social, and psychological) of the LCQ. The most bothersome/important aspects of cough (including chest pain, embarrassment, stigma, perceived annoyance to others, anxiety, and lack of control) were consistently reported as negatively impacting patients' abilities to interact with others, to complete daily tasks and activities, and to function normally.

- Cognitive debriefing: Patients were asked to provide their overall thoughts regarding each individual item of the LCQ, including overall relevance of the items and ability to complete the measure. All patients indicated that the measure and response options are appropriate and that it assesses the impacts most salient to their experiences with RCC/UCC.

All patients indicated that a reduction in cough frequency or cessation of cough is the most important treatment target and that a reduction in cough frequency would reduce the

significant negative impact of cough on their QoL as assessed by the LCQ total score. This study confirms the content validity of the LCQ in adults with RCC/UCC and that it is fit for the purpose of assessing the impact of cough across all 3 domains (physical, social, and psychological) of HRQoL in this patient population.

4.1.1.3 Efficacy Analyses and Statistical Methods

4.1.1.3.1 Cough Datasets Analyzed

Original dataset (used for the prespecified analyses): The original dataset was comprised of the coughs counted before database lock using both single- and dual-channel compression. The cough frequencies that comprise the original dataset were counted by blinded analysts before unblinding each Phase 3 study. In this dataset, the raw cough recordings were compressed, during the course of the pivotal studies, using dual-channel and single-channel compression: most of the raw recordings in the original dataset were compressed using dual-channel compression (92.8%), some were compressed using single-channel compression (4.0%), and a small percentage was unsuitable for compression (3.2%).

At the start of the Phase 3 program, only dual-channel compression was available, single-channel compression was added during the conduct of the Phase 3 studies. Following the CRL, Merck validated and applied only the single-channel method of compression. All compression and cough counting were done in a double-blind manner regardless of compression mechanism before unblinding the primary Phase 3 study results.

Recount dataset (used for posthoc supportive analyses): After the pivotal studies were completed and in response to the CRL, single-channel compression using the chest wall sensor was selected for the new validation study, as the chest wall sensor records fewer ambient sounds. After the new validation study was completed, single-channel compression was applied, as a single method, across all compressed recordings in Studies P027 and P030. These recordings were recounted by blinded analysts for the posthoc analyses. In the recount dataset, most raw recordings were compressed using single-channel compression (96.8%) and a small percentage remained uncompressed (3.2%) for this dataset.

4.1.1.3.2 Studies P027 and P030

For Studies P027 and P030, the primary efficacy endpoint was 24-hour cough frequency at Week 12 (Study P027) or Week 24 (Study P030).

The key secondary endpoints included awake cough frequency at the timepoint of the primary analysis, proportion of patients with a ≥1.3-point increase from baseline in LCQ total score at Week 24 (Study P030 only), and proportion of patients with a ≥30% reduction from baseline in 24-hour cough frequency at the timepoint of primary analysis.

Primary endpoint analysis:

Analyses were performed on log-transformed data (due to the known right-skewed distribution of cough frequency data) using a longitudinal ANCOVA method. The model included covariates of treatment, visit, treatment-by-visit interaction, gender, region, the log-transformed baseline value, and the log-transformed baseline value-by-visit interaction. An unstructured covariance matrix was used to model the correlation among repeated measurements. This analysis method is also referred to as a mixed-model repeated measures (MMRM) method. The model-estimated geometric mean ratios of post-baseline over baseline were reported for each treatment group, as well as the relative reductions (defined as differences in geometric mean ratios as a percentage of the placebo geometric mean ratio) between the gefapixant group and the placebo group.

Dataset: The prespecified analyses (using longitudinal ANCOVA) for Studies P027 and P030 were conducted on the original dataset.

Missing data: The prespecified longitudinal ANCOVA model for the evaluation of the primary efficacy endpoint was conducted on the Full Analysis Set [FAS] population and required a baseline value and at least one post-baseline value; thus imputation of missing data was not required for the primary analysis.

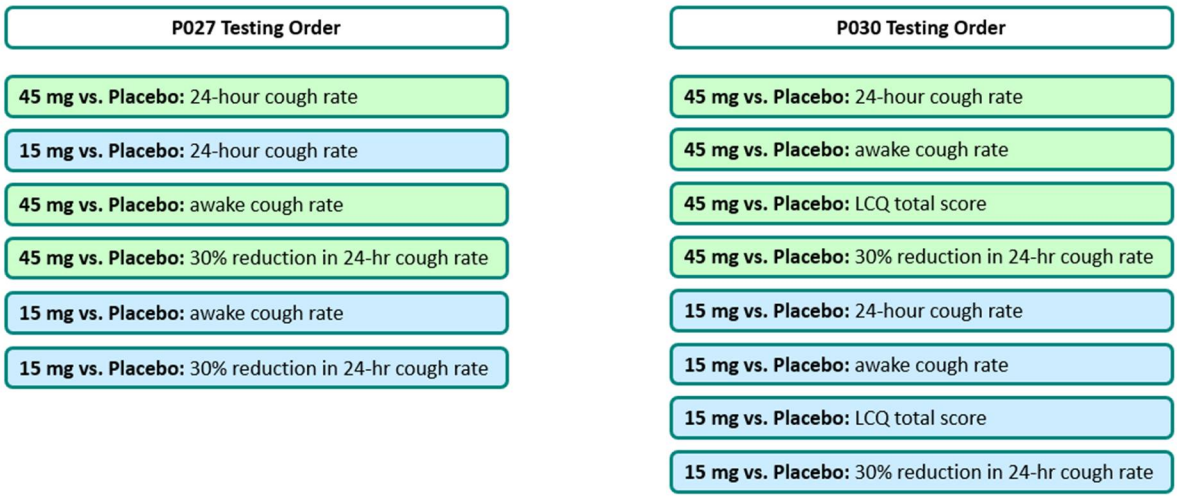
Sensitivity analyses: To further characterize the robustness of the primary efficacy results, tipping point analysis, and jump to reference multiple imputations were conducted as sensitivity analyses.

Key secondary endpoint analysis:

The awake cough frequency was analyzed using the same method as for the 24-hour cough frequency. The binary endpoints of LCQ response and ≥30% reduction in 24-hour cough frequency were analyzed using a logistic regression model, which included covariates for treatment, visit, the interaction of treatment-by-visit, gender, region, baseline of the underlying continuous response, and the interaction of baseline of the underlying continuous response by visit. The logistic regression model handled missing data, for patients who had a baseline value and at least one post-baseline value, through the likelihood function of all the observed data, where imputation of missing data is not required. In addition, the binary endpoints were also analyzed by the Miettinen and Nurminen (M&N) method stratified by gender and region, which imputed the missing data as nonresponders.

Multiplicity: The primary and key secondary efficacy endpoints for both doses in each study were tested using a prespecified fixed sequence to strictly control the Type I error (2-sided $\alpha = 0.0499$, adjusted using Haybittle-Peto rule for an interim analysis of futility). For both studies, the hypothesis testing started by comparing gefapixant 45 mg BID with placebo on 24-hour cough frequency (rate), then stepped down to test the next hypotheses in the sequence if the previous testing is significant. Details are presented in [Figure 2].

Figure 2
Multiplicity Strategy With Sequential Step-down Testing in P027 and P030



4.1.1.3.3 P027/P030 Pool

In the P027/P030 Pool, the clinical efficacy of gefapixant was evaluated through estimation of efficacy outcomes, including 24-hour cough frequency, awake cough frequency, proportion of patients with a ≥30% reduction from baseline in 24-hour cough frequency, and analyses of patient self-rated cough-specific HRQoL and cough severity endpoints (LCQ, CSD, and Cough Severity VAS scores). Efficacy analyses of objective cough endpoints in the P027/P030 Pool were provided for Week 12, the timepoint up to which cough data were available from both studies. Analyses of cough-specific HRQoL and cough severity endpoints were provided for Week 12 and Week 24.

The prespecified analyses (longitudinal ANCOVA) for the P027/P030 Pool were conducted on the original dataset for the objective cough frequencies. Analysis models for the P027/P030 Pool were consistent with the models for Studies P027 and P030, except that "trial" was added as an additional covariate. Point estimates for treatment differences and 2-sided 95% CI were provided. There was no adjustment for multiplicity, since there was no hypothesis testing for the pooled data.

The pooled efficacy data, including 24-hour cough frequency, awake cough frequency, and LCQ total scores, were analyzed in subgroups similar to those for the individual studies, using the same analysis approach for the overall population of the P027/P030 Pool.

Subgroup analyses: To further evaluate the effect of gefapixant to reduce 24-hour cough frequency, subgroup analyses were performed for baseline characteristics including but not limited to: gender, region (North America, Europe, Asia-Pacific, others), duration of cough (<10 years, ≥10 years), and baseline mean weekly Cough Severity VAS (<60 mm, ≥60 mm).

4.1.1.3.4 Additional Analyses

In addition to the prespecified analyses for Studies P027, P030, and the P027/P030 Pool, the following post hoc analyses were conducted to further explore the efficacy of gefapixant:

- Analyses of LCQ, Cough Severity VAS, and CSD data at Week 52 to further characterize persistence of efficacy.
- Summary of LCQ domain scores (physical, social, and psychological) over 52 weeks to further evaluate the contribution of individual domains to the LCQ total score.

4.1.1.3.5 Analyses in Response to the CRL

Posthoc Analyses of Objective Cough Frequency

In response to FDA's recommendations (and after unblinding), all originally dual-channel compressed cough recordings from the pivotal Phase 3 studies were recompressed using single-channel compression and then recounted by blinded cough analysts. Two different posthoc analyses were conducted using the recount dataset of cough frequencies as requested by regulatory authorities:

- Longitudinal ANCOVA: FDA requested this analysis method (which can also be called MMRM) on the recount dataset, as had been prespecified on the original dataset.
- MI+ANCOVA: EMA requested this analysis method for the original and recount datasets. In the MI+ANCOVA method, there is a single imputation for missing baseline values based on the stratification factors of gender and region (and within the same trial, for the pooled analyses only); multiple imputations are performed for the post-baseline values missing from the follow-up visits (m=50 imputed datasets), with covariates of: treatment, gender, region, and follow-up visit (and trial, for pooled analyses only). The ANCOVA model was then applied to the imputed dataset.
    - The MI+ANCOVA analyses included the 8.8% of Study P027 and 5.4% of Study P030 patients who were not included in longitudinal ANCOVA analysis due to missing data. MI+ANCOVA is a statistically valid approach whereby the entire efficacy population is used for characterizing the treatment effect and missing data are imputed based on the characteristics of patients with non-missing data. Therefore, such an analysis may be more informative than one which ignores missing data.
    - The MI+ANCOVA analysis method was applied to the original dataset of cough frequencies from Studies P027 and P030, for inclusion in the gefapixant product labeling in Europe (after EMA review, the European Commission has approved the use of gefapixant in RCC/UCC).

Thus, for these evaluations, the longitudinal ANCOVA analyses and MI+ANCOVA analyses were performed on both the original dataset and the recount dataset. The Efficacy Results section of this document provides all 4 sets of results for each of the cough frequency

endpoints: 24-hour cough frequency and awake cough frequency as prespecified, followed by 3 posthoc supportive analyses.

Posthoc Analyses of LCQ

- At FDA's request, Merck analyzed 2 additional thresholds (≥3.3 and ≥4.1 points) to define responders with a clinically meaningful change from baseline in the LCQ total score for Studies P027, P030, P027/P030 Pool, and for the Phase 3b Study P043.
- At FDA's request, Merck analyzed change from baseline in the LCQ physical domain score for Study P043.

4.1.1.4 Rationale for Dose Selection in Phase 3 Studies

Dose selection for Phase 3 cough studies was based on extensive modeling and simulation across the totality of the Phase 1 and 2 programs, including data from a randomized, placebo-controlled parallel-arm Phase 2b study in patients with RCC/UCC (Study P012) [29]. Based on these quantitative approaches, a low-dose regimen of gefapixant 15 mg BID was predicted to provide a clinically meaningful reduction in cough frequency with minimal incidence of taste-related adverse events and a minimal rate of discontinuations; a high-dose regimen of gefapixant 45 mg BID was predicted to provide maximal reduction in cough frequency, with an acceptable rate of taste-related adverse events and of discontinuations.

4.1.1.5 Relevance and Key Features of the Patient Population

P027/P030 Pool

Studies P027 and P030 were randomized, double-blind, placebo-controlled, parallel-group companion studies of gefapixant 15 mg BID and 45 mg BID in adult patients with RCC/UCC. These studies had identical entry criteria, dosing regimens, and endpoints. The duration of the main study period for Study P027 was 12 weeks; the duration of the main study period for Study P030 was 24 weeks.

A total of 2044 treated patients were evaluated in the P027/P030 Pool and 72.3% completed 52 weeks of study intervention.

Baseline characteristics for patients in Studies P027 and P030 were generally balanced across intervention groups and consistent with the demographics of the patients enrolled in the Phase 2 chronic cough studies (Studies P006, P010, P012). The mean age was 58.4 years, with approximately a third of the patients aged ≥65 years; 74.7% of the patients were female, and 79.6% were white. These demographic results show that patients enrolled in the Phase 3 program were representative of chronic cough patients seeking treatment at specialized cough clinics [10].

Baseline smoking status was similar across intervention groups; approximately 74% of patients never smoked and none were current smokers. The mean body mass index was

28.59 kg/m^2. Additional baseline factors were also generally balanced across intervention groups.

More patients had a primary diagnosis of RCC (61.5%) than UCC (38.5%). Patients had a mean duration of chronic cough of approximately 11 years prior to enrollment. The median 24-hour cough frequency at baseline was similar across the intervention groups (21.46 coughs/hr in the placebo group; 21.31 coughs/hr in the gefapixant 15 mg group; 19.19 coughs/hr in the gefapixant 45 mg group).

Medical history conditions were generally balanced across intervention groups. Patients who were classified as having RCC reported the following comorbid conditions: asthma (40.4%); gastroesophageal reflux disease (40.4%) and gastritis (4.5%); and upper airway conditions, including rhinitis allergic (16.4%), seasonal allergy (10.1%), upper airway cough syndrome (6.1%), and rhinitis (5.6%). The only other frequently reported condition (≥15% of patients) was hypertension (34.4%).

Among the most frequently reported prior medications were for chronic cough or comorbid conditions that may have been associated with chronic cough. These included medications for obstructive airway diseases (70.4%), acid-related disorders (54.7%), nasal preparations (53.1%), systemic antihistamines (35.2%), and cough and cold preparations (34.5%). Other frequently reported prior medications included ophthalmological agents (42.9%), analgesics (42.2%), corticosteroids, dermatological preparations (42.7%), and antidiarrheals, intestinal anti-inflammatory/anti-infective agents (30.1%). Among the most frequently reported medications with concomitant use during the trials were treatments related to chronic cough or to comorbid conditions that may have been associated with chronic cough and included drugs for obstructive airway diseases (58.5%), drugs for acid-related disorders (46.4%), and nasal preparations (43.9%). Other frequently reported concomitant medications were analgesics (52.4%) and ophthalmological agents (50.9%).

Study P043

The Phase 3b Study P043 enrolled patients with recent onset (<12 months) of RCC/UCC and focused on an assessment of cough from the patient's perspective, to evaluate if this population behaves similarly to a population with RCC/UCC for at least 1 year (as enrolled in Studies P027 and P030). Other than the duration of RCC/UCC, the definitions of RCC and UCC were the same in Study P043 as in the Phase 3 studies, as was the Cough Severity VAS inclusion criterion. The PROs used were the same as those used in Studies P027 and P030.

A total of 415 treated patients were evaluated and 89.9% completed 12 weeks of treatment. The majority of patients were female and white; the mean age of patients was 52.5 years and mean duration of chronic cough (>8 weeks) was 7.2 months. Overall, more patients had a diagnosis of RCC (70.8%) than UCC (29.2%).

Study P042

The Phase 3b Study P042 evaluated the efficacy of gefapixant in a patient population with RCC/UCC, consistent with Studies P027 and P030 (including the Cough Severity VAS inclusion criterion), but Study P042 patients also had C-SUI and were all female. A total of 375 treated patients were evaluated and 92.8% completed 12 weeks of treatment. The majority of patients were white, the mean age of patients was 56.4 years. Mean duration of chronic cough was 5.2 years; mean duration of C-SUI was 4.0 years. Overall, more patients had a diagnosis of RCC (77.1%) than UCC (22.9%).

4.1.2 Efficacy Results

Results for the primary and secondary cough frequency endpoints for Studies P027 and P030 are presented for the prespecified analyses (original dataset analyzed by longitudinal ANCOVA) along with results of 3 posthoc supportive analyses:

- Recount dataset analyzed by longitudinal ANCOVA
- Original dataset analyzed by MI+ANCOVA, and
- Recount dataset analyzed by MI+ANCOVA.

Based on the proposed label dose of 45 mg BID, the analyses presented in this section focus on the gefapixant 45 mg BID dose.

In both Studies P027 and P030, the baseline and post-baseline geometric means for cough frequencies in the recount dataset were slightly higher than the geometric means in the original dataset (data not shown). However, the results for the change from baseline using the geometric mean ratios (post-baseline/baseline) remained essentially unchanged across the original and posthoc analyses, as presented in this section.

The results for the primary and secondary endpoints of 24-hour cough frequency and awake cough frequency are presented for the prespecified and 3 posthoc supportive analyses [Sec. 4.1.2.1, 4.1.2.2]. LCQ results, including posthoc LCQ analyses, for Study P030, Study P027, the P027/P030 Pool, and Study P043, are presented in [Sec. 4.1.2.3]. Other PRO results from the P027/P030 Pool, Study P043, and Study P042 are presented in [Sec. 4.1.2.4].

4.1.2.1 Primary Endpoint – 24-Hour Cough Frequency

4.1.2.1.1 Study P027

The prespecified analysis (longitudinal ANCOVA applied to the original dataset) of the primary endpoint at Week 12 showed that gefapixant 45 mg BID reduced 24-hour cough frequency with a reduction relative to placebo of -18.45% (p=0.041) [Table 3, Panel A].

In the prespecified analysis, no statistically significant difference was identified for the gefapixant 15 mg BID group compared with the placebo group (data not shown in [Table 3], but shown in [Figure 3]).

Compared with the prespecified analysis, results of 3 posthoc supportive analyses showed similar cough frequency reductions for gefapixant 45 mg BID vs. placebo:

Longitudinal ANCOVA – recount dataset: Applying the longitudinal ANCOVA analysis to the recount dataset, the geometric mean ratios were consistent with the prespecified analysis, with a cough frequency reduction relative to placebo of -16.96% (nominal p=0.057) [Table 3, Panel B].

MI+ANCOVA – original dataset: Applying the MI+ANCOVA analysis to the original dataset, the geometric mean ratios were similar to the prespecified analysis results. The cough frequency reduction relative to placebo at Week 12 was -18.52% (nominal p=0.036) [Table 3, Panel C]. These results are the basis of the gefapixant approval by the European Commission on 18-SEP-2023.

MI+ANCOVA – recount dataset: Applying the MI+ANCOVA analysis to the recount dataset, the geometric mean ratios were similar to the prespecified analysis. The cough frequency reduction relative to placebo was -17.10% (nominal p=0.049) [Table 3, Panel D].

Cough Frequency Reduction Over Time

Consistent reductions from baseline in cough frequency over 24 hours compared with placebo were observed in the gefapixant 45 mg group from Week 4 through Week 12 in the prespecified analysis (longitudinal ANCOVA applied to the original dataset) [Figure 3] and in the posthoc analysis (MI+ANCOVA applied to the recount dataset) [Figure 4].

Table 3
Analysis of 24-Hour Cough Frequency
Study P027 (Week 12)

	PANEL A (Prespecified Analysis) Original Dataset – Longitudinal ANCOVA				PANEL B (Posthoc Analysis) Recount Dataset – Longitudinal ANCOVA			
	N	Geometric Mean Ratio (Post-Baseline/Baseline)† (95% CI)	Reduction Relative to Placebo (%) (95% CI)	*p*-Value	N	Geometric Mean Ratio (Post-Baseline/Baseline)† (95% CI)	Reduction Relative to Placebo (%) (95% CI)	*p*-Value
Placebo	222	0.47 (0.41, 0.54)			222	0.47 (0.41, 0.54)		
MK-7264 45 mg BID	217	0.38 (0.33, 0.44)	-18.45 (-32.92, -0.86)	0.041	217	0.39 (0.34, 0.45)	-16.96 (-31.45, 0.59)	0.057
	PANEL C (Posthoc Analysis) Original Dataset – MI+ANCOVA				**PANEL D (Posthoc Analysis) Recount Dataset – MI+ANCOVA**			
	N	Geometric Mean Ratio (Post-Baseline/Baseline)†† (95% CI)	Reduction Relative to Placebo (%) (95% CI)	*p*-Value	N	Geometric Mean Ratio (Post-Baseline/Baseline)†† (95% CI)	Reduction Relative to Placebo (%) (95% CI)	*p*-Value
Placebo	243	0.47 (0.40, 0.54)			243	0.46 (0.40, 0.54)		
MK-7264 45 mg BID	243	0.38 (0.33, 0.44)	-18.52 (-32.76, -1.28)	0.036	243	0.38 (0.33, 0.45)	-17.10 (-31.22, -0.06)	0.049

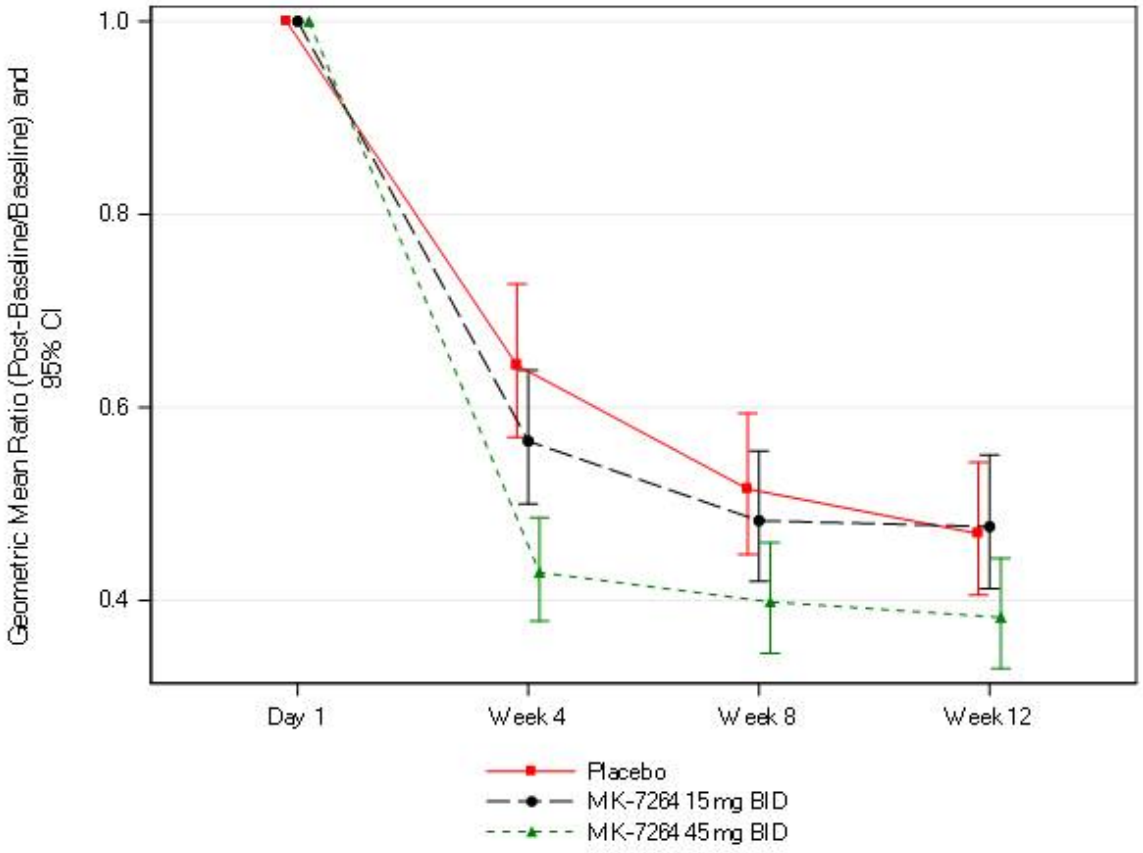
ANCOVA=Analysis of Covariance; CI=confidence interval; MI=multiple imputation; MK-7264=gefapixant; N=number of subjects included in the analysis.

Reduction relative to placebo is calculated: 100 (e^{DIFF} -1) where DIFF is the treatment difference (using the natural-log-transformed data) in change from baseline at Week 12.

†Values are model-based, using the Longitudinal Analysis of Covariance model consisting of the change from baseline in log-transformed 24-hour cough frequency at each post-baseline visit (up to Week 12) as response. The model includes treatment, visit, treatment-by-visit interaction, gender, region, log-transformed baseline value, and log-transformed baseline value-by-visit as covariates. The unstructured covariance matrix is used to model the correlation among repeated measurements.

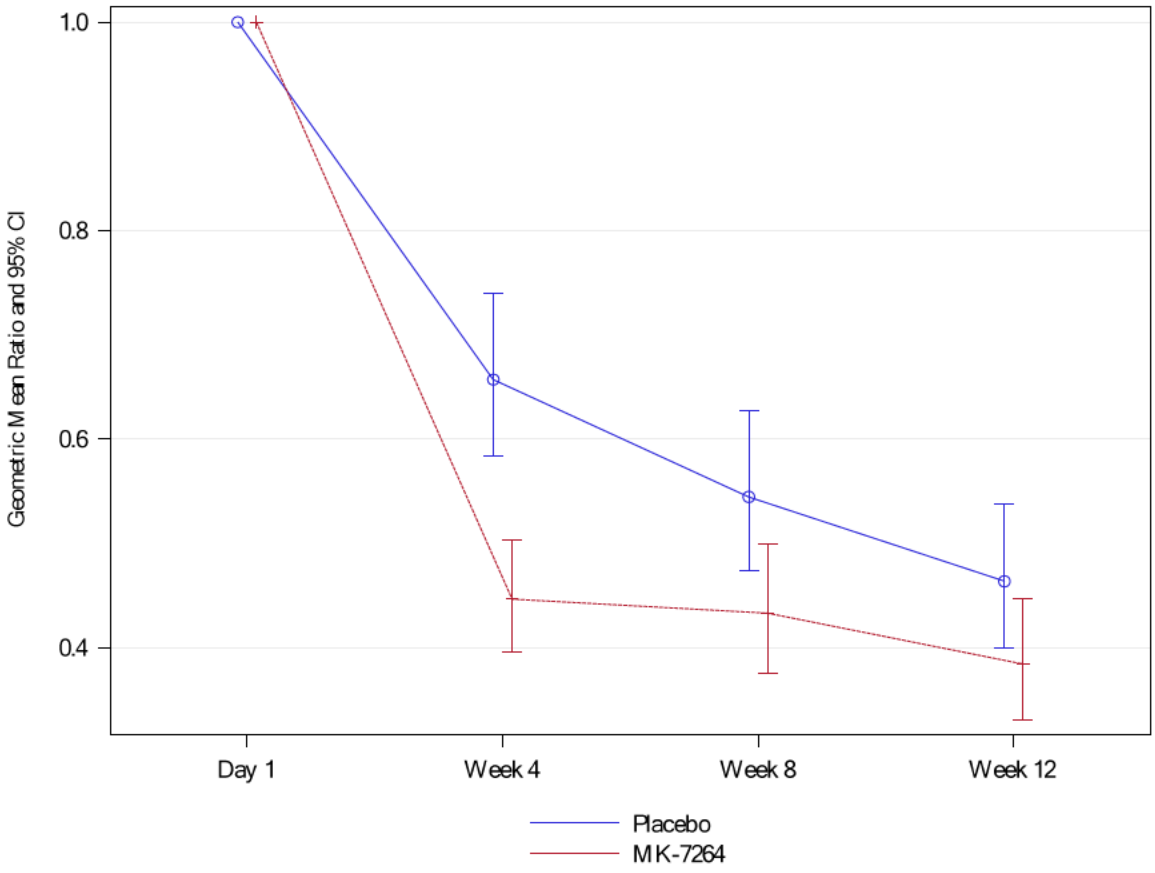
††Values are model-based after Multiple Imputation: Missing baseline values were imputed based on gender and region, followed by multiple imputation of the missing data (m = 50 imputed datasets) for all follow-up visits using treatment arm, gender, region, and the other follow-up visits as covariates. Following imputation, ANCOVA model was conducted at the time point of interest, adjusting for covariates of treatment, baseline, region, and gender.

Figure 3
Analysis of 24-Hour Cough Frequency Over Time for Gefapixant
Study P027
Prespecified Analysis (Original Dataset, Longitudinal ANCOVA)



ANCOVA=Analysis of Covariance; BID=twice daily; CI=confidence interval; MK-7264=gefapixant.

Figure 4
Analysis of 24-Hour Cough Frequency Over Time for Gefapixant 45 mg BID
Study P027
Posthoc Analysis (Recount Dataset, MI+ANCOVA)



ANCOVA=Analysis of Covariance; BID=twice daily; CI=confidence interval; MI=multiple imputation; MK-7264=gefapixant.

4.1.2.1.2 Study P030

The prespecified analysis (longitudinal ANCOVA applied to the original dataset) of the primary endpoint at Week 24 showed that gefapixant 45 mg BID reduced 24-hour cough frequency with a reduction relative to placebo of -14.64% (p=0.031) [Table 4, Panel A].

In the prespecified analysis, no statistically significant difference was identified for the gefapixant 15 mg BID group compared with the placebo group (data not shown in [Table 4], but shown in [Figure 5]).

Compared with the prespecified analysis, results of 3 posthoc supportive analyses showed similar cough frequency reductions for gefapixant 45 mg BID vs. placebo:

Longitudinal ANCOVA – recount dataset: Applying the prespecified analysis approach to the recount dataset, the geometric mean ratios were consistent with the prespecified analysis, with a similar cough frequency reduction relative to placebo of -14.63% (nominal p=0.030) [Table 4, Panel B].

MI+ANCOVA – original dataset: Applying the MI+ANCOVA analysis to the original dataset, the geometric mean ratios were similar to the prespecified analysis. The cough frequency reduction relative to placebo at Week 24 was -13.29% (nominal p=0.048) [Table 4, Panel C]. These results are the basis of the gefapixant approval by the European Commission on 18-SEP-2023.

MI+ANCOVA – recount dataset: Applying the MI+ANCOVA analysis to the recount dataset, the geometric mean ratios were similar to the prespecified analysis. The cough frequency reduction relative to placebo was -13.13% (nominal p=0.048) [Table 4, Panel D].

Cough frequency reduction over time
Consistent reductions from baseline in cough frequency over 24 hours compared with placebo were observed in the gefapixant 45 mg group from Week 4 through Week 24 in the prespecified analysis (longitudinal ANCOVA applied to the original dataset) [Figure 5] and in the posthoc analysis (MI+ANCOVA applied to the recount dataset) [Figure 6].

Table 4
Analysis of 24-Hour Cough Frequency
Study P030 (Week 24)

	PANEL A (Prespecified Analysis) Original Dataset – Longitudinal ANCOVA				PANEL B (Posthoc Analysis) Recount Dataset – Longitudinal ANCOVA			
	N	Geometric Mean Ratio (Post-Baseline/Baseline)† (95% CI)	Reduction Relative to Placebo (%) (95% CI)	*p*-Value	N	Geometric Mean Ratio (Post-Baseline/Baseline)† (95% CI)	Reduction Relative to Placebo (%) (95% CI)	*p*-Value
Placebo	419	0.43 (0.39, 0.48)			419	0.43 (0.39, 0.48)		
MK-7264 45 mg BID	409	0.37 (0.33, 0.41)	-14.64 (-26.07, -1.43)	0.031	409	0.37 (0.33, 0.41)	-14.63 (-25.98, -1.53)	0.030

	PANEL C (Posthoc Analysis) Original Dataset – MI+ANCOVA				PANEL D (Posthoc Analysis) Recount Dataset – MI+ANCOVA			
	N	Geometric Mean Ratio (Post-Baseline/Baseline)†† (95% CI)	Reduction Relative to Placebo (%) (95% CI)	*p*-Value	N	Geometric Mean Ratio (Post-Baseline/Baseline)†† (95% CI)	Reduction Relative to Placebo (%) (95% CI)	*p*-Value
Placebo	435	0.44 (0.39, 0.49)			435	0.44 (0.39, 0.49)		
MK-7264 45 mg BID	439	0.38 (0.34, 0.43)	-13.29 (-24.74, -0.10)	0.048	439	0.38 (0.34, 0.43)	-13.13 (-24.45, -0.12)	0.048

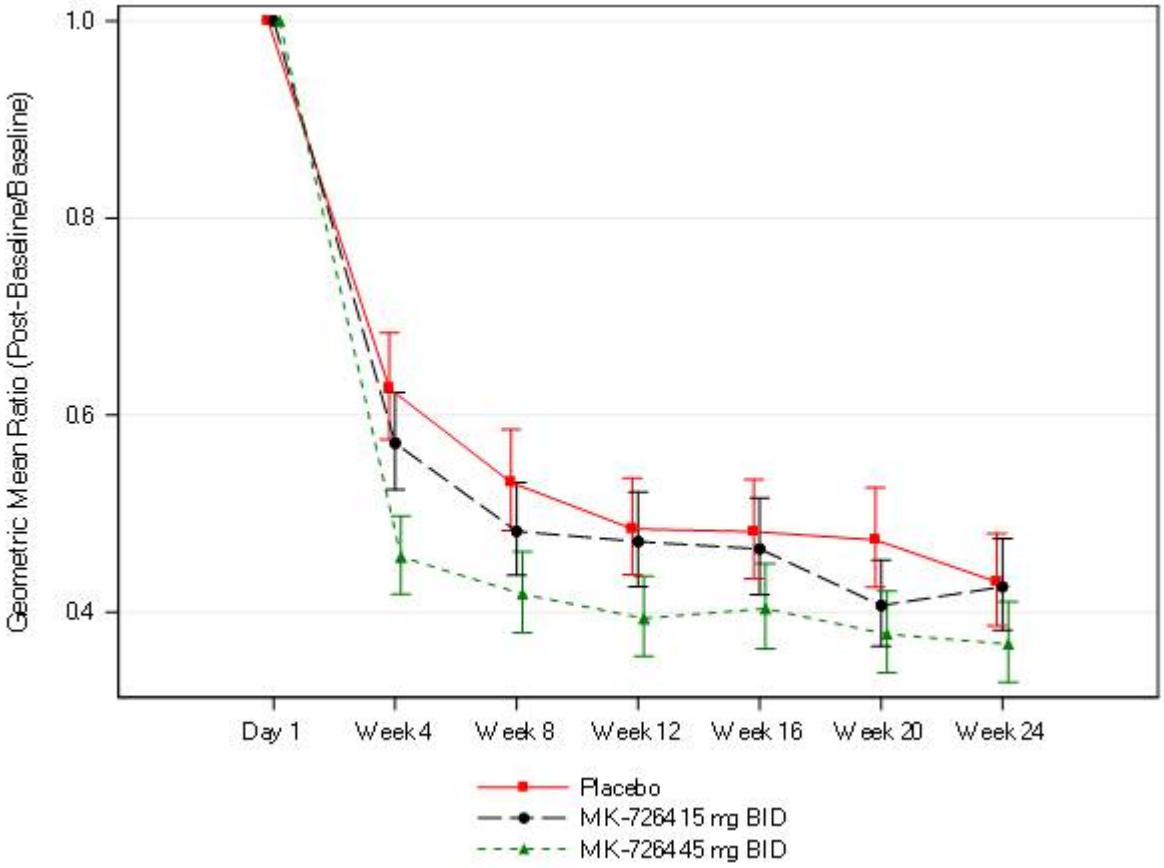
ANCOVA=Analysis of Covariance; CI=confidence interval; MI=multiple imputation; MK-7264=gefapixant; N=number of subjects included in the analysis.

Reduction relative to placebo is calculated: 100 (e^{DIFF} -1) where DIFF is the treatment difference (using the natural-log-transformed data) in change from baseline at Week 24.

†Values are model-based, using the Longitudinal Analysis of Covariance model consisting of the change from baseline in log-transformed 24-hour cough frequency at each post-baseline visit (up to Week 12) as response. The model includes treatment, visit, treatment-by-visit interaction, gender, region, log-transformed baseline value, and log-transformed baseline value-by-visit as covariates. The unstructured covariance matrix is used to model the correlation among repeated measurements.

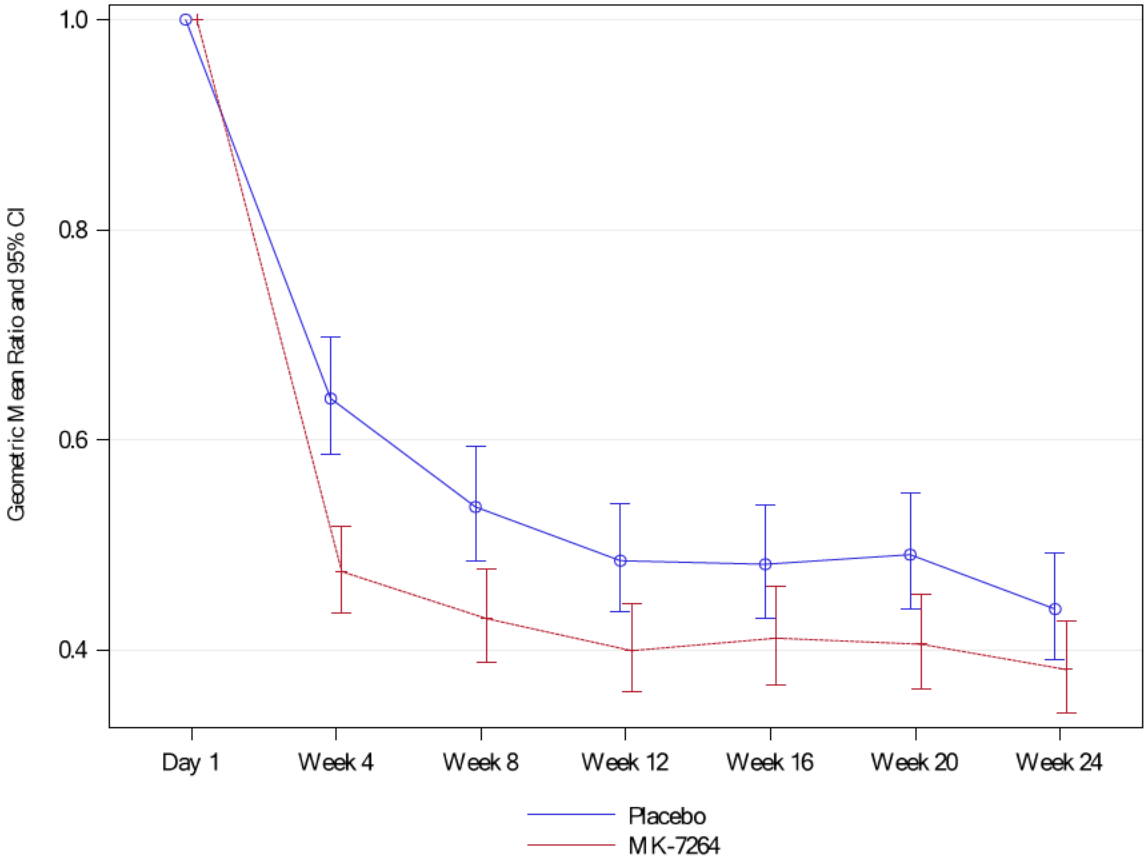
††Values are model-based after Multiple Imputation: Missing baseline values were imputed based on gender and region, followed by multiple imputation of the missing data (m = 50 imputed datasets) for all follow-up visits using treatment arm, gender, region, and the other follow-up visits as covariates. Following imputation, ANCOVA model was conducted at the time point of interest, adjusting for covariates of treatment, baseline, region, and gender.

Figure 5
Analysis of 24-Hour Cough Frequency Over Time for Gefapixant
Study P030
Prespecified Analysis (Original Dataset, Longitudinal ANCOVA)



ANCOVA=Analysis of Covariance; BID=twice daily; CI=confidence interval; MK-7264=gefapixant.

Figure 6
Analysis of 24-Hour Cough Frequency Over Time for Gefapixant 45 mg BID
Study P030
Posthoc Analysis (Recount Dataset, MI+ANCOVA)



ANCOVA=Analysis of Covariance; BID=twice daily; CI=confidence interval; MI=multiple imputation; MK-7264=gefapixant.

4.1.2.1.3 P027/P030 Pool

Treatment with gefapixant 45 mg BID for 12 weeks provides clinically meaningful reductions in 24-hour cough frequency from baseline relative to placebo.

- The prespecified analysis (longitudinal ANCOVA applied to the original dataset) showed that gefapixant 45 mg BID reduced 24-hour cough frequency with a reduction relative to placebo of -18.59% (95% CI: -27.06, -9.15) [30].

- Applying the MI+ANCOVA analysis to the recount dataset confirmed the treatment effect observed in the prespecified analysis with a similar reduction relative to placebo. The 24-hour cough frequency reduction of gefapixant 45 mg BID relative to placebo was -16.75% (95% CI: -25.11, -7.47).

4.1.2.2 Awake Cough Frequency

4.1.2.2.1 Study P027

In Study P027, the prespecified step-down procedure for multiplicity adjustment precluded statistical testing for the secondary endpoints at either dose, given that the gefapixant 15 mg BID dose did not reach statistical significance on the primary endpoint. Therefore, all *p*-values for the secondary endpoint analyses are considered nominal, with discussions of analysis results including point estimates and their 95% CI.

Results of the prespecified analysis (longitudinal ANCOVA applied to the original dataset) of the secondary endpoint at Week 12 showed that gefapixant 45 mg BID reduced awake cough frequency with a reduction relative to placebo of -17.68% (nominal p=0.056) [Table 5, Panel A].

In the prespecified analysis, no statistically significant difference was identified for the gefapixant 15 mg BID group compared with the placebo group (data not shown).

Compared with the prespecified analysis, results of 3 posthoc supportive analyses showed similar cough frequency reductions for gefapixant 45 mg BID vs. placebo [Table 5, Panels B, C, D].

Table 5
Analysis of Awake Cough Frequency
Study P027 (Week 12)

	PANEL A (Prespecified Analysis) Original Dataset – Longitudinal ANCOVA				PANEL B (Posthoc Analysis) Recount Dataset – Longitudinal ANCOVA			
	N	Geometric Mean Ratio (Post-Baseline/Baseline)† (95% CI)	Reduction Relative to Placebo (%) (95% CI)	*p*-Value	N	Geometric Mean Ratio (Post-Baseline/Baseline)† (95% CI)	Reduction Relative to Placebo (%) (95% CI)	*p*-Value
Placebo	222	0.46 (0.40, 0.53)			222	0.46 (0.40, 0.53)		
MK-7264 45 mg BID	217	0.38 (0.33, 0.44)	-17.68 (-32.57, 0.50)	0.056	217	0.39 (0.33, 0.45)	-16.26 (-31.20, 1.91)	0.076

	PANEL C (Posthoc Analysis) Original Dataset – MI+ANCOVA				PANEL D (Posthoc Analysis) Recount Dataset – MI+ANCOVA			
	N	Geometric Mean Ratio (Post-Baseline/Baseline)†† (95% CI)	Reduction Relative to Placebo (%) (95% CI)	*p*-Value	N	Geometric Mean Ratio (Post-Baseline/Baseline) †† (95% CI)	Reduction Relative to Placebo (%) (95% CI)	*p*-Value
Placebo	243	0.46 (0.39, 0.53)			243	0.45 (0.39, 0.53)		
MK-7264 45 mg BID	243	0.37 (0.32, 0.44)	-18.33 (-32.65, -0.96)	0.040	243	0.38 (0.32, 0.44)	-17.11 (-31.40, 0.16)	0.052

ANCOVA=Analysis of Covariance; CI=confidence interval; MI=multiple imputation; MK-7264=gefapixant; N=number of subjects included in the analysis.

Reduction relative to placebo is calculated: 100 (e^{DIFF} -1) where DIFF is the treatment difference (using the natural-log-transformed data) in change from baseline at Week 12.

†Values are model-based, using the Longitudinal Analysis of Covariance model consisting of the change from baseline in log-transformed 24-hour cough frequency at each post-baseline visit (up to Week 12) as response. The model includes treatment, visit, treatment-by-visit interaction, gender, region, log-transformed baseline value, and log-transformed baseline value-by-visit as covariates. The unstructured covariance matrix is used to model the correlation among repeated measurements.

††Values are model-based after Multiple Imputation: Missing baseline values were imputed based on gender and region, followed by multiple imputation of the missing data (m = 50 imputed datasets) for all follow-up visits using treatment arm, gender, region, and the other follow-up visits as covariates. Following imputation, ANCOVA model was conducted at the time point of interest, adjusting for covariates of treatment, baseline, region, and gender.

4.1.2.2.2 Study P030

Results of the prespecified analysis (longitudinal ANCOVA applied to the original dataset) of the secondary endpoint at Week 24 showed that gefapixant 45 mg BID reduced awake cough frequency with a reduction relative to placebo of -15.79% (nominal p=0.022) [Table 6, Panel A].

In the prespecified analysis, no statistically significant difference was identified for the gefapixant 15 mg BID group compared with the placebo group (data not shown).

Compared with the prespecified analysis, results of 3 posthoc supportive analyses showed similar cough frequency reductions for gefapixant 45 mg BID vs. placebo [Table 6, Panels B, C, D].

Table 6
Analysis of Awake Cough Frequency
Study P030 (Week 24)

	PANEL A (Prespecified Analysis) Original Dataset – Longitudinal ANCOVA				PANEL B (Posthoc Analysis) Recount Dataset – Longitudinal ANCOVA			
	N	Geometric Mean Ratio (Post-Baseline/Baseline)† (95% CI)	Reduction Relative to Placebo (%) (95% CI)	*p*-Value	N	Geometric Mean Ratio (Post-Baseline/Baseline)† (95% CI)	Reduction Relative to Placebo (%) (95% CI)	*p*-Value
Placebo	419	0.42 (0.38, 0.47)			419	0.43 (0.38, 0.47)		
MK-7264 45 mg BID	409	0.36 (0.32, 0.40)	-15.79 (-27.27, -2.50)	0.022	409	0.36 (0.32, 0.40)	-15.52 (-26.96, -2.28)	0.023
	PANEL C (Posthoc Analysis) Original Dataset – MI+ANCOVA				PANEL D (Posthoc Analysis) Recount Dataset – MI+ANCOVA			
	N	Geometric Mean Ratio (Post-Baseline/Baseline)†† (95% CI)	Reduction Relative to Placebo (%) (95% CI)	*p*-Value	N	Geometric Mean Ratio (Post-Baseline/Baseline)†† (95% CI)	Reduction Relative to Placebo (%) (95% CI)	*p*-Value
Placebo	435	0.43 (0.38, 0.48)			435	0.43 (0.38, 0.48)		
MK-7264 45 mg BID	439	0.37 (0.33, 0.42)	-14.31 (-25.95, -0.84)	0.038	439	0.37 (0.33, 0.42)	-13.82 (-25.36, -0.49)	0.043

ANCOVA=Analysis of Covariance; CI=confidence interval; MI=multiple imputation; MK-7264=gefapixant; N=number of subjects included in the analysis.

Reduction relative to placebo is calculated: 100 (e^{DIFF} -1) where DIFF is the treatment difference (using the natural-log-transformed data) in change from baseline at Week 24.

†Values are model-based, using the Longitudinal Analysis of Covariance model consisting of the change from baseline in log-transformed 24-hour cough frequency at each post-baseline visit (up to Week 24) as response. The model includes treatment, visit, treatment-by-visit interaction, gender, region, log-transformed baseline value, and log-transformed baseline value-by-visit as covariates. The unstructured covariance matrix is used to model the correlation among repeated measurements.

††Values are model-based after Multiple Imputation: Missing baseline values were imputed based on gender and region, followed by multiple imputation of the missing data (m = 50 imputed datasets) for all follow-up visits using treatment arm, gender, region, and the other follow-up visits as covariates. Following imputation, ANCOVA model was conducted at the time point of interest, adjusting for covariates of treatment, baseline, region, and gender.

4.1.2.2.3 P027/P030 Pool

Treatment with gefapixant 45 mg BID for 12 weeks provides clinically meaningful reductions in awake cough frequency from baseline relative to placebo.

- The prespecified analysis (longitudinal ANCOVA applied to the original dataset) showed that gefapixant 45 mg BID reduced awake coughs per hour frequency with a reduction relative to placebo of -17.38% (95% CI: -26.19, -7.51) [30].

- Applying the MI+ANCOVA analysis to the recount dataset confirmed the treatment effect observed in the prespecified analysis with a similar reduction relative to placebo. The awake coughs frequency reduction of gefapixant 45 mg BID relative to placebo was -15.85% (95% CI: -24.55, -6.15).

4.1.2.3 Leicester Cough Questionnaire

4.1.2.3.1 Study P030

In the prespecified analysis of Study P030 wherein the responder analysis for the LCQ total score (ie, ≥1.3-point increase from baseline) at Week 24 was a prespecified key secondary endpoint, a significantly (p=0.040) greater proportion of patients in the gefapixant 45 mg BID group were LCQ responders than in the placebo group [Table 7] [6]. At Weeks 12 and 52, similar results were observed wherein a greater proportion of patients in the gefapixant 45 mg BID group were LCQ responders compared with the placebo group. Summaries of the LCQ individual domain scores (physical, psychological, and social) over time indicate that scores from each of the individual domains contributed equally to the LCQ total score (data not shown). Of note, this study was powered to demonstrate statistical significance of the LCQ endpoint.

In the posthoc analysis requested by FDA for P030 using higher thresholds of change in the LCQ total score (≥3.3 and ≥4.1), there was a consistent trend of a greater proportion of LCQ responders observed for the gefapixant 45 mg BID group than placebo at Weeks 12, 24, and 52 [Table 7].

Table 7
Analysis of Subjects on Point Increase From Baseline in LCQ Total Score Over Time
Study P030
Full Analysis Set – Logistic Regression Model

Treatment	N	n	(%)	Difference† vs. Placebo (95% CI)	Odds Ratio† vs. Placebo (95% CI)
Week 12 – Threshold of 1.3					
Placebo	372	235	63.2		
MK-7264 45 mg BID	352	257	73.0	8.6 (1.53, 16.02)	1.51 (1.10, 2.06)
Week 12 – Threshold of 3.3 (posthoc)					
Placebo	372	154	41.4		
MK-7264 45 mg BID	352	185	52.6	10.7 (2.85, 18.66)	1.54 (1.14, 2.07)
Week 12 – Threshold of 4.1 (posthoc)					
Placebo	372	124	33.3		
MK-7264 45 mg BID	352	163	46.3	12.8 (5.07, 20.33)	1.72 (1.27, 2.33)
Week 24 – Threshold of 1.3†† (prespecified key secondary endpoint)					
Placebo	355	245	69.0		
MK-7264 45 mg BID	342	262	76.6	6.7 (-0.41, 13.47)	1.41 (1.02, 1.96)
Week 24 – Threshold of 3.3 (posthoc)					
Placebo	355	157	44.2		
MK-7264 45 mg BID	342	200	58.5	14.4 (6.34, 22.26)	1.78 (1.32, 2.41)
Week 24 – Threshold of 4.1 (posthoc)					
Placebo	355	139	39.2		
MK-7264 45 mg BID	342	169	49.4	10.2 (2.21, 18.11)	1.52 (1.12, 2.05)
Week 52 – Threshold of 1.3					
Placebo	334	229	68.6		
MK-7264 45 mg BID	322	267	82.9	13.3 (6.90, 19.98)	2.18 (1.52, 3.11)
Week 52 – Threshold of 3.3 (posthoc)					
Placebo	334	163	48.8		
MK-7264 45 mg BID	322	207	64.3	15.3 (7.10, 23.11)	1.87 (1.37, 2.55)
Week 52 – Threshold of 4.1 (posthoc)					
Placebo	334	145	43.4		
MK-7264 45 mg BID	322	181	56.2	13.1 (4.94, 21.37)	1.70 (1.24, 2.31)

BID=twice daily; CI=Confidence Interval; LCQ=Leicester Cough Questionnaire; MK-7264=gefapixant; N=Number of subjects with available data at the time point; n=Number of responders at the time point.

†Based on the logistic regression model. The covariates include treatment, visit, treatment-by-visit interaction, gender, region, baseline LCQ total score, and the interaction of baseline LCQ total score by visit.

†† *p*-value = 0.040 for MK-7264 45 mg BID vs. Placebo.

Threshold = change from baseline in LCQ total score ≥1.3, ≥3.3, or ≥4.1 points

4.1.2.3.2 Study P027

In the prespecified analysis of Study P027, the observed proportion of patients with a ≥1.3-point increase from baseline in LCQ total score (ie, LCQ responders) at the primary timepoint Week 12 was higher in the gefapixant 45 mg BID group than the placebo group [Table 8]. Analysis results at Weeks 24 and 52 were similar. Of note, this study was not powered to demonstrate statistical significance of the LCQ endpoint.

In the posthoc analysis requested by FDA for P027 using higher thresholds of change in the LCQ total score (≥3.3 and ≥4.1), similar results were observed wherein a greater proportion of LCQ responders was observed for the gefapixant 45 mg BID group than the placebo group at Weeks 12, 24, and 52 [Table 8].

Descriptive summaries of LCQ individual domain scores (physical, psychological, and social) over time indicate that scores from each of the individual domains contributed equally to the LCQ total score (data not shown).

Table 8
Analysis of Subjects on Point Increase From Baseline in LCQ Total Score Over Time
Full Analysis Set – Logistic Regression Model
Study P027

Treatment	N	n	(%)	Difference† vs. Placebo (95% CI)	Odds Ratio† vs. Placebo (95% CI)
Week 12 – Threshold of 1.3(prespecified secondary endpoint)					
Placebo	196	123	62.8		
MK-7264 45 mg BID	194	134	69.1	6.0 (-4.14, 16.11)	1.30 (0.85, 1.98)
Week 12 – Threshold of 3.3 (posthoc)					
Placebo	196	75	38.3		
MK-7264 45 mg BID	194	88	45.4	7.9 (-2.43, 18.40)	1.39 (0.92, 2.10)
Week 12 – Threshold of 4.1 (posthoc)					
Placebo	196	60	30.6		
MK-7264 45 mg BID	194	68	35.1	3.7 (-5.94, 13.40)	1.19 (0.77, 1.83)
Week 24 – Threshold of 1.3					
Placebo	193	124	64.2		
MK-7264 45 mg BID	185	129	69.7	6.1 (-4.09, 16.02)	1.31 (0.85, 2.00)
Week 24 – Threshold of 3.3 (posthoc)					
Placebo	193	87	45.1		
MK-7264 45 mg BID	185	83	44.9	1.2 (-9.61, 11.74)	1.05 (0.70, 1.59)
Week 24 – Threshold of 4.1 (posthoc)					
Placebo	193	68	35.2		
MK-7264 45 mg BID	185	74	40.0	6.2 (-3.76, 16.78)	1.31 (0.86, 2.01)
Week 52 – Threshold of 1.3					
Placebo	180	122	67.8		
MK-7264 45 mg BID	163	116	71.2	3.8 (-6.73, 13.70)	1.19 (0.76, 1.85)
Week 52 – Threshold of 3.3 (posthoc)					
Placebo	180	87	48.3		
MK-7264 45 mg BID	163	83	50.9	3.8 (-7.64, 14.40)	1.17 (0.76, 1.78)
Week 52 – Threshold of 4.1 (posthoc)					
Placebo	180	76	42.2		
MK-7264 45 mg BID	163	72	44.2	3.3 (-7.66, 14.11)	1.15 (0.75, 1.77)

BID=twice daily; CI = Confidence Interval; LCQ = Leicester Cough Questionnaire; MK-7264=gefapixant;
N=Number of subjects with available data at the time point; n=Number of responders at the time point.

†Estimated based on the logistic regression model. The covariates include treatment, visit, treatment-by-visit interaction, gender, region, baseline LCQ total score, and the interaction of baseline LCQ total score by visit.

Threshold = change from baseline in LCQ total score ≥1.3, ≥3.3, or ≥4.1 points

4.1.2.3.3 P027/P030 Pool

In the prespecified analysis of the P027/P030 Pool, the observed proportion of patients with a ≥1.3 point increase from baseline in LCQ total score (ie, LCQ responders) at Week 12, Week 24, and Week 52 [Table 9] was higher in the gefapixant 45 mg group than in the placebo group.

In the posthoc analyses of the P027/P030 Pool:

- Using higher thresholds of change in the LCQ total score (≥3.3 and ≥4.1), a greater proportion of LCQ responders is consistently observed for the gefapixant 45 mg BID group than placebo at Weeks 12, 24, and 52 [Table 9].Consistent with the individual studies discussed above, summaries of LCQ individual domain scores over time indicate that scores from each of the individual domains (physical, psychological, and social) contributed equally to the LCQ total score (data not shown).Results of the analyses of the LCQ domain scores demonstrate consistent benefit of gefapixant 45 mg BID group over placebo at Weeks 12, 24, and 52 on the 3 individual domains of the LCQ: physical, social, and psychological [Figure 7] [Figure 8] [Figure 9].

Table 9
Analysis of Subjects on Point Increase From Baseline in LCQ Total Score Over Time
Phase 3 Trials Pooled Across P027 and P030
Full Analysis Set – Logistic Regression Model

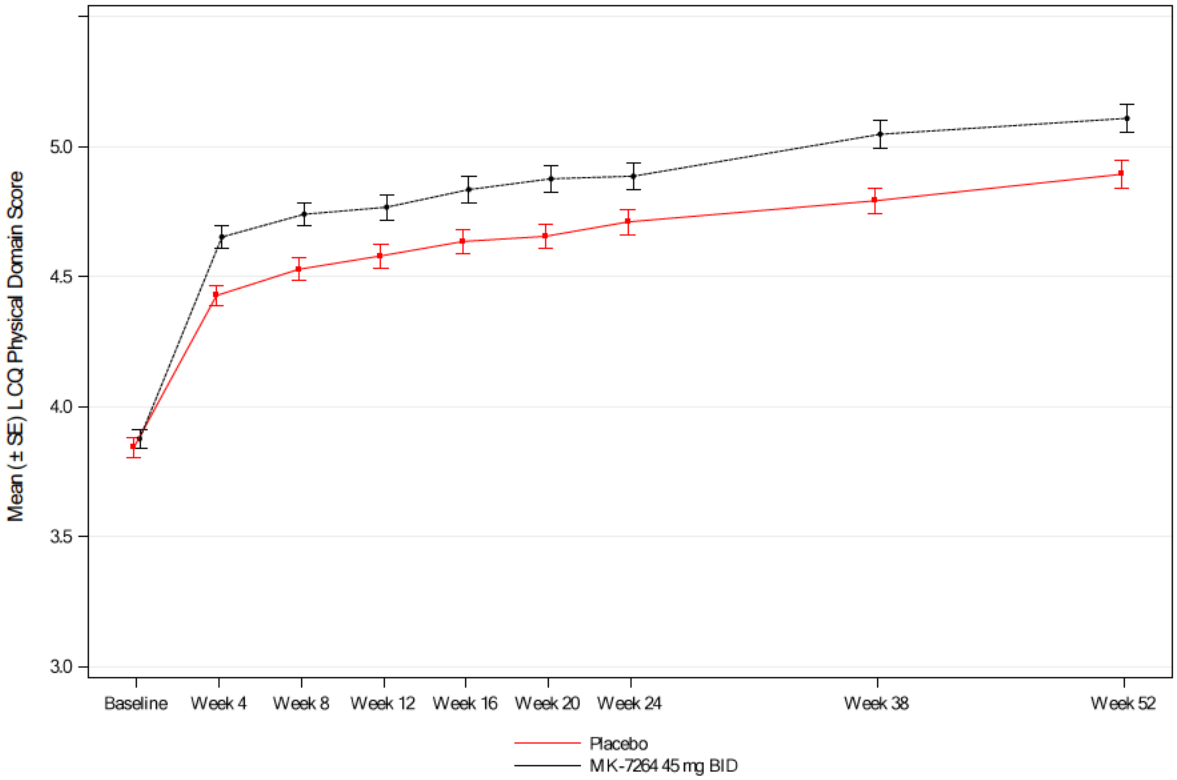
Treatment	N	n	(%)	Difference† vs. Placebo (95% CI)	Odds Ratio† vs. Placebo (95% CI)
Week 12 – Threshold of 1.3					
Placebo	568	358	63.0		
MK-7264 45 mg BID	546	391	71.6	7.8 (1.84, 13.62)	1.42 (1.11, 1.83)
Week 12 – Threshold of 3.3					
Placebo	568	229	40.3		
MK-7264 45 mg BID	546	273	50.0	9.7 (3.37, 15.91)	1.48 (1.17, 1.88)
Week 12 – Threshold of 4.1					
Placebo	568	184	32.4		
MK-7264 45 mg BID	546	231	42.3	9.6 (3.51, 15.47)	1.52 (1.19, 1.95)
Week 24 – Threshold of 1.3					
Placebo	548	369	67.3		
MK-7264 45 mg BID	527	391	74.2	6.5 (0.69, 12.17)	1.37 (1.06, 1.77)
Week 24 – Threshold of 3.3					
Placebo	548	244	44.5		
MK-7264 45 mg BID	527	283	53.7	9.7 (3.31, 16.09)	1.48 (1.16, 1.88)
Week 24 – Threshold of 4.1					
Placebo	548	207	37.8		
MK-7264 45 mg BID	527	243	46.1	8.7 (2.36, 14.90)	1.44 (1.13, 1.84)
Week 52 – Threshold of 1.3					
Placebo	514	351	68.3		
MK-7264 45 mg BID	485	383	79.0	10.4 (4.93, 16.10)	1.72 (1.31, 2.27)
Week 52 – Threshold of 3.3					
Placebo	514	250	48.6		
MK-7264 45 mg BID	485	290	59.8	11.5 (4.99, 17.98)	1.59 (1.24, 2.04)
Week 52 – Threshold of 4.1					
Placebo	514	221	43.0		
MK-7264 45 mg BID	485	253	52.2	9.8 (3.08, 16.18)	1.49 (1.16, 1.91)

BID=twice daily; CI=Confidence Interval; LCQ=Leicester Cough Questionnaire; MK-7264=gefapixant; N=Number of subjects with available data at the time point; n=Number of responders at the time point.

†Based on the logistic regression model. The covariates include treatment, visit, treatment-by-visit interaction, gender, region, baseline LCQ total score, and the interaction of baseline LCQ total score by visit.

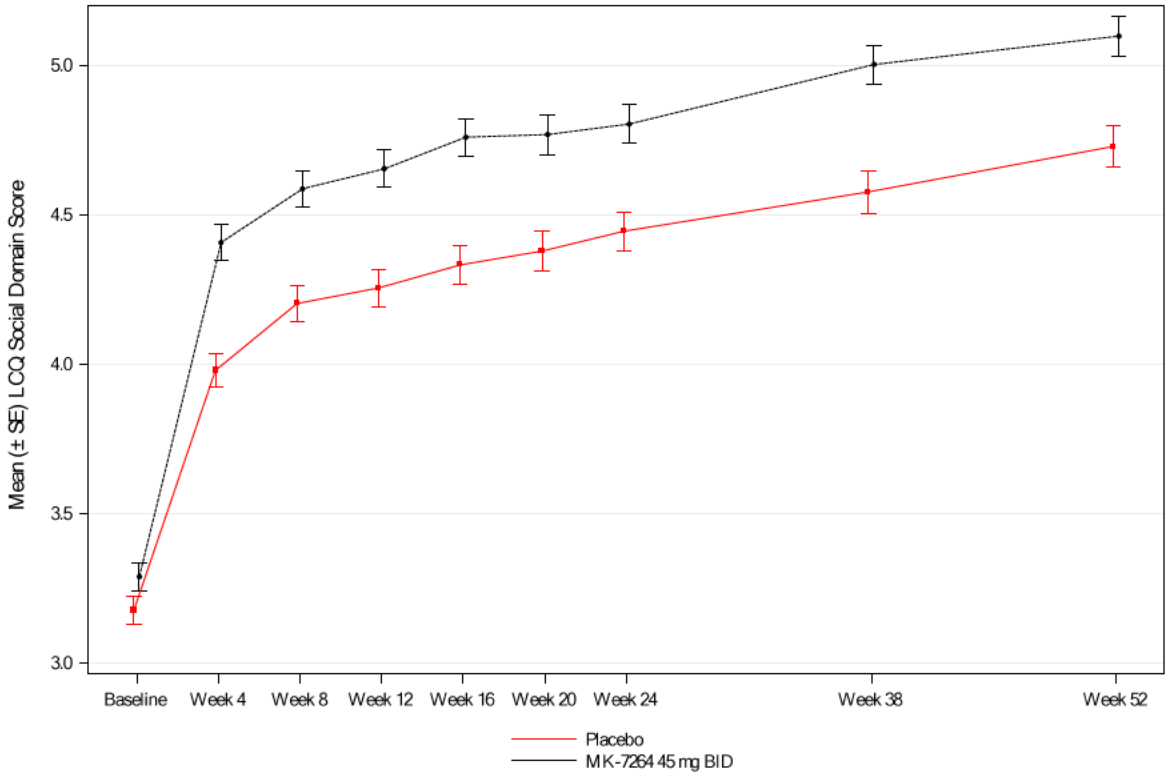
Threshold = change from baseline in LCQ total score ≥1.3, ≥3.3, or ≥4.1 points

Figure 7
Mean (± SE) LCQ Physical Domain Score
Phase 3 Trials Pooled Across P027 and P030
Full Analysis Set



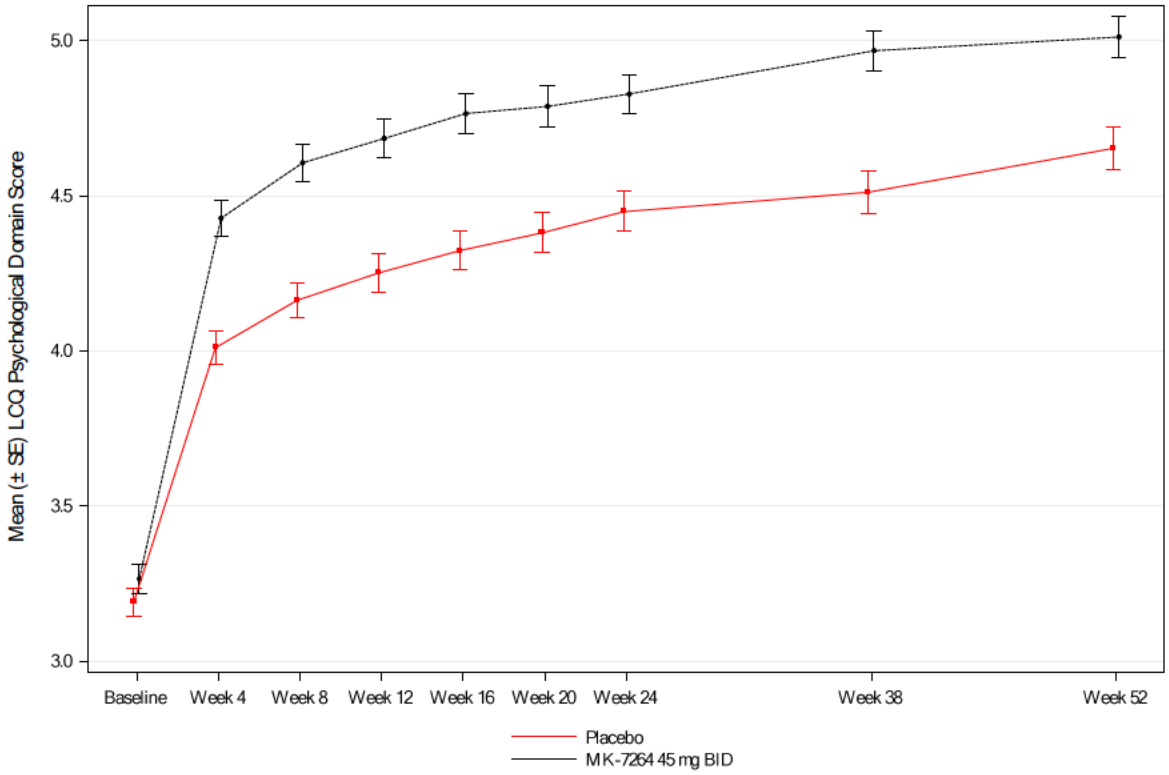
BID=twice daily; LCQ=Leicester Cough Questionnaire; MK-7264=gefapixant; SE=standard error.

Figure 8
Mean (± SE) LCQ Social Domain Score
Phase 3 Trials Pooled Across P027 and P030
Full Analysis Set



BID=twice daily; LCQ=Leicester Cough Questionnaire; MK-7264=gefapixant; SE=standard error.

Figure 9
Mean (± SE) LCQ Psychological Domain Score
Phase 3 Trials Pooled Across P027 and P030
Full Analysis Set



BID=twice daily; LCQ=Leicester Cough Questionnaire; MK-7264=gefapixant; SE=standard error.

4.1.2.3.4 Study P043

In the prespecified analysis of Study P043 at Week 12, the success criterion for superiority of gefapixant 45 mg BID in LCQ total score change from baseline compared with placebo was met, with a statistically significant treatment difference of 0.75 (95% CI: 0.06, 1.44; *p*=0.034), based on the LS mean [Table 10]; a higher score indicates better cough-specific HRQoL.

Posthoc analyses results showed:

- The proportion of patients with a ≥1.3-point increase from baseline in LCQ total score at Week 12 was higher in the gefapixant group than in the placebo group [Table 11].
- A higher proportion of patients achieved a ≥3.3- and ≥4.1-point increase from baseline in LCQ total score at Week 12 in the gefapixant group than the placebo group [Table 11].
- Change from baseline in LCQ physical domain score shows greater improvements over time in the gefapixant group compared with placebo. Summaries of the LCQ individual domain scores (physical, social, and psychological) over time show that the scores from each of the individual domains had similar contribution to the LCQ total score.

Table 10
Analysis of LCQ Total Score at Week 12
Study P043
Full Analysis Set

Treatment	N	Mean (SD) at Baseline[a]	Mean (SD) at Week 12[a]	Mean (SD) Change from Baseline (Week 12 – Baseline)[a]	Mean Change from Baseline[b] (Week 12 – Baseline) (95% CI)
Placebo	199	11.30 (2.80)	14.73 (3.48)	3.43 (3.74)	3.59 (3.09, 4.09)
MK-7264 45 mg BID	199	10.82 (3.08)	15.32 (3.91)	4.49 (3.91)	4.34 (3.84, 4.83)
Treatment Difference		**Estimated Difference[c] and (95% CI)**			***p*-Value**
MK-7264 45 mg BID vs. Placebo		0.75 (0.06, 1.44)			0.034

CI=Confidence Interval; LCQ=Leicester Cough Questionnaire; MK-7264=gefapixant; N=Number of patients included in the analysis; SD=Standard Deviation.

[a]Based on patients with non-missing values at both baseline and Week 12

[b]Based on the Longitudinal Analysis of Covariance Model consisting of the change from baseline in LCQ total score at each post-baseline visit (up to Week 12) as response. The model includes terms for treatment group (MK-7264 45 mg and Placebo), visit (Weeks 6 and 12), the interaction of treatment-by-visit, gender, and the baseline LCQ total score. The unstructured covariance matrix is used to model the correlation among repeated measurements.

[c]The estimated difference is the treatment difference in model-based mean change from baseline at Week 12.

Table 11
Posthoc Analysis of Subjects on Point Increase From Baseline in LCQ Total Score Over Time
Study P043
Full Analysis Set – Logistic Regression Model

Treatment	N	n	(%)	Estimated Difference† vs. Placebo (95% CI)	Estimated Odds Ratio† vs. Placebo (95% CI)
P043 (Week 6) – Threshold of ≥ 1.3					
Placebo	197	130	66.0		
MK-7264 45 mg BID	197	147	74.6	1.46 (0.92, 2.31)	7.8 (-13.13, 27.45)
P043 (Week 6) – Threshold of ≥ 3.3					
Placebo	197	83	42.1		
MK-7264 45 mg BID	197	94	47.7	1.18 (0.76, 1.82)	3.8 (-17.43, 25.98)
P043 (Week 6) – Threshold of ≥ 4.1					
Placebo	197	68	34.5		
MK-7264 45 mg BID	197	79	40.1	1.20 (0.77, 1.88)	4.1 (-18.40, 23.60)
P043 (Week 12) – Threshold of ≥ 1.3					
Placebo	193	126	65.3		
MK-7264 45 mg BID	193	154	79.8	2.02 (1.25, 3.26)	13.8 (-4.49, 35.18)
P043 (Week 12) – Threshold of ≥ 3.3					
Placebo	193	92	47.7		
MK-7264 45 mg BID	193	118	61.1	1.65 (1.08, 2.53)	12.4 (-11.92, 33.59)
P043 (Week 12) – Threshold of ≥ 4.1					
Placebo	193	79	40.9		
MK-7264 45 mg BID	193	100	51.8	1.46 (0.95, 2.24)	9.2 (-15.75, 29.89)

CI=Confidence Interval; LCQ=Leicester Cough Questionnaire; MK-7264=gefapixant; N=Number of subjects with available data at the time point; n=Number of responders at the time point.

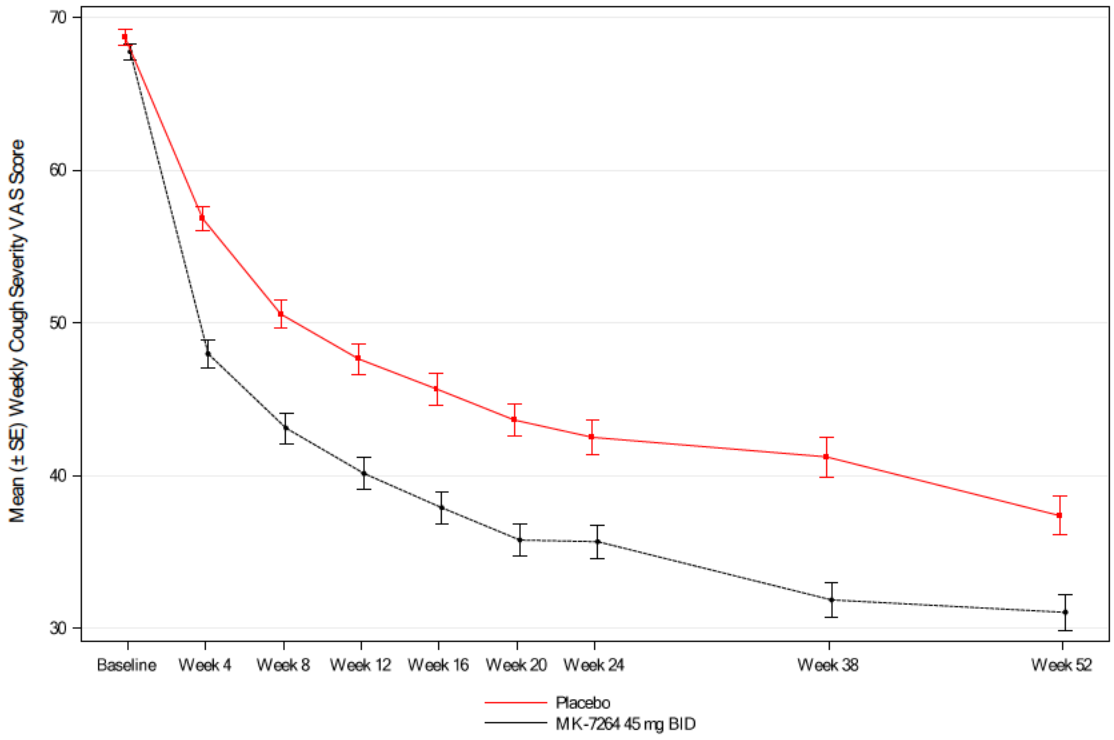
†Based on the logistic regression model. The covariates include treatment, visit, treatment-by-visit interaction, gender, region, baseline LCQ total score, and the interaction of baseline LCQ total score by visit.

4.1.2.4 Other PROs

4.1.2.4.1 P027/030 Pool (Cough Severity VAS, CSD)

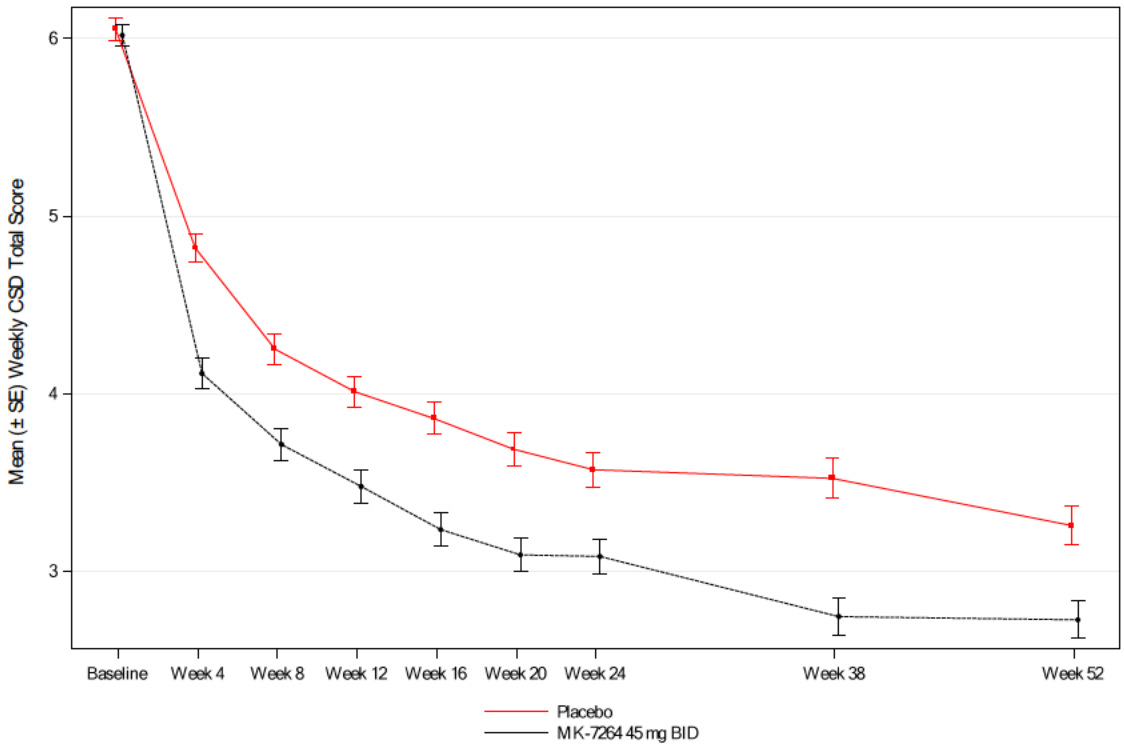
Least-squares mean scores in both the placebo and gefapixant groups improved over 52 weeks for both the Cough Severity VAS and CSD total score, with numerically greater improvement observed with gefapixant 45mg BID versus placebo [Figure 10] [Figure 11].

Figure 10
Mean (± SE) Weekly Cough Severity VAS Score Over Time
Phase 3 Trials Pooled Across P027 and P030
Full Analysis Set



BID=twice daily; SE=standard error, MK-7264=gefapixant; VAS=visual analog scale.

Figure 11
Mean (± SE) Weekly CSD Total Score Over Time
Phase 3 Trials Pooled Across P027 and P030
Full Analysis Set

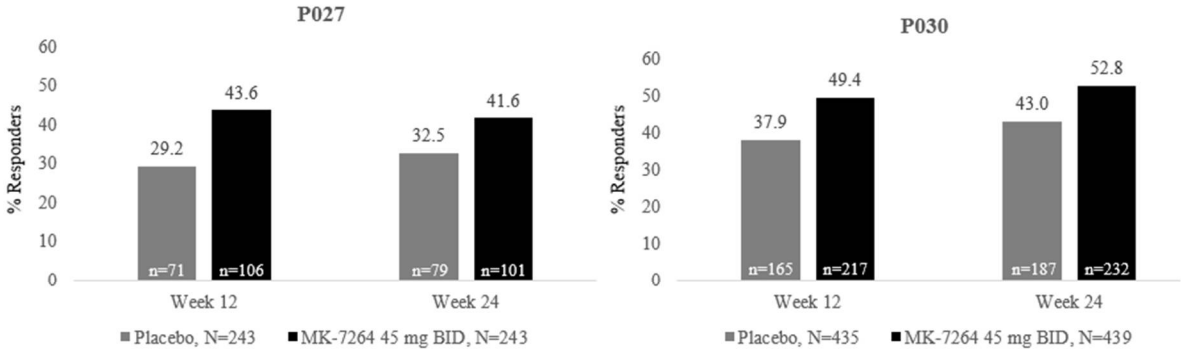


BID=twice daily; CSD=Cough Severity Diary; MK-7264=gefapixant; SE=standard error.

4.1.2.4.2 Studies P027 and P030 (PGIC)

In Studies P027 and P030, a greater proportion of patients in the gefapixant versus placebo groups (43.6% vs. 29.2% and 49.4% vs. 37.9%, respectively) rated their cough, on this 7-point Likert scale, as "much improved" or "very much improved" (ie, improvement responders) at Week 12 compared with the start of the study. Similar results were reported at Week 24 in both studies [Figure 12].

Figure 12
Analysis of PGIC Improvement Responders*
Full Analysis Set
Studies P027 and P030



*Improvement Responders = participants rating themselves as "very much improved" or "much improved" on PGIC

Treatment Difference MK-7264 45 mg BID vs Placebo (95% CI)	
Week 12	14.2 (5.69, 22.53)
Week 24	9.0 (0.38, 17.48)

Treatment Difference MK-7264 45 mg BID vs Placebo (95% CI)	
Week 12	11.5 (5.05, 17.94)
Week 24	9.9 (3.34, 16.36)

BID=twice daily; CI=confidence interval; MK-7264=gefapixant; PGIC=Patient Global Impression of Change.

4.1.2.4.3 Study P043 (Cough Severity VAS, CSD, PGIC)

- The gefapixant 45 mg BID group had a greater improvement in the mean change in Cough Severity VAS score from baseline compared with the placebo group at Week 12, with a treatment difference of -6.92 between the gefapixant and placebo treatment groups (95% CI: -11.88, -1.97; nominal *p*=0.006).

- The gefapixant group had a greater improvement in the CSD total score change from baseline compared with the placebo group at Week 12, with a treatment difference of -0.47 between the gefapixant 45 mg BID group and placebo treatment groups (95% CI: -0.88, -0.06; nominal *p*=0.026).

- For the PGIC improvement responders analysis at Week 12, there was a treatment difference of 8.8 percentage-points between the proportions of improvement responders in the gefapixant and placebo treatment groups (95% CI: 0.50, 17.11).

4.1.2.4.4 Study P042 (C-SUI Episodes, CSD, Cough Severity VAS, PGIC)

Primary Endpoint

- Treatment with gefapixant 45 mg BID was superior to placebo in the percent change from baseline in mean daily C-SUI episodes at Week 12 with a treatment difference of -11.67% percentage-points (95% CI: -19.67, -3.67, *p*=0.004). Percent changes from baseline in C-SUI episodes per day through Week 12 are shown in [Figure 13].

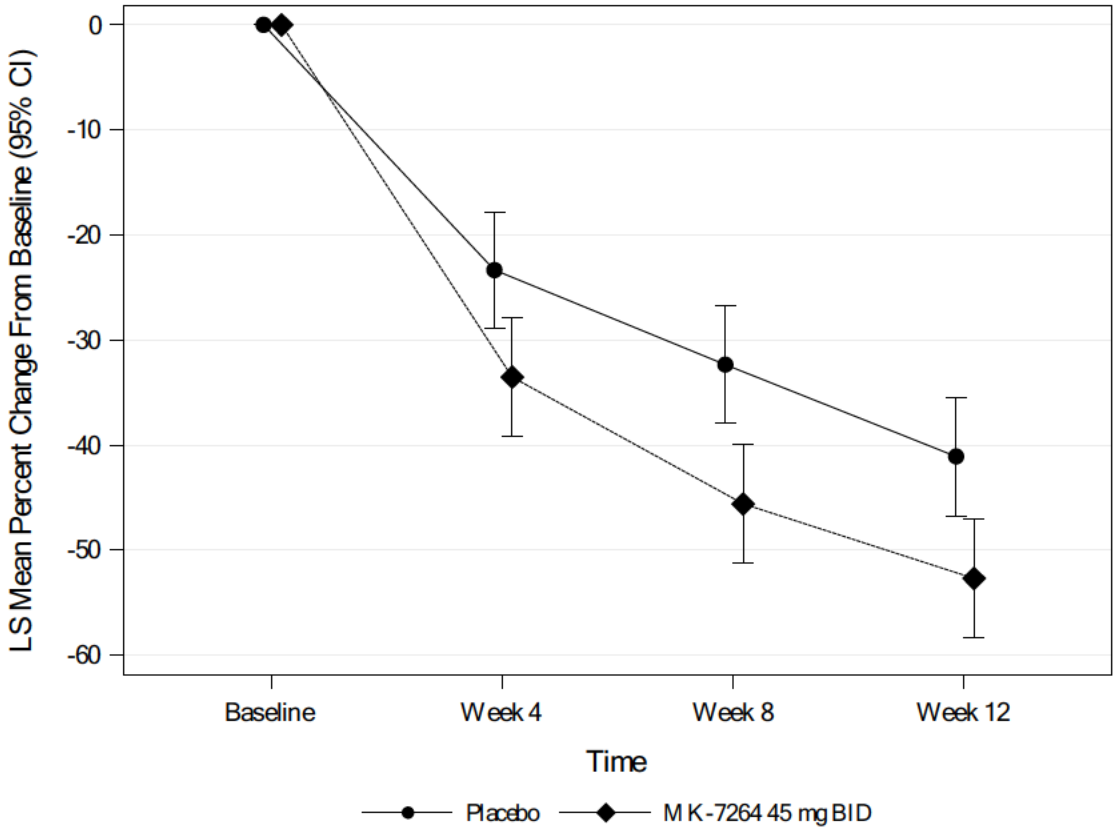
Secondary and Exploratory Endpoints

- The gefapixant group had greater CSD total score improvement, measured as change from baseline in mean weekly total score at Week 12, compared with the placebo group, with a treatment difference of -0.44 (95% CI: -0.85, -0.03).

- Improvement in mean change in Cough Severity VAS score from baseline at Week 12 was observed across both treatment groups, with a treatment difference of -3.83 (95% CI: -8.92, 1.26).

- In the gefapixant group, a greater proportion of patients reported improvement on the PGIC (defined in P042 as: “a little better”, “better”, or “much better”) at Week 12 compared with placebo, with a treatment difference of 11.1 percentage-points (95% CI: 2.31, 19.69).

Figure 13
Analysis of Daily Cough-Induced Stress Urinary Incontinence Episodes
7-day Average Over Time in Study P042
LS Mean Percent Change From Baseline and 95% CI
Full Analysis Set



BID=twice daily; CI=confidence interval: LS mean=least-squares mean; MK-7264=gefapixant.

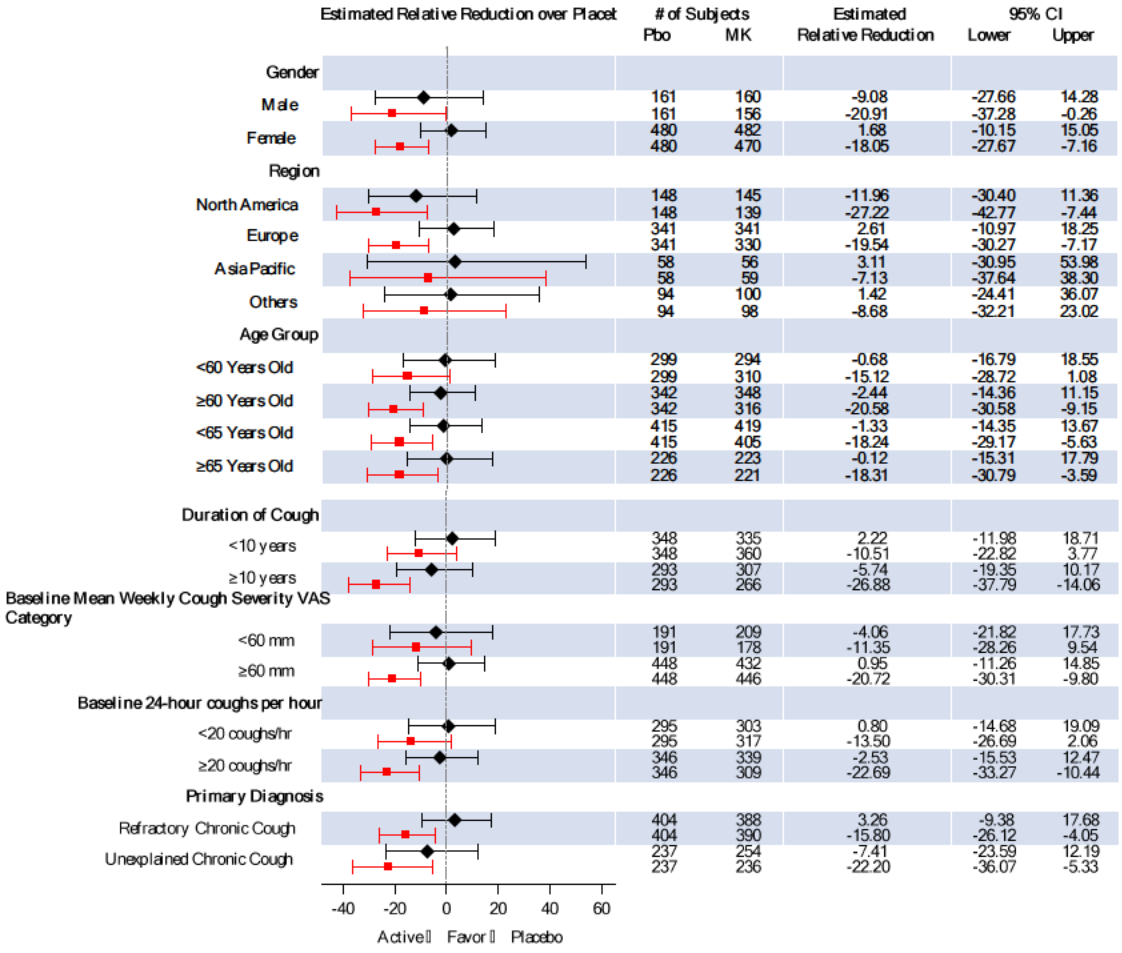
4.1.2.5 Subgroup Analyses

In the P027/P030 Pool, results of the prespecified analysis (longitudinal ANCOVA applied to the original dataset) for the reduction in 24-hour cough frequency, in patients treated with gefapixant 45 mg BID compared with placebo, were not affected by gender, age, region, primary diagnosis, duration of cough, baseline cough severity, or baseline cough frequency at Week 12 [Figure 14]. Analyses requested by FDA for additional subgroups, including race, ethnicity, additional age groups, BMI, and additional regions, were also generally supportive of the results of the primary analysis. Results of subgroup analyses in the number of patients with a ≥1.3-point increase from baseline in LCQ total score at Week 12 were generally consistent with the results of the primary analysis.

In the P027/P030 Pool, posthoc analysis (MI+ANCOVA applied to the recount dataset) results by subgroup were generally consistent with the results of the prespecified analyses (longitudinal ANCOVA applied to the original dataset) of 24-hour cough frequency at Week 12.

Results of subgroup analyses of the number of patients with a ≥1.3-point increase from baseline in LCQ total score at Week 12 were generally consistent with the results of the primary analysis.

Figure 14
Analysis of 24-Hour Coughs per Hour at Week 12 by Prespecified Subgroup
Estimated Relative Reduction Over Placebo (%) (95% CI)
Efficacy Pool Across P027 and P030 – Full Analysis Set
Prespecified Analysis (Original Dataset, Longitudinal ANCOVA)



Subgroups in this graph are prespecified subgroups.

4.1.2.6 Summary of Key Efficacy Results

Studies P027 and P030 individually:

- Prespecified analyses (longitudinal ANCOVA applied to the original dataset) demonstrated that treatment with gefapixant 45 mg BID resulted in clinically meaningful and statistically significant reductions in 24-hour cough frequency relative to placebo at Week 12 for Study P027 and at Week 24 for Study P030.

- Posthoc supportive analyses demonstrate consistent and clinically meaningful reductions in 24-hour cough frequency compared with the prespecified analyses.

- In Study P030, treatment with gefapixant 45 mg BID resulted in statistically significant improvement on the impact of cough on physical, social, and psychological aspects of HRQoL, as measured by the LCQ total score. In Study P027, similar analyses were supportive.

- Gefapixant 15 mg was not shown to be effective in reducing cough frequency.

P027/P030 Pool:

Based on the original submission and the prespecified analyses (longitudinal ANCOVA applied to the original dataset) in the P027/P030 Pool:

- Treatment with gefapixant 45 mg BID for 12 weeks provided clinically meaningful reductions from baseline in objective cough frequency. Treatment with gefapixant 45 mg BID resulted in greater improvement from baseline in objective cough frequency than placebo. These results were also generally consistent across the prespecified subgroups.

- The greater reduction in objective cough frequency by treatment with gefapixant 45 mg BID compared with placebo was supported by clinically meaningful improvements from baseline in cough-specific PRO endpoints. In addition to reducing the self-rated impact of cough on physical, social, and psychological aspects of HRQoL, treatment with gefapixant 45 mg BID resulted in greater improvement from baseline in the self-rated severity of cough at Weeks 12 and 24, compared with placebo.

- The 52-week data suggest that treatment with gefapixant 45 mg BID resulted in durable improvements from baseline in cough-specific patient-reported endpoints, including LCQ scores and cough severity. These improvements were greater in patients who received gefapixant 45 mg BID than in patients who received placebo.

Based on the cough data in the P027/P030 Pool that were recounted and underwent posthoc analyses (MI+ANCOVA applied to the recount dataset):

- Posthoc analyses results confirmed that treatment with gefapixant 45 mg BID for 12 weeks provided clinically meaningful reductions from baseline in objective cough frequency. Results confirmed the treatment effect observed in the prespecified analyses (longitudinal ANCOVA applied to the original dataset).

For LCQ, posthoc analyses performed to assess additional thresholds (≥3.3- and ≥4.1-point increases from baseline in total score) were consistent with the prespecified analyses (≥1.3-point increase from baseline). Results of the individual domain analyses of the P027/P030 Pool were aligned with the total score results. The LCQ results provide support for the clinical significance of the reductions in objective cough frequency observed for the gefapixant group.

Results of each of the other PRO endpoints intended to measure the impact of cough (Cough Severity VAS, CSD, and PGIC) provide support for the clinical significance of the reductions in objective cough frequency observed for the gefapixant group.

Additional Supportive Efficacy:

- P043 results demonstrated that gefapixant 45 mg BID was superior to placebo in improving LCQ total scores from baseline to Week 12 in patients with recent onset (<12 months) RCC/UCC. Results of other PRO endpoints were supportive of improvement of cough.

- P042 results demonstrated that gefapixant 45 mg BID was superior to placebo in reducing C-SUI episodes based on the percent change in mean daily C-SUI episodes, from baseline to Week 12, in patients with RCC/UCC and with C-SUI. Results of other PRO endpoints were supportive of improvement of cough.

4.1.2.7 Efficacy Conclusion

Based on the totality of data from the gefapixant development program, the data from the prespecified and posthoc analyses of cough frequency and supportive results of multiple PRO endpoints demonstrate that treatment with gefapixant 45 mg BID results in clinically meaningful improvement in 24-hour cough frequency and meets the standard for substantial evidence of effectiveness based on 2 adequate and well-controlled Phase 3 clinical trials of RCC/UCC. The 2 additional well-controlled Phase 3b trials support the efficacy and clinical meaningfulness established in the pivotal studies.

4.2 Overview of Clinical Safety

4.2.1 Methods for Safety Analyses

4.2.1.1 Phase 1 and Phase 2

Phase 1 and Phase 2 safety data are not integrated across study phases because of differences in dosing regimens and study populations. Phase 2 study designs are described in [Table 1].

Across the Phase 1 program in healthy participants (18 studies), safety observations are summarized by the following categories: participants who received any dose of gefapixant (referred to as the "gefapixant group"), participants who received gefapixant and another study medication (referred to as the "gefapixant + other group"), participants who received a study medication other than gefapixant (referred to as the "other group"), and participants who received placebo (referred to as the "placebo group"). An additional Phase 1 study is summarized individually: Study P039 was a Phase 1 double-blind, placebo-controlled, 2-period, crossover study to test the hypothesis that P2X3 antagonism could normalize sleep disordered breathing in participants with moderate to severe OSA. The study is presented separately because of differences in the participant population (OSA, noncough), and because of observed effects on SaO_2.

Because of the wide range of doses administered in the Phase 2 program, Phase 2 safety observations are summarized by gefapixant total daily dose (<100 mg TDD or ≥100 mg TDD) and placebo. Safety in Phase 2 is further characterized by patients with chronic cough and patients with indications other than chronic cough (including healthy participants) to compare the safety profiles of these population subsets.

4.2.1.2 Phase 3

P027/P030 Pool

The safety and tolerability assessment for gefapixant primarily focuses on the pooled 52-week results from the P027 and P030 pivotal studies (referred to as the P027/P030 Pool).

Results for the P027/P030 Pool are presented for gefapixant 45 mg BID (referred to as "gefapixant 45 mg"), gefapixant 15 mg BID (referred to as "gefapixant 15 mg"), and the placebo group. Safety was assessed in the APaT population, which includes all randomized patients who received at least 1 dose of gefapixant or placebo.

Phase 3 study designs are described in [Table 1].

4.2.1.3 Phase 3b Studies

Safety results from the Phase 3b study in patients with recent onset RCC/UCC (P043) and the Phase 3b study in patients with RCC/UCC and with C-SUI (P042) are presented individually. Results from these studies were not integrated with the P027/P030 Pool because

of differences in study design (dosing regimens, cough duration entry criterion, treatment duration, and study populations).

Phase 3b study designs are described in [Table 1].

4.2.1.4 Approach to Clinical Review of Adverse Events by Organ System or Syndrome

Clinical review of specific AEs across the P027/P030 Pool was based on preclinical observations, clinical observations, the mechanism of action of gefapixant, and class-related effects. These events of interest included taste-related AEs, paresthesia oral, hypoesthesia oral, renal and urinary events, pneumonia, lower respiratory tract infections, and hypersensitivity.

Taste-related AEs, including dysgeusia, ageusia, taste disorder, hypogeusia, and hypergeusia, were predefined as safety endpoints of special interest, and AEs of paresthesia oral and hypoesthesia oral were prespecified safety endpoints. PTs of loss of appetite, weight loss, thirst, and dehydration were evaluated as potential clinical sequelae of taste-related AEs.

Although not prespecified as safety endpoints, renal and urological events and the presence of urinary crystals were monitored throughout the clinical development program based on preclinical observations. Clinical evaluation included the review of PTs indicative of hematuria (PT: hematuria), crystalluria (PTs: crystal urine, crystal urine present, and crystalluria), and urolithiasis (PTs: nephrolithiasis, calculus urinary, calculus bladder, and ureterolithiasis). Specialized urine crystal analysis for identification of gefapixant crystals was conducted on urine samples that were confirmed to have crystals or unexplained hematuria.

The potential for protective cough reflex suppression was reviewed by evaluating pneumonia and lower respiratory tract infection AEs. To address the theoretical concern and subsequent clinical sequelae, specific pneumonia PTs, lower respiratory tract infection PTs, and respiratory tract infection PTs were reviewed.

Finally, a review of AEs for potential hypersensitivity was conducted. To minimize the potential for hypersensitivity, patients with a history of anaphylaxis or cutaneous adverse drug reaction to sulfonamide antibiotics or other sulfonamide-containing drugs were excluded from Studies P027 and P030. Specific AEs suggestive of hypersensitivity were reviewed, including, but not limited to PTs of hypersensitivity, rash, urticaria, dermatitis, lip swelling, and tongue pruritis.

4.2.2 Adverse Events

4.2.2.1 Phase 1

4.2.2.1.1 Studies in Healthy Participants

There were no clinically significant safety findings from the pool of the Phase 1 clinical studies in healthy participants. Results were generally consistent with those observed in the Phase 3 program.

A higher proportion of participants in the gefapixant group reported AEs and study intervention-related AEs, compared with the placebo group. All other AE summary measures were low and comparable across groups [Table 12]. The most frequently reported (≥10% of participants) AEs were:

- Gefapixant: dysgeusia (33.6%) and headache (11.9%).
- Placebo: none.

There were no deaths or SAEs.

No safety concerns related to gefapixant urinary crystallization were identified. No clinically significant drug-related abnormalities in complete blood count, ECG, physical examinations, or vital signs were observed.

Table 12
Adverse Events Summary
Gefapixant Clinical Pharmacology Studies (N=18 studies) by Treatment Categories

	MK-7264		MK-7264 + Other		Other		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	438		108		20		76		488	
with one or more adverse events	279	(63.7)	53	(49.1)	5	(25.0)	34	(44.7)	318	(65.2)
with no adverse event	159	(36.3)	55	(50.9)	15	(75.0)	42	(55.3)	170	(34.8)
with drug-related† adverse events	257	(58.7)	44	(40.7)	0	(0.0)	26	(34.2)	287	(58.8)
with serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	4	(0.9)	0	(0.0)	0	(0.0)	1	(1.3)	5	(1.0)
discontinued drug due to a drug-related adverse event	3	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.6)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

MK-7264=gefapixant.
† Determined by the investigator to be related to the drug.
Adverse events that occurred prior to first dose of study drug are excluded.
Source: P001, P002, P003, P007, P011, P017, P020, P022, P023, P024, P025, P026, P028, P032, P036, P037, P040, and P044.
P026 includes 18 subjects with renal impairment.

4.2.2.1.2 Study P039

A total of 22 patients with moderate to severe OSA who were not using PAP for at least 1 month, had a baseline SaO_2 ≥94%, and demonstrated an AHI response to hyperoxia, were randomized and received at least 1 dose of gefapixant in Study P039. Patients received either gefapixant 180 mg or placebo QHS for 7 days in Period 1, followed by a 7-day washout period, and then crossed over for the alternate intervention in Period 2 for 7 days.

Treatment with gefapixant had no effect on the primary endpoint of AHI. Among the exploratory endpoints were PSG pulse oximetry values, analyzed at baseline and following 7 days of gefapixant or placebo. The mean SaO_2, averaged across the sleep stages during the 8-hour polysomnography, was lower after 7 days of gefapixant relative to placebo (GMR [corresponding 90% CI] = 0.986 [0.977, 0.995]).

The most commonly reported AEs were consistent with those observed in the Phase 3 program. There were no SAEs, deaths, or discontinuations due to an AE. There were no clinically meaningful trends noted in laboratory values, vital signs, or ECGs in this study.

4.2.2.2 Phase 2

There were no clinically significant safety findings from the Phase 2 clinical studies. Results are generally consistent with those observed in the Phase 3 program.

Across the Phase 2 studies, AEs overall, study intervention-related AEs, discontinuations due to AEs, and discontinuations due to study intervention-related AEs were higher in the gefapixant ≥100 mg TDD group compared with the gefapixant <100 mg TDD and placebo groups [Table 13]. The most frequently reported (≥10% of patients) AEs were:

- Gefapixant ≥100 mg TDD: dysgeusia (41.1%), taste disorder (29.8%), ageusia (16.3%), nausea (12.6%), hypogeusia (12.4%), and headache (11.2%).
- Gefapixant <100 mg TDD: dysgeusia (16.8%) and upper respiratory tract infection (12.0%).
- Placebo: none.

The incidences of SAEs were low (<1.5%). Two SAEs had fatal outcomes: 1 event of acute respiratory failure in the gefapixant ≥100 mg TDD group and 1 event of pneumonia in the placebo group. The SAE of respiratory failure was assessed as possibly related to study intervention by the investigator. The SAE of pneumonia was assessed as not related to study intervention by the investigator.

There was no evidence of renal or urinary injury, urolithiases, or gefapixant crystalluria in the Phase 2 studies. No concerns for hypersensitivity were observed. Safety results in the

subset of patients with chronic cough were generally comparable with the subset of patients with indications other than chronic cough.

Table 13
Adverse Event Summary
Phase 2 Trials
All Subjects as Treated

	Placebo		MK-7264 < 100 mg Total Daily Dose		MK-7264 ≥ 100 mg Total Daily Dose		MK-7264 Combined	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	568		291		436		727	
with one or more adverse events	301	(53.0)	204	(70.1)	413	(94.7)	617	(84.9)
with no adverse event	267	(47.0)	87	(29.9)	23	(5.3)	110	(15.1)
with drug-related† adverse events	138	(24.3)	130	(44.7)	394	(90.4)	524	(72.1)
with serious adverse events	6	(1.1)	1	(0.3)	6	(1.4)	7	(1.0)
with serious drug-related† adverse events	0	(0.0)	1	(0.3)	3	(0.7)	4	(0.6)
who died	1	(0.2)	0	(0.0)	1	(0.2)	1	(0.1)
discontinued drug due to an adverse event	13	(2.3)	10	(3.4)	70	(16.1)	80	(11.0)
discontinued drug due to a drug-related† adverse event	6	(1.1)	9	(3.1)	65	(14.9)	74	(10.2)
discontinued drug due to a serious adverse event	2	(0.4)	0	(0.0)	2	(0.5)	2	(0.3)
discontinued drug due to a serious drug-related† adverse event	0	(0.0)	0	(0.0)	2	(0.5)	2	(0.3)

MK-7264=gefapixant.
† Determined by the investigator to be related to the drug.
Includes subjects from the following trials: P004, P005, P006, P009, P010, P012, P013, P014, P015, P016, P019, P021, P033, P034.
Subjects in crossover studies were counted more than once, in both active treatment and placebo groups, according to the treatment they were on at the onset of the adverse event.
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4.2.2.3 Phase 3 – P027/P030 Pool

The incidence of AEs overall in the P027/P030 Pool was higher in the gefapixant 45 mg group compared with the placebo group [Table 14]. The incidences of study intervention-related AEs, discontinuation of study intervention due to AEs, discontinuation of study intervention due to a study intervention-related AE, and discontinuation of study intervention due to a taste-related AE were higher in the gefapixant 45 mg group compared with the gefapixant 15 mg and placebo groups. The imbalances across intervention groups were primarily due to taste-related AEs.

Table 14
Adverse Event Summary
Safety Pool Across P027 and P030 Over the Period of 52 Weeks
All Subjects as Treated

	Placebo		MK-7264 15 mg BID		MK-7264 45 mg BID	
	n	(%)	n	(%)	n	(%)
Subjects in population	675		686		683	
with one or more adverse events	533	(79.0)	559	(81.5)	607	(88.9)
with no adverse event	142	(21.0)	127	(18.5)	76	(11.1)
with drug-related† adverse events	138	(20.4)	194	(28.3)	470	(68.8)
with serious adverse events	39	(5.8)	41	(6.0)	38	(5.6)
with serious drug-related† adverse events	1	(0.1)	0	(0.0)	1	(0.1)
who died	2	(0.3)	2	(0.3)	0	(0.0)
discontinued drug due to an adverse event‡	39	(5.8)	55	(8.0)	151	(22.1)
discontinued drug due to a drug-related† adverse event	21	(3.1)	31	(4.5)	131	(19.2)
discontinued drug due to a serious adverse event	8	(1.2)	10	(1.5)	2	(0.3)
discontinued drug due to a serious drug-related† adverse event	1	(0.1)	0	(0.0)	0	(0.0)
discontinued drug due to a taste-related adverse event	2	(0.3)	9	(1.3)	95	(13.9)

BID=twice daily; MK-7264=gefapixant.
† Determined by the investigator to be related to the drug.
‡ Subjects with one or more adverse events for which the action taken is listed as 'drug withdrawn'.

4.2.2.3.1 Common Adverse Events

In the P027/P030 Pool, the most frequently reported (≥10% of patients) AEs were [Table 15]:

- Gefapixant 45 mg: dysgeusia (41.1%), nasopharyngitis (17.6%), ageusia (14.6%), headache (14.5%), and hypogeusia (10.7%).
- Gefapixant 15 mg: nasopharyngitis (20.4%), headache (15.7%), and dysgeusia (11.4%).
- Placebo: nasopharyngitis (17.9%), and headache (14.5%).

Dysgeusia and ageusia were the most frequently reported taste-related AEs and the incidences were dose-related. The incidences of non-taste-related AEs were generally balanced across the intervention groups.

Table 15
Subjects With Specific Adverse Events
(Incidence ≥ 5% in One or More Treatment Groups)
Safety Pool Across P027 and P030 Over the Period of 52 Weeks
All Subjects as Treated

	Placebo		MK-7264 15 mg BID		MK-7264 45 mg BID	
	n	(%)	n	(%)	n	(%)
Subjects in population	675		686		683	
with one or more specific adverse events	533	(79.0)	559	(81.5)	607	(88.9)
with no specific adverse events	142	(21.0)	127	(18.5)	76	(11.1)
Gastrointestinal disorders	**172**	**(25.5)**	**203**	**(29.6)**	**250**	**(36.6)**
Diarrhoea	32	(4.7)	42	(6.1)	39	(5.7)
Dry mouth	17	(2.5)	22	(3.2)	45	(6.6)
Nausea	45	(6.7)	34	(5.0)	64	(9.4)
General disorders and administration site conditions	**62**	**(9.2)**	**59**	**(8.6)**	**91**	**(13.3)**
Infections and infestations	**334**	**(49.5)**	**348**	**(50.7)**	**315**	**(46.1)**
Bronchitis	35	(5.2)	40	(5.8)	29	(4.2)
Influenza	43	(6.4)	38	(5.5)	35	(5.1)
Nasopharyngitis	121	(17.9)	140	(20.4)	120	(17.6)
Upper respiratory tract infection	36	(5.3)	56	(8.2)	43	(6.3)
Urinary tract infection	34	(5.0)	48	(7.0)	28	(4.1)
Injury, poisoning and procedural complications	**86**	**(12.7)**	**82**	**(12.0)**	**79**	**(11.6)**
Investigations	**51**	**(7.6)**	**47**	**(6.9)**	**44**	**(6.4)**
Metabolism and nutrition disorders	**32**	**(4.7)**	**27**	**(3.9)**	**56**	**(8.2)**
Musculoskeletal and connective tissue disorders	**157**	**(23.3)**	**144**	**(21.0)**	**124**	**(18.2)**
Arthralgia	38	(5.6)	35	(5.1)	30	(4.4)
Back pain	44	(6.5)	44	(6.4)	37	(5.4)
Nervous system disorders	**175**	**(25.9)**	**240**	**(35.0)**	**468**	**(68.5)**
Ageusia	6	(0.9)	16	(2.3)	100	(14.6)
Dysgeusia	36	(5.3)	78	(11.4)	281	(41.1)
Headache	98	(14.5)	108	(15.7)	99	(14.5)
Hypogeusia	4	(0.6)	22	(3.2)	73	(10.7)
Taste disorder	3	(0.4)	10	(1.5)	61	(8.9)
Psychiatric disorders	**23**	**(3.4)**	**35**	**(5.1)**	**34**	**(5.0)**
Renal and urinary disorders	**35**	**(5.2)**	**45**	**(6.6)**	**46**	**(6.7)**
Respiratory, thoracic and mediastinal disorders	**147**	**(21.8)**	**146**	**(21.3)**	**182**	**(26.6)**
Cough	28	(4.1)	44	(6.4)	49	(7.2)
Oropharyngeal pain	29	(4.3)	26	(3.8)	37	(5.4)
Skin and subcutaneous tissue disorders	**64**	**(9.5)**	**47**	**(6.9)**	**63**	**(9.2)**

BID=twice daily; MK-7264=gefapixant.
Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

4.2.2.3.2 Deaths

Four deaths occurred in the P027/P030 Pool [Table 14]. Two deaths occurred in the gefapixant 15 mg group: 1 event of cardiopulmonary failure and 1 event of respiratory tract infection. The event of respiratory tract infection was reported after the post-treatment 14-day follow-up period. Two deaths occurred in the placebo group: 1 event of death and 1 event of accidental death. None of the deaths were considered to be related to study intervention by the investigator.

4.2.2.3.3 Other Serious Adverse Events

In the P027/P030 Pool, the incidence of SAEs overall was low (≤6.0%) and comparable across intervention groups [Table 16]. The incidences of individual SAEs were low; no individual SAE was reported in more than 3 patients in any intervention group. Two SAEs (hypoglycemia in the gefapixant 45 mg group and ureterolithiasis in the placebo group) were considered to be related to study intervention by the investigator.

Table 16
Subjects With Serious Adverse Events
(Incidence ≥ 3 Subjects With an Adverse Event in One or More Treatment Groups)
Safety Pool Across P027 and P030 Over the Period of 52 Weeks
All Subjects As Treated

	Placebo		MK-7264 15 mg BID		MK-7264 45 mg BID	
	n	(%)	n	(%)	n	(%)
Patients in population	675		686		683	
with one or more serious adverse events	39	(5.8)	41	(6.0)	38	(5.6)
with no serious adverse events	636	(94.2)	645	(94.0)	645	(94.4)
Cardiac disorders	**1**	**(0.1)**	**3**	**(0.4)**	**2**	**(0.3)**
Gastrointestinal disorders	**4**	**(0.6)**	**2**	**(0.3)**	**3**	**(0.4)**
General disorders and administration site conditions	**3**	**(0.4)**	**0**	**(0.0)**	**0**	**(0.0)**
Infections and infestations	**11**	**(1.6)**	**11**	**(1.6)**	**6**	**(0.9)**
Influenza	0	(0.0)	3	(0.4)	0	(0.0)
Pneumonia	0	(0.0)	3	(0.4)	1	(0.1)
Injury, poisoning and procedural complications	**1**	**(0.1)**	**3**	**(0.4)**	**8**	**(1.2)**
Musculoskeletal and connective tissue disorders	**3**	**(0.4)**	**6**	**(0.9)**	**5**	**(0.7)**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**3**	**(0.4)**	**5**	**(0.7)**	**2**	**(0.3)**
Nervous system disorders	**3**	**(0.4)**	**5**	**(0.7)**	**1**	**(0.1)**
Renal and urinary disorders	**3**	**(0.4)**	**2**	**(0.3)**	**3**	**(0.4)**
Respiratory, thoracic and mediastinal disorders	**7**	**(1.0)**	**2**	**(0.3)**	**5**	**(0.7)**
Vascular disorders	**2**	**(0.3)**	**3**	**(0.4)**	**2**	**(0.3)**

BID=twice daily; MK-7264=gefapixant.
Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if it meets the criterion in the report title.

4.2.2.3.4 Other Significant Adverse Events

The incidence of AEs leading to discontinuation of study intervention was higher in the gefapixant 45 mg group (22.1%) compared with the gefapixant 15 mg (8.0%) and placebo (5.8%) groups, primarily due to taste-related AEs [Table 14]. The most frequently reported (≥3% of patients) AEs leading to discontinuation of study intervention were:

- Gefapixant 45 mg: dysgeusia (8.6%) and ageusia (3.7%).
- Gefapixant 15 mg: none.
- Placebo: none.

4.2.2.3.5 Analysis of Adverse Events by Organ System or Syndrome

4.2.2.3.5.1 Taste-related AEs

The incidence of taste-related AEs was higher in the gefapixant 45 mg group (65.4%) compared with the gefapixant 15 mg (17.5%) and placebo groups (7.0%) [Figure 15]. The most frequently (>5% of patients) reported taste-related AEs were:

- Gefapixant 45 mg: dysgeusia (41.1%), ageusia (14.6%), hypogeusia (10.7%), and taste disorder (8.9%).
- Gefapixant 15 mg: dysgeusia (11.4%).
- Placebo: dysgeusia (5.3%).

Most of the taste-related AEs were considered related to study intervention by the investigator. Most (96.2%) taste-related AEs in the gefapixant 45 mg group were mild or moderate intensity. No taste-related SAEs were reported.

Study intervention discontinuation due to taste-related AEs was higher in the gefapixant 45 mg group (13.9%) compared with the gefapixant 15 mg (1.3%) and placebo (0.3%) groups. Of the discontinuations resulting from taste-related AEs in the gefapixant 45 mg group, half occurred during the initial 4 weeks of treatment.

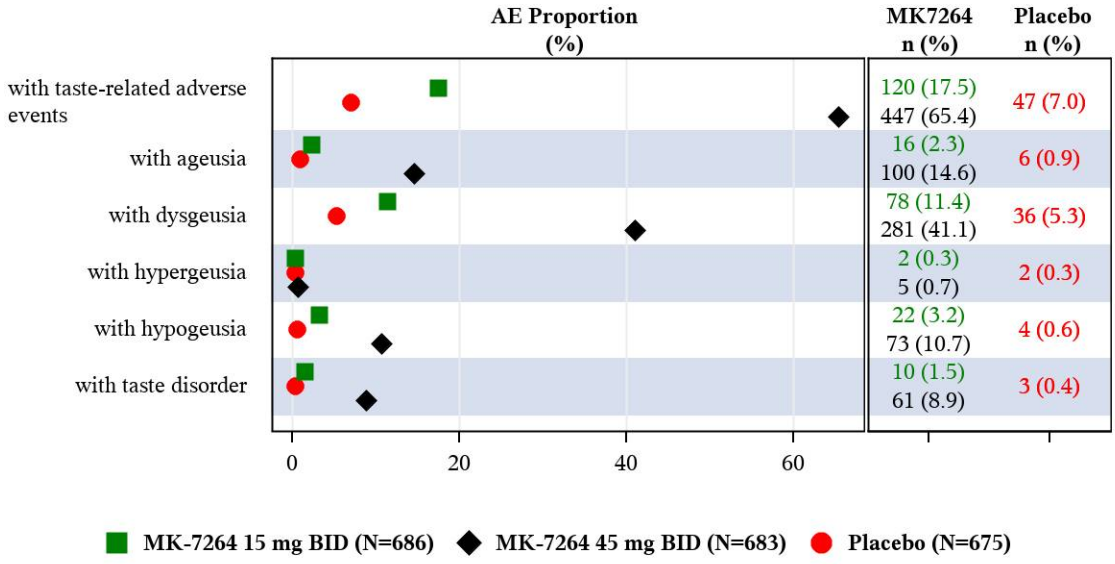
Among the patients in the gefapixant 45 mg group with any taste-related AE, median time to onset was 2.0 days after the first dose compared with 12.5 days in the gefapixant 15 mg and 33 days in the placebo groups.

For time to resolution of taste-related AEs in the gefapixant 45 mg group, 24.6% of patients resolved all taste-related AEs while on study intervention (ie, on or before the last dose) and median time to resolution for these patients was 65 days after AE onset; for patients with resolution of all taste-related AEs after discontinuing treatment, the median time to resolution was 5 days after the last dose. Overall, 96.0% (429/447) of the patients in the gefapixant 45 mg group resolved all taste-related AEs by database lock. Follow-up was conducted after database lock on the 4% (18/447) of patients in the gefapixant 45 mg group and the 14.9% (7/47) of patients in the placebo group with unresolved taste-related AEs. At the time of that follow-up, taste-related AE had resolved in 11 of the 18 patients in the gefapixant 45 mg group and 1 of the 7 patients in the placebo group with unresolved taste-related AEs at database lock. As such, 98.4% (440/447) of the patients in the gefapixant 45 mg group resolved all taste-related AEs at the time of follow-up [31].

The median duration of any taste-related AE was higher in the gefapixant 45 mg group (194.0 days) compared with the gefapixant 15 mg (134.0 days) and placebo groups (60.0 days).

The incidences of AEs representing potential clinical sequelae of taste-related AEs, including decreased appetite, weight decreased, abnormal loss of weight, dehydration, and thirst, were low (<4.0%) across the intervention groups. Blood urea increased was reported only in the gefapixant 15 mg group (0.1%). There were no clinically meaningful changes from baseline in weight.

Figure 15
Difference in Proportion of Subjects With Taste-Related Adverse Events
Safety Pool Across P027 and P030 Over the Period of 52 Weeks
All Subjects as Treated



BID=twice daily; MK-7264=gefapixant.

4.2.2.3.5.2 Other Adverse Events

Results from the P027/P030 Pool did not support a causal association for gefapixant with the AEs of hypoesthesia oral, paresthesia oral, renal and urinary AEs, pneumonia and lower respiratory tract infections, and AEs suggestive of hypersensitivity.

- The incidences of hypoesthesia oral and paresthesia oral were low (<3.5%) across all intervention groups.

- The overall incidence of specific renal and urinary AEs potentially associated with renal and urinary tract injury was low (<6.0%) across all intervention groups, and the individual incidences of hematuria, crystalluria, and urolithiasis PTs were low (<3.0%) across all intervention groups. Of the AEs specifically associated with renal and urinary tract injury, 5 patients reported SAEs. These SAEs were nephrolithiasis (1 patient in the gefapixant 45 mg and 1 patient in the placebo groups), calculus urinary (1 patient in the gefapixant 45 mg and 1 patient in the gefapixant 15 mg groups), and ureterolithiasis (1 patient in the placebo group). One patient in the gefapixant 45 mg group tested positive for gefapixant urinary crystals at the last study visit (Day 363, Week 52); however, the concentration of gefapixant in a simultaneous PK plasma sample was below the limit of quantification. A follow-up urine sample collected on Day 369 was negative for gefapixant urinary crystals. No adverse clinical sequelae attributable to urinary crystals were observed in this patient. Across all intervention groups, there were small mean changes from baseline in eGFR and in urea nitrogen, and no mean changes from baseline in creatinine.

- The overall incidence of AEs associated with pneumonia and lower respiratory tract infection was low (≤5%) across all intervention groups. Pneumonia SAEs were reported by 6 patients in the gefapixant 15 mg group, 1 patient in the gefapixant 45 mg group, and none in the placebo group. In all intervention groups, the incidences of lower respiratory tract infection and respiratory tract infection were low (<3.0%) and comparable. Respiratory tract infection SAEs were reported in 1 patient in the gefapixant 15 mg group and 1 patient in the placebo group.

- The overall incidence of hypersensitivity AEs was low (<6.5%) and comparable across intervention groups. The individual incidences of specific AEs suggestive of hypersensitivity were low (<2.5%) and comparable across the intervention groups. None were SAEs.

4.2.2.3.6 Other Observations Related to Safety

In the P027/P030 Pool, changes in clinical laboratory results were not clinically meaningful. Overall, there were no notable differences in mean changes over time in chemistry and hematology measurements across intervention groups.

Although a small percentage (<1%) of patients tested negative for urinary crystals at baseline and subsequently tested positive at Week 52, these changes were not clinically meaningful.

One patient in the gefapixant 45 mg group had a positive result for gefapixant urinary crystals and is discussed in [Sec. 4.2.2.3.5.2].

Overall, the incidences of laboratory findings that met predetermined criteria were low (<12%) and individual incidences were generally comparable across intervention groups. Laboratory evaluations related to renal function (ie, changes from baseline in eGFR, urea nitrogen, and creatinine) are discussed in [Sec. 4.2.2.3.5.2].

4.2.2.4 Phase 3b – Study P043 Safety Summary

Safety results were consistent with those observed in the Phase 3 program. The incidence of taste-related AEs was higher in the gefapixant group compared with the placebo group. One patient in the gefapixant group had a positive specialized urine crystal analysis result for gefapixant crystals on Day 87; no abnormal renal or other laboratory values were reported for this patient. A subsequent test on Day 130 was negative for gefapixant crystals. The incidence of SAEs was low and comparable between intervention groups. One death was reported in the placebo group. There were no clinically meaningful trends in laboratory values or vital signs in this study.

4.2.2.5 Phase 3b – Study P042 Safety Summary

Safety results were consistent with those observed in the Phase 3 program. The incidence of taste-related AEs was higher in the gefapixant group compared with the placebo group. The incidence of SAEs was low and comparable between intervention groups. No deaths occurred during this study. There were no clinically meaningful trends in laboratory values or vital signs in this study.

4.2.2.6 Summary of Key Safety Results

- Most AEs in patients who receive gefapixant were mild or moderate in intensity and the incidence of SAEs, overall, was low.

- Taste-related AEs were all nonserious, mostly mild or moderate in intensity and were the most frequently reported AEs in patients who received gefapixant 45 mg BID and are dose-related. Resolution of taste-related AEs occurred in most patients during treatment or after discontinuation of treatment. No clinically meaningful sequelae associated with taste-related AEs, such as loss of appetite, weight loss, or dehydration, were observed.

- The incidences of other AEs were generally balanced across gefapixant groups and placebo.

- The gefapixant 45 mg group had a higher incidence of discontinuations from study intervention than the gefapixant 15 mg group and placebo group, primarily due to taste-related AEs.

4.2.3 Safety Conclusion

Taste-related AEs, though reported frequently, have shown no evidence of clinically important sequelae and do not represent a significant safety concern. Taste-related AEs are a manageable tolerability issue and the totality of the safety data demonstrate that gefapixant administered as 45 mg BID in adults with RCC/UCC has a generally acceptable safety and tolerability profile.

5 BENEFIT-RISK ASSESSMENT

5.1 Analysis of Condition

5.1.1 Disease or Condition

Chronic cough, specifically RCC/UCC, is a debilitating illness. Patients with chronic cough may experience substantial physical, social, and psychological consequences because of excessive coughing. Patients with RCC/UCC are mostly female; the mean age in a recent publication was 55 years [10]. Patients with chronic cough may experience substantial physical consequences because of excessive coughing including sleep disturbance, breathlessness, C-SUI, and in some cases, more severe effects such as cough-induced rib fracture or syncope. In addition to frequent cough, patients often experience an irritation or "tickling" in the larynx and chest; this can be accompanied by chest tightness, dysphonia, or muscular pain. As these symptoms can persist for years, chronic cough can cause considerable social distress and social isolation for patients. Chronic cough patients report higher levels of depression, anxiety, fatigue, and somatic symptoms compared with noncoughers [13]. In addition, chronic cough patients report embarrassment, fear of a serious illness, and frustration as factors that impact their psychological well-being. Cough can affect patients every hour of every day and affect a wide range of basic activities such as eating, answering the telephone, work productivity, and activities of daily living [15] [3]. Furthermore, patients with chronic cough may lack the support and sympathy associated with other conditions [15].

5.1.2 Current Therapies

In the US, there is no medicinal product approved for the treatment of RCC/UCC. Many treatments such as gabapentin, dextromethorphan, low-dose morphine, and codeine are often prescribed off-label and are either associated with side effects, have addictive potential, or have limited evidence to support their use in chronic cough [32] [33].

As of 18-SEP-2023, gefapixant is approved for RCC/UCC in Japan, Switzerland, and the EU.

5.2 Benefits

A comprehensive assessment of the efficacy data in the gefapixant clinical development program demonstrates the clinical benefit of gefapixant in reducing cough frequency in patients with RCC/UCC, supported by both objective and subjective endpoints. In both Studies P027 and P030, statistical significance was achieved for the primary endpoint of reducing the number of coughs per hour over a 24-hour period, compared with placebo, after 12 and 24 weeks, respectively, in patients treated with gefapixant 45 mg BID (prespecified analysis: longitudinal ANCOVA applied to the original dataset). After the recount and reanalysis (longitudinal ANCOVA applied to the recount dataset), the reduction in 24-hour cough frequencies remained consistent in the gefapixant 45 mg group vs. placebo, with Study

P030 showing statistically significant difference (p=0.030) and Study P027 just missing statistical significance (p=0.057). A consistent treatment effect was observed across different analyses and datasets, and patients reported improvement in their condition across multiple Phase 3 and Phase 3b studies.

Furthermore, the clinical relevance of gefapixant 45 mg BID in reducing objective cough frequency was supported in both studies by the observed improvements on PROs. Study P030 was specifically designed and powered, along with other objective cough endpoints, to assess the impact of chronic cough on HRQoL as measured by the LCQ and was adjusted for multiplicity in the step-down procedure. A significantly greater proportion of patients treated with gefapixant 45 mg BID were defined as responders on the LCQ relative to the placebo-treated patients, in Study P030. These data indicate that gefapixant is effective in reducing both the frequency of cough and the impact of cough on patients' daily lives.

Results from the P027/P030 Pool confirm that gefapixant reduces 24-hour cough frequency in patients with RCC or UCC and demonstrated the consistency of results with respect to reducing cough frequency. Pooled data for the cough-specific PROs, including LCQ, Cough Severity VAS, and CSD showed consistent improvements compared with placebo through 52 weeks.

The population evaluated in the Phase 3 studies is consistent with the clinical demographics of RCC or UCC patients described in the published literature [7]. The mean duration of chronic cough for patients in the Phase 3 studies (11 years) reflects a chronic cough population that has likely exhausted currently available diagnostic modalities and treatments. Patients in the Phase 3 studies also had features consistent with CHS, a clinical syndrome often associated with RCC or UCC patients. Given the consistency in demographic information on similar chronic cough patients in the literature, the results of the Phase 3 program are likely applicable to patients seen in clinical practice.

The effect of gefapixant on a socially debilitating comorbidity in primarily women with chronic cough, stress urinary incontinence, was assessed in Study P042, and the effect of gefapixant on LCQ and Cough Severity VAS in patients with recent onset RCC/UCC was evaluated in Study P043. These studies are considered supportive evidence of efficacy for gefapixant, as evaluated by LCQ and other PROs. Although these 2 Phase 3b studies did not include objective cough frequency endpoints, the PROs support the clinically meaningful effect of gefapixant in patients with RCC or UCC.

In total, the data described demonstrate efficacy of gefapixant and thus meet the standard for substantial evidence of effectiveness based on 2 adequate and well-controlled clinical trials. The analyses of the recount dataset showed generally consistent results when compared to the original dataset. The accuracy and reliability of the VitaloJAK™ cough counting system was established and further substantiates the results of the cough recount dataset analyses. Individual efficacy results from the Phase 3b studies further support the clinically meaningful

effect of gefapixant on PROs, including the LCQ in Study P043 and reports of cough-induced SUI in Study P042, a socially debilitating complication of chronic cough.

5.3 Risks

A comprehensive evaluation of the safety and tolerability of gefapixant has been performed. The most frequently reported AEs in the gefapixant 45 mg group were taste-related and considered expected. Taste-related AEs were the most frequently reported AEs in the Phase 3 program and most were mild or moderate and none were SAEs. Taste-related AEs resolved in the vast majority of patients during treatment or after discontinuation of treatment and occurred early in the treatment course, allowing for reasonable monitoring in clinical practice. AEs representing potential clinical sequelae of taste-related AEs were evaluated; there were no clinically meaningful changes from baseline in weight, and AEs of loss of appetite, weight loss, and dehydration were low and comparable across the treatment groups, suggesting tolerability as the primary reason for treatment discontinuation.

Gefapixant contains a sulfonamide moiety, but is lacking an arylamine group (NH2) at the N4 position present in sulfonamide antimicrobials and is considered to be a nonsulfonylarylamine. Patients with a history of anaphylaxis or cutaneous adverse drug reaction (with or without systemic symptoms) to sulfonamide antibiotics or other sulfonamide-containing drugs were excluded from the Phase 3 studies. The potential for hypersensitivity was evaluated by reviewing AEs that could indicate hypersensitivity. Across intervention groups, the individual incidences of AEs of hypersensitivity or suggestive of hypersensitivity were low (<2.5%) and comparable across intervention groups; none were SAEs.

AEs reported under the SOC Investigations and the SOC Renal and urinary disorders, were evaluated for potential association with renal or urinary system injury. The overall incidence of specific renal and urinary AEs potentially associated with renal and urinary tract injury was low (<6.0%) across the intervention groups. The individual incidences of the AEs of hematuria, crystalluria, and urolithiasis were low (<3.0%) across all intervention groups.

5.4 Benefit-Risk Assessment

No drug is approved in the US for the treatment of RCC/UCC. The efficacy of gefapixant on objective and subjective cough measures as well as the safety of gefapixant up to 52 weeks in adults with RCC/UCC were well-characterized in Studies P027 and P030.

Results from the prespecified analyses using the original dataset demonstrated that gefapixant provided statistically significant and clinically meaningful improvement in 24-hour cough frequency. Results from the posthoc supportive analyses, including using the recount dataset, demonstrated clinically meaningful reductions in 24-hour cough frequency. Taken together with PRO results, these data confirm the conclusion that gefapixant provides clinically meaningful treatment benefit.

The totality of efficacy data across the Phase 2 studies, Phase 3 studies, and supplemented by the Phase 3b studies, provides substantial evidence of effectiveness of gefapixant for the treatment of RCC/UCC.

Taste-related AEs, the most frequently reported AEs, were all nonserious and most were mild or moderate in intensity. Because taste-related AEs were readily identified, resolved with discontinuation, and did not demonstrate clinically important sequelae, taste-related AEs are a manageable tolerability issue.

The overall benefit-risk of gefapixant is positive. Data from Phase 2 and Phase 3 efficacy data (both the original cough counts and the prespecified analyses and the recounts and posthoc analyses) as well as the Phase 3b studies, support the use of gefapixant of treatment of RCC/UCC in adults. This efficacy, balanced against the well-characterized safety profile for gefapixant, supports approval of gefapixant for the treatment of RCC/UCC in adults, a debilitating disease with no approved treatment, to fulfill the unmet need in this population.

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