20 July 2023
EMA/357321/2023 Corr.1
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lyfnua

International non-proprietary name: gefapixant

Procedure No. EMEA/H/C/005476/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

Abbreviation	Definition
ACCP	American College of Chest Physicians
ACE	Angiotensin-converting enzyme
AE	Adverse event
AHI	Apnea-hypopnea Index
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APaT	All participants as treated
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BID	Twice daily
BMI	Body mass index
BTS	British Thoracic Society
CC	Chronic cough
CHS	Cough hypersensitivity syndrome
CI	Confidence interval
CNS	Central nervous system
COVID-19	Coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CSD	Cough severity diary
CSF	Cerebrospinal fluid
CSR	Clinical study report
CT	Computed tomography
CTD	Common technical document
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EQ5D-5L	EuroQoL Five Dimensions Five Level questionnaire
E-R analysis	Exposure-response analysis
FAS	Full analysis set
FDA	United States Food and Drug Administration
GERD	Gastroesophageal reflux disease
HARQ	Hull Airway Reflux Questionnaire
HRQoL	Health-related quality of life
HRV-16	Human rhinovirus type 16
IND	Investigational new drug
IPF	Idiopathic pulmonary fibrosis
IPF	Idiopathic pulmonary fibrosis

iSAP	Integrated statistical analysis plan
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
LCQ	Leicester cough questionnaire
LLT	Lowest level term
MI	Multiple Imputation
M&N	Miettinen and Nurminen
MCID	Minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
OSA	Obstructive sleep apnoea
PAP	Positive airway pressure
PD	Pharmacodynamics
PGIC	Patient global impression of change
PK	Pharmacokinetics
Pop-PK	Population pharmacokinetics
PRO	Patient-reported outcome
PSG	Polysomnography
PT	Preferred term
QD	Once a day
QHS	Daily at bedtime
QoL	Quality of life
RCC	Refractory chronic cough
SAE	Serious adverse event
SaO2	Oxygen saturation
SAP	Statistical analysis plan
SCE	Summary of clinical efficacy
SCS	Summary of clinical safety
SD	Standard deviation
SF-12	12-Item Short Form health survey
SOC	System organ class
sSAP	Supplemental statistical analysis plan
TDD	Total daily dose
UACS	Upper airway cough syndrome
UCC	Unexplained chronic cough
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
VAS	Visual analogue scale
WPAI	Work productivity and activity impairment questionnaire

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Merck Sharp & Dohme B.V. submitted on 2 February 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Lyfnua, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 October 2019.

The applicant applied for the following indication: Lyfnua is indicated in adults for the treatment of refractory or unexplained chronic cough.

1.2. Legal basis, dossier content and multiples

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

The application for Lyfnua was submitted along with the application for Gefzuris, subject to compliance with Article 82.1 of Regulation (EC) No 726/2004. However, the MAA for Gefzuris was withdrawn by the applicant during the assessment.

1.3. Information on Paediatric requirements

Pursuant to Article 7 Regulation (EC) No 1901/2006, the application included an EMA Decision P/0380/2019 on the granting of a (product-specific) waiver.

Pursuant to Article 11(1)(b) of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0380/2019 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4.2. New active substance status

The applicant requested the active substance gefapixant contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Scientific advice

Scientific advice was sought in December 2019 (EMA/CHMP/SAWP/85718/2020) on the selection of starting material and key reactants for gefapixant citrate drug substance. The applicant has followed the recommendations of CHMP and provided the requested additional data.

Concerning the clinical aspects of this development, scientific advice was received from the CHMP in 2017, and the final advice letter was issued in July 2017, EMA/CHMP/SAWP/432855/2017. The advice included a variety of questions related to both pre-clinical and clinical. With regards to the non-clinical aspects discussed, questions on the completed and planned toxicity studies were put forward and agreed by the CHMP, but at the same time interest was drawn to the formation of crystals in the urine and associated histopathology changes in the urinary tract. In that context, the importance of conducting the 6-month carcinogenicity study in rasH2 mice was conveyed to the applicant, and it was noted that detailed histopathological analysis should be performed to clearly demonstrate (the absence of) an association of precipitates and tumour formation. Since then, the applicant has followed advice and studied non-clinical carcinogenicity in two species.

With regard to the clinical aspects of this development, several issues raised by the company were acknowledged and agreed upon by the CHMP for the proposed replicate phase 3 trials in chronic cough, such as the use of the VitaloJAK™ to measure cough frequency (but not as the sole or single primary endpoint), the justification of the doses (with remarks on the definition of the target population), the size of the safety database, the proposed pooling of efficacy and safety data, the inclusion of Cough Severity Diary (CSD) and Cough Severity Visual Analogue Scale (VAS) as secondary endpoints. Regarding the PRO measurements, it was also advised to include a CSD cut-off of 2.7 (corresponding to PGIC ratings of much or very much improved), which was followed by the company.

Several recommendations were included in the CHMP advice, that were not all followed by the applicant. Importantly, it was conveyed that a sole primary endpoint was not considered sufficient to document clinical relevance. The inclusion of an adequately validated subjective/functional variable ensuring patient relevance (PRO) as co-primary endpoints was advised instead, as well as the incorporation of the Patient Global Impression of Change (PGIC) as a secondary endpoint. In contrast, both phase III studies in this submission do not include a co-primary endpoint, and the PGIC was included as an exploratory endpoint only. It was already indicated during the SA that the efficacy should be demonstrated convincingly for both endpoints, and improvements seen in these endpoints must be statistically significant and clinically relevant (clinically relevant threshold should be prespecified).

Given that the target condition would require long-term or chronic treatment, it has been further noted in the SA procedure that maintenance of treatment effect and absence of tolerance needs to be shown. To that end, the applicant proposed to expand the duration of one of the trials to 6 months. This was noted by the CHMP, but it was also strongly preferred to perform a randomised withdrawal study following stable verum treatment, randomising predefined responders to active treatment or placebo. The relapse of symptoms according to pre-specified criteria should be the trial endpoint. Also, rebound and withdrawal reactions required attention in the form of off-treatment data.

In conclusion, the main issues that are not in line with the given SA are the absence of a co-primary endpoint and a withdrawal study. The applicant also did not proceed with an active comparator study as initially discussed. (For completeness of this section, it is also noted that advice recommending application to the PDCO for a full paediatric waiver was also given to the applicant in 2019 (EMEA/H/SA/4046/1/2019/PED/II)).

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Elita Poplavska

The appointed CHMP co-rapporteur had no such prominent role in Scientific advice relevant for the indication subject to the present application.

The application was received by the EMA on	2 February 2021
The procedure started on	25 February 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	19 May 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 May 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	31 May 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 June 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	11 August 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	23 September 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	14 October 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	12 November 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	03 December 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 December 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	16 December 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	21 December 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all	13 January 2022

CHMP and PRAC members on	
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	21 January 2022
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	27 January 2022
Applicant's clock stop extension request adopted on	21 July 2022
Working Party experts were convened to address questions raised by the CHMP The CHMP considered the views of the Working Party as presented in the minutes of this meeting.	05-09 September 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 March 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	19 April 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	20 April 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	26 April 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 May 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	08 June 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	16 June 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	22 June 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 June 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	07 July 2023

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Lyfnua on	20 July 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS).	20 July 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The claimed indication for this medicinal product is: Gefapixant is indicated in adults for the treatment of refractory or unexplained chronic cough.

Cough is the most common physical complaint for which patients seek medical attention, accounting for up to 38% of outpatient pulmonary consultations in the US. In Europe, a survey administered to adults with chronic cough indicated that 72% of respondents had seen a doctor at least 3 times for their cough, yet only 53% had received a suggested diagnosis for their cough. The estimated prevalence of chronic cough ranges from approximately 4% to 11%. Overall, the proportion of patients with a chronic cough that is either refractory to the treatment of any underlying condition or unexplained ranges from 2.7% to 46%, demonstrating that the epidemiology of RCC and UCC is not well understood.

2.1.2. Epidemiology

Cough was only recently perceived as a clinical entity besides as a symptom from other respiratory diseases (European Respiratory Society Guideline on Chronic Cough). Cough is a protective reflex to prevent aspiration into the lung and to enhance airway clearance. It is a multistep process that begins with the activation of airway sensory neurons by chemical or mechanical stimuli. The vagus nerve contains functionally distinct subsets of sensory neurons such as Aδ- and C-fibres that contribute to the initiation of the cough reflex.

Because of their sensitivity to mechanical and acidic stimuli, Aδ-fibres are believed to protect the lower airways against accumulated secretions or aspiration events. C-fibres are activated in response to inflammation or the presence of chemical irritants and have thus been proposed as the appropriate target for the development of therapies to treat cough presenting as a medical complaint.

Chronic cough observed in refractory chronic cough (RCC) and unexplained chronic cough (UCC) is potentially related to activation of C-fibres *via* binding of extracellular ATP to P2X3 receptors. However, the exact role of this P2X3 receptor in cough is still unclear. P2X3 receptors are ATP-gated ion channels found on sensory C-fibres in the nodose derived neurons of the vagal nerve in the airways. ATP is released from airway mucosal cells under conditions of inflammation, and the binding of extracellular ATP to P2X3 receptors is sensed as a damage signal by C-fibres, with subsequent activation. ATP is released from airway mucosal cells under conditions of inflammation, and the binding of extracellular ATP to P2X3 receptors is sensed as a damage signal by C fibres, with subsequent activation.

2.1.3. Clinical presentation, diagnosis

About 5-10% of the adult population has a pathologically excessive and protracted cough. A cough that pertains for longer than 8 weeks in adults, it considered chronic cough. Chronic cough has a major effect on the quality of life, such with co-morbidities such as incontinence, cough syncope and dysphonia. These co-morbidities can, for example, results in social isolation, interference with speech and depression. While many different diseases are associated with chronic cough, the clinical presentation of the cough is very similar. The patients often complain of high sensitivity to inhalation of

environmental irritants such as perfumes, bleaches and cold air. This is suggestive of increased sensitivity of the neuronal pathways mediating cough. Some patients cough on a daily basis over many years, while in others, the disorder has a relapsing and remitting course. Chronic cough is traditionally divided in:

- Asthmatic cough/eosinophilic cough
- Reflux cough
- Postnasal drip syndrome/upper airways cough syndrome
- Iatrogenic cough (use of ACE-inhibitors)

Patients with a chronic cough in whom conditions associated with cough cannot be identified despite a thorough diagnostic workup are considered to have Unexplained Chronic Cough (UCC).

2.1.4. Management

The assessment and treatment of cough is summarised in the below figure from "the guideline on the diagnosis and treatment of chronic cough in adults and children" from the European Respiratory Society (ERS).

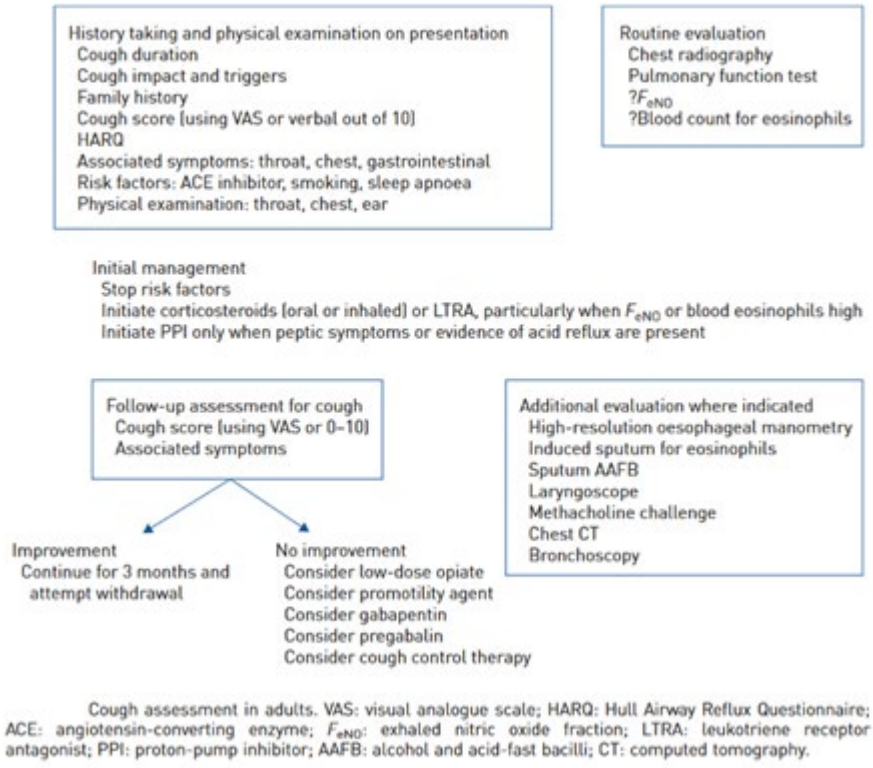


Figure 1 Cough assessment and treatment in adults

A proportion of patients have a persistent cough despite thorough investigation and treatment according to the published practice guidelines. These patients have a:

1. Refractory chronic cough (RCC) if they have a cough-associated condition, but the conventional treatments do not work;
2. Unexplained chronic cough (UCC) when no diagnosable cause for the cough has been found (despite extensive assessment for common and uncommon cases).

Many treatments for chronic cough, such as gabapentin, dextromethorphan, low-dose morphine, and codeine are used and are associated with considerable side effects and/or have limited data to support their use. However, the inconsistency of results, lack of reliable outcome measures, and low overall strength of evidence resulted in the inability to draw firm conclusions on the comparative effectiveness of these agents.

2.2. About the product

Gefapixant (MK-7264 is mainly used in this report, but AF-219, RO4926219 are used as well) is a first in class, non-narcotic, peripherally active, selective antagonist of the P2X3 receptor. Gefapixant also has activity against the P2X2/3 receptor subtype. The applicant for gefapixant requests an indication in adult patients with RCC or UCC. The recommended dose of gefapixant is one 45 mg tablet taken orally twice daily with or without food.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as a film-coated tablet containing 45 mg of gefapixant. The product contains the citrate salt.

Other ingredients are: tablet core: collodial anhydrous silica (E551), crospovidone (E1202), hypromellose (E464), magnesium stearate (E470b), mannitol (E421), microcrystalline cellulose (E460), sodium stearyl fumarate film coat: hypromellose (E464), titanium dioxide (E171), triacetin (E1518), iron oxide red (E172), carnauba wax (E903.

The product is available in opaque white PVC/PE/PVdC blisters with push through aluminium lidding foil, as described in section 6.5 of the SmPC.

2.3.2. Active Substance

2.3.2.1. General information

The chemical name of gefapixant citrate is 2,4-diamino-5-[4-methoxy-2-(propan-2-yl)-5-sulfamoylphenoxy]pyrimidin-1-ium 3-carboxy-2-(carboxymethyl)-2-hydroxypropanoate (citrate salt) corresponding to the molecular formula $C_{14}H_{19}N_5O_4S \cdot C_6H_8O_7$. The active substance has a molar mass of 545.52 g/mol and the following structure:

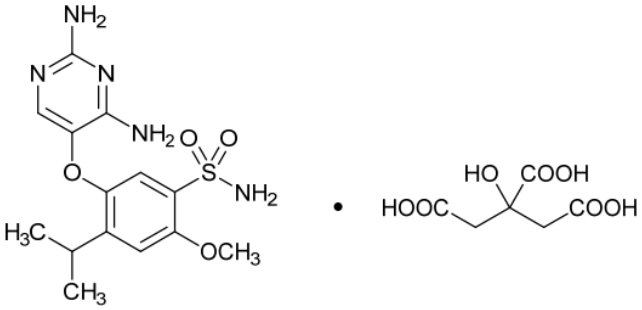


Figure 2: active substance structure

The chemical structure of gefapixant was elucidated by a combination of ultraviolet-visible absorption spectrophotometry, infrared absorption spectroscopy, nuclear magnetic resonance spectroscopy, mass spectrometry and elemental analysis.

The solid state properties of the active substance were measured by single crystal X-ray crystallography, differential scanning calorimetry and thermogravimetric analysis.

The active substance is a white to light yellow non-hygroscopic powder.

Gefapixant has a non - chiral molecular structure.

Polymorphism has been observed for gefapixant citrate.

Gefapixant citrate is a low solubility compound for a human dose of 45 mg. and is pH dependent (decrease at pH above 5).

Permeability of gefapixant was determined to be low with moderate bioavailability.

Based on the above solubility and the permeability data, gefapixant citrate is considered a BCS class IV compound (i.e., low aqueous solubility at neutral pH and low permeability at a human dose of 45 mg).

2.3.2.2. Manufacture, characterisation and process controls

Gefapixant citrate is obtained from a single manufacturer and it is synthesised in four synthetic steps using linear synthesis and three purification steps, using a well-defined starting material with acceptable specifications.

A justification for the designated starting material was provided in line with the requirements of ICH Q11. The acceptability of the starting material was discussed as part of the Scientific Advice procedure (EMA/CHMP/SAWP/85718/2020).

Adequate in-process controls are applied during the synthesis. The specifications and control methods for two isolated intermediate products, the starting material and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

Proven acceptable ranges (PARs) have been defined. The proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs. It was confirmed that only one process parameter will be deliberately changed from its set-point within its PAR. However, no design space or model-based controls are claimed by the applicant.

2.3.2.3. Specification

The active substance specification includes tests for: appearance, identity (IR), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), particle size (laser diffraction), glycolic acid content (HPLC), and citrate content (titration).

The active substance specifications are based on the active substance critical quality attributes (CQA).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch analysis data of the active substance which were produced in support of development, clinical, safety, and stability programs are provided. This includes data on 19 batches, 5 of which are commercial scale from the proposed manufacturer. The results are within the specifications and consistent from batch to batch.

2.3.2.4. Stability

Stability data from three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: identity by IR, description, assay, water, related compounds, physical form by XPRD and particle size distribution. The chromatographic methods used for stability studies were validated and stability-indicating. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications.

Photostability testing following the ICH guideline Q1B was performed on one batch.

Results on stress conditions on acidic, basic (caustic), free radical, oxidative, thermal and photolytic stress conditions were also provided.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable in the proposed container.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

The finished product is a pink, 10.32 mm round and convex immediate release film-coated tablet debossed with "777" on one side and plain on the other side. Film coating is non-functional. The product is available in 45 mg strength, and it is intended for twice-daily use.

Pharmaceutical development of the finished product contains QbD elements. The aim of pharmaceutical development was to develop a physically and chemically stable formulation with the intended biopharmaceutical properties consistent with the quality target product profile (QTPP). The safety, efficacy, and patient compliance requirements were also used to inform the dosage form design, primary packaging design, and critical quality attribute (CQA) selection.

The formulation and manufacturing development have been evaluated through the use of risk assessment, multi and single factors studies.

The proposed commercial formulation contains gefapixant citrate and compendial excipients. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. or

Commission Regulation (EU) No. 231/2012 standards (for iron oxide). There are no novel excipients used in the finished product formulation.

A high-throughput excipient screen was conducted on physical mixtures of the active substance with commonly used excipients to evaluate their chemical and physical stability under accelerated stress conditions. With the results of the excipient compatibility screening study and prior knowledge, mannitol and microcrystalline cellulose were selected. In addition, gefapixant citrate is compatible with hypromellose, crospovidone, colloidal silicon dioxide, sodium stearyl fumarate, and magnesium stearate. Gefapixant formulation is also compatible with the components of the film coating system as demonstrated by the commercial site stability studies. Discussion on functionality related characteristics of the excipients was provided during the procedure.

The comparison of dissolution profiles between clinical Phase III and commercial formulation in media across the physiological pH range (pH 1.2, pH 4.5 and 6.8)–were presented. All batches met the proposed specification limit. Additionally, bioequivalence between these two formulations was demonstrated by means of in an open-label, two-part, two-period crossover studies (P040).

The chosen manufacturing process for the final formulation containing gefapixant citrate is a standard dry tabletting manufacturing process starting with blending and lubrication, followed by a dry compression and film coating.

The proposed manufacturing process consistently provides a final product meeting CQAs. PARs have been defined for the following steps of the medicinal product manufacture: blending, lubrication, compression and film coating. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs. No regulatory flexibility for the control strategy such as operational flexibility within multi-variate design spaces or the use of process analytical technology for in-process control are proposed or requested.

The primary packaging is PVC/PE/PVdC blisters with push through aluminium lidding foil. The material complies with Ph.Eur. and Commission Regulation (EU) 10/2011. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.3.3.2. Manufacture of the product and process controls

The manufacturing process consists of seven main steps: blending, lubrication, compression, film coating, bulk packaging, primary and secondary packaging. The process is considered to be a standard manufacturing process. Commercial process validation was not carried out. The validation scheme / process performance qualification has been submitted and this approach is acceptable.

The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.3.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identity (NIR, HPLC, UV), assay (NIR, HPLC), degradation products (HPLC), uniformity of dosage units (NIR, HPLC) and dissolution (HPLC).

The proposed specification for the finished product is in line with ICH Q6A and is acceptable for this type of dosage form.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk

assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (in response to the major objection raised in this regard) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report-Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch analysis results are provided on 8 (5 of which are commercial scale) batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

2.3.3.4. Stability of the product

Stability data on three commercial scale batches of finished product stored for up to 36 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging representative to the one proposed for marketing.

Samples were tested for assay, degradation products, description, dissolution, disintegration, hardness, water content, and water activity at each time point. Microbial quality is tested Physical stability by X-ray powder diffraction (XRPD) is tested.

No significant changes have been observed at any storage condition.

In accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In addition, three commercial scale batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is considered stable when exposed to light.

An open dish stability study was carried out in lieu of a formal in-use study as it represents a worst-case condition. The open dish study results support that the finished product is stable and therefore the product can be considered stable for up to 9 months in open dish at 25ºC / 60% RH and does not require any additional precautionary labeling statements.

Based on available stability data, the proposed shelf-life of 3 years, with no special storage conditions, as stated in the SmPC (section 6.3) is acceptable.

2.3.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The major objection identified on the risk assessment on the presence of nitrosamines was resolved in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3.6. Recommendations for future quality development

Not applicable.

2.4. Non-clinical aspects

2.4.1. Introduction

Gefapixant has been evaluated in a comprehensive nonclinical safety assessment programme that included safety pharmacology studies, genotoxicity studies, repeat dose oral tolerability and toxicity studies, developmental and reproductive toxicity studies, and carcinogenicity studies in animal models, as well as *in vitro* phototoxicity to support oral administration in humans. All impurities/degradation products were either assessed in toxicology studies or were below the ICH [ICH Q3A(R2); ICH Q3B(R2)] qualification thresholds and have been assessed for mutagenic potential according to ICH M7 guidance.

Overall, the nonclinical development programme was conducted in accordance with International Conference for Harmonisation (ICH) guidance.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

Gefapixant binds to P2X3 homotrimers and P2X2/3 heterotrimer channels. Binding to rat P2X3 and human recombinant P2X3 and P2X2/3 was measured in CHOK1 and 1321N1 cell lines as inhibition of intracellular calcium flux. The IC_{50} values for rat P2X3 and human P2X2/3 ranged from 66 nM to 214 nM. Gefapixant hydrochloride showed the highest binding affinity for human P2X3 with an IC value of 28 nM. Gefapixant did not bind to other P2X channels.

In rat dorsal route ganglions (P2X3) and rat nodose ganglion neurons (P2X2/3) antagonism of α,β-MeATP-induced currents were shown after exposure to gefapixant, with pKi values of 8.3 and 6.9 respectively. Similarly, antagonism of induced currents in HEK-293 cells expressing recombinant human P2X3 and P2X2/3 channels was shown, with KD values of 140 and 250 nM, respectively. It can be concluded that gefapixant binds to P2X3 and P2X2/3 channels with high affinity and specificity. P2X3-containing receptors are ATP-gated ion channels and are primarily expressed on the C and Aδ-sensory fibres. These fibres are also present in upper and lower airways and apparently are involved in airway sensitisation and cough.

A number of animal studies has been performed, using different models for a wide variety of diseases. These include different rat models of pain: Formalin-induced nocifensive behaviour, mechanical hyperalgesia, iodoacetate-induced osteoarthritis, chronic constriction injury and models of neuropathic pain. In these models, a reduction of pain-induced behaviour was observed after single or repeated doses of gefapixant. Effects on bladder contraction reflex were studied in rat models of micturition. Different dosing regimens and administration routes were evaluated, which resulted in variable outcomes, where not all endpoints were affected consistently. Overall, some effect on inhibition of bladder contraction could be seen. Several other studies were conducted in rat models of abdominal constriction, paw oedema, colon hypersensitivity and hypertension. In these models, effects of gefapixant treatment were seen on abdominal contraction (decreased) and hypertension (reduced blood pressure, heart rate), whereas no effects were observed on paw oedema and colon hypersensitivity.

2.4.2.2. Secondary pharmacodynamic studies

In a secondary pharmacology *in vitro* screen of 73 receptors, ion channels and enzymes, no significant binding was observed for gefapixant when tested up to 10 µM. A further screen of 121 kinases also revealed no significant binding. It can be concluded that gefapixant has no off-target binding potential and is specific for the P2X channels.

2.4.2.3. Safety pharmacology programme

Gefapixant was negative in the hERG channel assay at concentrations up to 100 µM, which is 147-fold above the clinical C_{max}. When tested *in vivo* in dogs, there were no effects on the ECG recordings. At all dose levels, there was a slight decrease in blood pressure and heart rate. This effect is likely due to the pharmacological action of gefapixant since decreases in blood pressure, and heart rate were also seen in the Spontaneous Hypertension Rat (SHR) model as described in the primary pharmacodynamics section. In conclusion, no adverse effects on the cardiovascular system have been observed at doses resulting up to a C_{max} 59-fold above the clinical C_{max}. The respiratory system was evaluated in rats. The only effect observed was a decrease in tidal volume at the high dose of 1680 mg/kg. The safety factor at the NOAEL is 16, based on C_{max}. There were no effects on the central nervous system in rats when tested up to 2000 mg/kg, leading to 10-fold and 19-fold the human AUC and C_{max}, respectively. Evaluation of urinary electrolyte excretion in rats showed a transient increase in total urinary excretion of sodium and/or chloride and a transient decrease in potassium excretion at doses up to 2000 mg/kg. Gefapixant caused a dose-dependent delay in gastric emptying at ≥500 mg/kg and decreased intestinal motility at 2000 mg/kg.

2.4.2.4. Pharmacodynamic drug interactions

No studies on pharmacodynamic drug interactions have been performed.

2.4.3. Pharmacokinetics

Methods of analysis

The applicant provided validation reports for the analytical methods used, demonstrating the suitability of the methods, storage, and handling for the purpose of analysis of gefapixant. Specific and sensitive bioanalytical assays were developed and validated for the quantitative determination of gefapixant in mouse, rat, dog, and rabbit plasma, as well as in rat milk. The methods for quantification of gefapixant utilised an automated 96-well format protein precipitation of drug from plasma, followed by liquid chromatography (together with internal standard) using reversed-phase chromatography and subsequent MS/MS detection employing an electrospray interface in the positive ion mode. Metabolites were characterised by high-resolution mass spectrometry with radioactivity detection, and their proposed identity was based on exact mass and MS/MS fragmentation patterns.

Absorption

The absorption of a single 2 mg/kg oral or IV dose of gefapixant in fasted female WH rats showed a bi-phasic decline after dosing, with a moderate distribution volume $V_{d,ss}$ (4.22 L/kg), clearance CL_p (29.5 mg/min/kg) and terminal elimination half-life $t_{1/2}$ (4.4 h). Upon oral dosing, T_{max} was fast with 1.5 hours, whereas bioavailability was low (38.3%), although the oral dosing study was limited in the amount of data points, which might influence this value.

Subsequent studies with increasing oral doses of gefapixant in the formulation selected for GLP toxicity studies (0.5% hydroxypropyl methylcellulose containing 0.4% polysorbate 80 in water) showed dose-proportional increases in gefapixant exposure from 100 mg/kg to 250 mg/kg, and a less than dose-proportional increase in exposure from 500 mg/kg to 6000 mg/kg (administered as 3000 mg/kg BID).

In dogs, single-dose studies with 0.5 mg/kg of an oral or IV dose of gefapixant in fasted female Beagle dogs showed a bi-phasic decline. The PK of gefapixant in dogs was characterised by a low CL_p (2.4 mL/min/kg), a low $V_{d,ss}$ (0.64 L/kg), and a moderate terminal $t_{1/2}$ (~4 hours). The oral bioavailability of gefapixant was 81.5%. Subsequent studies where the formulation of gefapixant was prepared in 0.5% hydroxypropyl methylcellulose containing citric acid (selected for GLP toxicity studies) provided sufficient exposures for toxicology studies despite exhibiting less than dose-proportional increases from BID dosing of 25 mg/kg and 300 mg/kg.

The potential effect of gastric pH on the pharmacokinetics of gefapixant was evaluated in dogs. Studies were conducted in dogs pre-treated with either pentagastrin (resulting in lower gastric pH) or famotidine (pH neutralisation). Following administration of gefapixant prepared in a non-acidified formulation as a solution, a 4-fold increase in gefapixant exposure was observed in pentagastrin-treated dogs, but no increase was observed in famotidine-treated dogs, indicating that a low gastric pH resulted in increases in exposure to gefapixant. Indeed, when gefapixant was administered as a tartaric acid-containing tablet, no difference in gefapixant exposure was observed in pentagastrin-treated dogs or famotidine-treated dogs.

Concerning multiple-dose studies, in rat and dog, no evidence for accumulation was observed, whereas mouse repeated-dose studies showed evidence indicating potential accumulation of gefapixant.

Distribution

The *in vivo* tissue distribution of [^{14}C]gefapixant was investigated in the rat from 2 up to 168 hours (male, albino Wistar Hannover) or 2 up to 672 (male, pigmented Long-Evans) hours post-dosing and assessed quantitatively by measuring radioactivity in autoradioluminograms. In Long-Evans rats, upon oral administration of 20 mg/kg, tissue to plasma ratios (T/P) were similar to or greater than 1 for most tissues, except central nervous tissue, bone, lens and abdominal fat at 2, 6 and 10 hr post-dose.

The highest observed T/P ratios were observed in the large intestine wall, cecum mucosa and non-glandular stomach wall at 2 and 6 hours as a result of oral dosing. The majority of tissues were below LLOQ (0.0675 µg equiv/g) by 36 h post-dose, indicating rapid elimination, and at 672 h post-dose, all tissues were below BQL. Pigmented and non-pigmented skin showed similar T/P ratios, which were both below LLOQ after 36 hours. In Wistar Hannover rats, upon oral administration of 20 mg/kg, tissue to plasma ratios showed significant distribution to the endocrine and metabolic/excretory tissues, as well as the gastrointestinal tract. The highest T/P ratios were observed in the small intestinal wall and liver, with other tissues showing T/P ratios similar to or greater than in plasma, except central nervous tissue, bone, eye, lens, and abdominal fat at 2 hours. The majority of tissues were below LLOQ by 168 post-dose.

Since the T/P ratio for the uveal tract of the eyes increased threefold in LE compared to WH rats, gefapixant appeared to be associated with melanin binding. However, this association appeared to be reversible, based on the observation that the T/P ratio returned to below LLOQ levels by 672 hours post-dose in LE rats. Also, pigmented skin showed similar T/P ratios compared to non-pigmented skin, with no radiolabel being detected for both skin samples after 36 hours.

The distribution of gefapixant to the central nervous system was evaluated in rats following a single P.O. dose of 90 mg/kg, a subcutaneous (SC) dose of 30 mg/kg, or an IV infusion of 62.3 mg/kg over an 8-h period. In all these studies, the brain-to-plasma concentration ratios were approximately 0.05, suggesting that gefapixant distribution in the brain was limited to blood volume in the brain. In pregnant rats, the placental transfer of gefapixant was investigated following 100 or 225 mg/kg TID oral dosing of gefapixant from gestation day 6 through 18. Plasma concentrations of gefapixant were determined in maternal and foetal plasma samples collected 0.5 and 1-hour post-dose on gestation day 18. The ratios of foetal to maternal plasma concentration of gefapixant were approximately 0.15 to 0.21, indicating the placental passage of gefapixant in rats. In pregnant rabbits, the placental transfer of gefapixant was investigated following 400 or 1500 mg/kg oral dosing of gefapixant from gestation day 7 through 20. Plasma concentrations of gefapixant were determined in maternal and foetal plasma samples collected 1 and 2-hour post-dose on gestation day 20. Gefapixant crossed rabbit placenta, with mean gefapixant foetal/maternal plasma concentration ratios that ranged from approximately 0.18 to 0.25 at 1- and 2-hours post-dose.

Using equilibrium dialysis, the plasma protein binding of gefapixant was investigated for mice, rats, rabbits, dogs and humans. The fraction unbound (F_u) ranged from 33.9 to 51.9 % for these species, with F_u for human plasma at 45.3%. No concentration-dependent plasma protein binding was observed for the concentrations tested (0.1, 1 and 10 µM for human plasma and 1, 10 and 50 µM for animal plasma). The F_u of gefapixant did not appear to be concentration-dependent at a clinically relevant steady state concentration, which is covered within the tested range. Gefapixant bound mostly to human serum albumin, with 25% of gefapixant being detected as an unbound fraction.

The blood/plasma partitioning of gefapixant was determined *in vitro* with fresh whole blood and plasma from nonclinical species and humans. The blood-to-plasma concentration ratio was 1.26 (rat), 0.83 (dog), and 1.11 (human) at 0.3 µM gefapixant, indicating gefapixant partitioning into red blood cells in rat and human blood. No concentration-dependence in the blood to plasma concentration ratio was observed in human blood at the concentration range tested (0.1 – 5.0 µM).

Female rats were administered gefapixant by orally, beginning on Day 6 of gestation (GD 6) continuing through Day 10 of lactation (LD 10). Concentrations of gefapixant were determined in maternal plasma and milk samples collected at 0.5 and 1 h post-dose on lactation day 10. Following the 300 mg/kg and 675 mg/kg daily doses, concentrations of gefapixant in milk at 1 h post-dose were 3.6- and 4.0-fold higher than maternal plasma concentrations, respectively, indicating the distribution of gefapixant into milk of lactating rats.

Metabolism

Gefapixant was mainly eliminated *via* urinary excretion of the unchanged compound, with metabolism observed as a minor elimination pathway in rat, dog and human. The primary biotransformation pathways observed in the ADME studies included hydroxylation, O-demethylation, dehydrogenation, oxidation and direct glucuronidation. Secondary biotransformation pathways included glucuronidation of O-demethylated metabolite as well as the formation of a metabolite that was O-demethylated and dehydrogenated.

The *in vivo* biotransformation of gefapixant was assessed following single dosing of [^{14}C]gefapixant at 20 mg/kg orally in intact and bile-duct cannulated (BDC) rats, intravenous dosing at 2 mg/kg in BDC rats, and oral dosing at 1 mg/kg in BDC dogs and at 50 mg in humans. No multiple dosing studies were reported. In plasma, unchanged gefapixant was the most abundant drug-related component in all three species (87% in humans, 100% in dogs and 100% in rats of the total ^{14}Cdrug-related AUC in plasma). Circulating metabolites in human plasma included three low to moderately abundant molecules:
M1 (glucuronide of O-demethylated gefapixant), M5 (directly glucuronidated parent) and M13 (hydroxylated). These accounted for respectively 1.0%, 6.3% and 5.8% in human, whereas in both rat and dog the metabolites M1 and M5 were not detected, while M13 was detected only by mass spectrometry. In addition, in humans, the metabolites M8 (dehydrogenated) and M11 (oxidated) were only detected by mass spectrometry and thus not quantified. These two metabolites were detected in dog also only by mass spectrometry and were not detected at all in rat. Taken together, the five metabolites observed in human plasma accounted for ~13% of the total ^{14}Cdrug-related AUC in plasma in humans, *versus* ~87% for unchanged gefapixant. The most abundant metabolite in human plasma was M5, which was detected at 6% of the total drug label-related AUC in plasma; therefore, none of the human metabolites constitutes a major metabolite, and no further nonclinical characterisation was required. Apart from human plasma, urine and faeces, M5 was detected only in rat bile and not in dog at all. However, M5 was a direct glucuronide of gefapixant and therefore was not considered to require further investigation. M13 represented 6% of the ^{14}C drug-related AUC. This metabolite was considered not to require additional investigation since it was detected by mass spectrometry in both rat and dog in plasma, urine and faeces. The results from the other species indicated that in rat, M1 and M5 were identified only in bile, suggesting other routes of elimination for rat metabolism for these metabolites, whereas M1 and M5 were not detected in dog plasma, bile or faeces at all, indicating that this pathway was absent in dog. In the rat, the pathways involved in metabolism included oxidation, hydroxylation, O-demethylation and a combination of O-demethylation and dehydrogenation; in the dog hydroxylation, oxidation and dehydrogenation were observed, whereas in human, oxidation, hydroxylation and both direct and secondary glucuronidation were observed.

In excreta, following an IV dose of [^{14}C]gefapixant to BDC rats, the majority of the dose (~68% of dose) was recovered from urine. Almost all radioactivity in urine was recovered as unchanged gefapixant (~65% of dose). The remainder of the dose was recovered in bile (10% of the dose) and faeces (17% of the dose). In both bile and faeces, unchanged gefapixant was responsible for the majority of the recovered radioactivity, indicating significant intestinal excretion of unchanged gefapixant in rats. Together, these results show that excretion of intact gefapixant was the main route of gefapixant elimination, with only a minor role for metabolism. Metabolites M9 and M11 (with oxidation at the diaminopyrimidine moiety), as well as M6 and its glucuronides (M2 and M3), were observed as minor metabolites in excreta, totalling less than 10% of the dose.

After P.O. administration of [^{14}C]gefapixant to BDC rats, the recovered dose in faeces, urine, and bile was 63%, 31%, and 6%, respectively. The predominant radioactive component in excreta was gefapixant, accounting for 62% of the dose in faeces, 29% in urine, and 3% in bile. Metabolite M1

(a glucuronide of M6) as well as metabolites M2, M3, M6, M9, and M11 collectively accounted for less than 6% of the dose. Several minor oxidative metabolites and glucuronide conjugates (M4, M5, M7, M8, M10, and M13) were detected by mass-spectrometry only. Following P.O. administration of [^{14}C]gefapixant to BDC dogs, the recovered dose in faeces, urine and bile was 16%, 72% and 6%, respectively. Again, unchanged gefapixant constituted the majority of the radioactivity in these excreta, accounting for 16%, 66% and 6% of the dose. An oxidative metabolite M11 was detected in urine (6% of the dose), and minor metabolites M4, M6, M7, and M13 were detected in excreta by HRMS only.

In humans, a similar pattern of excretion was observed: after P.O. administration of [^{14}C]gefapixant, 76% and 23% of the dose was recovered in urine and faeces, respectively. Gefapixant was the major drug-related component in all excreta, accounting for 64% and 20% of the dose in urine and faeces, respectively. Similar to rats and dogs, in humans, excretion of unchanged gefapixant *via* urine appeared to be the main elimination pathway, with a minor role for metabolism (14% of the dose was recovered as metabolites in all excreta, mainly as secondary metabolites). The metabolites detected in urine included oxidative products and glucuronide conjugates (M1, M5, M8, M11, and M13). Metabolites detected in faeces were M5, M6, M11, and M13. All the metabolites detected in human excreta and plasma were observed in either rat and/or dog (although some only by high-resolution mass spectrometry) and were <10% of drug-related plasma exposure based on the radiometric peak area.

Gefapixant incubated with rat, dog, monkey, and human microsomes at 1 µM revealed very slow metabolism in these microsomes for all species tested.

In hepatocytes of the mouse, rat, rabbit, dog and human, 10 µM of [^{14}C]gefapixant showed low metabolism in all species, and its metabolic profile was qualitatively similar across all species. Multiple mono-oxidations, O-demethylation, and glucuronic acid conjugations of parent and metabolites were the major routes of metabolism identified. All metabolites observed in human liver preparations were also detected in nonclinical species.

Excretion

In rat, dog and human, the excretion of [^{14}C]gefapixant-associated radioactivity was predominantly through the renal (urinary) pathway as unchanged gefapixant.

In rats dosed intravenously with 2 mg/kg [^{14}C]gefapixant, the urinary pathway accounted for 40% to ~68% of the radioactivity recovered, with the faecal (biliary) pathway contributing ~20 to 27%. In the study showing ~68% of renal elimination, metabolite profiling analysis of excreta showed that unchanged gefapixant was the major component in all excreta and that excretion of intact parent in urine (~65% of dose), faeces (~16%), and bile (~5%) were the major routes of gefapixant elimination. The presence of unchanged gefapixant in faeces indicated intestinal secretion of the parent compound. Rats dosed orally with 20 mg/kg [^{14}C]gefapixant showed that ~37% of the radioactivity was excreted *via* the urinary pathway, with ~63% of radioactivity being recovered in faeces. The intestinal secretion observed in the IV dosing study suggested that the fraction of absorption could be much higher than 36%. Experimental recoveries were 79% for the first IV study, with 97 and 100 % recoveries for the other two studies. Similar to rats, dogs dosed intravenously with 2 mg/kg [^{14}C]gefapixant showed that the majority of radioactivity (~52%) was recovered from urine. Moreover, dogs dosed orally with 1 mg/kg [^{14}C]gefapixant showed the majority of radioactivity was recovered in urine (~72%). Metabolite profiling analysis of excreta showed that the unchanged parent compound was the predominant radioactive component in bile (~6% of the dose), urine (~66% of the dose), and faeces (~16% of the dose). For this study, the experimental recovery was found to be 99%.

Humans dosed with 50 mg of [^{14}C]gefapixant *via* an oral dose showed renal excretion as well, with ~76% of the radioactivity recovered in urine and ~23% recovered in faeces. In urine and faeces, unchanged gefapixant accounted for 64 and 20% of the dose, respectively, indicating a minor role in metabolite excretion. The experimental recovery was 99% for this study.

Other pharmacokinetic studies

In order to identify the urinary concentrations of gefapixant associated with crystal formation in repeat-dose toxicity studies, rats were dosed SC with 200 mg/kg gefapixant, and the urinary gefapixant concentrations were measured in ureter catheterised rats. Following a single SC administration of 200 mg/kg gefapixant, the maximum urine concentration was 2.27 mg/mL. At this concentration of gefapixant, numerous crystals were observed in urine collected directly from the ureters. In another study conducted following a single SC administration of 200 mg/kg of gefapixant, the maximum urine concentration was 0.41 mg/mL. A single urine crystal was observed in one of the four rats. Finally, following a single oral administration of gefapixant at 500 mg/kg, no crystals were detected in urine isolated from the ureter despite the concentration achieved in the urine of 1.50 mg/mL.

Given the detection of crystals composed of gefapixant in the urine from the rat and dog toxicity studies, the solubility of gefapixant was evaluated in urine obtained from rat, dog, and human. Gefapixant solubility was strongly pH-dependent in human urine. The steady-state urine solubility, at pH 5 to pH 7, the normal pH range in human urine, ranged from ~0.03 to ~0.11 mg/mL, but solubility was much higher at acidic pH values (>10 mg/mL).

2.4.4. Toxicology

2.4.4.1. Single dose toxicity

Oral single dose treatment was well-tolerated in mouse (up to 2000 mg/kg) and rat (up to 500 mg/kg). No animals died in these studies. In rat, at 2000 mg/kg one female had a calculus within a thickened urinary bladder concurrent with histopathological signs of hyperplasia, inflammation, crystal-forming and superficial necrosis of transitional epithelium and necrosis of smooth muscle of the urinary bladder. The NOAEL was 2000 and 500 mg/kg for the mouse and rat, respectively.

2.4.4.2. Repeat dose toxicity

Rat

Gefapixant was tested in rats in repeat-dose toxicity studies up to 6 months of duration with a maximum recovery period of two months. In the non-pivotal and one-month study, dosing was performed once each day. However, twice per day dosing was used for a subsequent one-month study and increased to three times per day dosing for the 3 months and half-year study in the rat. The main target organs of toxicity in rats were the kidney, ureter, and urinary bladder. Urinary crystals were formed in a dose-dependent manner and often observed at all doses tested. Crystalluria was associated with adverse effects observed in these organs. Adverse effects observed across studies included increased kidney weight, increases in BUN and serum creatinine levels, histopathological findings in kidney, ureter, and urinary bladder, including distended tubules, degeneration of epithelial cells lining tubules, papillary necrosis and inflammation in the interstitium in the kidney, dilatation and inflammation of the ureter and transitional cell hyperplasia in the urinary bladder. Inflammation was associated with increased higher mean total leukocyte, neutrophil, and monocyte counts. In addition, in several repeat-dose toxicity studies, mandibular salivary gland weight was increased, associated

with vacuolation of the salivary gland at the highest doses tested. This effect was not accompanied by any related clinical signs and fully reversible after 1- and 2-months recovery. A clear aetiology of the vacuolation in the salivary gland was not established. At the highest dose levels tested (>20-fold exposure at MRHD), some animals were sacrificed under moribund conditions, including observed clinical signs (hypoactivity, paleness, ataxia, irregular respiration, piloerection, hunched posture, and/or squinting prior to death). After the recovery phase, all observed effects were reversed or were almost resolved (kidney at highest doses tested). Crystal formation was more severe in female rats than at the same dose in males, possibly due to higher plasma exposures compared to male rats. The exposure margin at the NOAEL in the three- and six-month rat repeat dose toxicity studies was ≥3.5-fold exposure at MRHD.

Dog

Repeat-dose toxicity studies in Beagle dog were performed up to nine months with 2 months of recovery. In the pivotal studies, dosing was performed twice each day. Only minimal toxicity was observed in the dog at exposure margins of >35-fold exposure at MRHD. The effects observed included crystalluria, which was more pronounced in females. Additional adverse effects observed were related to obstruction by crystalluria, including unilateral calculus in kidney, ureter and/or urinary bladder, inflammation in the kidney and urinary bladder and hyperplasia in the urinary bladder (at exposures approximately 50-fold exposure at MRHD). The exposure margin at the NOAEL in beagle dogs was approximately 20-fold the exposure at MRHD.

Mouse

Gefapixant was in general well tolerated in mice after exposure up to three months with an exposure margin of up to 10-fold exposure at MRHD of 45 mg/day. Urinary crystals were observed in both males and females in the 3-month study. In a one-month study, three animals showed macroscopic and microscopic findings in the kidney, ureter, and urinary bladder, including one female with a moribund condition showing clinical signs and papillary necrosis in both kidneys, was associated with the moribund condition. These findings were not reproduced in the three-month study.

Crystalluria: Based on several investigative studies, it was shown that precipitation of crystals in the kidney, ureter and urinary bladder across species is possibly due to minimal solubility of gefapixant at physiological urine pH, primary excretion of gefapixant in the kidney and the fact that the chemical structure contains a sulphonamide moiety. Sulphonamide containing drugs is known to cause crystalluria and occasional calculi due to their poor solubility and high urinary excretion, favouring crystallisation in the urine. Higher incidences of crystals and crystal related nephropathy in female rats at high doses was driven by slightly higher systemic exposure (AUC) and C_{max} values likely leading to higher urinary concentration and crystal formation in female rats. Regarding dog, crystal related nephropathy was observed in a limited number of animals, and the incidence was comparable between males and females in the one week and 3-month toxicity studies. In addition, although in the 9-month study a higher incidence of urinary crystals was observed in females, no associated increase related in histopathological findings were observed in females. It was concluded that data from gefapixant studies in both rats and dogs show no evidence of sex difference in sensitivity to crystalluria and related nephropathy.

Due to the lower exposure and lower excretion in the clinical setting compared to values in the repeat dose toxicity animal studies, the applicant expects that the finding of crystalluria is of limited clinical relevance. In general, in the repeat-dose toxicity studies across species effects consisted mainly of crystalluria induced adverse outcome on the kidney, ureter and urinary bladder. Also, female animals seemed to be more sensitive than male animals.

2.4.4.3. Genotoxicity

Gefapixant was found to be negative in the bacterial reverse mutation assay, the human peripheral blood lymphocyte chromosome aberration assay, and the *in vivo* chromosomal aberration assay in rats bone marrow. In the human peripheral blood lymphocyte chromosome aberration assay, at the highest tested concentration of 1000 µg/mL with metabolic activation (3h treatment, 21h recovery) a slight significant difference in %S-cells was observed compared to the vehicle control. However, the incidence of the control was very low within historical control values (0.0%), and the incidence of the 1000 µg/mL sample (3.0%) was within historical control (0.0%-5.0%). Therefore, it is agreed that the result form this test can be considered negative. Overall, it can be concluded that gefapixant did not show any genotoxic potential in the pivotal genotoxicity assays.

2.4.4.4. Carcinogenicity

Carcinogenicity was assessed in rasH2 transgenic mice in a half-year chronic exposure study. There was no increase in carcinogenic potential by gefapixant compared to the negative controls, up to a dose of 500 mg/kg/day. Furthermore, as in the repeat-dose toxicity studies in mice, no further gefapixant related findings were observed. Only C_{max} was measured in this study before necropsy (high dose 2200 ng/mL), which was in a similar order of magnitude as can be expected from the repeat-dose toxicity studies with these rasH2 transgenic mice.

A second carcinogenicity study was performed in Wistar Han rats, in which animals were treated for two years with gefapixant up to 300 mg/kg/day. A trend for an increased incidence of adenoma of the pars distalis of the pituitary gland was observed in males at all dose levels compared to control. However, this finding was within the historical control range. Furthermore, incidences of this adenoma were higher in females compared to males for all treatment groups, including vehicle and water control. It is agreed that this finding is not considered to be test article related.

Other non-neoplastic findings were similar to the findings observed in the repeat-dose toxicity studies in rats and were related to the presence of crystals in the urinary tract at high dose. Effects included findings related to local irritation, inflammation and hyperplasia. The NOAEL in the two-year rat carcinogenicity study had an exposure margin based on $AUC_{0\text{-}24h}$ of approximately 8-fold exposure at MRHD.

2.4.4.5. Reproductive and developmental toxicity

No effects on male or female fertility or early embryonic development were observed in rats up to an exposure margin of 11-fold for females and 13-fold for males, compared to exposure at MRHD. In the embryo-foetal developmental toxicity study in rats, foetal body weight was slightly decreased (up to 7%) in the presence of maternal toxicity, including decreased body weight gain and food consumption. At the developmental NOAEL, the exposure margin was 6-fold exposure at MRHD. The rabbit embryo-foetal developmental toxicity study did not show any adverse effect related to gefapixant up to an exposure margin of 35 fold MRHD. Maternal toxicity, including 1 female abortion at the highest dose tested and body weight (gain) loss and decreased food consumption, were observed dose-dependently at high and mid-dose. The exposure margin for developmental toxicity was approximately 35-fold exposure at MRHD.

In the pre- and post-natal developmental toxicity study in rats, dose dependent maternal toxicity was observed, including effects on body weight, food consumption, clinical signs, gefapixant associated effects on the kidney, ureter, and urinary tract. At the highest dose tested, two litters had complete litter loss, due to severe maternal toxicity resulting in poor maternal care to the pups. No effects on

development, sexual maturation, behavioural endpoints, or other parameters were observed in the F1 group. The maternal exposure at the NOAEL for pre and postnatal development was approximately 11-fold exposure at MRHD.

2.4.4.6. Toxicokinetic data

In general, for mouse, rat, and dog, increases in gefapixant dose resulted in less than dose-proportional increases in AUC and C_{max} values. In rat and dog, no evidence for accumulation was observed, whereas mouse repeated-dose studies showed evidence for accumulation. In mouse, the exposure multiples ranged from 2.7-9.9 for AUC values and from 4.4-48 for C_{max} values. In rat, exposure multiples based on AUC values ranged from 2.4-17, and exposure multiples based on C_{max} values ranged from 5.6-22. In the dog, exposure multiples based on AUC values ranged from 19-24, and exposure multiples based on C_{max} values ranged from 17-27. It can therefore be concluded that adequate exposure was maintained to evaluate safety in the toxicologic studies.

2.4.4.7. Local Tolerance

Gefapixant was classified as non-irritant in the bovine corneal opacity and permeability test (BOCP) and the EpiDerm MTT viability assay.

2.4.4.8. Other toxicity studies

Based on the negative outcome of primary and secondary pharmacology related to targets of liability potential, negative CNS safety pharmacology studies, low gefapixant distribution to rat CNS and absence of dependence related observations in the repeat-dose toxicity studies in rat and dog, it is unlikely gefapixant will increase the risk of dependence.

2.4.5. Ecotoxicity/environmental risk assessment

Table 1 Summary of main study results

Substance (INN/Invented Name): Gefapixant			
CAS-number (if available): 1015787-98-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 107	0.879	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	0.879	not B
Persistence	ready biodegradability	Not readily biodegradable; $DT_{50,\ activated\ sludge}$ = 74.0 d; OECD 314B not adequate for P assessment	vP
	DegT50	$DT_{50,\ water}$ = 15/10 d; (r/r) $DT_{50,\ sediment}$ >1000 d (both systems; r/r) $DT_{50,\ system}$ = >1000 d (both systems; r/r) Sediment shifting 81-86%	r=river DT_{50} values corrected to 12°C. Conclusion: vP
Toxicity	NOEC algae NOEC crustacea NOEC fish	≥1.4 mg/L 5.3 mg/L ≥3.9 mg/L	Not T

	CMR	Not assessed			-
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surface\ water}$, default	0.45	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	$K_{oc\ sludge}$ = 73.4, 153 L/kg $K_{oc\ soil}$ = 3811, 3390 and 5060 L/kg			
Biodegradation in active sludge	OECD 314B	$DT_{50,\ activated\ sludge}$ = 74.0 d			Elimination rate constant = 0.00937 day^{-1}
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = 6.4/4.3 d (r/r) $DT_{50,\ sediment}$ = >1000d (both systems; r/r) $DT_{50,\ system}$ = >1000d (r/r) % shifting to sediment = 81-86%			r=river Reported DT_{50} values at 21 °C. Significant shifting to sediment (and NER) observed.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*R. subcapitata*	OECD 201	NOEC	≥1.4	mg/L	No effects observed
Daphnia magna. Reproduction Test	OECD 211	NOEC	5.3	mg/L	Offspring released
Fish, Early Life Stage Toxicity Test/*P. promelas*	OECD 210	NOEC	≥3.9	mg/L	No effects observed
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥1000	mg/L	Respiration
Phase IIb Studies					
Sediment dwelling organism/ *C. riparius*	OECD 218	NOEC	≥550	mg/kg_{dw}	Male/female combined development rate, normalised to 10% o.c.

The Log Kow of gefapixant is lower than 4.5. A further PBT assessment is not required. PEC_{sw} is 0.45 µg/L, which exceeds the action limit of 0.01 µg/L. The applicant did not seek to refine the F_{pen}. A Phase II assessment is warranted. Gefapixant is not PBT, nor vPvB. Considering the above data, gefapixant is not expected to pose a risk to the environment.

2.4.6. Discussion on non-clinical aspects

Based on the non-clinical data provided, gefapixant has an inhibitory effect on ATP induced currents in P2X3 and P2X2/3 channels. However, an inhibitory effect on otherwise (mechanical and chemical) induced currents has not been investigated. More information on the specificity of gefapixant for ATP induced cough comes from published trial data, in which it was shown that gefapixant increased the ATP threshold and distilled water threshold to elicit a cough response; but that it had no effect on the threshold for the cough response for capsaicin and citron acid (chemical stimulant). This is reassuring from a safety perspective.

In conclusion, the claimed specificity of gefapixant for ATP induced cough is a complex area under research which is not fully understood at the present time. A risk for inhibition of protective cough

induced by a mechanical or chemical stimulus cannot be ruled out in patients that are responsive to gefapixant, based on the current data. A credible explanation behind the observed gender differences on gefapixant exposure (from data from safety pharmacology studies) was provided – emesis after oral administration of the drug substance may affect the given outcome measure. A reasonable and comprehensive justification for not performing tissue distribution study in female individuals of non-clinical species has been provided by the applicant and is considered appropriate by the CHMP.

The applicant provided a discussion on the effects of sex, exposure and the occurrence of crystalluria in the rat and dog repeat-dose toxicity studies. Regarding the rat, the applicant concludes that higher incidence of crystals and crystal related nephropathy in female rats at high doses is driven by slightly higher systemic exposure (AUC) and C_{max} values, likely leading to higher urinary concentration and crystal formation in female rats. Regarding the dog, the applicant argues that crystal related nephropathy was observed in a limited number of the animals, and the incidence was comparable between males and females in the one week and 3-month toxicity studies. In addition, although in the 9-month study, a higher incidence of urinary crystals was observed in females, no associated increase related to histopathological findings were observed in females. The applicant concludes that data from gefapixant studies in both rats and dogs show no evidence of sex difference in sensitivity to crystalluria and related nephropathy. This is agreed by the CHMP. In addition, the applicant states that in the phase 3 study, no events of crystalluria have been reported as serious adverse events, and that when crystalluria was observed, occurrence was similar between male and female patients.

The applicant has provided discussion and clarification regarding the findings of salivary gland vacuolation. The minimal to mild vacuolation of salivary gland epithelium was observed in the rat studies. It was not accompanied by any degenerative or inflammatory changes and was fully reversible after a 4 or 8-week recovery period. However, the clear aetiology of the vacuolation in the salivary gland is unknown. According to the applicant this finding was likely an adaptive change rather than an injury and was therefore considered a non-adverse finding.

The applicant has explained that incidences of emesis were comparable between the vehicle-treated and gefapixant-treated dogs in toxicity studies of longer duration. Furthermore, the emesis was not harmful because, throughout the 28-day treatment period, animals at this dose did not show evidence of dehydration, changes in food consumption or body weight or any findings in the gastrointestinal tract. Given the lack of gefapixant-related emesis in the chronic duration study in dogs at doses of up to 35-fold the human clinical exposure, it can be considered not relevant in humans. In addition, the safety data from the clinical study indicate that the incidence of vomiting observed in the gefapixant 45 mg BID dose group was low (< 4.5%) and comparable to the placebo-treated group.

The applicant has provided a justification for the chosen testing strategy for the phototoxic potential evaluation of gefapixant, and it is considered valid.

A discussion on the uveal tract binding mechanism of gefapixant was also supplied and admittedly, the reason for the apparent higher binding of gefapixant to melanin in the uveal region of the eye as compared to the skin remains unknown. However, given the following considerations that (i) melanin binding and retinal toxicity are two separate entities, (ii) photochemical characteristics of gefapixant provided by the applicant and the fact that wavelengths below 400 nm (those absorbed by gefapixant, i.e., between 290 and 350 nm) do not reach the retina of the adult human eye, it can be concluded that the possibility of phototoxicity of gefapixant is low.

The water solubility of gefapixant was determined internally in a non-GLP study. An OECD 105 Water Solubility study is not required and, therefore, was not conducted. Of note, the non-GLP results were inadvertently reported as µg/L in the original environmental risk assessment; however, the units were incorrect. The actual solubility of gefapixant is pH dependent. At physiological pH in aqueous buffered solutions, the solubility varies from 140 mg/L at pH 5.23 to 10 mg/L at pH 8.1. Solubility increases

significantly under acidic conditions; at pH 1.5, the solubility is >113 g/L. All aquatic toxicity tests were performed at or below the water solubility limit of gefapixant. The provided information was considered acceptable for submission.

Although the adaptation of the DFOP-derived DT_{50} values is agreed upon, it should be noted that the recalculated DT_{50} values are likely an underestimation of the actual degradation half-lives. These DT_{50} values were estimated to be 723 and 444 days, respectively. Furthermore, as the study was performed at 21°C, recalculation to 12°C should also have been performed. Nevertheless, as the slow-phase DFOP DT50 values for the total systems, including the %AS in NER are >1000 days, the conclusion on the persistence of the substance remains unchanged (vP) and the adaptations are considered acceptable.

Gefapixant is not a PBT substance. Considering the above data, it is not expected to pose a risk to the environment.

2.4.7. Conclusion on the non-clinical aspects

The non-clinical pharmacodynamics, pharmacokinetics, toxicology and environmental risk assessment aspects of gefapixant have been adequately addressed. All non-clinical concerns of the CHMP were resolved.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 2 Tabular overview of clinical studies

Study ID	Phase	Country/ Region	Study Title	Study design	Dosing regimen	Study population	Participant exposure
7264-001 [Ref. 5.3.3.1: P001MK7264]	1	New Zealand	A single-center, single-ascending dose, randomized, observer-blinded, placebo-controlled, parallel study to investigate the safety, tolerability and pharmacokinetics of RO4926219 following oral administration in healthy subjects.	Single center, randomized, observer-blinded, placebo-controlled, parallel ascending, single-dose study in healthy subjects	Single oral suspension dose of 10-, 30-, 100-, 200-, 300-, 450-, 900-, or 1800-mg MK-7264 or placebo, in the fasted state Single oral tablet dose of 460-mg MK-7264 or placebo, in the fasted state Single oral tablet dose of 460-mg MK-7264 or placebo, in the fed state	Healthy male and female participants Age range: 18 to 48 years Indication: Pain	MK-7264 10, 30, 100, 200, 300, 450, 460, 900, or 1800 mg: 80
7264-002 [Ref. 5.3.3.1: P002MK7264]	1	New Zealand	A single-center, randomized, observer-blinded, multiple ascending-dose, placebo-controlled, parallel study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of RO4926219 following 14-days oral administration in healthy subjects.	Single center, randomized, observer-blinded, placebo-controlled, multiple-ascending dose, parallel study in healthy subjects	BID oral doses of 100, 300 and 900 mg or placebo for 14 days, in the fed and fasted states	Healthy male participants Age range: 18 to 58 years Indication: Pain	MK-7264 100 mg BID: 8 MK-7264 300 mg BID: 8 MK-7264 900 mg BID: 8
7264-003 [Ref. 5.3.3.1: P003MK7264]	1	New Zealand	A Single-Center, Randomized, Observer-Blinded, Multiple-Dose, Placebo-Controlled, Parallel Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AF-219 Following 14-Days of Oral Administration in Healthy Subjects	Single center, randomized, observer-blinded, placebo-controlled, multiple-dose, parallel study in healthy subjects	BID oral doses of 1800 mg or placebo for 14 days, in the fed and fasted states	Healthy male and female participants Age range: 20 to 60 years	MK-7264 1800 mg BID: 8
7264-007 [Ref. 5.3.3.3: P007MK7264]	1	USA	A Randomized, Placebo-Controlled Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of 3-Weeks Oral Administration of AF-219 in Healthy Adult and Elderly Subjects	Single center, randomized, double blind, placebo controlled, dose escalating, parallel group study in healthy adult and elderly subjects	BID oral doses of 300 mg for 7 days followed by a dose escalation to 600 mg BID for 14 days, or placebo for 21 days	Healthy male and female participants Age range: 20 to 78 years	MK-7264 300 and/or 600 mg BID: 28
7264-011 [Ref. 5.3.1.2: P011MK7264]	1	USA	A Study in Healthy Subjects to Assess the Effect of Intragastric pH and Fasting on the Multiple-Dose Pharmacokinetics of AF-219	Single center, open label, partially randomized, 11-period, 2-treatment sequence crossover study in healthy subjects	BID oral doses of 25, 50, and 150 mg for 2 days, in fasted and fed states BID oral doses of 50 and 150 mg with 40 mg BID omeprazole for 2 days in fasted and fed states	Healthy male and female participants Age range: 20 to 51 years	MK-7264 25, 50, and/or 150 mg BID: 18 Omeprazole 40 mg BID: 18
7264-017 [Ref. 5.3.1.2: P017MK7264]	1	UK	A Study in Healthy Male Subjects Designed to Evaluate the Pharmacokinetic Profile of AF-219 Following Administration of Modified Release Prototype Formulations, to Evaluate the Relationship Between the Pharmacokinetic Profile of AF-219 in the Fed State and Also Evaluate the Effect of Proton Pump Inhibitors on the Pharmacokinetic Profile of AF-219	Single center, open label, randomized study in healthy subjects	Single oral doses of 50 and 100 mg tablet and multiparticulate formulations in the fasted and fed states	Healthy male participants Age range: 23 to 59 years	MK-7264 50 or 100 mg tablet and/or multiparticulate: 20

7264-020 [Ref. 5.3.1.2: P020MK7264]	1	USA	A Study in Healthy Subjects to Assess the Multiple-Dose Pharmacokinetics of Two AF-219 Formulations	Single center, open-label, partially randomized, 6-period, 2-treatment sequence, crossover, healthy subjects	BID oral doses of 25 mg for 1 day and 50 mg (original and citric acid formulation) for 2 days in the fed state BID oral doses of 25 mg for 4 days and 50 mg (original and citric acid formulation) for 2 days with 20-mg QD omeprazole in the fed state	Healthy male and female participants Age range: 19 to 52 years	MK-7264 25, 50 and/or 150 mg BID: 14 Omeprazole 20 mg QD: 14
7264-022 [Ref. 5.3.3.1: P022MK7264]	1	USA	A 14-Day Study in Healthy Subjects to Assess the Multiple-Dose Pharmacokinetics of AF-219	Single center, double-blind, randomized, parallel group, placebo-controlled study in healthy subjects	BID oral doses of 7.5, 15, 30, and 50 mg or placebo for 14 days in the fed state	Healthy male and female participants Age range: 18 to 55 years	MK-7264 7.5, 15, 30, and 50 mg BID: 32
7264-023 [Ref. 5.3.1.2: P023MK7264]	1	USA	A Study in Healthy Subjects to Assess the Multiple-Dose Pharmacokinetics of Three AF-219 Formulations (F01, F03-L, and F03-M)	Single center, open-label, randomized, parallel group, 6-period, single-sequence study healthy male and female subjects	BID oral doses of 15 and 30 mg of the F01 and F03 formulations for 15 days with and without coadministration of omeprazole	Healthy male and female participants Age range: 18 to 53 years	MK-7264 15 and 30 mg BID: 32 Omeprazole 20 mg QD or 40 mg BID: 32
7264-024 [Ref. 5.3.3.3: P024MK7264]	1	Japan	Single and multiple dose study to assess the safety, tolerability and pharmacokinetics of MK-7264 in healthy Japanese male subjects	Part 1 and 2: Randomized, double-blind, placebo-controlled Part 3: Randomized, open-label, cross-over	Part 1: MK-7264: 15-100 mg po single dose Part 2: MK-7264: 15-50 mg po BID for 15 days (only morning dose on Day 15) Part 3: MK-7264: 50 mg po single dose	Males Age range : 21 to 45 years Healthy Japanese subjects Indication: Cough	Part 1: single dose MK-7264 15 mg: 6 MK-7264 30 mg: 6 MK-7264 50 mg: 6 MK-7264 100 mg: 6 Part 2: BID for 15 days (only morning dose on Day 15) MK-7264 15 mg: 6 MK-7264 30 mg: 6 MK-7264 50 mg: 6 Part 3: single dose MK-7264 50 mg: 14

7264-025 [Ref. 5.3.1.2: P025MK7264]	1	USA	A Study to Determine the Relative Bioavailability and PK Drug Interaction of Two Formulations of MK-7264 50 mg tablets and Apo-Omeprazole 40 mg DR capsules in Healthy Adults Type of Trial: BA, DI Indication: Cough	Open-label, five-period, five-treatment, fixed-sequence, relative bioavailability and pharmacokinetic drug interaction study	A: 50 mg MK 7264 (F02); po; single-dose, fasting B: 50 mg MK-7264 (F04); po; single-dose, fasting C: 50 mg MK-7264 (F04); po; single-dose, fed D: 50 mg MK-7264 (F04); po; single-dose, fasting after Omeprazole 40 mg; po; multiple dose E: 50 mg MK-7264 (F02); po; single-dose, fed	Males and females Age: 18-65 years Indication: Cough	A: 50 mg MK-7264 (F02): 14; open label B: 50 mg MK-7264 (F04): 13; open label C: 50 mg MK-7264 (F04): 13; open label D: 50 mg MK-7264 (F04) and 200 mg Omeprazole: 12; open label E: 50 mg MK-7264 (F02): 10; open label

7264-032 [Ref. 5.3.1.2: P032MK7264]	1	USA	A Study to Characterize the Pharmacokinetic Performance of Different Formulations of MK-7264 in Healthy Adult Subjects under Fed and Fasted Conditions	2-Stage Adaptive Study Under Fasted and Fed Conditions: Single-Dose, Four-Period, Open-Label, Randomized Crossover in the First Stage followed by Single-Dose, Two-Period, Open-Label, Fixed-Sequence (if necessary) Study in the Second Stage	A: 1 × 45 mg (IR F04 tablet) oral dose of MK-7264 B: 1 × 60 mg (MR1; 4-hour release tablet) oral dose of MK-7264 C: 1 × 45 mg (MR2; 4-hour release tablet) oral dose of MK-7264 D: 1 × 45 mg (MR3; 8-hour release tablet) oral dose of MK-7264	Males and females Age range: 18 to 65 years Healthy subjects Indication: Cough	IR F04, 45 mg MK-7264 tablet: 14 MR1, 60 mg MK-7264 tablet: 12 MR2, 45 mg MK-7264 tablet: 13 MR2, 45 mg MK-7264 tablet: 13
7264-036 [Ref. 5.3.3.4: P036MK7264]	1	USA	A two-period fixed sequence study to evaluate the effects of pyrimethamine, a potent inhibitor of MATE1/2K, on the pharmacokinetics of MK-7264 in healthy adults	Open-label, 2-period, fixed sequence, drug-drug interaction (DDI) study	Period 1: Single oral dose of MK-7264 45 mg Period 2: Single oral dose of pyrimethamine 50 mg 3 hours before a single oral dose of MK-7264 45 mg	Males and females Age range: 18 to 55 years Healthy subjects Indication: Chronic cough	MK-7264 45 mg: 12 Pyrimethamine 50 mg: 12
7264-039 [Ref. 5.3.4.2: P039MK7264]	1	USA, Belgium	A Randomized Double-Blind Clinical Trial to Evaluate the Effects of MK-7264 in Participants with Obstructive Sleep Apnea	Randomized, placebo-controlled, crossover, double-blind, multi-site study of MK-7264 in participants with OSA	MK7264 (180 mg) po or matching placebo (0 mg) orally once daily at bedtime for 7 days in Periods 1 and 2	Males and female Participants with moderate to severe OSA Age range: 39 to 68 years Indication: Obstructive sleep apnea	MK 180 mg/day: 22 PBO: 0 mg/day: 20
7264-040 [Ref. 5.3.1.2: P040MK7264]	1	USA	An Open-Label, Two-Part, Two-Period Crossover Study to Determine Bioequivalence Between Gefapixant (MK-7264) F04A and F04B Formulations at 45 mg and 15 mg Single Doses in Healthy Participants	Single-center, bioequivalence, pharmacokinetic, safety, tolerability, crossover assignment, open-label, intervention	Part 1: Subjects were randomized to receive 45 mg gefapixant F04A and gefpaixant F04B. Part 2: Subjects were randomized to receive 15 mg gefapixant F04A and gefpaixant F04B. Washout: at least 5 days between dosing in each part.	Part 1: 45 mg Gefapixant F04B/45 mg Gefapixant F04A Age: 19 to 48 Part 2: 15 mg Gefapixant F04B/15 mg Gefapixant F04A Age: 22 to 50 Indication: Chronic cough	Below is a list of the number of subjects that received at least 1 dose of the following treatments: Part 1: 45 mg Gefapixant F04B and 45 mg Gefapixant F04A: 20 Part 2: 15 mg Gefapixant F04B and 15 mg Gefapixant F04A: 20
7264-044 [Ref. 5.3.3.4: P044MK7264]	1	USA	A Two-Period Fixed Sequence Study to Evaluate the Effects of Multiple-Dose Gefapixant (MK-7264) on the Single-Dose Pharmacokinetics of Pitavastatin in Healthy Adult Participants	Single center, pharmacokinetic, safety, fixed sequence assignment, open label, intervention	Period 1: Participants received a single oral dose of 1 mg pitavastatin on Day 1. Period 2: Participants received oral doses of 45 mg gefapixant twice a day on Days 1 to 4 with a single oral dose of 1 mg pitavastatin coadministered with the morning dose of gefapixant on Day 2. Washout: at least 4 days between the pitavastatin dose in Period 1 and the first gefapixant dose in Period 2.	Healthy male and female participants. Age: 19 to 54 Indication: Chronic cough	Below is a list of the number of participants that received at least 1 dose of the following treatments: Period 1: Pitavastatin Alone: 20 Period 2: Pitavastatin + Gefapixant: 20
7264-004 [Ref. 5.3.5.1: P004MK7264]	2	USA	A Four-Week, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study Evaluating the Safety and	Multi-center, randomized, double-blind, placebo-controlled study	MK-7264 600 mg BID po or placebo	Males and females Age range: 40 to 79 years	MK-7264 300 mg BID: 85 MK-7264 600 mg BID: 11

			Efficacy of AF-219 in Subjects with Osteoarthritis of the Knee		The initial MK-7264 dose of 600 mg BID po was amended to 300 mg BID po. Duration of treatment: 4 weeks	Indication: moderate to severe pain associated with osteoarthritis of the knee	Placebo BID: 94
7264-005 [Ref. 5.3.5.1: P005MK7264]	2	USA	A Four-Week, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study Evaluating the Safety and Efficacy of AF-219 in Female Subjects with Interstitial Cystitis /Bladder Pain Syndrome	Multi-center, randomized, double-blind, placebo-controlled study	MK-7264 600 mg BID po or placebo The initial MK-7264 dose of 600 mg BID po was amended to include a 6-day titration schedule. Participants titrated their dose in 50 mg increments from 50 mg BID up to the highest tolerated dose (maximum of 300 mg BID) over a 6-day period, then maintained that dose for the duration of the study. Duration of treatment: 4 weeks	Female participants Age range: 20 to 75 years Indication: interstitial cystitis/bladder pain syndrome	MK-7264: 54 Placebo: 51
7264-006 [Ref. 5.3.5.1: P006MK7264]	2	UK	A Study to Assess the Efficacy of AF-219, a P2X3 Receptor Antagonist, in Subjects with Chronic Cough (EPiCC)	Single center, randomized, double-blind, placebo-controlled, 2-period, crossover study	MK-7264 600 mg BID po or placebo Duration of treatment: 14 days	Males and females Age range: 24 to 70 years Indication: chronic cough	MK-7264 600 mg BID/placebo: 24
7264-009 [Ref. 5.3.5.1: P009MK7264]	2	UK	A Randomised, Double-Blind, Double-Dummy, Placebo-Controlled, Three-Way Cross-over Study to Evaluate the Effect of AF-219 on Methacholine Hyper-Reactivity in Subjects with Asthma	Single-center, randomized, double-blind, double-dummy, placebo-controlled, 3-way crossover study	MK-7264 50 mg BID po or placebo MK-7264 300 mg BID po or placebo Duration: 3.5 days x 3	Males and females Age range: 21 to 62 years Indication: methacholine challenge in participants with asthma	MK-7264 50 mg BID: 19 MK-7264 300 mg BID: 19 Placebo: 20
7264-010 [Ref. 5.3.5.1: P010MK7264]	2B	USA	A Dose Escalation Study to Assess the Efficacy and Tolerance of AF-219 in Subjects with Refractory Chronic Cough	Multi-center, randomized, double-blind, placebo-controlled, crossover, dose escalation study	Cohort 1: MK-7264 dose escalation 50, 100, 150, 200 mg BID po or placebo. Two 16-day (four 4-day) treatment periods (MK-7264 or placebo) with 3-7 days washout between the 2 study periods Cohort 2: MK-7264 dose escalation 7.5, 15, 30, 100 mg BID po or placebo. Two 16-day (four 4-day) treatment periods (MK-7264 or placebo) with 14-21 days washout between the 2 study periods	Males and females Age range: 23 to 76 years Indication: RCC	Cohort 1: MK-7264/Placebo: 28 Cohort 2: MK-7264/Placebo: 30
7264-012 [Ref. 5.3.5.1: P012MK7264]	2B	USA, UK	A 12-Week Study to Assess the Efficacy and Safety of MK-7264 (AF-219) in Subjects with Treatment Refractory Chronic Cough	Multicenter, randomized, double-blind, parallel-group, placebo-controlled	MK-7264 7.5 mg or MK-7264 20 mg or MK-7264 50 mg or matching placebo administered twice daily (BID) for 84 days (12 weeks)	Males and females Age range: 22 to 79 years Indication: Participants with chronic cough	MK-7264 7.5 mg: 63 MK-7264 20 mg: 63 MK-7264 50 mg: 63 Placebo: 63
7264-013 [Ref. 5.3.5.1: P013MK7264]	2A	UK	Phase 2a, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Efficacy, Safety and Tolerability of MK-7264 on Acute Cough in Participants with Induced Viral Upper Respiratory Tract Infection	Single-center, randomized, double-blind, parallel, placebo-controlled study	MK-7264: 45 mg BID for 7 days	Males and females Age range: 18 to 53 years Indication: Participants with acute cough with induced viral upper respiratory tract infection	MK-7264 45 mg: 23 Placebo: 23

7264-014 [Ref. 5.3.5.1: P014MK7264]	2	UK	A Study to Assess the Effect of MK-7264 (AF-219) on Cough Reflex Sensitivity in Both Healthy and Chronic Cough Subjects	Single-center, randomized, double-blind, 2-period, crossover study	Treatment Sequence A: 1 dose of placebo in Treatment Period 1, followed by 1 dose of MK-7264 100 mg in Treatment Period 2. Treatment Sequence B: 1 dose of MK-7264 100 mg in Treatment Period 1, followed by 1 dose of placebo in Treatment Period 2.	Males and females Age range: 26 to 73 years Indication: Healthy and Chronic Cough Subjects	MK-7264 100 mg: 36 Placebo: 36
7264-015 [Ref. 5.3.5.1: P015MK7264]	2	UK	A Study to Assess the Effect of AF 219 on Cough Reflex Sensitivity in Both Healthy and Chronic Cough Subjects	Multi-center, randomized, double-blind, placebo-controlled, 4 period crossover, single dose	Duration of treatment: Four 1-day treatment periods, with at least a 48-hour washout period between treatments.	Males and females Age range: 19 to 74 years Indication: cough reflex sensitivity	Cohort 1: MK-7264 300 mg Placebo: 26 Cohort 2: MK-7264 50 mg Placebo: 24
7264-016 [Ref. 5.3.5.1: P016MK7264]	2B	USA	A Randomized Placebo-Controlled Study to Assess the Efficacy and Safety of AF-219, a P2X3 Receptor Antagonist, in Subjects with Idiopathic Pulmonary Fibrosis (IPF) with Persistent Cough	Multicenter, randomized, double-blind, placebo-controlled, crossover	One oral tablet of MK-7264 50 mg or matching placebo administered BID for 14 days, or one oral tablet of MK-7264 50 mg was administered BID for 10 days followed by MK-7264 150 mg for 4 days.	Males and females Age range: 47 to 86 years Indication: Subjects with IPF with persistent cough	MK-7264 50 mg: 47 MK-7264 150 mg: 4 Placebo: 45
7264-019 [Ref. 5.3.5.2: P019MK7264]	2	USA	A Study to Assess the Tolerability of a Single Dose of AF-219, a P2X3 Receptor Antagonist, in Subjects with Idiopathic Pulmonary Fibrosis (IPF)	Single-center, open-label, single-dose study	single dose MK-7264 150 mg	Males and femlaes Age range: 53 to 68 years Indication: Subjects with IPF	MK-7264 150 mg: 6
7264-021 [Ref. 5.3.5.1: P021MK7264]	2	USA	A Randomized, Parallel, Double-Blind Study to Assess the Efficacy and Tolerability of AF-219 in Subjects with	Multi-center, randomized, parallel-group, double-blind, placebo-controlled study	MK-7264 15 mg BID MK-7264 30 mg BID MK-7264 50 mg BID	Males and females Age range: 41 to 73 years	MK-7264 15 mg BID: 8 MK-7264 30 mg BID: 5
			Treatment Refractory Chronic Cough		Placebo Duration of treatment: 8 weeks	Indication: RCC	MK-7264 50 mg BID: 6 Placebo: 4
7264-033 [Ref. 5.3.5.1: P033MK7264]	2	Japan	Phase 2 study, Randomized, Double-Blind, Placebo-Controlled 4-Week Clinical Study, to Evaluate the Efficacy and Safety of MK-7264 in Adult Japanese Participants with Unexplained or Refractory Chronic Cough	Multi-center, parallel-group, randomized, double-blind, placebo-controlled study	MK-7264 45 mg BID or Placebo Duration of treatment: 4 weeks	Males and females Age range: 29 to 77 years Indication: RCC or UCC	MK-7264 45 mg BID: 11 Placebo: 12
7264-027 [Ref. 5.3.5.1: P027MK7264]	3	North America, Central America, South America, Europe, Asia-Pacific	A Phase 3, Randomized, Double-blind, Placebo-controlled, 12-month Study to Evaluate the Efficacy and Safety of MK-7264 in Adult Participants with Chronic Cough (PN027)	Multicenter, randomized, double-blind, placebo-controlled, parallel assignment	MK-7264 45 mg po BID in Main Study (12 weeks) and Extension Study (40 weeks) MK-7264 15 mg po BID in Main Study (12 weeks) and Extension Study (40 weeks) Placebo po BID in Main Study (12 weeks) and Extension Study (40 weeks)	Males and females aged Age range: 19 to 89 years Indication: RCC or UCC	MK-7264 45 mg: 243 MK-7264 15 mg: 244 Placebo: 243
7264-030 [Ref. 5.3.5.1: P030MK7264]	3	North America, Central America, South America, Europe, Asia-Pacific, South Africa	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 12-Month Study to Evaluate the Efficacy and Safety of MK-7264 in Adult Participants with Chronic Cough (PN030)	Multicenter, randomized, double-blind, placebo controlled, parallel assignment	MK-7264 45 mg po BID in Main Study (24 weeks) and Extension Study (28 weeks) MK-7264 15 mg po BID in Main Study (24 weeks) and Extension Study (28 weeks) Placebo po BID in Main Study (24 weeks) and Extension Study (28 weeks)	Males and females Age range: 19 to 88 years Indication: RCC or UCC	MK-7264 45 mg: 439 MK-7264 15 mg: 440 Placebo: 435

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

The clinical pharmacology programme consists of 17 completed clinical pharmacology studies, in which a total of 408 healthy subjects and 18 subjects with renal impairment received at least 1 dose of

gefapixant. The effects of key intrinsic factors were evaluated in healthy adult subjects and patients with renal impairment. In addition, 7 Phase 1 trials evaluated the biopharmaceutical aspects. Moreover, reports covering *in vitro* data and population pharmacokinetic analysis are submitted.

Two gefapixant API forms – free base and citrate salt – were used during the clinical formulation development. Gefapixant free base was developed to support early phase clinical trials, while gefapixant citrate was used in late clinical formulation development. Considering the 45 mg strength and the recommended dose of 45 mg b.i.d., gefapixant free base and gefapixant citrate can be considered low solubility drugs, based on BCS classification. The free base has a lower solubility at pH 5.0 than citrate salt, i.e., 0.3 mg/ml vs. 9.3 – 12.1 mg/ml. Considering the low permeability of the drug, gefapixant is a BCS Class IV drug (low solubility/low absorption).

Fully validated analytical methods have been applied for the analysis of gefapixant in plasma, urine and dialysate. Validation proved that the method was specific, precise, and accurate. Stability was shown covering study sample handling and storage.

A pooled population pharmacokinetic analysis (report 05HB0V) was performed across Phase 1, Phase 2b, and Phase 3 trials with gefapixant at a 45 mg b.i.d. dose. The final structural population PK model is a 2-compartment model that includes a linear elimination from the central compartment, a first-order absorption, and a lag time. The residual variability is modelled *via* an additive and proportional error model. The IIV was estimated for the Ka (CV = 85.7%), the Vc (CV = 12.7%), and the apparent clearance (CV = 27.1%). The prediction-corrected (pc)-VPC for Phase 1 data and Phase 2/3 data showed that the final model could predict the observed median and 5^{th} and 95^{th} percentiles of observed gefapixant concentrations with good accuracy. Based on stepwise covariate analysis, eGFR, age, body weight, and sex were statistically significant covariates of gefapixant pharmacokinetics. Although statistically significant, the magnitude of age, sex, weight, and race on gefapixant pharmacokinetics was < 20% and not clinically relevant.

As data obtained from different formulations were included in the popPK, the applicant was requested to discuss the applicability of data obtained with early formulations, their inclusion in pop-PK models and whether formulation was used as a covariate in the analysis. From the response it was indicated that different formulations have been used across these studies. The population pharmacokinetic analysis was based on studies with F02 and/or the F04 / F04A / F04B formulations, respectively, whereas the formulation F01 was used for preliminary PK estimations only, but not in the final population PK analysis. As the F02 formulation was reformulated to avoid exposure differences under the fasted conditions, the food effect as a covariate was retained in the population PK model for the F02 formulation, and in general the approach is considered to be appropriate. However, the percent coefficient of variation (CV%) for absorption rate constant (Ka) is considerably high – 85.7 % suggesting considerable inter-individual variability. As different formulations have been used, their impact on absorption, next to other possible factors, cannot be excluded. It was requested to support that a slower absorption rate is not associated with lower exposure. Considering applicant's response, although comparable t_{max} values were observed (range 1.0 – 4.0) hampering a good evaluation of a difference in absorption rate on the exposure, no food effect or a PPI effect on the F04 formulation is observed (study P025) and overall PK indicates that variability in exposure is moderate. Moreover, the exposure-efficacy relation is not steep and the effect of a difference in AUC (5^{th} – 90^{th} percentile) may be considered relatively small.

Absorption

In vitro permeability data indicate that gefapixant is a low permeability drug. Absolute bioavailability has not been evaluated, and based on the ADME study, the *in vivo* bioavailability is estimated to be at least 78%. It is expected that the pharmacokinetics of gefapixant is not different between healthy subjects and patients with refractory chronic and unexplained chronic cough. This is confirmed in the

popPK analysis, showing that after accounting for the intrinsic covariates age, body weight and gender, there was no difference in gefapixant exposure between healthy subjects and subjects with chronic cough.

Gefapixant is a substrate for P-gp but did not inhibit P-gp.

After oral administration, gefapixant t_{max} values are observed after about 1 - 4h. No effect of food has been observed for the F04 formulation. Considering the small changes in excipients in the commercial F04B formulation compared to the F04 formulation, a comparable food effect is expected for the F04B formulation. The SmPC indicate that the tablet may be dosed without regard to food, which is appropriate.

After single doses up to 450 mg and over the multiple b.i.d. dose range of 7.5 – 200 mg, linear pharmacokinetics is observed. As the recommended dose is 45 mg b.i.d., dose proportionality or non-proportionality in the pharmacokinetics is not of concern. No unexpected accumulation is observed after multiple dosing b.i.d. dosing. Steady-state was reached within 2 - 3 days. The accumulation ratio was about 1.5-fold.

Gefapixant pharmacokinetics shows a moderate inter-subject variability in AUC and C_{max} of about 23 and 29% under fasting conditions. Intra-subject variability was not evaluated; however, the ANOVA CV (as an indication of the intra-subject variability) in the bioequivalence study with the F04A and F04B tablet was 7 and 16%, respectively for AUC and C_{max}, indicating that gefapixant can be considered a low variability drug.

Different formulations were used in the clinical programme, i.e., a suspension, F01 and F02 tablets with gefapixant free base, F04 prototype tablets, F04A Phase 3 tablets and F04B commercial tablet formulations. The F04, F04A, and F04B formulations contained the gefapixant citrate salt. Due to the addition of citric acid, the F02 formulation had significantly less PPI effects than the F01 formulation. The direct compression tablet F04 formulation was developed for enhanced shelf stability, and this formulation was chosen for commercial use (F04B without citric acid). The relative difference in exposure under fasting and fed conditions is about -30% and -15%, respectively, for the F01 formulation compared to the suspension formulation at a 450 mg single dose. The suspension formulation was only used in early development in study P001. The relative difference in exposure under fasting and fed conditions is about -20 to -25% for the F02 formulation compared to the F01 formulation; however, dosed at a 150 mg b.i.d. dose. At a dose of 50 mg b.i.d., bioequivalence could be shown between the F01 and F02 tablet under fed conditions. The prototype F04 tablet formulation (s.d. 50 mg) was bioequivalent (AUC and C_{max}) with the F02 formulation under fed conditions.

Bridging of the 50 mg F04 tablet to the dose-proportional Phase 3 F04A 15 and 45 mg tablets was based upon comparable dissolution, which is acceptable. However, only dissolution data have been provided at a pH of 1.2 and 6.8, showing more than 85% dissolved within 15 min. Additional dissolution data at a pH of 5.0 has been submitted, showing slower dissolution for the F04 tablet, however, in vivo study comparison of exposure data following single oral dose administration of the F04 and F04A formulation in adult subjects showed comparable AUC and C_{max} values.

In the pivotal studies P010, P012, P014, P015, P027 and P030 7.5, 20 and 50 mg F01 and F02 tablets have been used and the F04A 15 and 45 mg tablets. The tablets were administered under fed conditions, so based upon studies P020, P025 and P040, there are no issues concerning exposure and possible bridging of the clinical results between these studies. However, 7.5 and 20 mg tablets were used, and the support of bridging of these formulations has been requested and addressed by the applicant during evaluation.

Distribution

Gefapixant *in vitro* plasma protein binding is about 55% and not dependent on the concentration and drug-drug interactions due to protein displacement are not expected with gefapixant. Based upon limited animal data, gefapixant may cross the blood-brain barrier to a low extent, and it may transfer over the placenta and excrete into mother milk. The popPK estimated V/F is 133.8 l (Vc 101 l and Vp 32.8 l), after b.i.d. administration of 45 mg.

In vitro, gefapixant was metabolised at very low rates in human liver microsomes. Mono-oxidation, O-demethylation and glucuronic acid conjugation were the major routes of metabolism observed. The involvement of CYP450 in the metabolism of gefapixant could not be determined due to the high metabolic stability of gefapixant.

Following a single oral ^{14}C-gefapixant labelled dose to healthy adult male subjects over a 1-week collection period, total recovery was 98.9% of the dose with the majority of radioactivity recovered in urine (76.4% of the dose), and a moderate amount recovered in faeces (22.6% of the dose). Gefapixant accounted for 64% and 20% of the dose in urine and faeces, respectively. In plasma, gefapixant was the major component, accounting for about 88% of the total drug-related material in a sample representative of the exposure in a 24 h period. Minor metabolites were detected in plasma (M1, M5, M8, M11 and M13), and no metabolite in plasma was greater than 10% of the drug-related material based on the radiometric peak area. Minor metabolites were detected in urine ((M1, M5, M8, M11 and M13) and faeces (M5, M6, M11 and M13), each < 4.2% of the dose).

These data indicate that metabolism is a relatively minor pathway of elimination, with approximately 15% of an oral dose appearing in urine and faeces as metabolites.

Elimination

The observed clearance was 14.8 l/h. Based on the population-PK analysis integrating Phase 1, 2, and 3 data, the geometric mean Cl/F is 10.8 l/h. Renal clearance was approximately 8.7 l/h, indicating that renal clearance is the major elimination pathway. The observed CLr was greater than the GFR for unbound gefapixant, indicating the involvement of active tubular secretion. The latter is confirmed *in vitro*, i.e., gefapixant is a substrate of MATE1 and MATE2K, P-gp, and BCRP transporters. After reaching peak levels, gefapixant plasma concentrations decline according to a biexponential disposition manner with a terminal $t_{1/2}$ of approximately 6 to 10 hours.

Special populations

Based upon pharmacokinetic data and population pharmacokinetic analysis, no clinically significant effect of body weight and ethnicity (Japanese subjects) on the pharmacokinetics is observed.

In the population pharmacokinetic analysis gender was identified as a significant covariate, and females had about 18% and 22% higher AUC and C_{max} compared to males. After accounting for eGFR, age and gender were no longer significant factors in the model.

Gefapixant exhibited low metabolic turnover following incubation with liver microsomes or hepatocytes. Consistent with the *in vitro* results, metabolism was observed as a minor route of elimination in the human ADME study, with approximately 14% of a dose of ^{14}C-gefapixant recovered as metabolites in urine and feces. Therefore, no study was done to evaluate pharmacokinetics in subjects with hepatic impairment. The SmPC indicated that patients with hepatic impairment have not been studied, but no dose recommendation is given. As hepatic elimination is a relatively minor pathway, a dose adjustment based on hepatic impairment is not required.

Pharmacokinetic studies in humans indicate renal excretion is the major elimination pathway for gefapixant in humans (i.e., about 64% of the dose was excreted unchanged in urine following a 50 mg

single dose). A pronounced effect on the pharmacokinetics of gefapixant due to a renal impairment is observed, i.e. in subjects with a moderate and severe impaired renal function and in subjects with ESRD not on hemodialysis, AUC_{0-t} increased 3.2-, 4.1- and 4.4-fold, respectively. In the popPK analysis, renal function was also indicated as a significant covariate for gefapixant exposure, i.e., in subjects with mild, moderate and severe renal impairment, the exposure was estimated to increase 1.2-, 1.5- and 1.9-fold. Thus, there is a pronounced difference of the impact of an impaired renal function observed in the study and the estimation by the popPK analysis. This difference was considered to be due to the higher average eGFR values in normal participants in the renal impairment study P026 (median eGFR 122 ml/min/1.73 m^2; n=6) compared to those in population PK analysis (mean eGFR 105 ml/min/1.73 m^2; n=650). As a result, the subjects with RCC/UCC with normal renal function showed higher exposures than did the healthy subjects in study P026, and the observed exposure fold change in the subjects with renal impairment may have been overestimated in study P026. According to the applicant, the population-PK analysis, which included 1555 participants with chronic cough and 122 healthy participants, may reflect a more realistic prediction of the effects of renal impairment on exposures in the intended population. Subjects with ESRD requiring haemodialysis and on haemodialysis showed a 23% lower exposure compared to subjects not on haemodialysis, indicating increased clearance due to haemodialysis.

Based on the estimated clinically relevant bounds for efficacy and safety (0.7 – 2.0) and based on the estimated increase in exposures by popPK analysis, no dose adjustment is necessary for subjects with a mild and moderate renal impairment.

Although the estimated increase in exposure in subjects with severe renal impairment was 1.9-fold and within the clinically relevant upper bound of 2.0, the exposure would lie primarily above the exposure range observed in Phase 3 studies. According to the applicant, adjusting the dose to bring the projected exposures within the range of clinical exposures seen in the Phase 3 studies will be most appropriate to limit unnecessary taste-related AEs. The projected steady-state C_{max} and AUC following 45-mg q.d. dosing in subjects with severe renal impairment are comparable to the projected C_{max} and AUC following 45 mg b.i.d. dose in subjects with normal renal function, and a comparable efficacy is expected. Therefore, the SmPC recommends a 45 mg q.d. dose in patients with severe renal impairment.

It is indicated that insufficient data are available in patients with end-stage renal disease requiring dialysis to make gefapixant dosing recommendations.

Pharmacokinetic interaction studies

In vitro data show that gefapixant is not a substrate for CYP enzymes. Gefapixant is a substrate MATE1, MATE2K, P-gp and BCRP. I*n vivo* metabolism is a minor pathway for gefapixant elimination and the potential for clinically meaningful drug interactions for gefapixant with co-administration of inhibitors or inducers of CYP-enzymes or uridine 5'-diphosphoglucuronic acid glucuronosyl transferase (UGT) enzymes is considered low.

Inhibition of P-gp- and BCRP-mediated renal excretion of gefapixant could not be tested clinically as there are no specific inhibitors for which the necessary degree of inhibition could be achieved at physiologic doses. Active tubular secretion is estimated to contribute to no more than 50% of the total clearance, and as such, an increase in gefapixant exposure resulted from transporter inhibition would not be clinically significant, according to the applicant. Considering the maximal possible effects on absorption (+25%) combined with the effect on renal clearance (factor 2), a potentially significant effect of P-gp and BCRP inhibitors on gefapixant pharmacokinetics cannot be ruled out. This issue has been further addressed by the applicant. In terms of oral absorption, the fraction absorbed for gefapixant was determined to be at least 78% in the human ADME study (P028), such that absorption is not limited to any significant extent by efflux mechanisms in the gut and the potential impact of P-gp

or BCRP inhibition is anticipated to be limited. As for the elimination of gefapixant, it was estimated that active secretion (i.e. by transporters) contributed to less than 50% of the total clearance. As demonstrated in P036, a portion of active secretion is mediated by MATE1 and/or MATE2K. Given the observed involvement of MATE1 and/or MATE2K on active secretion as well as contribution from glomerular filtration, the potential impacts of P-gp or BCRP inhibition toward gefapixant elimination is minimised. Taken together, co-administration of inhibitors of P-gp or BCRP is not expected to lead to clinically relevant drug interactions.

The inhibition of intestinal P-gp is expected to be of minimal effect on gefapixant exposure, as the fraction absorbed for gefapixant is at least 78%, so an increase caused by P-gp inhibition alone would not be clinically significant.

In a single-dose study, the MATE1/MATE2K inhibitor pyrimethamine (50 mg, administered 3 h before gefapixant 45 mg) increased gefapixant AUC by 24%, which is considered not clinically relevant. The SmPC indicates no dose adjustment in case pyrimethamine is co-administered with gefapixant, as the change in exposure is considered not clinically relevant, which is agreed.

Concomitant use of the proton pump inhibitor omeprazole did not have a clinically meaningful effect on gefapixant pharmacokinetics. However, omeprazole has a pronounced effect on the exposure of the F01 formulation, and the extent of the effect depends on the gefapixant dose, fed/fast condition and omeprazole dose. At a 50 mg dose, the exposure decreased 31 – 60%. For the F02 formulation containing the free base and citric acid was added as an excipient, the effect of omeprazole was less pronounced, and at a dose of 25 - 50 mg, exposure increased 3 – 8%. A comparable effect was observed for the F04 formulation containing the citrate salt at a 50 mg dose (fast), with a 3% decrease in exposure. The latter results are also considered applicable to the commercial F04B formulation taking into account the quantitative and qualitative compositions.

Considering the use of different formulations in the clinical studies and considering the pronounced different effect of a PPI on the exposure, the applicant was requested to indicate if PPIs have been used in the clinical studies. It appeared that in the Phase 3 studies, the F04 formulation has been used, for which no significant PPI effect was observed. This is also applicable for the F02 formulation used in Phase 2 studies at a relevant dose of 25 – 50 mg. Thus, although PPIs were used in these studies, a significant effect on pharmacokinetics is not expected based on data from previous (interaction) studies.

In vitro, the potential of gefapixant to cause CYP inhibition or induction is low, and therefore it is unlikely that gefapixant would affect the CYP-mediated metabolism of other drugs. The inhibition potential of gefapixant concerning P-gp, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, and BSEP was evaluated *in vitro* using specific cell lines expressing these transporters. Based upon the observed *in vitro* IC_{50} values, gefapixant may inhibit OATP1B1, OCT1, MATE1 and MATE2K, although for the latter 2, values were just around the cut-off threshold for a possible *in vivo* interaction.

Gefapixant (45 mg b.i.d.) did not affect the pharmacokinetics of the OATP1 substrate pitavastatin (1 mg).

In light of a potential safety concern associated with precipitation in the urinary tract which could lead to inflammation and subsequent hyperplasia, it was requested to discuss potential effects of medicinal products/ food affecting urinary pH. It appeared that solubility of gefapixant is pH-dependent, with the lowest solubility in in the physiologic pH range for human urine. The steady-state aqueous solubility at pH 5 to pH 7, which is the normal pH range in human urine, was around 0.13 mg/mL, while at more acidic or alkaline conditions solubility tended to be increased, which suggests that medicinal products/ food products that could affect urinary pH are not expected to increase the risk of precipitation in the urine.

Interactions are sufficiently described in section 4.5. of the SmPC.

Pharmacokinetics using human biomaterials

Not applicable.

2.5.2.2. Pharmacodynamics

Mechanism of action

Gefapixant is a first-in-class, non-narcotic, peripherally active, oral selective antagonist of the P2X3 receptor. Gefapixant also has activity against the P2X2/3 receptor subtype. Chronic cough observed in RCC and UCC is potentially related to activation of C-fibres *via* binding of extracellular ATP to P2X3 receptors. P2X3 receptors are ATP-gated ion channels found on sensory C fibres of the vagus nerve in the airways. C-fibres are activated in response to inflammation or chemical irritants and, when activated, initiate a cough reflex. ATP is released from airway mucosal cells under conditions of inflammation, and the binding of extracellular ATP to P2X3 receptors is sensed as a damage signal by C fibres, with subsequent activation. Studies conducted in animal models indicate that antagonism of either P2X3- or the closely related P2X2/3 receptor subtype reduces the responsiveness of C-fibre sensory neurons to ATP.

Primary and Secondary pharmacology

Study MK7264-015: Study P015 is a Phase 2 study that examined the effect of MK-7264 50 mg and 300 mg on cough reflex sensitivity of both capsaicin and ATP to access the cough reflex sensitivity in healthy volunteers and chronic cough patients. It is a one-dose, double-blind, randomised, 4-period, crossover study in male and female healthy and chronic cough subjects (Table 3).

Table 3 Study design of cohort 1 (300 mg)

Cohort 1				
	Capsaicin		ATP	
	Tx Period 1	Tx Period 2	Tx Period 3	Tx Period 4
Sequence A	PBO	AF-219 300 mg	PBO	AF-219 300 mg
Sequence B	AF-219 300 mg	PBO	AF-219 300 mg	PBO

* similar design for cohort 2 with 50 mg of AF-219 (=MK-7264)

Participants were all non-smokers (given up smoking in the past 6 months and less than 10 (healthy subjects) or 20 (chronic cough subjects) pack-years. All participants had a maximal cough frequency evoked by challenge agent (E_{max}) ≥4 following the capsaicin challenge at Screening. Healthy subjects had to have a forced expiratory volume in 1 second FEV1 ≥80% at Screening. The chronic cough subjects had to have a treatment-refractory cough for at least one year (cough that is unresponsive to at least 8 weeks of targeted treatment for identified underlying triggers, including reflux disease, asthma, and post-nasal drip) and cough for which no objective evidence of an underlying trigger could be determined. A total of 50 subjects were randomised. In Cohort 1, 26 subjects received 1 dose of MK-7264 300 mg. In Cohort 2, 24 subjects received at least one dose of MK-7264 50 mg.

The co-primary endpoints of cough reflex sensitivity were the maximal cough response (E_{max}) observed on inhalation of any concentration of tussive agent and the concentration of tussive agent causing 50% of the maximal cough response (ED_{50}).

Results: Pharmacodynamic modelling of the capsaicin- and ATP-evoked cough data showed similar results (Table 4 and Table 5). For capsaicin-evoked cough, the modelling detected a very small (<1

cough), but statistically significant reduction in E_{max}, i.e., the maximum number of coughs evoked was reduced for healthy subjects and chronic cough subjects during MK-7264 treatment compared with placebo. There was no significant effect on ED50.

For ATP-evoked cough, E_{max} was not achieved by the maximum ATP concentration inhaled; therefore, only effects on ED50 were estimated. There was a significant increase in ED50, i.e., reduced cough reflex sensitivity, for both healthy subjects and chronic cough subjects during MK-7264 treatment compared with placebo; the reduction in ED50 during treatment was higher for chronic cough subjects who received 300 mg compared with chronic cough subjects who received 50 mg and healthy subjects.

Table 4 Summary of Parameter Estimates (E_{max}, ED50, and E0) Based on the Final Model for the Capsaicin-Evoked Cough Challenge

	Placebo			Treatment		
	Healthy Subjects	Chronic Cough Subjects		Healthy Subjects	Chronic Cough Subjects	
Parameter	Male	Male	Female	Male	Male	Female
Emax	4.14	4.14	7.57	3.66	3.37	6.17
ED50	33	33	9.56	33	33	9.56
E0	0.036	0.33	0.33	0.036	0.33	0.33
n	26	5	18	26	5	18

Source: 16.1.10; Table 1 and Table 4

Table 5 Summary of parameter estimates (E_{max}, ED50, and E0) based on the final model for the ATP-evoked cough challenge

	Placebo			Treatment					
				AF219 50 mg			AF219 300 mg		
	Healthy Subjects	CC Subjects		Healthy Subjects	CC Subjects		Healthy Subjects	CC Subjects	
Parameter	Male	Male	Female	Male	Male	Female	Male	Male	Female
Emax	2.35	2.35	5.4	2.35	2.35	5.4	2.35	2.35	5.4
ED50	54.9	54.9	8.63	119.13	155.92	24.51	119.13	192.7	30.29
E0	0.015	0.17	0.17	0.015	0.17	0.17	0.015	0.17	0.17
n	26	4	18	26	4	18	26	4	18

CC = chronic cough

Source: 16.1.10; Table 5 and Table 8

ATP did not evoke as many coughs as capsaicin, and in many subjects, C5 was not achieved for subjects on placebo treatment (i.e., the maximum concentration of ATP elicited <5 coughs). For analysis, a C5 concentration of double the maximum dose is generally imputed, as the C5 is known to be above the maximum concentration, but a decrease in sensitivity with MK-7264 (increase in C5) could not be detected in these circumstances. A significant (unadjusted $p<0.05$) reduction in cough reflex sensitivity induced by inhalation of ATP was observed for MK-7264 in chronic cough subjects, i.e., C2 (i.e., the maximum concentration of ATP eliciting 2 coughs) was increased at both 50 mg and 300 mg MK-7264 doses and C5 was increased at 50 mg AF 219. However, in healthy subjects, no effect of MK-7264 on cough reflex sensitivity to ATP for C5 was observed at either dose; an increase in C2 was observed only for the 50 mg dose.

Study MK7264-014: Study 014 is a similar phase 2 study as Study 015. It is a randomised, double-blind, 2-period, crossover study of MK-7264 in healthy subjects and subjects with refractory or unexplained chronic cough. This study was exploratory for the cough reflex sensitivity assessment and not designed to assess the efficacy of MK-7264 in subjects with chronic cough. Participants were all non-smokers for at least 5 years. Healthy subjects had to have a forced expiratory volume in 1 second FEV1 ≥80% at Screening. The chronic cough subjects had to have a treatment-refractory cough for at least one year, cough for which no objective evidence of an underlying trigger could be determined and demonstrated significant cough symptoms by a score greater than 20/70 on the HARQ. The participant

received a single dose as 2 MK-7264 tablets, 50mg tablets (100 mg total) and 2 placebo tablets, divided over two treatment periods and in Sequence A (first placebo) or B (first MK-7264). A total of 36 subjects were randomised, and all completed the study. Overall, most subjects were female (88%), and healthy subjects (37.8 years) were younger than chronic cough subjects (61.1 years). Chronic cough subjects had a median history of cough of 12 years. Cough reflex sensitivity is measured by standard clinical methodology incorporating ATP, capsaicin, citric acid, and distilled water cough challenges.

The co-primary endpoints are those concentrations of challenge agents that induce 2 or more (C2), and 5 or more (C5) coughs, respectively. These were the average C2 and C5 (concentrations inducing at least 2 coughs and 5 coughs, respectively) across 3-time points.

Results: The results of the ATP cough challenge in chronic cough subjects showed a difference in the concentration required to induce C2 and C5 during the combined Treatment Periods 1 and 2 between MK-7264 and placebo groups ($p<0.001$ and $p=0.007$, respectively) (Table 6). In healthy subjects, there was no difference in the concentration required to induce C2 between the MK-7264 and placebo groups]; however, a significant difference was observed in the concentration required to induce C5 between the MK-7264 and placebo groups ($p=0.003$) (Table 7). There were no observed meaningful differences in cough responses to capsaicin and citric acid challenge agents in the MK-7264 *vs* placebo groups for either healthy or chronic cough subjects during the combined Treatment Periods 1 and 2 and in Treatment Periods 1 and 2 individually.

Table 6 MRMM analysis for C2 and C5 based on natural log-transformed data - chronic cough subjects - FAS Set

	C2		C5	
	MK-7264 100 mg N=24	Placebo N=24	MK-7264 100 mg N=24	Placebo N=24
ATP (mM)				
Geometric Mean[1]	18.1	3.9	33.9	9.2
LS Mean Difference (MK-7264 – Placebo)		1.54		1.30
p-value		0.0006		0.0067
Ratio[2]		4.65		3.68
95% CI (Ratio)		(2.0, 10.8)		(1.5, 9.2)

Table 7 MRMM analysis for C2 and C5 based on natural log-transformed data - healthy subjects - FAS Set

	C2		C5	
	MK-7264 100 mg N=24	Placebo N=24	MK-7264 100 mg N=24	Placebo N=24
ATP (mM)				
Geometric Mean[1]	120.2	49.5	272.5	113.5
LS Mean Difference (MK-7264 – Placebo)		0.89		0.88
p-value		0.1125		0.0029
Ratio[2]		2.43		2.40
95% CI (Ratio)		(0.8, 7.4)		(1.4, 4.0)

Secondary Pharmacodynamics: Gefapixant blocked hERG potassium currents with an IC_{20} and IC_{50} of >100,000 nM (35,400 ng/mL, 148x the clinical C_{max} free concentrations at 45 mg bid) and, therefore, did not provide any signal of concern.

In the non-clinical studies, no significant hemodynamic or ECG findings and no evidence of QTc interval prolongation were noted at doses of 15, 70, and 200 mg/kg in the conscious dog telemetry study. Concentration-QT analysis was performed using data from a single dose (P001) and multiple-dose (P007) Phase 1 trials to assess the effect of gefapixant doses on the QTc interval. Data from P001 provided the broadest range of doses (10 mg to 1800 mg) with the highest exposure margin >15-fold (8168 ng/mL) over the predicted steady-state mean C_{max} (531 ng/mL) for 45 mg BID. This trial also had an adequate placebo sample size and robust ECG sampling. The results showed no effect on the QTc interval up to single doses of 1800 mg.

Results: The predicted mean placebo population-based QTc (QTcP]) and Fridericia-corrected QTc (QTcF) time-matched change from baseline estimate at C_{max} and corresponding 90% CIs for 1800 mg administered in healthy male adults as a single dose in the fasted state were 3.64 (-0.39, 7.66) and 2.45 (-1.74, 6.63), respectively, with the upper 90% CI limits falling below 10 milliseconds (msec).

Data from P007 included both healthy and elderly adult male and female participants in a multiple-dose (600 mg BID for 14 days) setting with the largest exposure margin >6-fold (3481 ng/mL) over the predicted steady-state mean C_{max} (531 ng/mL) for 45 mg BID. The results showed no effect on the QTc interval up to multiple doses of 600 mg BID. The predicted mean placebo corrected QTcF time-matched change from baseline estimate at C_{max} and corresponding 90% CIs following gefapixant 600 mg BID administered to healthy adult and elderly males and females for 14 days was - 2.60 (-5.87, 0.68), with the upper 90% confidence limit falling below 10 msec.

2.5.3. Discussion on clinical pharmacology

Pharmacokinetics

Pharmacokinetics were in general sufficiently addressed. A 45 mg formulation with gefapixant as citrate salt was selected based upon a rather extensive development programme. This formulation appeared not to have a food effect, and bioavailability was not affected by the administration of a PPI. Gefapixant is metabolised to a small extent (<20%), and the interaction potential, i.e., being a victim drug or acting as a perpetrator, is low. As renal excretion is the major elimination route, renal impairment is identified as a significant covariate. To prevent too high exposures in patients with severe renal impairment, a dose reduction to 45 o.d. is recommended. No major objections are identified concerning pharmacokinetics.

Primary pharmacology

In the PD studies, an effect of MK-7264 treatment on the ATP induced cough sensitivity was seen. However, the effect sizes for all tested doses 50, 100 and 300 mg were small, and the clinical relevance is questioned. Especially the effect of the 50mg dose is very modest. Furthermore, the studies have some serious setbacks (E_{max} not reached, C5 not reached, not all data available) that hamper a robust conclusion on the results.

Secondary pharmacology

In *in vitro* data and non-clinical studies, there were no signals to expect QTc prolongation. Therefore, a dedicated QTc study is not considered necessary. Instead, concentration-QT modelling was performed. which confirmed that gefapixant does not prolong QTc interval as in these models the upper 90% confidence limit was falling below 10 msec.

2.5.4. Conclusions on clinical pharmacology

The clinical pharmacology testing concerning PK, PD effects of gefapixant is considered to be sufficient. Results are adequately reflected in the product information and in the agreed RMP. The CHMP did not consider any measures necessary to be addressed in the post-marketing phase.

2.5.5. Clinical efficacy

The key efficacy data originate from 2 controlled Phase 3 studies:

- Study MK7264-027: Evaluate Efficacy and Safety of 15 and 45 mg in patients with chronic cough – main study 12 weeks
- Study MK7264-030: Evaluate Efficacy and Safety of 15 and 45 mg in patients with chronic cough – main study 24 weeks

Supportive efficacy data are from:

- phase 2 studies assessing different doses of MK-7264:
  - Study MK7264-006 – Efficacy of 600mg in patients with chronic cough – 14 days
  - Study MK7264-010: Dose Escalation for Efficacy and Tolerance with doses between 7.5mg and 200mg in patients with RCC
  - Study MK7264-012: Efficacy and Safety of 7.5mg, 20mg and 50 mg in patients with chronic cough – 12 weeks
  - Study MK7264-021: Efficacy and Tolerability of 15mg, 30mg and 50mg in patients with RCC – 8 weeks
- top line results of two phase 3b studies
  - Study MK7264-042 – A 12 week placebo controlled trial to evaluate the efficacy of Gefapixant 45 mg in cough induced stress urinary incontinence in adult female participants with RCC or UCC
  - Study MK7264-043 – a 12 week placebo controlled trial to evaluate the efficacy of Gefapixant 45 mg in recent onset choric cough (< 12 months duration of RCC or UCC

2.5.5.1. Dose response studies

The recommended therapeutic dose of gefapixant is 45 mg BID, adjusted to 45 mg QD in the setting of severe Renal Impairment. The proposed gefapixant dose was evaluated based on the totality of data from individual trials and pooled analyses. A wide-dose range of gefapixant was evaluated in Phase 1 trials to establish safety/tolerability in healthy participants.

- 600 mg BID in a Phase 2a proof-of-concept trial in participants with cough (P006)
- 7.5 mg to 200 mg BID in a Phase 2a dose-escalation trial (P010)
- 7.5, 20, and 50 mg BID compared with placebo in a 1:1:1:1 Phase 2b trial (P012)

The PK and PD of gefapixant evaluated in 2 of these Phase 2 trials (P010 and P012) were used for population-PK and exploratory exposure-response analyses, and doses of 15 mg.

Dose Selection for Phase 2 Programme

No preclinical model for cough was available at the time of dose selection for Phase 2. Preclinical models that targeted pain associated with arthritis or bladder distension suggested that clinical doses in the range of 300 mg to 600 mg BID would achieve a pharmacologic effect. At the time of Phase 2

start, approximately 140 participants had received at least 1 dose of gefapixant in 4 Phase 1 trials. These doses (up to maximum exposure at 1800 mg BID for 14 days) were generally well tolerated in Phase 1. The initial dose tested in the Phase 2a proof-of-concept trial (P006) was 600 mg BID for 14 days, effectively reducing cough frequency. However, in this trial for cough (P006), participants had difficulty tolerating taste-related AEs, causing some participants to discontinue treatment at doses of 300 mg BID and higher.
Therefore, Study P010, a randomised, double-blind, placebo-controlled cross over, dose-ranging Phase 2a study in participants with RCC, initially evaluated a 50 mg to 200 mg BID dose range. However, no dose-response in the reduction of cough frequency. Therefore, a lower dose range of 7.5 mg to 50 mg BID was added. The Phase 2b Study P012 similarly tested doses of 7.5, 20, and 50 mg BID against placebo in four parallel groups of participants with RCC. The data from these 2 Phase 2 trials demonstrated a dose-dependent decrease in the cough frequency and improvement in participant-reported outcomes with doses ranging from 7.5 mg to 50 mg BID. Participants in these trials also experienced a dose-related increase in the taste-related AEs.

Dose Selection for Phase 3 Programme

The phase 3 programme tested 2 doses against placebo. The selected doses were 45 mg bid and 15 mg bid. The 45 mg dose was selected based on a near-maximal effect with a tolerable safety profile. The 15 mg dose was selected as it was the minimal effective dose. The selection of the dose was based on exposure-safety models based on data collected in n= 812 patients that participated in several clinical phase 1 and 2 trials, including studies P010 and P012.

The cough rate reduction increased from 7.5 mg to 30 mg and then plateaued at higher doses. Guided by the explorative analysis, the placebo model was used to account for the unconfounded drug effect, and the cough rate was modelled using an E_{max} function. The influence of proton-pump inhibitor use, underlying disease, history of chronic cough and age and gender were investigated using a standard SCM analysis. The effects of the intrinsic and extrinsic factors were evaluated on the model parameters baseline, placebo effect and drug effect (E_{max}). Gender was the only significant predictor for baseline cough rate and was retained in the model.

The taste data from P012 was only used for the model development as it has data from a longer duration (12 weeks) relative to P006 (4 days/treatment arm). The taste disturbance endpoint for the modelling was assessed from the structured taste questionnaire that was administered to subjects only if a subject experienced a taste-related adverse event to determine "How frequently do you experience the taste effect after taking each dose of medication", which is scaled from 1 to 5 with 1 representing never and 5 representing always. The taste disturbance endpoint was rederived to a binary end point- either the subjects had the taste effect irrespective of the frequency or not. Logistic regression was applied and an E_{max} model was shown to describe the exposure-response relation for taste disturbance best. All three exposure parameters were evaluated and C_{max} performed relatively better compared to AUC and C_{trough}. However, given that AUC is relatively less prone to prediction bias than C_{max}, only sparse concentration sampling at trough was performed with P012 and since AUC, C_{max}, and C_{trough} were highly correlated, AUC was considered as the most robust exposure driver for E-R relationship. A fit for purpose TTE drop-out model was developed to facilitate trial simulations and predict reasonable drop-out patterns over the clinically relevant dose range (0 – 50 mg). Due to limited drop-out data and low power model discrimination, model selection was largely guided by scientific plausibility rather than statistical significance. A simple one-parameter constant hazard model with an E_{max} model to account for the effect of AUC described the data adequately.

Simulations were performed to simulate the impact of important covariates on the exposure and to characterise the dose-response profile for cough reduction, taste effects and drop-out for a range of doses (0 – 50 mg, in steps of 2.5 mg) under consideration for Phase 3. A virtual population (n=250)

was obtained by randomly sampling patients from the available Phase 2 trial population with the covariate vectors of interest. The final popPK model was utilised to obtain individual PK parameters (CL, F1, V etc). For each dose level of interest, the PK parameters were used to obtain exposure estimates (AUC) for each patient. The simulations considered inter-individual variability and covariate effects. The placebo adjusted 24 h cough rate globally changes from baseline, placebo adjusted taste disturbance incidence, and the fraction of patients in the study at day 84 were simulated in the virtual population utilising the estimated PK exposures and the final E-R models. For each dose level, the median response was calculated. This procedure was repeated 1000 times by incorporating parameter uncertainty for estimated fixed effect parameters of the E-R models. For each dose level, median, 5th and 95th percentiles of cough, taste and drop-out outcomes from these 1000 runs were calculated to estimate the median and 90% CI, see Figure 3.

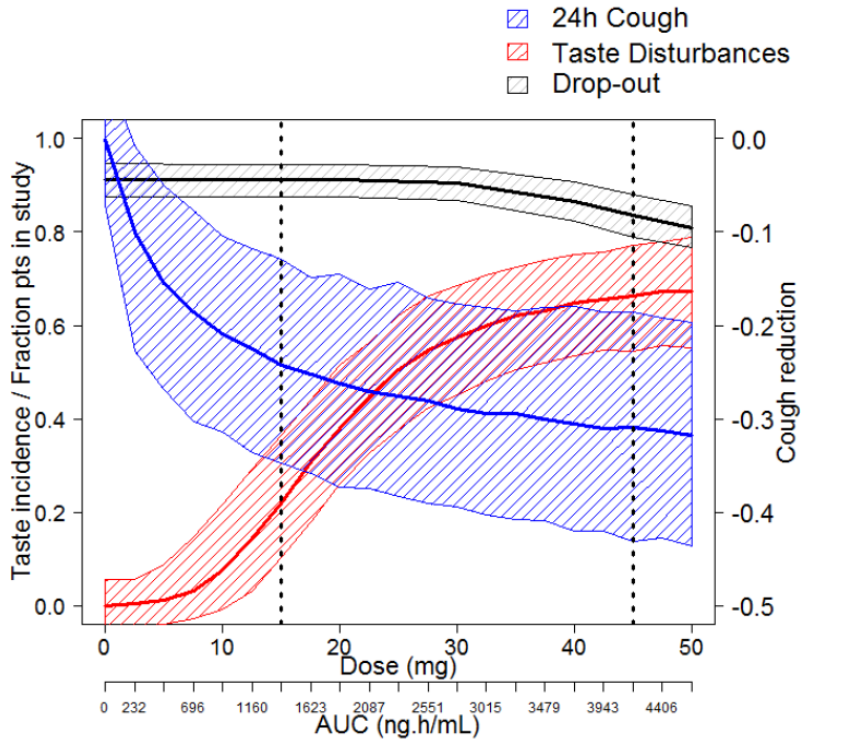


Figure 3 Integrated dose-response profile for cough reduction, taste disturbances and drop-out

MK-7264-010: A Dose Escalation Study to Assess the Efficacy and Tolerance of MK-7264 (AF-219) in Subjects with Refractory Chronic Cough

Study MK-7264-010 was a randomised, double-blind, placebo-controlled, crossover, dose-escalation study of MK-7264 in subjects with refractory or unexplained chronic cough. The study included a high dose cohort (50mg-200mg, cohort 1) and a low dose cohort (7.5mg – 50 mg, cohort 2) to identify a dose that would decrease cough with minimal to no effect on taste. Enrolment in the second cohort did not begin until enrolment in the first dosing cohort had been completed. Each dosing cohort consisted of two 16-day treatment periods (MK-7264 or placebo). For cohort 1, there was a 3-7 day washout period; for cohort 2, there was a 14-21 day washout period.

A total of 59 subjects were enrolled. In Cohort 1, 28 subjects received at least 1 dose of MK-7264; 92.9% received at least one dose of MK-7264 200 mg. In Cohort 2, 30 subjects received at least one dose of MK-7264; 100.0% received at least one dose of MK-7264 50 mg. Mean exposure was 17 days

in either the MK-7264 or placebo group. Mean exposure was 16 days while in either the MK-7264 or placebo group. For cohort 1, three subjects discontinued the study due to AEs and one subject in cohort 2 discontinued due to AEs.

Mean age across Periods 1 and 2 and for cohorts 1 and 2 was similar, approximately 63 years old. More women than men participated in the study; most subjects were White and non-Hispanic.

The primary endpoint was the mean change of baseline in awake objective cough frequency (per hour), using a mixed model repeated measures (MMRM) analysis to evaluate the results from this two-period cross-over study. The derived change in Awake cough frequency measured at each dose were the repeated measures. The mixed-effect model included Period, Treatment, Dose Level, and all interaction terms as the fixed effects. Contrasts were constructed to compare the active treatment to the placebo for each individual dose level. The primary endpoints and responder analyses (≥ 30, 50 and 70% cough reduction) were performed.

Results

Cohort 1 - At the end of treatment, mean (SD) change from Baseline in Awake cough frequency (Periods 1 and 2 combined) was -26.5 (37.79) cough/h in the MK-7264 50 mg dosing level compared to -0.4 (12.53) cough/h in the placebo group.

Based on the mixed-effects model with period, treatment, dose level, and all interaction terms as fixed effects and baseline as a covariate for change from baseline, Awake cough frequency was significantly reduced from the Baseline for all MK-7264 dosing groups compared to placebo ($p<0.001$). The period/sequence effect was significant ($p=0.047$), so the results for each period were also summarised. For 50 mg dosing level, the LS mean difference (95% CI) was -22.6 (- 34.4, -10.8) cough/h for Periods 1 and 2 combined, -29.7 (-46.5, -12.9) cough/h at Period 1, and -15.4 (-32.0, 1.1) cough/h at Period 2.

Based on the mixed model analysis based on log-transformed data statistically significant reduction in Awake Cough Frequency for all MK-7264 dosing levels was observed compared to placebo (p-value <0.008). The difference between MK-7264 and placebo was also estimated by percent change, which is calculated by 100 (ediff - 1), where diff =LS mean difference from mixed model of change from baseline based on log-transformed data. The significant percent change was -41.2% (95% CI: -59.3%, -15.1%) relative to placebo for 50 mg and the percent change was -52.0%, -46.9%, and - 57.1% relative to placebo for 100 mg, 150 mg, and 200 mg, respectively.

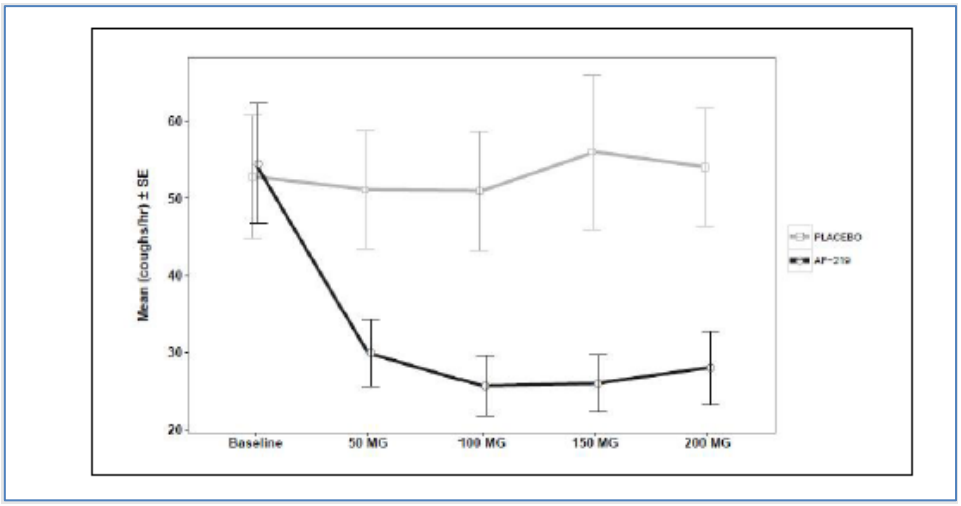


Figure 4 Awake objective cough frequency (Periods 1 and 2 combined): cohort 1 – FAS (AF-219 = MK-7264)

Cohort 2 - At the end of treatment, mean (SD) change from Baseline in Awake cough frequency (Periods 1 and 2 combined) was -24.3 (35.48) cough/h in the MK-7264 50 mg dosing level compared to 1.1 (23.39) in the placebo group. Based on the mixed-effects model for change from baseline, Awake cough frequency was significantly reduced from Baseline ($p<0.001$) for MK-7264 30 mg and 50 mg doses. LS mean difference (95% CI) was -24.6 (-37.1, -12.0) for 30 mg and - 23.8 (-35.9, -11.7) for 50 mg. MK-7264 7.5 mg and 15 mg doses reduced Awake cough frequency compared with placebo by LS mean (95% CI) was -6.9 (-18.0, 4.3) and -9.0 (-18.3, 0.3), respectively. The period/sequence effect was not significant ($p=0.129$).

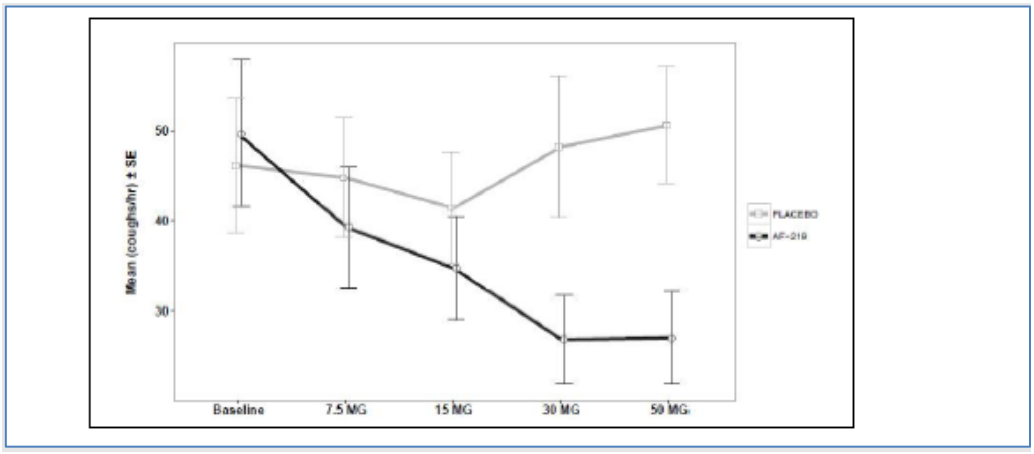


Figure 5 Awake objective cough frequency (Periods 1 and 2 combined): cohort 2 – FAS (AF-219 = MK-7264)

Based on the mixed model analysis based on log-transformed data, a statistically significant reduction in Awake Cough Frequency for MK-7264 15 mg, 30 mg, and 50 mg was observed compared to placebo (p-value <0.027). The difference between MK-7264 and placebo was also estimated by percent change, which is calculated by 100 (ediff - 1), where diff =LS mean difference from a mixed model of change from baseline based on log-transformed data. The significant percent change was -55.9% (95% CI: -71.9% - 30.8%) relative to placebo for 50 mg and the percent change was -14.7%, -25.2%, and -37.1% relative to placebo for 7.5 mg, 15 mg, and 30 mg, respectively.

Three responder variables were define based on the magnitude of percent change from baseline Awake objective cough frequency.

Cohort 1 - For the 50 mg dosing level (Periods 1 and 2 combined), MK-7264 had greater response rates compared to the placebo group: 58.3% vs. 12.0% for ≥30% decrease in cough frequency, 46.2% vs. 0% for ≥50% decrease, and 34.6% vs. 0% for ≥70% decrease.

Cohort 2 - For the 50 mg dosing level, MK-7264 had greater response rates compared to the placebo group: 55.2% vs. 22.2% for ≥30% decrease in cough frequency, 41.4% vs. 11.1% for ≥50% decrease, and 31.0% vs. 3.7% for ≥70% decrease.

Secondary Endpoint Results:

Daily Cough Severity Diary

At the end of treatment (Periods 1 and 2 combined), both cohorts showed a statistically significant improvement in the Daily Cough Severity dairy for the MK-7264 100 mg, 150 mg and 200 mg doses, while numeral improvements were observed for the MK-7264 50 mg dose.

Cough Severity by Visual Analog Scale

Cohort 1 - At the end of treatment (periods 1 and 2 combined), a statistically significant reduction was observed for the 100 mg, 150 mg and 200 mg dose, while numerical improvements were observed for the MK-7264 50 mg dose

Cohort 2 - At the end of treatment (periods 1 and 2 combined), statistically significant reductions with placebo were observed for the 30 mg and 50 mg dose.

MK-7264-012: A 12-Week Study to Assess the Efficacy and Safety of (AF-219) MK-7264 in Subjects with Treatment Refractory Chronic Cough

This was a 12-week randomised, parallel, double-blind, placebo-controlled study of MK-7264 in subjects with treatment-refractory or unexplained chronic cough. Two-hundred and fifty-three subjects who met entry criteria were randomly assigned to MK-7264 (dosing 7.5 mg, 20 mg, 50 mg) or matching placebo for up to 84 days. Of the 31 (12.3%) subjects who discontinued prematurely, one subject was discontinued due to 'investigator decision' before study treatment was started, and the majority discontinued due to adverse events. In the 50 mg arm, 20.6% discontinued compared to 79% in the placebo arm.

The study diagram is depicted in Figure 6.

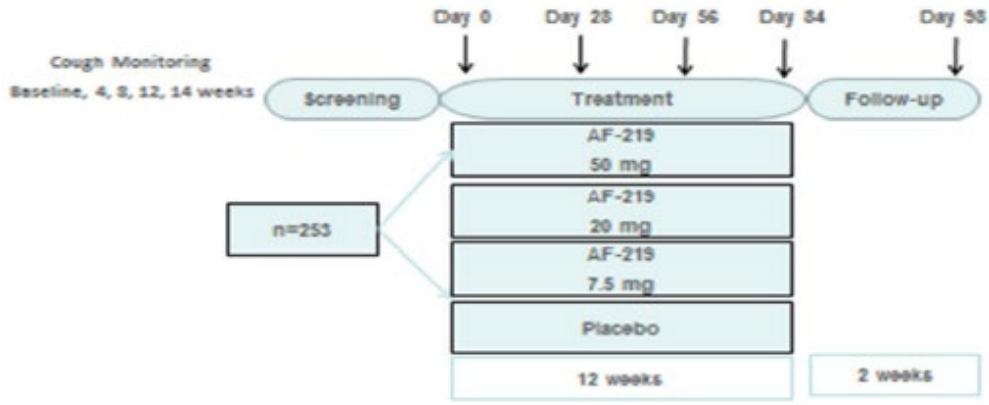


Figure 6 Study diagram P012

Patients were included with a Chest radiograph or CT thorax within the last 5 years, not demonstrating any abnormality considered to be significantly contributing to the chronic cough, and with a diagnosis of refractory chronic cough or unexplained cough for at least 1 year. They also had to have a score of ≥ 40mm on the Cough Severity VAS at Screening.

Patients were excluded when they were a smoker or had given up smoking in the past 6 months prior to study entry. Initiation of treatment with an angiotensin-converting enzyme (ACE)-inhibitor within 4 weeks prior to the Baseline Visit (Day 0) or during the study was not allowed, and FEV1/FVC < 60% was also not allowed. Other exclusion criteria were for example, respiratory tract infection in last 4 weeks, history of bronchiectasis or cystic fibrosis, opioid use in last week, requirement of prohibited medications.

The primary endpoint was the change from baseline in awake cough frequency after MK-7264 therapy at each dose studied after 12 weeks (Day 84) of treatment. The primary endpoint was analysed using a mixed model repeated measures (MMRM) analysis (log-transformed awake cough frequency). The primary efficacy endpoint comparisons for all active doses *versus* placebo were controlled for multiplicity (for the three comparisons of MK-7264 50 mg to placebo, MK-7264 20 mg to placebo, and MK-7264 7.5 mg to placebo on the primary efficacy endpoint in a hierarchical manner). All other efficacy endpoints were tested at the 0.05 level of significance without multiplicity adjustment.

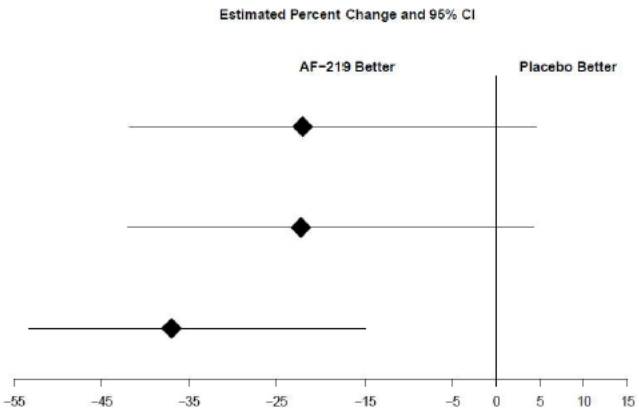
Results

More women than men participated in the study; most subjects were white and non-Hispanic. Subjects' history of smoking and their FEV1/FVC ratio were similar across treatment groups. All other baseline characteristics were also generally similar across the treatment groups.

Primary Endpoint (Awake Cough Frequency at Week 12):

The primary efficacy hypothesis of the study was met. At Week 12, there was a significant reduction in awake cough frequency in the MK-7264 50 mg group compared to placebo (p = 0.003). The percent change from baseline in awake cough frequency was -37% (95% CI: -53.3% to -14.9%) relative to placebo. The percent changes from baseline in awake cough frequency in the MK-7264 20 mg (-22.2%, p=0.093) and 7.5 mg (-22.0%, p=0.097) groups at Week 12 were not statistically significant compared to placebo (Figure 7).

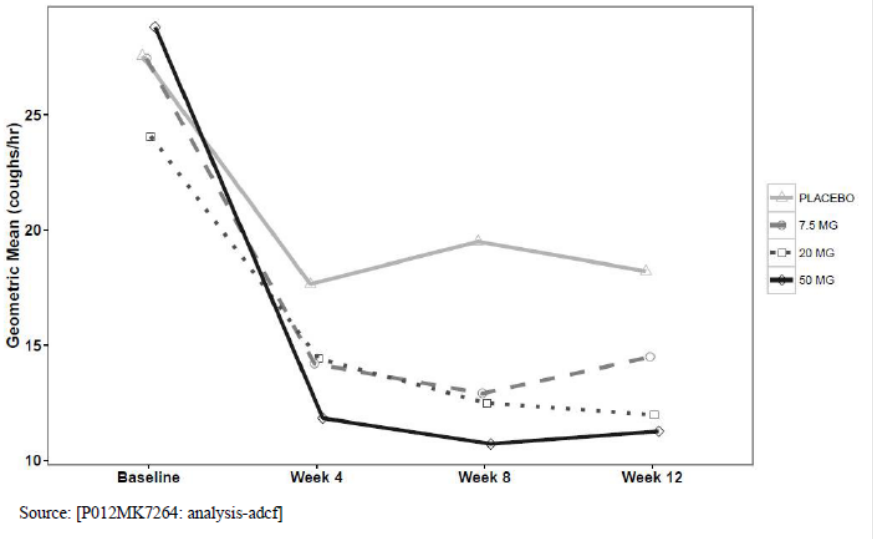
AF-219 Does Levels	Estimated %Change (95% CI)	p-value
7.5 MG	-22 (-41.8, 4.6)	0.0971
20 MG	-22.2 (-42, 4.3)	0.0928
50 MG	-37 (-53.3, -14.9)	0.0027



%Change = 100(e**diff -1), diff = least square mean difference (AF-219 – Placebo) from mixed model of change from baseline (natural log-transformed data)
FAS=Full Analysis Set; CI=Confidence Interval

Figure 7 Estimated percent change of awake cough frequency MK-7264 (AF-219) dose relative to placebo at week 12 (FAS)

At Week 12, the geometric mean of the awake cough frequency (c/hr) was 11.3 in the MK-7264 50 mg group, 12.0 in the MK-7264 20 mg group, and 14.5 in the MK-7264 7.5 mg group, compared to 18.2 in the placebo group (Figure 8).



Source: [P012MK7264: analysis-adcf]

Figure 8 Geometric mean of awake cough frequency

The percent of subjects who met the various responder criteria for awake cough frequency at Week 12 is depicted below (Figure 9).

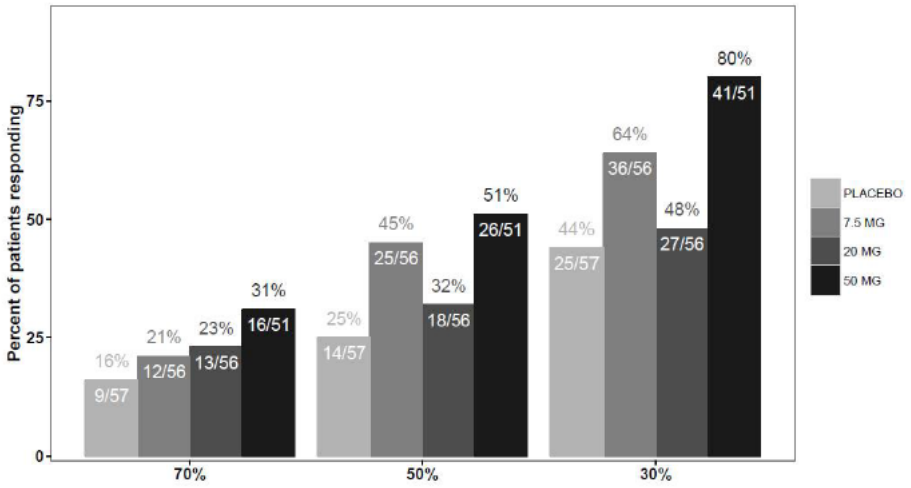


Figure 9. Responder analysis of awake cough frequency at week 12

Key secondary outcomes

The key secondary endpoints (awake cough frequency at week 4 and 8; 24h cough frequency and Cough Severity VAS) support the primary outcome with statistically significant improvements with placebo observed with the high dose with gefapixant 45 mg and numerical improvements with the two lower doses of 20 mg and 7.5 mg.

Discussion on the dose-response studies

The dosing of gefapixant was investigated in two randomised, double-blind, placebo-controlled Phase 2 studies (P010, P012) in patients with refractory or unexplained cough. The dose selection is based on clinical outcome measures, i.e., the reduction of cough frequency. No additional pharmacodynamic parameters, i.e., the ATP or capsaicin threshold for the induction of cough or capsaicin was investigated.

The dose escalation Study P010 identified the dosages on the steep part of the dose-response curve. It showed that the MK-7264 50 mg bid dose resulted in the maximal effect on the cough reduction. A higher dose did not result in a much larger benefit.

The 7.5 mg, 20 mg and 50 mg bid dosages were investigated in the study P012 to provide l 12-week treatment data to support the dose selection for the pivotal phase III phase.

Study 012 showed a significant reduction in awake cough frequency in the MK-7264 50 mg group compared to placebo (p = 0.003), while numerical improvements were observed with the lower posology of 20 mg and 7.5 mg. The results are supported with secondary outcomes including the Cough severity VAS, a patient reported outcome.

Conclusion

The design of the studies is adequate to support the selected dosages in the range of 7.5 mg and 50 mg bid. Further support for the dose selections (i.e., 15 mg bid and 45 mg bid) is provided by the exposure-effect simulations.

2.5.5.2. Studies to validate the cough recording procedure

Introduction

For the two main studies, a new outcome measure was used, i.e., the relative reduction in cough count per hour measured during a 24-hour period. Coughs were recorded using a VitaloJAK recording device. Where possible these recordings were compressed to remove silence and non-cough sounds, and the coughs were tagged by trained cough analysts for counting.

During the assessment procedure, concerns were raised by the CHMP relating to the validation of the VitaloJAK cough counting system. While the VitaloJAK is validated as an FDA cough recording device and is a CE marked medical device, the full system including the compression cough counting algorithm and manual cough tagging by multiple trained cough analysts has not been adequately validated against what was considered to be the "gold standard" for manual cough count: the uncompressed cough recordings.

The results from the two main studies were based on cough count data which were compressed using a combination of the version 2.0 compression algorithm with dual channel processing, version 3.0 algorithm with dual channel processing, and version 3.0 algorithm with single channel processing. During assessment, the applicant developed and conducted a (1) study to validate the Recordings Compressed with Software Algorithm WH03 v3.0, Single Channel Processing and (2) a study to evaluate the inter-rater reliability of cough counting. The CHMP consulted the Methodology Working Party (MWP), to receive input on specific questions regarding both study protocols (see section 2.5.6).

Description of the validation studies

I. Validation of 24-Hour Cough Frequencies Ascertained Using Recordings Compressed with Software Algorithm WH03 v3.0, Single Channel Processing and Proprietary Phase 3 Data

During the main studies P027 and P030, three different software compression algorithms were used i.e., Version 2.0 is dual compression channel (based on data from 2 microphones); Version 3.0 had two variations: single channel (compressing based on the recording from the chest sensor only) and dual channel. The applicant decided only to validate the single channel compression algorithm WHO3 v3.0, because this compression algorithm was considered closest to the "gold standard" of uncompressed recording. This algorithm removes less of the uncompressed recording compared with both dual compression algorithms, while, in addition, a previous validation study showed less variation in cough counts than with dual channel compressions.

Objective

The primary objective of the study was to measure the agreement between the 24-hour cough frequencies (coughs per hour) from uncompressed cough recordings and recordings compressed using WH03 v3.0 single channel processing.

Methods

Cough recordings from studies P027 and P030, including those with quality events (per Vitalograph SOPs), ≥ 20 hours were eligible for inclusion. Recordings were randomly selected based on subject ID from all visits (baseline and post-baseline recordings) using a random seed to be approximately representative of the age, sex, and underlying aetiology of the cough (refractory chronic cough and unexplained chronic cough), as well as approximately evenly distributed across quintiles of cough

counts observed in the Phase 3 trials. Only one recording per participant included in the primary efficacy analysis was selected.

Recordings were selected across each quintile of cough counts per 24-hour recording observed in the Phase 3 data: Q1 0-100, Q2 101-210, Q3 211-366, Q4 367-655, Q5 656-25331. About equal numbers of recordings within each quintile were selected for inclusion. Slightly more recordings were selected from Q5 than in the other quintiles, as there was a concern that the highest range of cough counts in the phase 3 trials was not adequately represented in the original validation study.

Each individual cough analyst tagged coughs for one of the two formats (uncompressed or compressed) for any selected recording to eliminate potential bias from an analyst remembering a particular recording that he/she has tagged before in a different format. Cough analysts were blinded to tags on recordings in other formats and were trained using the same Vitalograph SOPs used throughout the Phase 3 P027 and P030 clinical trials. All cough analysts received the same training and certification. They were blinded to treatment assignment and previous cough counts for a given recording.

Statistical Analyses

As a primary analysis, a modified Bland-Altman plot with percent difference plotted against the gold standard was performed. In this study, the percent difference (the difference between the 24-hour cough frequencies from the uncompressed and compressed files (using WH03 v3.0, single channel processing) divided by the uncompressed 24-hour cough frequencies*100) is used to assess the degree of agreement between 24-hour cough frequencies from compressed recordings *versus* 24-hour cough frequencies in uncompressed recordings.

Considering the experts' opinions, the applicant proposed a 10% maximal allowed difference (MAD), but based on health authority feedback, the applicant used 5% as the MAD for the Bland-Altman plot. The Limits of agreement are the range of values within which 95% of the percent differences are expected, assuming a normal distribution. These limits are calculated as mean percent difference ± 1.96 x standard deviation of percent difference, assuming a normal distribution of the within subject percent differences in 24-hour cough frequencies between uncompressed and compressed recordings. The 95% confidence limits (CI) of the 95% LOA were calculated as LOA ± 1.96 x $\sqrt{(3/n)}$ x S, where S is the standard deviation of percent difference. If the upper limit of the 95% CI of upper LOA and the lower limit of the 95% CI of lower LOA were within MAD of percent difference (for this study, MAD = 5%), then the applicant concluded there was agreement in cough counts between compress and uncompressed records.
The LOA along with the corresponding 95% confidence intervals was plotted and reported in a table. The protocol also described various alternative methods in case normally distribution of the data was not achieved i.e., Deming/Passing Bablok analyses and a sensitivity analysis using alternative limits agreement based on a folded normal or half normal distribution. This latter sensitivity analysis was not performed.

Matlab and an excel lookup table were used to compare the cough tag positions between the 24h uncompressed and compressed recordings. This software was developed to compare cough counts from two or more cough analysts. It reports tags from the two recordings as matching if they are within 1000 sample points (125msec) of each other. This time window was chosen based on the typical length of cough sounds which is 200-300msec, and therefore, a second explosive cough sound could not be performed in this time window. For each recording the lookup table generated a table documenting the number of matched tags, tags present in the 24h recording but not the compressed and also tags present in the compressed but not 24h recording.
A second piece of software (validation software) utilised the 'output file' data to determine which of the unmatched tags in the 24h files were removed by the WH03 algorithm i.e., the sound was no

longer present in the compressed file, and therefore could not be tagged. This process also determined which sounds tags in the 24h files were retained by the algorithm but not subsequently tagged by the cough analyst in the compressed file.

Based on the processes described above all tags can be classified as follows:

1. Matched tags; tags present within both the 24h and compressed files for the same cough sound

2. Tags present in the 24h recording file but not the compressed, subclassified as

    a. algorithm removed

    b. algorithm retained

3. Tags present in the compressed recording but not the 24h recording file

Results

The main results of this validation study are shown in the Bland-Altman Plots on different scales in (Figure 10, Figure 11, and Figure 12). Each point represents one recording. In Figure 10, the Bland-Altman plot shows the LOA and several points outside the pre-specified MAD of 5% (shown in red and with the bolded line). The outliers outside the MAD appear at low cough frequencies. A comparison of Figure 10 and Figure 12 demonstrates that at the low cough frequencies, a small absolute difference can translate to a high relative percentage difference.

The points are approximately evenly distributed above and below 0, although the mean of the differences is slightly above 0 suggesting that, on average, the uncompressed recordings result in a higher cough count than the compressed recordings.

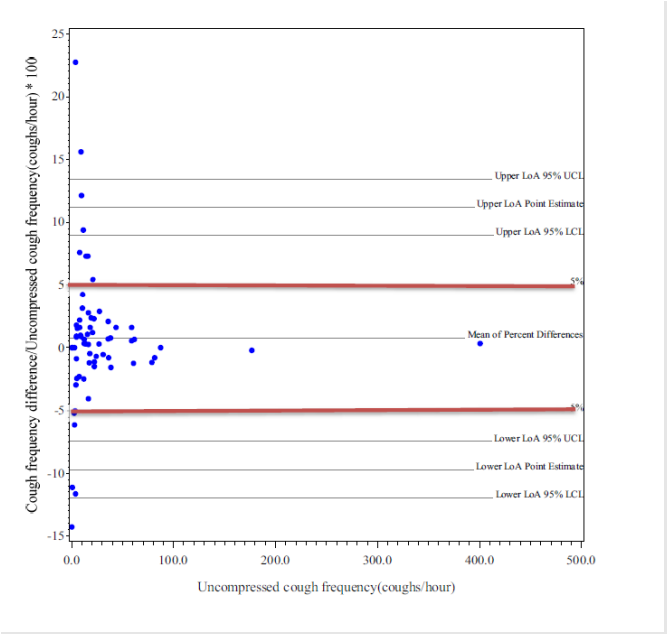


Figure 10. Bland-Altman plot of cough frequencies, Percent difference scale

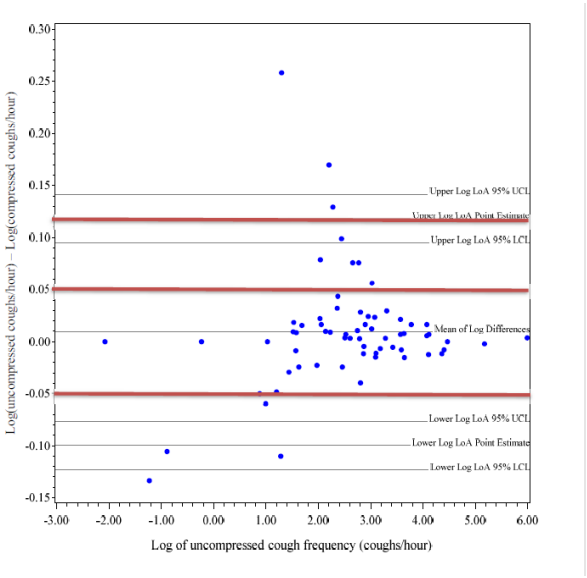


Figure 11. Bland-Altman plot of cough frequencies, log scale

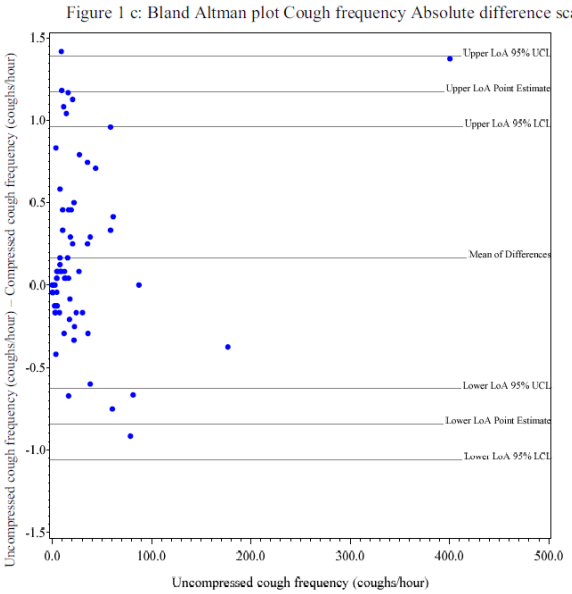


Figure 12. Bland-Altman plot of cough frequencies, absolute difference scale

The applicant performed an investigation into the recordings that had a discrepancy outside the 5% MAD. There were no clear patient characteristics that were associated with these recordings. Furthermore, based on the analysis of the position of the cough tags, it was determined that most of the discrepancies were due to a difference in the cough analyst and not the removal of any cough-like sounds from the compressed recording from the uncompressed recording. In 2/13 recordings it was determined that the discrepancy was primarily due to the algorithm, and in an additional one recording the discrepancy was a combination of both the algorithm and manual cough count.

II. Inter-rater Reliability of Cough Counting for Cough Recordings

This cross-sectional study assessed and documented the inter-rater reliability among blinded trained cough analysts to identify coughs from the uncompressed and compressed recordings (WH03 v3.0, single channel processed). A total of 20 recordings of 20 subjects were randomly selected from studies P027 and P030 across each quintile of cough counts. The selection of recordings was the same as for the study that validated the compression algorithm. Recordings that were included in the validation study were not eligible for the inter-rater reliability study.

Eight cough analysts were randomly selected from a pool of cough analysts trained using the same Vitalograph SOPs used throughout the two phase 3 clinical trials, and would therefore, be reflective of the population of cough analysts. All cough analysts received the same training and certification. Each cough analyst tagged both the compressed and non-compressed data from each of the 20 cough recordings. The order of the compressed or non-compressed recording was random and there was a timeframe of at least four weeks before the same analyst counted the other version of the same cough recording.

Statistical Analysis

The intraclass correlation was reported for all uncompressed and compressed recordings in this inter-rater reliability study. In this analysis, the intraclass correlation (ICC), ICC type (2,1) was calculated to assess the inter-rater reliability. The case 2 model is a two-way random effects model that was used to calculate the ICC, considering that both recording and cough analyst effects were random.

ICC type (2,1) represents that the intention to: generalise the reliability results to any raters who possess the same characteristics as the selected raters in the reliability study, that it is interested in absolute agreement between the analysts, and that it is interested in a single measurement (not a mean of multiple measurements).Observed agreement between cough analysts as measured by ICC (2,1) ≥0.996 was set as the threshold to conclude sufficient inter-rater reliability.

The percent coefficient of variation (PCV=100*standard deviation/mean) across analysts was also calculated for each recording. As an exploratory objective, Bland-Altman plots were also used to assess agreement between cough counts from compressed and uncompressed recordings, as was done in the compression algorithm validation study.

Results

The ICC was ≥0.996 for both compressed and uncompressed recordings, respectively, indicating that the study met the success criteria, see below.

Table 8 Intraclass correlation

Compression status	ICC	Bootstrapped 2.5th percentile
Compressed	0.99975	0.99941
Uncompressed	0.99978	0.99954

All except for one recording had a percent of coefficient of variation (% CV) of <5%; the only exception referred one missed cough by 1 of the 7 analysts in a recording that only reported 4 cough counts. As with the validation of the compression algorithm, the largest %CV was observed in the recordings with the lowest cough frequencies.

Discussion on the validation studies

The applicant provided the results from two validation studies: i.e. a validation study of the 24-Hour Cough Frequencies Ascertained Using Recordings Compressed with Software Algorithm WH03 v3.0, single channel processing, an inter-rater reliability study, which was also based on recordings compressed with Software Algorithm WH03 v3.0, single channel processing.

Single channel compression algorithm WHO3 V3.0: Based on the results from the validity of the compression algorithm, it is concluded that the Recordings Compressed with Software Algorithm WH03 v3.0, single channel processing is valid. Although there were some compressed recordings that were outside the maximum acceptable difference, these were from patients with a low cough frequency which meant that a small absolute difference resulted in a high difference on the relative percent scale. Furthermore, an investigation of these discrepancies identified that most of the discrepancies were due to the analyst differences and not the removal of relevant cough-like sounds by the algorithm.

It is important to note that the version 2.0 and version 3.0 compression algorithms for the dual channel processing were not part of the validation study. The results for the primary and secondary endpoints that were provided in the CSR are based on data containing around 90% of recordings that were compressed using dual channel processing.

Inter-rater reliability: Based on feedback received from the CHMP Methodology Working Party (MWP), the applicant prepared a protocol version and final report, for which the primary measurement of interest was the intraclass correlation coefficient. The results from the inter-rater reliability study support a conclusion that the level of agreement between cough analysts is acceptable when compression algorithm WHO 3 V3 is used. Similar to what was observed in the validation study of the

compression algorithm, the differences in the low cough frequency recordings resulted in a larger coefficient of variation.

Overall conclusion

Based on the validation studies based on the recordings compressed with Software Algorithm WH03 v3.0, single channel processing, V3.0 it can be concluded that the full VitaloJAK system is valid for use in the clinical studies.

2.5.5.3. Main studies

The core efficacy data originate from Phase 3 Studies MK7264-027 and MK7264-030, which are almost duplicate studies except for their treatment duration of the main study phase, that is 12 weeks and 24 weeks, respectively, when the main efficacy endpoints were measured. Both studies were followed by a blinded extension period of 40 weeks (study P027) or 24 weeks (study P030). In the extension period, additional patient reported outcomes and safety data were collected.

Title of studies

- *Study MK7264-027: A Phase 3, Randomised, Double-blind, Placebo-controlled, 12-month Study to Evaluate the Efficacy and Safety of MK-7264 in Adult Participants with Chronic Cough (PN027).*
- *Study MK7264-030: A Phase 3, Randomised, Double-Blind, Placebo-Controlled, 12-Month Study to Evaluate the Efficacy and Safety of MK-7264 in Adult Participants with Chronic Cough (PN030).*

Methods

- **Study Participants**

Both studies have the same inclusion and exclusion criteria. These studies planned to enrol male and female participants at least 18 years of age with chronic cough >1 year and a diagnosis of refractory chronic cough or unexplained chronic cough according to the American College of Chest Physician (ACCP) guidelines. Participants were eligible to be included in the study only if all the following criteria applied:

Inclusion criteria

1. Normal Chest radiograph or computed tomography scan of the thorax (within 5 years of Screening/Visit 1 and after the onset of chronic cough)
2. Have chronic cough for 1 year and a diagnosis of refractory chronic cough or unexplained chronic cough.
    a. Refractory Chronic Cough was defined as participants who have had a clinical evaluation that suggested a comorbid condition that may be related to cough (e.g., gastroesophageal reflux disease [GERD], asthma, or upper airway cough syndrome), the participant has received appropriate diagnostic work-up and therapy according to ACCP (American College of Chest Physicians guidelines), and the participant continues to cough.
    b. Unexplained Chronic Cough was defined as participants who have had a clinical evaluation of their cough per ACCP guidelines, and this evaluation has not suggested a comorbid condition that may be related to cough.

3. Have a score of ≥40 mm on the Cough Severity VAS at both the Screening and Baseline visits.

Exclusion Criteria

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

1. Current smoker.
2. Individuals who have given up smoking within 12 months of Screening/Visit 1.
3. Former smokers with a pack/year history greater than 20 pack-years.
4. Forced expiratory volume in 1 second (FEV1)/ forced vital capacity (FVC) ratio <60%.
5. History of upper or lower respiratory tract infection or recent clinically significant change in pulmonary status within 4 weeks of Screening/Visit 1.
6. History of chronic bronchitis, defined as a cough that produces a clinically significant amount of sputum (greater than approximately 1 tablespoon of phlegm) that occurs every day for at least 3 months in a row, with those periods occurring at least 2 years in a row.
7. Individuals who are currently taking an angiotensin converting enzyme inhibitor or have taken an angiotensin converting enzyme inhibitor within 3 months of Screening/Visit 1.
8. Estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2 (using the Chronic Kidney Disease Epidemiology Collaboration [CKD EPI] formula at Screening/Visit 1.
9. Screening systolic blood pressure >160 mm Hg or a diastolic blood pressure >90 mm Hg.
10. History of cutaneous adverse drug reaction to sulphonamides with or without systemic symptoms or history of anaphylaxis to sulphonamides.
11. Has a known allergy/sensitivity or contraindication to MK-7264 or its excipients.

Participants were also to refrain from the consumption of alcohol 24 hours prior to and after all study visits (including the PK sampling visits). On intermediate days, alcohol consumption was limited to no more than approximately 3 alcoholic beverages per day. Participants were to abstain from strenuous exercise and avoid noisy environments while the VitaloJAK monitor was attached over a 24-hour period. However, participants were allowed to participate in light recreational activities.

- **Treatments**

In both studies, patients were randomised to receive either active MK-7264 45 mg, active 15 mg MK-7264 or placebo, approximately 12 hours apart.

- **Objectives**

Primary Objective

- To evaluate the efficacy of MK-7264 in reducing cough frequency as measured over a 24-hour period at week 12 (P027) or week 24 (P030).

  Primary hypothesis: At least one MK-7264 dose is superior to placebo in reducing coughs per hour (over 24 hours) at Week 12 (study P027) or at week 24 (study P030).

Secondary objectives

- To evaluate the efficacy of MK-7264 in reducing cough frequency as measured while awake during a 24-hour period

- To evaluate the efficacy of MK-7264 based on the proportion of participants with a clinically significant reduction from baseline in 24-hour coughs per hour
- To evaluate the efficacy of MK-7264 in improving self-rated cough severity (CSD and Cough Severity VAS)
- To evaluate the ability of MK-7264 to provide a clinically significant improvement in cough specific quality of life (LCQ)

Three exploratory objectives have also been outlined in the study protocol:

- To evaluate the efficacy of gefapixant based on the proportion of participants with a clinically significant reduction from baseline in cough frequency
- To evaluate the impact of gefapixant on generic health-related quality of life, work productivity, and global rating of change
- To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analysed for association with clinical data collected in the study

Outcomes/endpoints

Outcomes/endpoints P027

Primary efficacy endpoint

- Change from baseline in (log-transformed) 24-hour coughs per hour (i.e., average hourly cough frequency based on 24-hour sound recordings) at Week 12

Secondary endpoints

- Change from baseline in (log-transformed) awake coughs per hour at Week 12
- The proportion of participants who received a ≥30% reduction in (log-transformed) 24-hour coughs per hour at Week 12
- The proportion of participants with a ≥1.3-point reduction from baseline in mean weekly cough severity diary (CSD) total score
- The proportion of participants with a ≥2.7-point reduction from baseline in mean weekly CSD total score
- The proportion of participants with a ≥30 mm reduction from baseline in Cough Severity Visual Analog Scale (VAS) score
- The proportion of participants with a ≥1.3-point increase from baseline in Leicester Cough Questionnaire (LCQ) total score

Exploratory endpoints

- The proportion of participants with ≥50% and ≥70% reduction from baseline in 24-hour coughs per hour
- The proportion of participants with ≥30%, ≥50%, and ≥70% reduction from baseline in awake coughs per hour

Outcomes/ endpoints Study P030

Primary Efficacy endpoint

- Change from baseline in (log-transformed) 24-hour coughs per hour (i.e., average hourly cough frequency based on 24-hour sound recordings) at Week 24

Secondary Efficacy endpoint

- Change from base line in (log transformed) awake coughs per hour at Week 24
- The proportion of participants with a ≥1.3-point increase from baseline in LCQ total score at Week 24
- The proportion of participants with a ≥30% reduction from baseline in 24-hour coughs per hour at Week 24
- The proportion of participants with a ≥1.3-point reduction from baseline in mean weekly CSD total score at Week 24
- The proportion of participants with a ≥2.7-point reduction from baseline in mean weekly CSD total score at Week 24
- The proportion of participants with ≥30 mm reduction from baseline in Cough Severity VAS score at Week 24

Exploratory endpoints:

- Proportion of participants with ≥50% and ≥70% reduction from baseline in 24-hour coughs per hour
- Proportion of participants with ≥30%, ≥50%, and ≥70% reduction from baseline in awake coughs per hour

Description of the assessment for the primary efficacy endpoint

Method of cough counts: The cough data for the primary analyses were collected by the VitaloJAK system. The VitaloJAK system consists of Audio-recording device, a Web-portal, compression algorithm and human cough counts. The VitaloJAK audio recording device has been FDA cleared as an audio recording system and is CE marked. The Web-portal, compression algorithm and manual cough counts are not FDA cleared but supported with an additional validation study.

Audio-recording system: Cough counts were measured using a digital recording device (VitaloJAK). Microphones were affixed to the participant's chest wall and attached to the participant's clothing; the device provides high fidelity recordings and facilitates signal processing to identify and quantify cough accurately. The device uses two input channels - the first records sounds from the lungs and trachea through a chest contact sensor, which is attached to the skin at the top of the sternum. The second channel captures ambient sounds through a lapel air microphone. Data were collected for a 24-hour recording period when the participant was both awake and asleep.

Compression algorithm: The collected digital recordings were processed in a centralised reading centre, where recordings are condensed using a computer algorithm (compression algorithm) before human analysts identified and tagged individual coughs. The compression algorithm was developed to remove the non-cough sounds and silent parts for the recording to facilitate the readout by analysts.

During the main study, a total of three different versions of the compression algorithm were used:

- Version 2.0 dual compression channel (based on data from 2 microphones i.e., one chest and one lapel microphone)
- Version 3.0 dual channel
- Version 3.0 single channel (compression based on the recording from the chest sensor only)

Single channel compression algorithm WHO3V3.0: After CHMP's concerns had been raised during the evaluation about the validity of the data generated by these compression algorithms, the applicant validated the compression algorithm Version 3.0 single channel compression algorithm, resulting in a recount of about 90% of the originally presented data. The efficacy results based on this data set are referred to as "recount data set."

Cough count analyses: After a training period, the cough analysts performed a manual cough count on the compressed data, or uncompressed data in cases where it was not possible to apply the compression algorithm. The analysts listened to both audio channels simultaneously and inspects the visual waveforms: the use of concurrent review of both an audio presentation and visual wave form of the cough sound (i.e., characteristic explosive phase followed by an auditory phase) facilitates discrimination of true cough events from other forceful ambient noises. The cough sounds were manually tagged by the cough analysts and counted. The analysts reviewed the data in a blinded manner.

Quality checks cough monitoring

Original data

During the study, the cough analysts were subject to continuous monitoring to ensure the quality. Recordings to be recounted were selected at random from each set of cough counts that the analyst had worked on in the previous week. A comparison between the original and recounted results was made. If the QA results were not within the acceptable limits, i.e., 5% of the counted and the recounted segments are outside the limits of ±4 coughs per hour, an investigation was conducted to determine the source of poor agreement.

From the Phase 3 studies, an Intra class correlation ICC (case 1, each subject is measured by a different set of k randomly selected raters) was calculated on hourly segment randomly selected recordings chosen for recounting once the trial was completed to assess the interrater reliability.

- In Protocol 27, the ICC was 0.999. The mean difference between analysts was -0.00791coughs/hour (range -28 to + 19)
- Protocol 30, the ICC was 0.998. The mean difference between analysts was 0.0447 coughs/hour (range -32 to +72)

Recount data

Following the validation of the single channel compression algorithm v3.0, all other recordings that were compressed using either of the two dual channel algorithm versions were recompressed and recounted (>90% of recordings).
During the recount, the applicant performed a stricter QA process check during recount. The recordings were broken into blocks of ~ 220 recordings. Once all recordings in a block were analysed, 20 recordings were selected at random from the block and recounted blind by a second analyst. The Intraclass Correlation Coefficient (ICC) for each block was calculated and plotted longitudinally to ensure the process is in control; per SOP if the ICC fell to 0.9965 or lower, additional investigation would be required. Bland-Altman Plots using limits of agreement of +/-50 coughs per session were used as a monitoring tool.

Description of assessment scales for secondary endpoints

Cough severity diary (CSD): The CSD is a 7-item, disease-specific electronic PRO measure with a recall period of "today". A CSD total score, and 3 domain scores (frequency, intensity, disruption) can be calculated. A mean improvement of 1.3 and 2.7 points in the mean weekly CSD total score was observed for those reporting themselves on the PGIC as at least "minimally improved" and "much improved", respectively.

Cough severity Visual Analog Scale (VAS): The Cough Severity VAS is a single-item question asking the participant to rate the severity of their cough "today" using a 100 mm VAS anchored with "No Cough" at 0 and "Extremely Severe Cough" at 100. Based on the results from MK-7264 Protocol 012, analyses to define a clinically meaningful reduction in cough severity indicated that a reduction of ≥30 mm was found to be predictive of patient-reported improvement in cough as rated on the PGIC questionnaire.

Leicester Cough Questionnaire (LCQ): The LCQ is a 19-item cough-specific HRQoL questionnaire that contains three domains (physical, psychological, and social), calculated as a mean score for each domain ranging from 1 to 7 and a total score ranging from 3 to 21. Each item on the LCQ assesses symptoms or the impact of symptoms on HRQoL over the past two weeks using a 7-point Likert scale ranging from 1 to 7. Higher scores indicate better HRQoL. Data obtained from the LCQ intended to provide information on the impact of chronic cough on patients' daily lives, beyond objective cough counts and severity. An increase of the LCQ score ≥ 1.3 points is considered the minimal clinically important difference (MCID).

- **Sample size**

P027: The sample size calculations were based on the primary and key secondary efficacy endpoints, with the following assumptions based on Protocol 012 data:

1. 24-hour coughs per hour at Week 12

- Relative reductions in change from baseline in 24-hour coughs per hour at Week 12 are 20% in MK-7264 15 mg BID and 30% in MK-7264 45 mg BID
- The common standard deviation (SD) of the change from baseline in log-transformed 24-hour coughs per hour is 0.7
- The number of coughs per hour follows an approximately log-normal distribution

2. Awake coughs per hour at Week 12

- Same assumptions as to the primary efficacy endpoint of 24-hour coughs per hour at Week 12

3. Proportion of participants with ≥30% reduction from baseline in 24-hour coughs per hour at Week 12

- The proportion of responders in 24-hour coughs per hour at Week 12 is 54%, 66%, and 73% in placebo, MK-7264 15 mg BID, and MK-7264 45 mg BID, respectively

Based on the assumptions above, Table 9 provides power for the primary and key secondary efficacy endpoints with a total of 720 participants (240 participants per treatment group). All calculations are based on a 2-sided α=0.0499 significance level. The dropout rate is expected to be 12% at Week 12.

Table 9 Power for primary and secondary endpoints

Endpoints (At Week 12)	Power in MK-7264 45 mg BID Group	Power in MK-7264 15 mg BID Group
24-hour coughs per hour	>99%	91%
Awake coughs per hour	91%	82%
Proportion of participants with a ≥30% reduction from baseline in 24-hour coughs per hour	89%	65%

P030: Under the same assumptions, Table 10 provides the power calculations for the primary and key secondary efficacy endpoints with 1290 participants (430 participants per treatment group). All calculations were based on a 2-sided α=0.0499 significance level. The dropout rate was expected to be 20% at Week 24. Unlike study P027, the difference in the LCQ responder rate with placebo was included as a secondary outcome.

Table 10 Power for the primary and key secondary endpoints, Study P030

Endpoints (At Week 24)	**Power in MK-7264 45 mg BID Group**	**Power in MK-7264 15 mg BID Group**
24-hour coughs per hour	>99%	98%
Awake coughs per hour	98%	97%
Proportion of participants with ≥1.3-point increase from baseline in LCQ total score	81%	56%
Proportion of participants with ≥30% reduction from baseline in 24-hour coughs per hour	55%	50%

BID = twice daily; LCQ = Leicester Cough Questionnaire

- **Randomisation and Blinding (masking)**

Randomisation occurred centrally using an interactive response technology (IRT) system. There were 3 study intervention arms. Participants were assigned randomly in a 1:1:1 ratio to MK-7264 45 mg BID, MK-7264 15 mg BID, or placebo. Randomisation was be stratified according to the following factors: gender and geographical region (North America, Europe, Asia-Pacific, other).

A double-blinding technique with in-house blinding was used. The participant, the investigator, and the sponsor involved in the study intervention administration or clinical evaluation were unaware of the group assignments. Since MK-7264 45 mg and 15 mg differed in appearance and had corresponding matching placebos, participants received two study treatment bottles.

- **Statistical methods**

Estimand

The objective of this study was to examine the reduction in 24-hour coughs/hour across gefapixant and placebo at Week 12 (P027) or at Week 24 (P030) in patients with UCC or RCC, regardless of treatment/study discontinuation or the use of prohibited medication. The variable to address the clinical question was the change from baseline in 24-hour coughs per hour at Week 12 (P027) or at Week 24 (P030). Intercurrent events were to be handled through a treatment policy strategy. It was intended that data continue to be collected after treatment discontinuation and/or during usage of prohibited medication and were used as-is in the analysis.

Efficacy analysis populations

- Primary analyses as proposed by the applicant

The FAS population was to serve as the primary population for the analysis of efficacy data in this study. The FAS population consisted of all randomised participants who had taken at least 1 dose of the study intervention. For the original analyses presented in the CSR, inclusion in the primary and secondary analyses required that participants provided a baseline measurement and at least 1 post-baseline measurement during the treatment period.

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

Participants are included in the treatment group to which they are randomised to analyse efficacy data using both the FAS and PP populations.

- Additional efficacy analysis population (CHMP specified)

Additional efficacy analysis population was requested during the assessment, this being the ITT population of all participants randomised to one of the three arms regardless of whether they had baseline or post-baseline data available. It was considered that the use of the ITT population more closely reflects the treatment policy estimand. Officially, this ITT efficacy analysis population is a modified ITT (mITT) because a very small number of participants (2 in study P027 and 3 in study P030) were randomised to double-blind treatment but were not treated.

Analysis of the primary endpoint

Cough monitoring was conducted for baseline and 24 hours after administering the study intervention on Weeks 4, 8, and 12 and Week 24 (P030). The primary efficacy endpoint of this study was 24-hour coughs per hour at Week 12 (P027) or at Week 24 (P030). As the change from baseline in 24-hour coughs per hour was expected to have a skewed and wide distribution, the data were log-transformed before analysis for the primary approach. The primary analysis of the primary endpoint was on the natural log scale of the cough rate data. The variable of change from baseline in log-transformed 24-hour coughs per hour was used to analyse the primary endpoint. A negative result indicates a decrease in cough rate, while a positive result indicates an increase in cough rate.

The primary analysis approach was conducted using the longitudinal ANCOVA model. In this model, the response vector consists of the change from baseline in log-transformed 24-hour coughs per hour at each post-Baseline visit. The model includes factors for the treatment group, visit, the interaction of treatment group by visit, gender, and region, and the log-transformed baseline value and the interaction of log-transformed baseline value by the visit as covariates. The model uses all available 24-hour coughs per hour data at Baseline and Weeks 4, 8 and 12. Contrasts are constructed to compare each of the 2 MK-7264 treatment groups to the placebo group at each post-Baseline visit. The least-squares mean change from baseline (in log scale) with the associated standard errors are displayed for each treatment group. Estimated treatment differences (MK-7264 − placebo) along with corresponding 95% CIs are presented for each MK-7264 treatment group. In addition, the geometric mean of the 24-hour coughs per hour will be presented by the treatment group and by visit. The percent difference in the change from baseline between MK-7264 and placebo will be estimated by 100*(diff − 1), where diff is the difference provided by the analysis of the log-transformed variable.

Observation of zero coughs per hour will be replaced by a cough rate of 0.1/hour to calculate geometric means. If this rule is used, the table will have a footnote detailing the participant(s) and treatment group(s) who had zero coughs observations per hour.

Data Handling Rules for Cough Data: In general, each 24-hour session starts with awake status and is composed of an awake monitoring period and a sleep monitoring period. If a participant did not have a sleep time available before the end of the recording session, it would be considered that the participant was awake during the entire session. The last monitoring period of a session will be censored after the end time of the session. The cough data will contain all cough events occurring during that 24-hour monitoring period, as well as the information about "sleep time" and "awake time". Any session with a duration of recording <20 hours was to be considered missing. If a session had a duration of less than 24 hours but not less than 20 hours, the 24-hour coughs per hour was to be based on the actual duration of the session.

Secondary Efficacy Analysis

The continuous secondary efficacy endpoints were analysed using a similar longitudinal ANCOVA model as used for the primary efficacy analysis. Responder endpoints were analysed by the logistic regression model. The logistic regression model included terms for treatment group, visit, the interaction of treatment group by visit, gender, region, baseline, and baseline interaction by visit for the underlying continuous response.

Subgroup analyses

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

- Gender (Male, Female)
- Region (North America, Europe, Asia-Pacific, Others)
- Age group (<60 years, ≥60 years old)
- Duration of cough (in years) (<10 years, ≥10 years)
- Baseline Cough Severity VAS (<60 mm, ≥60 mm)
- Baseline 24-hour coughs per hour (<20 coughs/hr, ≥20 coughs/hr)

An additional subgroup analysis for primary diagnosis (Refractory chronic cough, Unexplained chronic cough) was included in the supplementary SAP. At request of the CHMP, a *post hoc* post randomisation subgroup was defined with or without taste disorders. A similar longitudinal ANCOVA model as the primary efficacy endpoint was be performed. For each subgroup, summary statistics including mean, SD, and 95% CIs will be provided each treatment group.

Handling of Missing Data (P027 and P030)

Missing Data Sensitivity Analyses

The statistical approach used for the primary analysis assumes that data are missing at random (MAR). In this study, it was expected that missing at random and missing completely at random (MAR/MCAR) mechanisms will underlie most of the missingness, and the proportion of data missing not at random (MNAR), driven solely by unobserved values of the study endpoints, will be small.

In addition to the analysis approach specified in the above-mentioned primary efficacy endpoint analysis section, the following sensitivity analyses will be used to assess the robustness of the primary analysis to deviation from the missing-at-random assumption:

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

Tipping-point Multiple-imputation Analysis: In a tipping-point analysis, missing data were first imputed for all visits under the MAR assumption, and then the worsening/shift is applied to the imputed values in the active arms. To reflect the worse performance after early withdrawal, this delta-shift (worsening) is increased until the result is no longer statistically significant. The scientific plausibility of the tipping region was evaluated.

On-treatment Subset Analysis: In this analysis, cough sessions collected after a participant has discontinued treatment are excluded.

Supplemental Estimand

For the supplemental estimand the following strategies to handling intercurrent events were outlined:

- Treatment discontinuation was handled by the *hypothetical strategy* as if the treatment discontinuation did not occur. So, measurements taken after treatment discontinuation were not used.
- The treatment policy strategy handled the usage of prohibited medication. Data were collected and used as normal during the usage of prohibited medication.
- Other attributes were identical to those in the primary estimand.
- An "on-treatment sensitivity analysis" was conducted for this supplemental estimand.

Additional analyses (CHMP requested)

The following analyses were requested for the original data set to enable the inclusion of the mITT population in the analysis:

For both Studies P027 and P030, the applicant was requested to plan and perform additional analyses that best target the treatment policy estimand. These additional analyses should include all patients from the mITT population (it is recommended that a valid imputation approach be used to account for the missing baseline measurements, and it is reasonable to assume that these are MAR). In response to this request, the applicant provided results from a constrained longitudinal analysis. This analysis was deemed to be equivalent to using multiple imputation followed by an ANCOVA (MI+ANCOVA), which was also requested. For the MI + ANCOVA approach missing baseline data were imputed using a single imputation strategy (independent of treatment) and then for post-baseline missing data, a multiple imputation procedure (m = 50 imputations) was specified with treatment, region, gender, and all visits as covariates.

As a sensitivity analysis, it was also requested that the applicant explores the possibility of applying the J2R method where the reference group is the set of participants from the same treatment arm who have discontinued treatment and continued to provide follow up data in the study. If this was not feasible given the small numbers, then it was suggested that the option of using a pooled reference group be explored (i.e., grouping eligible continuing participants across all treatment arms or from both Phase III studies).

Re-analysis of the current sensitivity analyses (i.e., with placebo as reference) that includes all patients from the mITT population was also requested. The applicant was also requested to re-perform the supplemental analyses that target the hypothetical estimand strategy and includes all patients from

the mITT population. In order to strengthen the plausibility of the MAR assumption, the inclusion of additional auxiliary variables in the imputation model was encouraged.

Interim Efficacy Analysis

One planned interim efficacy analysis was to be conducted for futility when approximately 40% of participants had either completed or discontinued before completing the main study period. The futility analysis was to be based on the primary endpoint of 24-hour coughs per hour at Week 12. The criteria adopted for the futility rule was based on the conditional power (CP), which is the conditional probability of rejecting the null hypothesis given the observed data at the time of the interim analysis. When the CP at the interim analysis is low, it is unlikely that the predefined primary objective will be achieved. The decision criteria were: If CP <20% for both treatment arms (which translates to an approximate 10% reduction in 24-hour coughs per hour, or less, assuming observed variability is similar to what was assumed based on the Protocol 012 data), strong consideration should be given to stopping the study for futility. Otherwise, the study will continue with both doses of MK-7264.

Considerations for Multiple Comparison Adjustments (P027 and P030)

Due to the interim analysis for futility, an α-spending of 0.0001 was applied to the 2-sided Type I error rate of 0.05 for the primary and secondary hypotheses based on the Haybittle-Peto method. Multiplicity adjustment was be made for testing two doses on the primary and the key secondary endpoints for the analysis

Study P027

• H11: MK-7264 45 mg BID is superior to placebo in reducing 24-hour coughs per hour at Week 12

•H12: MK-7264 15 mg BID is superior to placebo in reducing 24-hour coughs per hour at Week 12

•H21: MK-7264 45 mg BID is superior to placebo in reducing awake coughs per hour at Week 12

•H31: MK-7264 45 mg BID is superior to placebo on the proportion of participants with a ≥30% reduction from baseline in 24-hour coughs per hour at Week 12

•H22: MK-7264 15 mg BID is superior to placebo in reducing awake coughs per hour at Week 12

•H32: MK-7264 15 mg BID is superior to placebo with respect to the proportion of participants with a ≥30% reduction from baseline in 24-hour coughs per hour at Week 12.

Study P030: The multiplicity adjustment criterion was updated based on the available information prior to the database lock of P030. Testing of hypotheses will be performed as follows:

•H11: MK-7264 45 mg BID is superior to placebo in reducing 24-hour coughs per hour at Week 24.

•H21: MK-7264 45 mg BID is superior to placebo in reducing awake coughs per hour at Week 24.

•H31: MK-7264 45 mg BID is superior to placebo on the proportion of participants with a ≥1.3-point increase from baseline in LCQ total score at Week 24.

•H41: MK-7264 45 mg BID is superior to placebo with respect to the proportion of participants with a ≥30% reduction from baseline in 24-hour coughs per hour at Week 24.

To strongly control the Type-I error rate for this family, a step-down testing procedure will be applied in the order specified above. Each hypothesis will be formally tested only if the preceding one is significant at p = 0.0499 level.

Results

Study MK7264-027

- **Participant flow**

A total of 1073 participants were screened, and 732 were randomised across 156 global study sites. All nonrandomised participants were screen failures, with a non-eligible Cough Severity VAS score being the most common reason for screen failure. Two screen failure participants (1 in the placebo group, 1 in the gefapixant 45 mg group) were randomised in error and did not receive study intervention. Excluding the 2 participants randomised in error, all randomised participants received at least 1 dose of the study intervention. Most participants (79.6%) completed the study, and 517 (70.8%) completed the study intervention regimen.

Main study period (i.e., up till week 12): The number of patients that discontinued treatment in the main study part was higher in gefapixant 45 mg (61/244 (25.1 %) compared with the other two groups (28/244 (11.5 %) for the gefapixant 15 mg group and 30/243 (12.3%) for the placebo group. The most common reasons for treatment discontinuation were AEs (n=55 (7.5%) total study population) and withdrawal by subject (n=62 (8.2%) total population). More patients in the gefapixant 45 mg group n=40(16.5%) discontinued due to an AE, than in the other treatment groups (gefapixant 15 mg n=8 (3.3%), placebo n=7 (2.95%) most discontinuations were due to taste-related AEs. Other reasons for discontinuation of study intervention were similar across groups and discontinuation categories.

Overall trial period (i.e. main period + extension period): At the end of the trial, a total of 96/243 (39.5 %) of the gefapixant 45 mg group, 57/244 (23.4%) of the gefapixant 15 mg group and 60/241 (24.1 %) of the placebo group discontinued the trial (Figure 13).

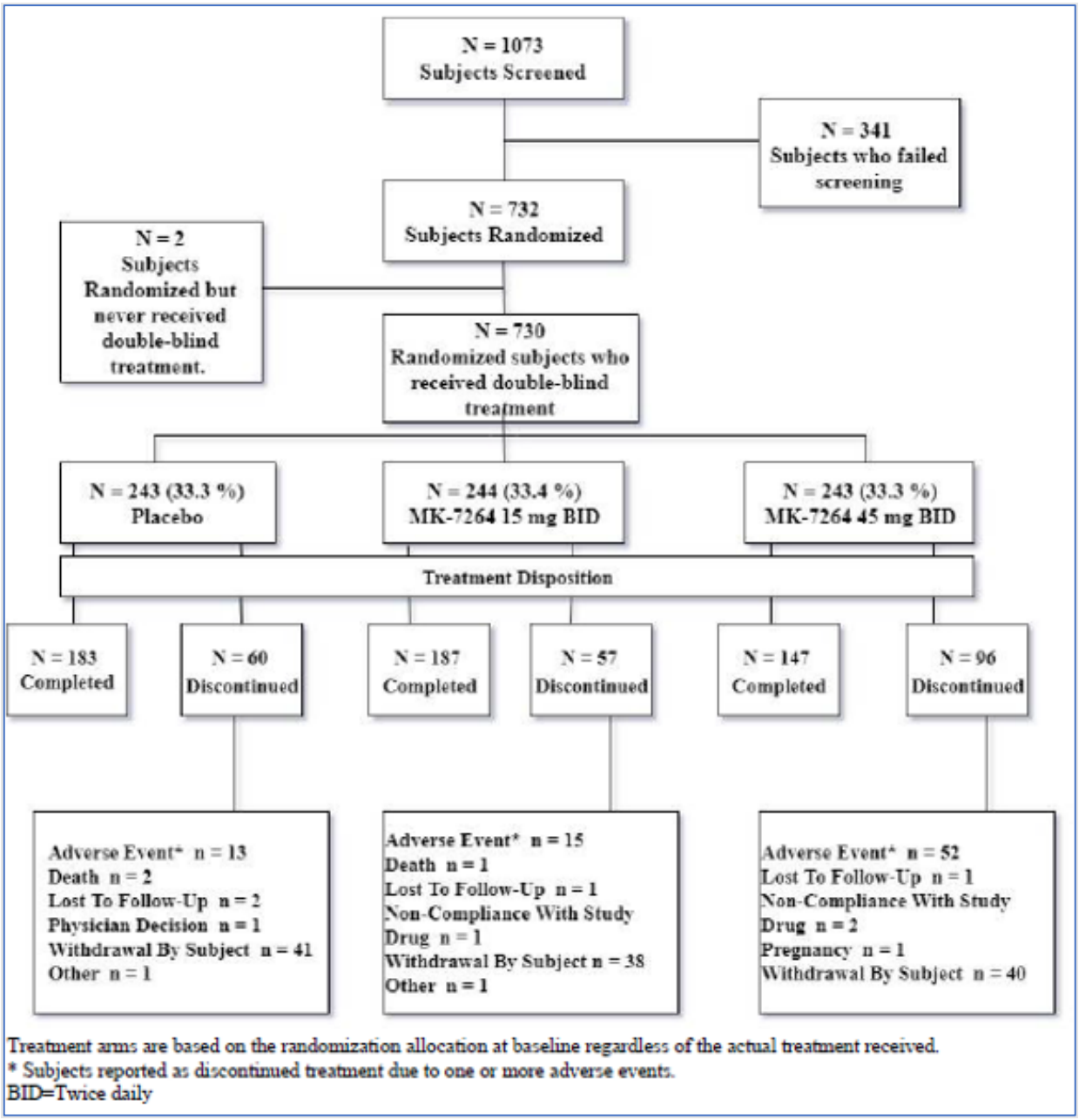


Figure 13 Disposition of subjects: All subjects as randomised in study P027

- **Recruitment**

The study was conducted at 156 sites in: USA, Argentina, Canada, Czech Republic, Denmark, France, Hungary, Israel, Poland, Japan, Peru, South Korea, Spain, Taiwan, Turkey, UK, and Ukraine. The study period was from 14 March 2018 (first participant first visit) up to 24 April 2019 (last participant last visit). The date of the CSR was 01 Dec 2020.

- **Conduct of the study**

Study 027 included 3 amendments. The first amendment was made before the inclusion was started (13 Dec 2017). The second amendment more specifically described that patients should receive appropriate treatment for at least 2 months before enrolment. The amendment also allowed the inclusion of patients with a lower GFR (17 Sept 2018). The last amendment (26 April 2019) was restricted to a few countries (UK, USA Ukraine, DE, PL). The amendment described that the extension

follows up period was followed by a 3 month off treatment follow-up up period to explore the impact of withdraw in MK 7264 therapy in a participant who has been treated for 1 year.

- **Baseline data**

The baseline demographic and disease characteristics were generally well balanced across intervention groups; the mean number of coughs per hour over 24 hours at baseline was slightly higher in the placebo group mean (SD) 38.7 (79.4) cough /hour than the gefapixant groups mean (SD): 26.8 (21.2) and 28.5 (3.7) coughs/h. Most participants were female (74%), white (78%), and had a long duration of chronic cough (≥ 10 years (46%); the mean age of participants was 59.0 years. Overall, more participants had a primary diagnosis of RCC (59%) than UCC (41%); the primary diagnosis was balanced across intervention groups. The reported medical history conditions were generally balanced across intervention groups. Participants who were classified as having RCC had a comorbid condition that may have been associated with chronic cough. The most frequently reported comorbidities were asthma (40.7%), gastroesophageal reflux disease (40.5%), and rhinitis allergic (19.7%). Other frequently reported comorbid conditions known to be associated with chronic cough included seasonal allergy (8.8%), upper airway cough syndrome (6.8%), rhinitis (5.1%), chronic gastritis (3.2%), and dyspepsia (1.8%). Compliance with the study intervention regimen was high across the intervention groups, with 95.1% of participants being >80% compliant.

- **Numbers analysed**

The following analyses sets are defined:

Efficacy analyses

Full analyses set (FAS): defined by the applicant as all randomised participants who have taken at least 1 dose of the study intervention and provided a baseline measurement and at least 1 post-baseline measurement (i.e., a 24 h cough registration) during the treatment period (Table 11).

(Modified) ITT population: All participants who were randomised and who have taken at least 1 dose of the study intervention. Also referred to as the 'Treated' population in some tables.

Please refer to Table 13 for numbers included in the analyses related to cough counts.

Per protocol (PP) PP: population excludes participants due to important deviations from the protocol that may substantially affect the results of the primary efficacy endpoint. Potential deviations that may result in the exclusion of a participant from the PP population will be specified in the sSAP.

Safety analysis: All Participants as Treated (APaT) population which consists of all randomised participants who received at least one dose of study.

Table 12 Summary of efficacy population analysed (All subjects randomised baseline week 12, Study P027)

	Placebo		MK-7264 15 mg BID		MK-7264 45 mg BID		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in Population	244		244		244		732	
Treated	243	(99.6)	244	(100.0)	243	(99.6)	730	(99.7)
FAS population	243	(99.6)	244	(100.0)	243	(99.6)	730	(99.7)
Per-Protocol population	219	(89.8)	206	(84.4)	209	(85.7)	634	(86.6)
Subjects included in the analysis of 24-hour coughs per hour at Week 12	222	(91.0)	227	(93.0)	217	(88.9)	666	(91.0)
Subjects included in the analysis of awake coughs per hour at Week 12	222	(91.0)	227	(93.0)	217	(88.9)	666	(91.0)
Subjects included in the analysis for ≥ 30% reduction from baseline in 24-hour coughs per hour at Week 12	222	(91.0)	227	(93.0)	217	(88.9)	666	(91.0)

FAS = full analysis set;
The denominator for percentages is based on the number of randomized subjects.

Source: [P027MK7264: adam-adsl; adeff]

Table 13 Number of participants of ITT, mITT, included in original primary analysis, and with available data at the post-baseline timepoints week 4, 8 and 12. Percentages shown are the percentage of the ITT, Study P027

	ITT	mITT	Included in primary analysis	week 4	week 8	week 12
Treatment arm	n	n (%)	n (%)	n (%)	n (%)	n (%)
Placebo	244	243 (99.6)	222 (91.4)	217 (89.3)	208 (85.6)	205 (84.3)
15 mg	244	244 (100)	227 (93.0)	224 (91.8)	218 (89.3)	210 (86.1)
45 mg	244	243 (99.6)	217 (89.3)	207 (85.2)	199 (81.9)	194 (79.9)

- In the placebo group, 244 participants were randomised, 243 were treated, 222 (91%) had at least one baseline, and one postbaseline measurement for cough frequency, 199 (81.6%) completed the study, 183 (75.3%) completed the trial intervention regimen, and 60 (24.7%) discontinued trial intervention.
- In the gefapixant 15 mg group, 244 participants were randomised and treated**,** 227 (93%) had at least one baseline and one postbaseline measurement for cough frequency, 200 (82.0%) completed the study, 187 (76.6%) completed the trial intervention regimen, and 57 (23.4%) discontinued trial intervention.
- In the gefapixant 45 mg group, 244 participants were randomised, 243 were treated, 217 (88.9%) had at least one baseline, and one postbaseline measurement for cough frequency, 184 (75.4%) completed the study, 147 (60.5%) completed the trial intervention regimen, and 96 (39.5%) discontinued trial intervention.

In general, the number of protocol deviations was overall balanced between the treatment groups in both trials.

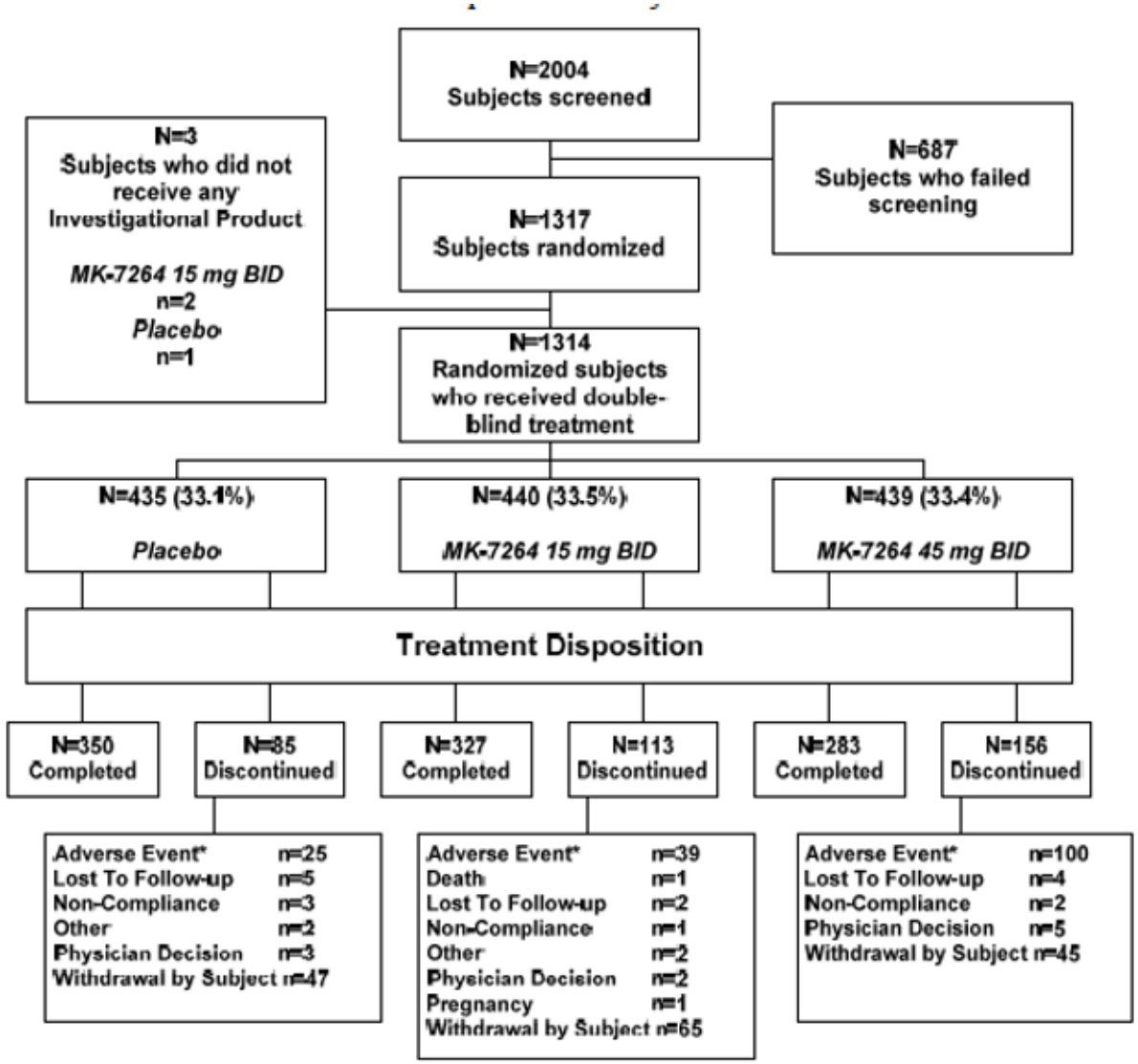
Study MK7264-030

- **Participant flow**

A total of 2,004 participants were screened; 1,317 participants were randomised across 158 global study sites in 20 countries. All nonrandomised participants were screen failures, with a non-eligible Cough Severity VAS score being the most common reason for screen failures. Three screen failure participants were randomised in error and did not receive study intervention. Excluding the 3 participants randomised in error, all randomised participants received at least 1 dose of the study intervention. Most participants (83.9%) completed the study, and 960 (73.1%) completed the study intervention regimen.

Main study period (i.e., up till week 24): The proportion of participants who discontinued treatment in the main study was higher in the gefapixant 45 mg group (125/439 (28.5%) than in the gefapixant 15 mg (82/440 (18.6%) and placebo group (66/435 (15.2%). The most common reasons for treatment discontinuation were AEs (n=164 (12.5%) total study population P030) and withdrawal by subject (n=157 (11.9%) total population P030). More patients in the gefapixant 45 mg group (n= 88 (20%) discontinued treatment compared with the other treatment groups gefapixant 15 mg (n 34 7.7% and placebo (n=21 (4.8%) respectively); most discontinuations were due to taste-related AEs. Other reasons for discontinuation of study intervention were similar across groups and discontinuation categories

Overall trial period (i.e., main period + extension period): At the end of the trial, a total of 156/439 (35.5%) of the gefapixant 45 mg, 113 /440 (25.7%) of the gefapixant 15 mg group and 85 /435 (19.5%) of the placebo group discontinued the trial (Figure 14).



Treatment arms are based on the randomization allocation at baseline regardless of the actual treatment received.
* Subjects reported as discontinued treatment due to one or more adverse events.

BID=twice daily

Source: [P030MK7264: adam-adsl; adbase]

Figure 14 Consort diagram of disposition of subjects in study P030

- **Recruitment**

The study was conducted at 175 sites in: Australia, Canada, China, Colombia, Czech Republic, Denmark, Germany, Guatemala, Hungary, Israel, Italy, Malaysia, New Zealand, Peru, Poland, South Africa, Turkey, United Kingdom, Ukraine, and United States. The study period was from 15 March 2018 (first participant first visit) up to 20 August 2020 (last participant last visit). The date of the CSR was 02 Dec 2020.

- **Conduct of the study**

Study P030 had the same amendments as mentioned in study P027 (dated 13 Dec 2017, 18 Sept 2018 and 26 April 2019) and two additional amendments that were restricted to China in order to achieve the locally required sample size, while the low dose group was removed from the follow up extension.

- **Baseline data**

The baseline demographic and disease characteristics were generally well balanced across intervention groups, including baseline smoking status. Most participants were female (75%), white (80%) and had a long duration of chronic cough (≥ 10 years) (44%); the mean age of participants was 58.1 years. Overall, more participants had a primary diagnosis of RCC (63%) than UCC (37%); the primary diagnosis was balanced across intervention groups. The reported medical history conditions were generally balanced across intervention groups. Participants who were classified as having RCC had a comorbid condition that may have been associated with chronic cough. As such, gastroesophageal reflux disease (40.3%), asthma (40.2%), and rhinitis allergic (14.5%) were among the most frequently reported medical history conditions. Other reported comorbid conditions known to be associated with chronic cough included seasonal allergy (10.8%), rhinitis (5.9%), upper-airway cough syndrome (5.6%), chronic gastritis (4.5%), and dyspepsia (2.8%). Compliance with the study intervention regimen was high across the intervention groups, with approximately 95% of participants being >80%.

- **Numbers analysed**

Analysis sets for the ITT, mITT, FAS and PP populations have a similar definition as in study P027. With regard to the numbers analysed at week 4, 8, 12, and 24 the numbers are as depicted in (Table ***14***, Table ***15***).

Table 14 Summary of efficacy population analysed (All subjects randomised baseline week 24, Study P030)

	Placebo		MK-7264 15 mg BID		MK-7264 45 mg BID		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in Population	436		442		439		1317	
Treated	435	(99.8)	440	(99.5)	439	(100.0)	1314	(99.8)
FAS population	435	(99.8)	440	(99.5)	439	(100.0)	1314	(99.8)
Per-Protocol population	411	(94.3)	406	(91.9)	401	(91.3)	1218	(92.5)
Subjects included in the analysis of 24-hour coughs per hour at Week 24	419	(96.1)	415	(93.9)	409	(93.2)	1243	(94.4)
Subjects included in the analysis of awake coughs per hour at Week 24	419	(96.1)	415	(93.9)	409	(93.2)	1243	(94.4)
Subjects included in the analysis for ≥ 1.3-point increase from baseline in LCQ total score at Week 24	406	(93.1)	404	(91.4)	399	(90.9)	1209	(91.8)
Subjects included in the analysis for ≥ 30% reduction from baseline in 24-hour coughs per hour at Week 24	419	(96.1)	415	(93.9)	409	(93.2)	1243	(94.4)

FAS = full analysis set; LCQ = Leicester Cough Questionnaire.
The denominator for percentages is based on the number of randomized subjects.

Source: [P030MK7264: adam-adsl; adeff; adqs]

Table 15 Number of participants in the ITT, mITT, included in the original primary analysis, and with available data at the post-baseline timepoints week 4, 8, 12 and 24. Percentages shown are the percentage of the ITT with available data, study P030

	ITT	mITT	Included in primary analysis	week 4	week 8	week 12	Week 16	Week 20	Week 24
Treatment arm	n	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Placebo	436	435 (99.8)	419 (96.1)	412 (94.5)	398 (91.2)	383 (87.8)	382 (87.6)	366 (83.9)	368 (84.4)
15 mg	442	440 (99.5)	415 (94.0)	409 (92.5)	389 (88.0)	373 (84.4)	367 (83.0)	362 (81.9)	363 (82.1)
45 mg	439	439 (100.0)	409 (93.1)	403 (91.8)	377 (86.0)	363 (82.7)	355 (80.9)	345 (78.6)	347 (79.0)

- In the placebo group, 436 participants were randomised, 435 were treated, 419 (96.1%) had at least one baseline, and one postbaseline measurement for cough frequency, 382 (87.6%) completed the study, 350 (80.5%) completed the trial intervention regimen, and 85 (19.5%) discontinued trial intervention.
- In the gefapixant 15 mg group, 442 participants were randomised, 440 were treated, 415 (93.9%) had at least one baseline, and one postbaseline measurement for cough frequency, 368 (83.3%) completed the study, 327 (74.3%) completed the trial intervention regimen, and 113 (25.7%) discontinued trial intervention.
- In the gefapixant 45 mg group, 439 participants were randomised, 439 were treated, 409 (93.2%) had at least one baseline and one postbaseline measurement for cough frequency, 355 (80.9%) completed the study, 283 (64.5%) completed the trial intervention regimen, and 156 (35.5%) discontinued trial intervention.

In general, the number of protocol deviations was overall balanced between the treatment groups.

- **Outcomes and estimation**

A series of analyses for the primary and secondary endpoints were conducted in both studies.

The results from all these analyses are provided in this document in the following order:

I. Original data set: Analyses based on the full analysis set (FAS) as defined by the applicant and using the longitudinal analysis of covariance model for continuous outcomes. This is

the pre-specified analysis in the protocol and the results were reported as primary in the CSR.

II. **Original data set: Based on the mITT population, analysed according to the multiple imputation + ANCOVA for continuous outcomes. For binary endpoints derived from continuous outcomes, a multiple imputation approach was used followed by the relevant analysis.**

This method is preferred by the CHMP as this analysis does not exclude patients who had missing baseline or missing post baseline data. Therefore, this analysis is considered to more closely estimate the treatment effect of the treatment policy estimand.

III. Recount data set: The recount data set includes cough count data that are based only on version 3.0 of the compression algorithm, which was used in the additional validation studies. The analysis method is the same as is specified in I, using the FAS.

IV. Recount data set: As specified in II, using the mITT population. It is noted that there may be some numerical differences for some analyses like the PRO outcomes, that are not affected by the recount of the coughs. This is because the multiple imputation procedure was re-run for the recount data. For completeness, the provided results have also been presented.

To ensure transparency, the full set of results are presented for the primary endpoint and the LCQ responder rate in Study P030, which are both included in the SmPC. For the other endpoints, only the results based on the original dataset and including the mITT population are presented (i.e., data set II).

Study MK-7264-027

Primary endpoint – 24-Hour Coughs per Hour at week 12 (study P027)

I. Original data: FAS, longitudinal ANCOVA model

At baseline, the geometric mean of the number of coughs per hour over a 24 h period was 18.24 for the 45 mg dose, 19.86 for the 15 mg dose and 22.83 for placebo. At week 12, the model based geometric mean ratio (95%) was 0.38 (0.33, 0.44) for the 45 mg group, 0.48 (0.41, 0.55) for the 15 mg group and 0.47 (0.41, 0.54) for placebo. (Table 16), indicating a within treatment improvement of 62%, 53% and 53% respectively.

At Week 12, the number of coughs per hour over a 24-hour period were significantly reduced in the gefapixant 45 mg group compared with the placebo group (p=0.041), with an estimated relative reduction of the geometric mean ratio was -18.45% (-32.92, -0.86). The number of coughs per hour over 24 hours was not significantly reduced in the gefapixant 15 mg group (1.56 (-16.13, 22.99); p=0.874) (Table 16 , Figure 15).

The within-group reduction from baseline in 24-hour coughs per hour at Week 12 in the gefapixant 45 mg group in Study P027 was consistent with the treatment benefit observed in Study P012 (around 60%). However, study P027 showed a smaller placebo-corrected reduction in 24-hour coughs per hour at Week 12 than that observed in the Phase 2b Study P012.

The placebo response observed at Week 4 was similar to that observed in Study P012 at Week 4; however, in Study P027, the placebo response continued to increase in magnitude over time.

Table 16 Analysis of 24-hour coughs per hour at week 12 (Full analysis set baseline week 12)

Treatment	N	Geometric Mean at Baseline[‡]	Geometric Mean at Week 12[‡]	Geometric Mean Ratio (Week 12/Baseline)	Model[†] Based Geometric Mean Ratio (Week 12/Baseline) (95% CI)
Placebo	222	22.83	10.33	0.45	0.47 (0.41, 0.54)
MK-7264 15 mg BID	227	19.86	9.66	0.49	0.48 (0.41, 0.55)
MK-7264 45 mg BID	217	18.24	7.05	0.39	0.38 (0.33, 0.44)

Treatment Difference	Estimated Relative Reduction (%)[††] and (95% CI)	p-Value
MK-7264 15 mg BID vs. Placebo	1.56 (-16.13, 22.99)	0.874
MK-7264 45 mg BID vs. Placebo	-18.45 (-32.92, -0.86)	0.041

N = Number of participants included in the analysis. CI = Confidence Interval.
[‡]Based on subjects with non-missing values at both baseline and Week 12.
[†]Based on the Longitudinal Analysis of Covariance Model consisting of the change from baseline in log-transformed 24-hour coughs per hour 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.
[††]The estimated relative reduction (relative to Placebo) is calculated by 100 (e**DIFF -1). Here DIFF is the treatment difference in change from baseline at Week 12, as provided by the analysis of the log transformed data.
Note: observations with 0 coughs per hour were replaced by a cough rate of 0.1/h; One subject (1 timepoint) in MK-7264 45 mg BID had 0 coughs per hour.

Source: [P027MK7264: adam-adeff]

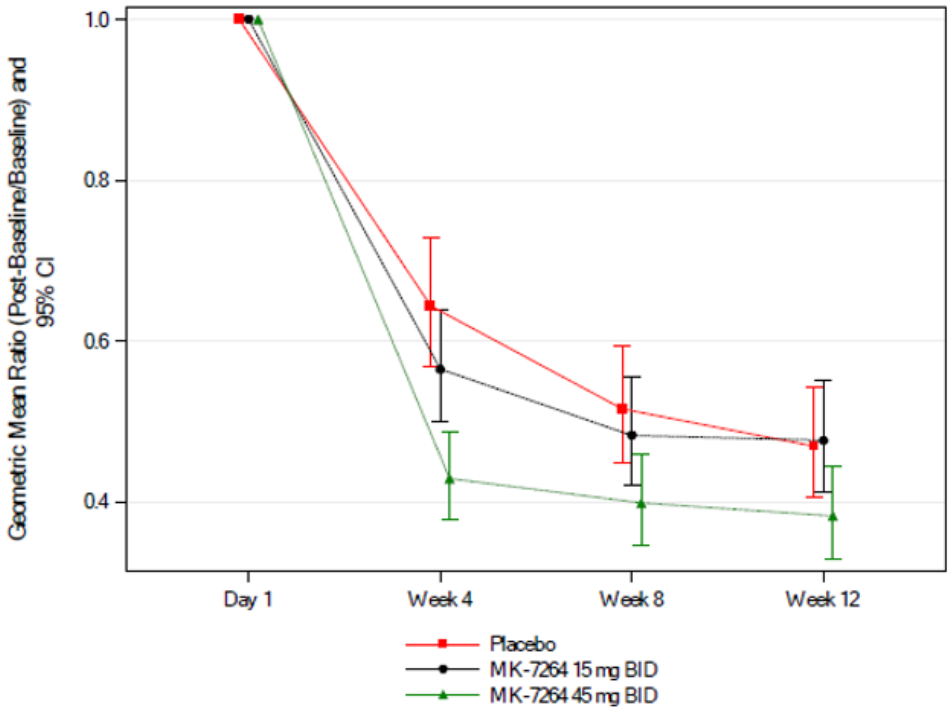


Figure 15 Analysis of 24-hour coughs per hour over time; model-based geometric mean ratio (post baseline/baseline) and 95% CI (full analysis set baseline week 12)

II. Original data: mITT, Multiple Imputation (MI) + ANCOVA

Table 17 presents results from the MI+ANCOVA analysis including the mITT population.

At week 12, the model-based geometric mean ratio (95%) was 0.39 (0.34, 0.45) for the 45 mg group, and 0.48 (0.42, 0.55) for placebo. The estimated relative reduction was between gefapixant 45 mg and placebo -18.52% (95% CI: -32.76, -1.28) (Table 17). Results from the constrained longitudinal analysis also performed by the applicant were -19.05% (-33.09, -2.06), p = 0.030.

Table 17 Analysis of 24-hour coughs per hour at week 12, (mITT, MI + ANCOVA)

Treatment	N	Estimated Relative Reduction (%)† and (95% CI)	p-Value
Placebo	243		.
MK-7264 15 mg BID	244	-0.04 (-17.11, 20.56)	0.997
MK-7264 45 mg BID	243	-18.52 (-32.76, -1.28)	0.036

N = Number of participants included in the analysis. CI = Confidence Interval.

†The estimated relative reduction (relative to Placebo) is calculated by 100 (e**DIFF -1). Here DIFF is the treatment difference in change from baseline at Week 12, as provided by the analysis of the log-transformed data.

Differences in LS mean of change from baseline at the time point of interest in the full FAS population. 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 is conducted at the time point of interest, adjusting for covariates of treatment, baseline, region, and gender.

Sensitivity analyses provided in the CSR

Sensitivity analyses were performed using a jump-to-reference approach, using placebo arm as the reference group as well as a tipping-point analysis.
For the jump-to-reference multiple imputation analysis the estimated relative reduction for the 45mg group compared with placebo was -16.36 (95% CI: -31.96, 2.82) and for the jump-to-reference *via* pattern mixture approach the relative reduction was -16.67 (95% CI: -30.01, -0.78). The tipping point analysis showed that the point where the primary comparison of the 45 mg group *versus* placebo was no longer statistically significant, occurred between 6% and 7% of worsening applied to the missing data imputation in the 45mg group.

The Clinical Study Report also describes a supplemental estimand strategy. In this supplemental strategy, a hypothetical estimand strategy is applied for treatment discontinuations (i.e., any data after treatment discontinuation are set to missing, and only available on-treatment data are included in the analysis. The table below presents the results from this approach. The estimated relative reduction for the 45mg group compared with placebo was -21.92% (95% CI: -36.11, -4.58). In the PP analyses, the Estimated Relative Reduction (%) MK-7264 45 mg vs. Placebo from baseline to week 12 was not statistically significant (-17.56 (95% CI -33.18, 1.72, p=0.072)).

Table 18 On-treatment subset analysis, Study P027

Treatment	N	Geometric Mean at Baseline§	Geometric Mean at Week 12§	Geometric Mean Ratio (Week 12/Baseline)	Model† Based Geometric Mean Ratio (Week 12/Baseline) (95% CI)
Placebo	221	22.92	10.36	0.45	0.47 (0.41, 0.55)
MK-7264 15 mg BID	225	19.86	9.79	0.49	0.49 (0.42, 0.56)
MK-7264 45 mg BID	208	18.34	6.79	0.37	0.37 (0.32, 0.43)

Treatment Difference	Estimated Relative Reduction (%)†† and (95% CI)	p-Value
MK-7264 15 mg vs. Placebo	2.80 (-15.29, 24.75)	0.779
MK-7264 45 mg vs. Placebo	-21.92 (-36.11, -4.58)	0.016

N = Number of participants included in the analysis. CI = Confidence Interval.

§Based on subjects with non-missing values at both baseline and Week 12.

†Based on the Longitudinal Analysis of Covariance Model consisting of the change from baseline in log-transformed 24-hour coughs per hour 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.

††The estimated relative reduction (relative to Placebo) is calculated by 100 (e**DIFF -1). Here DIFF is the treatment difference in change from baseline at Week 12, as provided by the analysis of the log transformed data.

Source: [P027MK7264: adam-adeff]

Additional sensitivity analyses requested by the CHMP

In line with the request for the analyses to include the mITT population and to target the treatment policy estimand, additional sensitivity analyses were requested. These included a jump to reference with off-treatment as reference group for imputation, and a jump to reference with the placebo group as the reference group. For the jump to reference with off-treatment as reference group the estimated relative reduction was estimated to be -19.80% (-33.69, -3.00), p = 0.023. For the jump to reference with placebo as the reference group this was -17.34% (-32.80, 1.67) p = 0.071.

Additional analyses were also requested to target the secondary estimand strategy – the hypothetical estimand. This included an MI+ ANCOVA approach including the mITT population; estimated relative reduction: -20.45% (-35.16, -2.42), p = 0.028 and a jump to reference with placebo as reference; estimated relative reduction: -18.35% (-33.93, 0.90) p = 0.060.

III. Recount data: FAS, longitudinal ANCOVA model

The analysis of recount efficacy data was performed for the primary endpoint of 24-hour cough rate using the longitudinal analysis of covariance model adjusted for covariates of treatment, visit, the interaction of treatment by visit, gender, region, log-transformed baseline value, and interaction of log-transformed baseline value by visit. An unstructured covariance matrix, as well simpler covariance structures of Toeplitz, compound symmetry, first-order autoregressive in the model were used to model the correlation among repeated measurements to examine the consistency of results across different covariance matrix assumptions. Full results are presented in Table 19.

Geometric means at baseline and Week 12 were slightly higher than original geometric means in each treatment group, but the geometric mean ratio remained the same. Using the unstructured covariance matrix in the model, for the primary endpoint of 24-hour cough rates, the relative difference over placebo was -16.96% (95% CI -31.34, 0.59) p=0.057.

Table 19 Analysis of 24-hour coughs per hour at week 12, recount data with longitudinal ANCOVA model study P027

Treatment	N	Geometric Mean at Baseline†	Geometric Mean at Week 12†	Geometric Mean Ratio (Week 12/Baseline)†	Covariance Structure	Model†† Based Geometric Mean Ratio (Week 12/Baseline) (95% CI)
Placebo (CSR)	222	22.83	10.33	0.45	Unstructured	0.47 (0.41, 0.54)
Placebo (Recount)	222	23.59	10.63	0.45	Unstructured	0.47 (0.41, 0.54)
					Toeplitz	0.46 (0.40, 0.53)
					CS	0.46 (0.41, 0.53)
					AR(1)	0.46 (0.40, 0.52)
MK-7264 15 mg BID (CSR)	227	19.86	9.66	0.49	Unstructured	0.48 (0.41, 0.55)
MK-7264 15 mg BID (Recount)	227	20.89	10.22	0.49	Unstructured	0.48 (0.42, 0.56)
					Toeplitz	0.48 (0.42, 0.55)
					CS	0.48 (0.42, 0.55)
					AR(1)	0.48 (0.42, 0.54)
MK-7264 45 mg BID (CSR)	217	18.24	7.05	0.39	Unstructured	0.38 (0.33, 0.44)
MK-7264 45 mg BID (Recount)	217	18.93	7.39	0.39	Unstructured	0.39 (0.34, 0.45)
					Toeplitz	0.38 (0.33, 0.44)
					CS	0.38 (0.34, 0.44)
					AR(1)	0.38 (0.33, 0.44)

Treatment Difference	Covariance Structure	Estimated Relative Reduction (%)§ and (95% CI)	p-Value
MK-7264 15 mg BID vs. Placebo (CSR)	Unstructured	1.56 (-16.13, 22.99)	0.874
MK-7264 15 mg BID vs. Placebo (Recount)	Unstructured	3.12 (-14.54, 24.42)	0.748
	Toeplitz	3.42 (-13.14, 23.14)	0.705
	CS	3.33 (-13.22, 23.02)	0.713
	AR(1)	3.74 (-12.89, 23.53)	0.680
MK-7264 45 mg BID vs. Placebo (CSR)	Unstructured	-18.45 (-32.92, -0.86)	0.041
MK-7264 45 mg BID vs. Placebo (Recount)	Unstructured	-16.96 (-31.45, 0.59)	0.057
	Toeplitz	-17.14 (-30.66, -0.98)	0.039
	CS	-17.14 (-30.65, -0.99)	0.038
	AR(1)	-17.21 (-30.75, -1.03)	0.038

N = Number of subjects included in the analysis. CI = Confidence Interval. CS = Compound Symmetry. AR(1) = First-Order Autoregressive.
†Based on subjects with non-missing values at both baseline and Week 12.
††Based on the Longitudinal Analysis of Covariance Model consisting of the change from baseline in log-transformed 24-hour coughs per hour 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 estimated relative reduction (relative to Placebo) is calculated by 100 (e**DIFF -1). Here DIFF is the treatment difference in change from baseline at Week 12, as provided by the analysis of the log transformed data.

IV. Recount data: mITT, MI+ANCOVA

Table 20 and Table 21 present the results for the recount data with the mITT population and MI+ANCOVA approach. At baseline, the geometric mean was 18.36 for the 45 mg dose and 22.80 for placebo; while at week 12, the geometric mean ratio was 0.39 for the 45 mg dose and 0.39 for

placebo (Table 20); the estimated relative reduction to placebo was -17.10 % (95% CI -31.22, -0.06), p=0.049 (Table 21). Figure *16* illustrates the geometric mean ratio over time for study P027.

Table 20 Summary of 24-hour coughs per hour over time at week 12- Study P027- Full analyses set - Recount data - MI + ANCOVA.

Timepoint	Treatment	N	Geometric Mean at Baseline	Geometric Mean at Post-Baseline	Geometric Mean Ratio (Post-Baseline/Baseline)
P027					
Baseline	Placebo	232	22.80		
	MK-7264 15 mg BID	235	20.69		
	MK-7264 45 mg BID	237	18.36		
Week 12	Placebo	205	23.59	10.63	0.45
	MK-7264 15 mg BID	210	20.89	10.22	0.49
	MK-7264 45 mg BID	194	18.93	7.39	0.39

Table 21 Analysis of 24-hour coughs per hour at week 12 – Study P027- Full analyses set - Recount data - MI + ANCOVA

Treatment	N	Estimated Relative Reduction (%)† and (95% CI)	p-Value
Placebo	243		.
MK-7264 15 mg BID	244	1.20 (-15.77, 21.58)	0.899
MK-7264 45 mg BID	243	-17.10 (-31.22, -0.06)	0.049

N = Number of participants included in the analysis. CI = Confidence Interval.

†The estimated relative reduction (relative to Placebo) is calculated by 100 (e**DIFF -1). Here DIFF is the treatment difference in change from baseline at Week 12, as provided by the analysis of the log-transformed data.

Differences in LS mean of change from baseline at the time point of interest in the full FAS population. 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 is conducted at the time point of interest, adjusting for covariates of treatment, baseline, region, and gender.

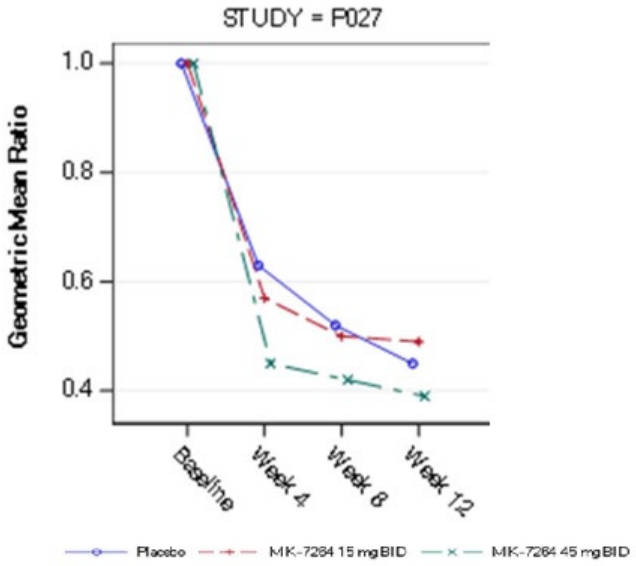


Figure 16 Summary of -24 hour coughs per hour over time - Geometric mean ratio (post- baseline /baseline; study P027- Full analyses set- Recount data-MI+ANCOVA)

- ***Secondary endpoints***[1]

In Study P027, the prespecified step-down procedure for multiplicity adjustment precluded statistical testing for the secondary endpoints at either dose, given the observed lack of efficacy on the primary endpoint for the gefapixant 15 mg BID dose. The following descriptive endpoints were observed.

Awake coughs per hour at week 12

II. **Original data: mITT, MI + ANCOVA**

At Week 12, the gefapixant 45 mg group had a significant reduction in awake coughs per hour compared with the placebo group, resulting in estimated relative reduction of -18.33 % (95% CI (-32.62, -0.96), p=0.04 (

Table 22).

Table 22 Analysis of awake cough per hour (study P027, mITT multiple imputation +ANCOVA - week 12)

Treatment	N	Estimated Relative Reduction (%)† and (95% CI)	p-Value
P027 (Week 12)			
Placebo	243		.
MK-7264 15 mg BID	244	1.35 (-16.19, 22.55)	0.890
MK-7264 45 mg BID	243	-18.33 (-32.65, -0.96)	0.040

N = Number of participants included in the analysis. CI = Confidence Interval.

*†The estimated relative reduction (relative to Placebo) is calculated by 100 (e**DIFF -1). Here DIFF is the treatment difference in change from baseline at Week 12 for P027, at Week 24 for p030, and at Week 12 for Pooled, as provided by the analysis of the log-transformed data.*

Differences in LS mean of change from baseline at the time point of interest in the full FAS population. 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 study, treatment arm gender, region and the other follow-up visits as covariates. Following imputation, ANCOVA model is conducted at the time point of interest, adjusting for covariates of study, treatment, baseline, region, and gender.

Responder analyses: ≥ 30% reduction from baseline in 24-h coughs

II. Original data: mITT, MI

A slight increase in the proportion of participants with ≥30% reduction from baseline in 24-hour coughs per hour at Week 12 was observed in the gefapixant 45 mg group (71.4%) compared to the placebo group (66.5%): the estimated difference with placebo was 4.91% (95% CI not provided). The estimated odds ratio *vs* placebo was 1.26 (95% CI 0.83, 1.01), p=0.277).

[1] The rank order for the description of the secondary outcome measures is based on the hierarchical testing of study P030.

Cough Severity Diary

II Original data: mITT, MI

At week 12, the observed proportion of participants with a ≥1.3-point reduction from baseline in mean weekly CSD total score was higher in the gefapixant 45 mg (60.5%) than in the placebo group 52.5%). The estimated difference between the 45 mg group and placebo was 7.28% (95% CI not provided). The estimated odds ratio *vs* placebo was 1.38 (95% CI 0.95, 2.03). At week 12, the observed proportion of participants with a ≥2.7-point reduction from baseline in mean weekly CSD total score was higher in the gefapixant 45 mg (35.8%) than in the placebo group (28.8%). The estimated difference between the 45 mg group and placebo was 7.02 % (95% CI not provided). The estimated odds ratio *vs* placebo was 1.38 (95% CI 0.93, 2.05).

At week 12, the observed percentage of participants with a ≥30 mm reduction from baseline in mean weekly Cough Severity VAS score was higher in the gefapixant 45 mg (39.1%) than in the placebo group (29.6%). The estimated difference between the 45 mg and placebo was 9.23% (95% CI not provided). The estimated odds ratio relative to placebo was 1.53 (95% CI 1.03, 2.27).

Leicester Cough Questionnaire (LCQ)

II Original data: mITT, MI

At week 12, the observed percentage of participants with a ≥1.3-point increase from baseline in LCQ total score was higher in the gefapixant 45 mg (66.7%) than in the placebo group (61.7%). The estimated difference between the 45 mg and placebo group was 5.25 % (95% CI not provided), with an estimated odds ratio *vs* placebo of 1.26 (95% CI 0.84-1.89).

Ancillary analyses

Subgroup analyses were available for

- The primary efficacy variable i.e., reduction from baseline in 24 cough/h at week 12
- ≥ 1.3 LCQ responder rate (at week 24)

Primary efficacy outcome: 24 h cough/h baseline to week 12

II Original data: MI + ANCOVA

The subgroup analyses showed a general consistent improvement in the reduction of 24/h coughs /h of gefapixant 45 mg over placebo, with the exception of the small subgroup of patients from North America. (Table 23)

Table 23 Analysis of coughs per hour by subgroups estimated relative reduction over placebo (%) (95% CI) - Multiple imputation full analysis set -Study P027 - Baseline to Week 12

	Gefapixant 45 mg (N)	Placebo (N)	Estimated relative reduction over placebo (95% CI)
Gender			
Male	63	62	-17.95 (-43.97, 20.16)
Female	180	181	-18.37 (-34.68, 2.01)
Age (years)			

	Gefapixant 45 mg (N)	Placebo (N)	Estimated relative reduction over placebo (95% CI)
<60	112	115	-17.59 (-40.13, 13.45)
≥ 60	131	128	-20.57 (-36.10, -1.27)
	Age (years)		
< 65	148	146	-17.04 (-36.67, 8.67)
≥ 65	95	97	-17.53 (-35.75, 5.87)
Region			
North America	56	56	2.09 (-32.90, 55.30)
Europe	121	121	-25.53 (-43.02, -2.68)
Duration of cough			
<10 years	134	127	-14.23 (-33.24, 10.21)
≥ 10 years	109	116	-24.61 (-43.79, 1.13)
Baseline mean weekly cough severity VAS category			
<60 mm	71	62	-20.95 (-47.16, 18.26)
≥ 60 mm	172	179	-16.64 (-33.19, 4.00)
Baseline number of coughs/hr			
<20 cough/h	121	96	-18.85 (-39.34, 8.55)
≥ 20 cough /h	116	136	-16.22 (-35.22, 8.35)
Primary diagnosis			
RCC	139	148	-7.95 (-25.33, 13.47)
UCC	104	95	-33.25 (-53.20, -4.79)
Taste related adverse events			
With taste related adverse events	144	11	-28.62 (-63.46, 39.45)
Without taste related adverse event	292	232	-11.39 (-31.17, 14.07)

N = Number of participants included in the analysis. CI = Confidence Interval.

[†]The estimated relative reduction (relative to Placebo) is calculated by 100 (e**DIFF -1). Here DIFF is the treatment difference in change from baseline at Week 12, as provided by the analysis of the log-transformed data.

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 is conducted at the time point of interest, adjusting for covariates of treatment, baseline, region, and gender.

≥ 1.3 LCQ responder rate (at week 12)

II Original data: MI

The results of the subgroup analyses are provided in Table **24** for the improvement in the LCQ ≥ 1.3-point increase for study P027 at week 12. Most subgroups showed an improvement in the LCQ responder rate at week 12.

Table 24 Analysis of subjects with ⩾1.3 point increase from baseline in LCQ total score at Week 12 by subgroup (P027; Full analyses set multiple imputation)

	Gefapixant 45 mg N* (%)*		Placebo N (%)		Estimated % difference With placebo†	Estimated Odd ratio vs placebo 95% CI
	Gender					
Male	63	57.4	62	54,4	3.01	1.13 (0.52, 2.45)
Female	180	70.6	181	64.5	6.11	1.32 (0.82, 2.13)
Age (years)						
<60	112	69.4	115	62.9	6.52	1.34 (0.74, 2.43)
≥ 60	131	61.4	128	59.0	2.40	1.11 (0.63, 1.93)
Age (years)						
< 65	148	70.1	146	60.5	9.56	1.53 (0.90, 2.59)
≥ 65	95	58.5	97	60.7	-2.18	0.91 (0.48, 1.76)
Region						
North America	56	67	56	58.2	8.84	1.46 (0.63, 3.39)
Europe	121	62.3	121	66.7	4.38	1.21 (0.68, 2.16)
Duration of cough						
<10 years	134	64.5	127	60.9	3.57	1.17 (0.66, 2.06)
≥ 10 years	109	68.6	116	61.4	7.19	1.37 (0.76, 2.49)
Baselines mean weekly cough severity VAS category						
<60 mm	71	68.6	62	60.2	8.39	1.44 (0.65, 3.23)
≥ 60 mm	172	66.0	179	63.7	2.36	1.11 (0.69, 1.78)
Baseline number of coughs/hr						
<20 cough/h	121	62.5	96	62.8	0.99	0.99 (0.51, 1.90)
≥ 20 cough /h	116	68.3	136	61.0	7.27	1.38 (0.79, 2.41)
Primary diagnosis 429						
RCC	139	64.2	148	62.1	2.10	1.10 (0.64, 1.89)
UCC	104	66.5	95	59.7	6.80	1.34 (0.71, 2.54)
Taste related events						
With taste related AE	142	68.9	9	65.3	3.54	1.17 (0.23, 5.93)
Without taste related AE	101	61.7	234	61.8	5.75	1.00 (0.59, 1.68)

N* = Number of subjects included in the analysis. % * = Model-based percent responders at Week 12 CI = Confidence Interval. LCQ = Leicester Cough Questionnaire.

† Missing baseline values were imputed based on gender and region, followed by multiple imputation of the missing data (m = 50 imputed dataset) for all follow-up visits using treatment arm, study, gender, region, and the other follow-up visits as covariates. Following imputation, logistic regression is conducted on the dichotomised scores at Week 12, adjusting for covariates of treatment, study, baseline underlying continuous score, region, and gender.

Study MK-7264-030

Primary endpoint – 24-Hour Coughs per Hour at week 24

I. Original data: FAS, longitudinal ANCOVA model

At baseline, the geometric mean of the number of coughs per hour over a 24 h period was 18.55 for the 45 mg dose, 19.35 for the 15 mg dose and 19.48 for placebo. At week 24, the model-based geometric mean ratio (95%) was 0.37 (0.33, 0.41) for the 45 mg group, 0.43 (0.38, 0.47) for the 15

mg group and 0.43 (0.39, 0.48) for placebo, indicating a within treatment improvement of 63 %, 57% and 57% respectively.

At Week 24, the number of coughs per hour over a 24-hour period was significantly reduced in the gefapixant 45 mg group compared with the placebo group (p=0.031), with an estimated relative reduction of the geometric mean ratio -14.64% (-26.07, -1.43) (*Table 25*). The number of coughs per hour over 24 hours was not significantly reduced in the gefapixant 15 mg group (-1.14 (-14.27, 14.02); p=0.875).

Like in study P027, the placebo response observed at Week 4 was similar to that observed in Study P012 at Week 4; however, in Study P030, it continued to increase in magnitude over time. The magnitude of the observed placebo response was similar in Studies P030 and P027. The within-group reduction from baseline in 24-hour coughs per hour at Week 24 in the gefapixant 45 mg group in Study P030 was consistent with the treatment benefit observed in Study P012.

Overall, the placebo-corrected reduction in 24-hour coughs per hour at Week 24 was smaller than that observed in Phase 2b Study P012 at Week 12.

Table 25 Analysis of 24-hour coughs per hour at week 24 (full analysis set baseline at week 24) study P030

Treatment	N	Geometric Mean at Baseline†	Geometric Mean at Week 24†	Geometric Mean Ratio (Week 24/Baseline)†	Model†† Based Geometric Mean Ratio (Week 24/Baseline) (95% CI)
Placebo	419	19.48	8.34	0.43	0.43 (0.39, 0.48)
MK-7264 15 mg BID	415	19.35	8.10	0.42	0.43 (0.38, 0.47)
MK-7264 45 mg BID	409	18.55	6.83	0.37	0.37 (0.33, 0.41)

Treatment Difference	Estimated Relative Reduction (%)§ and (95% CI)	p-Value
MK-7264 15 mg BID vs. Placebo	-1.14 (-14.27, 14.02)	0.875
MK-7264 45 mg BID vs. Placebo	-14.64 (-26.07, -1.43)	0.031

N = Number of subjects included in the analysis. CI = Confidence Interval.

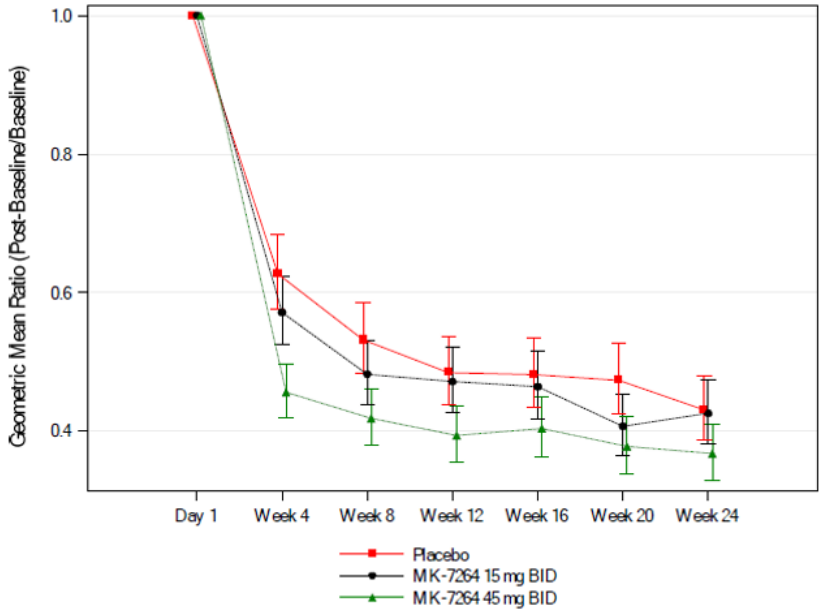
†Based on subjects with non-missing values at both baseline and Week 24.

††Based on the Longitudinal Analysis of Covariance Model consisting of the change from baseline in log-transformed 24-hour coughs per hour 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.

§The estimated relative reduction (relative to Placebo) is calculated by 100 (e**DIFF -1). Here DIFF is the treatment difference in change from baseline at Week 24, as provided by the analysis of the log-transformed data.

Note: observations with 0 coughs per hour were replaced by a cough rate of 0.1/h; this included 1 subject (1 timepoint) in Placebo, 1 subject (2 timepoints) in MK-7264 15 mg BID, and 2 subjects (1 timepoint each) in MK-7264 45 mg BID.

Source: [P030MK7264: adam-adeff]



Source: [P030MK7264: adam-adeff]

Figure 17 Model base geometric mean ratio (post-baseline/baseline) and 95% CI (full analysis set baseline to week 24), study P030

II Original *data: mITT, MI+ANCOVA*

Table 26 presents the results from the MI+ANCOVA approach with the mITT population accounted for. The estimated relative reduction was -13.29% (95% CI: -24.74, -0.10), p = 0.048. For the constrained longitudinal analysis also performed by the applicant, the estimated relative reduction was -13.95% (95% CI: -25.48, -0.64), p = 0.041.

Table 26 Analysis of 24-hour coughs per hour at week 24, mITT, MI+ANCOVA

Treatment	N	Estimated Relative Reduction (%)† and (95% CI)	p-Value
Placebo	435		.
MK-7264 15 mg BID	440	0.54 (-12.79, 15.91)	0.941
MK-7264 45 mg BID	439	-13.29 (-24.74, -0.10)	0.048

N = Number of participants included in the analysis. CI = Confidence Interval.

†The estimated relative reduction (relative to Placebo) is calculated by 100 (e**DIFF -1). Here DIFF is the treatment difference in change from baseline at Week 12, as provided by the analysis of the log-transformed data.

Differences in LS mean of change from baseline at the time point of interest in the full FAS population. 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 is conducted at the time point of interest, adjusting for covariates of treatment, baseline, region, and gender.

Sensitivity analyses

Sensitivity analyses were performed using a jump-to-reference approach, using placebo arm as the reference group as well as a tipping-point analysis. For the jump-to-reference multiple imputation analysis, the estimated relative reduction for the 45mg group compared with placebo was -12.55 (95% CI: -24.44, 1.23), and for the jump-to-reference *via* pattern mixture approach, the relative reduction was -12.56 (95% CI: -22.61, -1.21). The tipping point analysis showed that the point where the primary comparison of the 45 mg group *versus* placebo was no longer statistically significant occurred between 6% and 7% of worsening applied to the missing data imputation in the 45mg group.

The CSR also describes a supplemental estimand strategy. In this supplemental strategy, a hypothetical estimand strategy is applied for treatment discontinuations (i.e., any data after treatment discontinuation are set to missing, and only available on-treatment data are included in the analysis (Table 27) presents the results from this approach. The estimated relative reduction for the 45mg group compared with placebo was -15.75% (95% -27.43, -2.19).

Table 27 On-treatment subset analysis, Study P030

Treatment	N	Geometric Mean at Baseline†	Geometric Mean at Week 24†	Geometric Mean Ratio (Week 24/Baseline)†	Model†† Based Geometric Mean Ratio (Week 24/Baseline) (95% CI)
Placebo	417	19.47	8.34	0.43	0.44 (0.39, 0.49)
MK-7264 15 mg BID	409	19.74	8.11	0.41	0.43 (0.38, 0.48)
MK-7264 45 mg BID	394	18.91	6.78	0.36	0.37 (0.33, 0.41)

Treatment Difference	Estimated Relative Reduction (%)§ and (95% CI)	p-Value
MK-7264 15 mg vs. Placebo	-2.71 (-15.85, 12.47)	0.710
MK-7264 45 mg vs. Placebo	-15.75 (-27.43, -2.19)	0.024

N = Number of subjects included in the analysis. CI = Confidence Interval.

†Based on subjects with non-missing values at both baseline and Week 24.

††Based on the Longitudinal Analysis of Covariance Model consisting of the change from baseline in log-transformed 24-hour coughs per hour 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.

§The estimated relative reduction (relative to Placebo) is calculated by 100 (e**DIFF -1). Here DIFF is the treatment difference in change from baseline at Week 24, as provided by the analysis of the log-transformed data.

Note: observations with 0 coughs per hour were replaced by a cough rate of 0.1/h; this included 1 subject (1 timepoint) in Placebo, 1 subject (2 timepoints) in MK-7264 15 mg BID, and 2 subjects (1 timepoint each) in MK-7264 45 mg BID.

Source: [P030MK7264: adam-adeff]

In the PP analyses, the Estimated Relative Reduction (%) MK-7264 45 mg vs. Placebo result was -16.39 (95% CI -27.96, -2.95, p=0.019).

Additional sensitivity analyses requested by the CHMP

In line with the request for the analyses to include the mITT population and to target the treatment policy estimand, additional sensitivity analyses were requested. These included a jump to reference with off-treatment as reference group for imputation, and a jump to reference with the placebo group as the reference group.

For the jump to reference with off-treatment as reference group the estimated relative reduction was estimated to be -13.78% (-25.40, -0.34), p = 0.045. For the jump to reference with placebo as the reference group this was -13.00% (-25.20, 1.19), p = 0.071.

Additional analyses were also requested to target the secondary estimand strategy – the hypothetical estimand. This included an MI_+ ANCOVA approach including the mITT population; estimated relative reduction: -12.73% (-24.74, 1.19), p = 0.071 and a jump to reference with placebo as reference; estimated relative reduction: -12.20% (-25.42, 3.36), p = 0.118.

III Recount data: FAS, longitudinal ANCOVA

At baseline the geometric mean of the number of coughs per hour over a 24 h period was 19.38 for the 45 mg dose, 20.23 for the 15 mg dose and 20.39 for placebo. At week 24, the model based geometric mean ratio (95%) was 0.37 (0.33, 0.41) for the 45 mg group, 0.42 (0.38, 0.47) for the 15 mg group and 0.43 (0.39, 0.48) for placebo., indicating a within treatment improvement of 63%, 58% and 57% respectively.

At Week 24, the number of coughs per hour over a 24-hour period were significantly reduced in the gefapixant 45 mg group compared with the placebo group p= 0.031, with an estimated relative reduction of the geometric mean ratio was -14.63 (-25.98, -1.53), p=0.030 (Table 28). The number of coughs per hour over 24 hours was not significantly reduced in the gefapixant 15 mg group 2.71 % (-15.55, 12.08, p=0.70).

Table 28 Analysis of 24-hour coughs per hour at week 24; full analysis set Study P030

Treatment	N	Geometric Mean at Baseline[†]	Geometric Mean at Week 24[†]	Geometric Mean Ratio (Week 24/Baseline)[†]	Covariance Structure	Model[††] Based Geometric Mean Ratio (Week 24/Baseline) (95% CI)
Placebo (CSR)	419	19.48	8.34	0.43	Unstructured	0.43 (0.39, 0.48)
Placebo (Recount)	419	20.39	8.70	0.43	Unstructured	0.43 (0.39, 0.48)
					Toeplitz	0.43 (0.39, 0.48)
					CS	0.43 (0.39, 0.48)
					AR(1)	0.43 (0.39, 0.47)
MK-7264 45 mg BID (CSR)	409	18.55	6.83	0.37	Unstructured	0.37 (0.33, 0.41)
MK-7264 45 mg BID (Recount)	409	19.38	7.13	0.37	Unstructured	0.37 (0.33, 0.41)
					Toeplitz	0.37 (0.33, 0.41)
					CS	0.37 (0.33, 0.41)
					AR(1)	0.37 (0.33, 0.41)

Treatment Difference	Covariance Structure	Estimated Relative Reduction (%)[‡] and (95% CI)	p-Value
MK-7264 45 mg BID vs. Placebo (CSR)	Unstructured	-14.64 (-26.07, -1.43)	0.031
MK-7264 45 mg BID vs. Placebo (Recount)	Unstructured	-14.63 (-25.98, -1.53)	0.030
	Toeplitz	-14.59 (-25.05, -2.66)	0.018
	CS	-14.96 (-25.37, -3.11)	0.015
	AR(1)	-14.08 (-24.76, -1.89)	0.025

N = Number of subjects included in the analysis. CI = Confidence Interval. CS = Compound Symmetry. AR(1) = First-Order Autoregressive.

[†] Based on subjects with non-missing values at both baseline and Week 24.

[††] Based on the Longitudinal Analysis of Covariance Model consisting of the change from baseline in log-transformed 24-hour coughs per hour 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 estimated relative reduction (relative to Placebo) is calculated by 100 (e**DIFF -1). Here DIFF is the treatment difference in change from baseline at Week 24, as provided by the analysis of the log transformed data.

IV Recount data: mITT, MI + ANCOVA

Table 29 and Table 30 present the results for the recount data with the mITT population and MI+ANCOVA approach. At baseline, the geometric mean was 19.31 for the 45 mg dose and 20.20 for placebo; At week24 the geometric mean ratio was 0.37 for the 45 mg dose and 0.43 for placebo (Table 29). At week 24 the estimated relative reduction to placebo was -13.13% (95% CI -24.45, -0.12), p=0.048 (Table 29, Table 30). *Figure 19* illustrates the geometric mean ratio over time for study P030.

Table 29 Summary of 24-hour coughs per hour over time full analysis set Study P030 at week 12 and 24 - full analyses set- recount data - MI + ANCOVA

Timepoint	Treatment	N	Geometric Mean at Baseline	Geometric Mean at Post-Baseline	Geometric Mean Ratio (Post-Baseline/Baseline)
Baseline	Placebo	432	20.20		
	MK-7264 45 mg BID	434	19.31		
Week 12	Placebo	383	20.78	10.16	0.49
	MK-7264 45 mg BID	363	19.58	7.91	0.40
Week 24	Placebo	368	20.39	8.70	0.43
	MK-7264 45 mg BID	347	19.38	7.13	0.37
N = Number of subjects with non-missing values at baseline and at the post-baseline timepoint.					

Table 30 Analysis of 24-hour coughs per hour at week 24- study P030- full analysis - recount data)- MI + ANCOVA

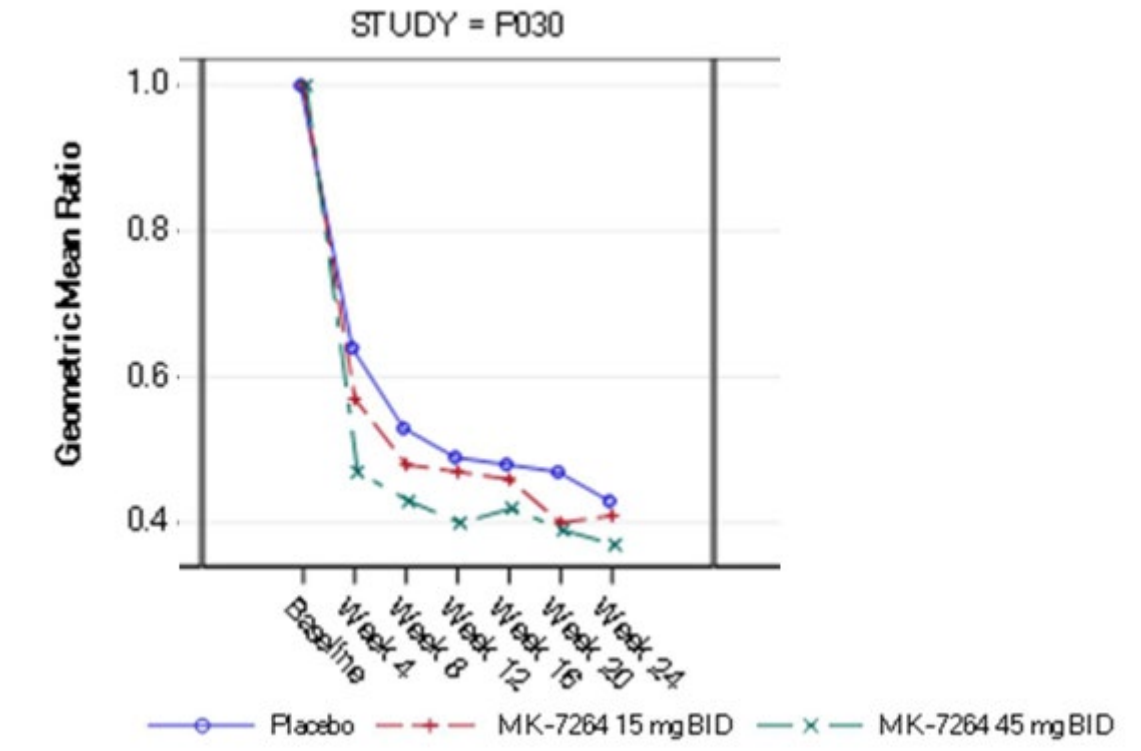
Treatment	N	Estimated Relative Reduction (%)† and (95% CI)	p-Value
Placebo	435		.
MK-7264 15 mg BID	440	-0.91 (-14.07, 14.26)	0.900
MK-7264 45 mg BID	439	-13.13 (-24.45, -0.12)	0.048

N = Number of participants included in the analysis. CI = Confidence Interval.

†The estimated relative reduction (relative to Placebo) is calculated by 100 (e**DIFF -1). Here DIFF is the treatment difference in change from baseline at Week 24, as provided by the analysis of the log-transformed data.

Differences in LS mean of change from baseline at the time point of interest in the full FAS population. 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 is conducted at the time point of interest, adjusting for covariates of treatment, baseline, region, and gender.

Figure 18 Summary of 24-hour coughs per hour over time - geometric mean ratio study P030 (post-baseline /baseline) – full analyses set- Recount data MI + ANCOVA



- ***Secondary endpoints***

In Study P030, the prespecified step-down procedure for multiplicity adjustment was formally stopped at the fourth step at which the results for the ≥ 30% reduction in cough rate for 45mg *vs* placebo were not statistically significant. Other endpoints lower in the hierarchy are considered to be descriptive.

Awake coughs per hour

II Original data: mITT MI + ANCOVA

At Week 24, the gefapixant 45 mg group had a significant reduction in awake coughs per hour compared with the placebo group, resulting in an estimated relative reduction of -14.31 % (95% CI [-25.95, -0.84], p=0.038). The gefapixant 15 mg BID group showed a small numerical improvement over placebo concerning reducing the number of awake coughs per hour at Week 24, with an estimated relative reduction of -1.21%, 95% CI [-14.14, 138]) (**Table 31**).

Table 31 Analyse of awake cough per hour, multiple imputation P030- week 24

Treatment	N	Estimated Relative Reduction (%)[†] and (95% CI)	p-Value
Placebo	435		.
MK-7264 15 mg BID	440	-1.21 (-14.24, 13.80)	0.866
MK-7264 45 mg BID	439	-14.31 (-25.95, -0.84)	0.038

N = Number of participants included in the analysis. CI = Confidence Interval.
*[†]The estimated relative reduction (relative to Placebo) is calculated by 100 (e**DIFF -1). Here DIFF is the treatment difference in change from baseline at Week 12 for P027, at Week 24 for p030, and at Week 12 for Pooled, as provided by the analysis of the log-transformed data.*
Differences in LS mean of change from baseline at the time point of interest in the full FAS population. 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 study, treatment arm gender, region and the other follow-up visits as covariates. Following imputation, ANCOVA model is conducted at the time point of interest, adjusting for covariates of study, treatment, baseline, region, and gender.

Leicester Cough Questionnaire (LCQ)

I. Original data: FAS

At baseline, the mean (SD) LCQ total score was 104 (3.1) for the 45 mg dose, 10.4 (2.9) for the 15 mg dose and 10.4 (3.0) for placebo. At week 24, the mean (SD) score was 14.8 (3.9), 14.3 (4.1) and 13.9 (4.0) respectively.

At week 24, the proportion of participants with a ≥1.3-point increase from baseline in LCQ total score was higher in the gefapixant 45 mg (76.6%) and 15 mg groups (75%) than in the placebo group (69.0%); only the gefapixant 45 mg group showed a significant (p=0.040) improvement in cough-specific HRQoL at Week 24 (Table 32).

Table 32 Analysis of responder type for the LCQ ⩾ 1.3 increase -week 24 – study P030- full analysis set - MI logistic regression model study P030

Treatment	N	n	(%)	Estimated Difference[†] vs. Placebo (95% CI)	Estimated Odds Ratio[†] vs. Placebo (95% CI)	p-Value
≥1.3 Point Increase from Baseline in LCQ Total Score P030 (Week 24)						
Placebo	355	245	69.0			
MK-7264 15 mg BID	352	264	75.0	5.72 (1.00, 10.43)	1.34 (0.97, 1.85)	0.077
MK-7264 45 mg BID	342	262	76.6	6.67 (2.32, 10.84)	1.41 (1.02, 1.96)	0.040

N=number of subjects with available data at the time point; n=Number of responders at the time point. CI= Confidence Interval. LCQ= Leicester Cough Questionnaire. NA= Not applicable.
[†]based on the logistic regression model. The covariates include treatment, visit, treatment-by-visit interaction, gender, region, baseline continuous variable, and the interaction of baseline continuous variable by visit.

When the patients with missing data were included as non-responders (Miettinen and Nurminen Method), the number of responders and the differences became smaller: gefapixant 45 mg (62.5%), 15 mg (63.3%) and placebo 59%. The estimated difference between the 45 mg and placebo was 3.3 % (95% CI - 3. 27, 9.94).

At Week 52, the observed proportion of participants with a ≥1.3-point increase from baseline in LCQ total scores was higher in both gefapixant groups than the placebo group, 45 mg group (82.9%), 15 mg group (79.1%) and placebo 68.6%). The estimated difference with placebo was 13.30 % (95% CI is not provided). When the patients with missing data were included as non-responders, the number of responders and the differences became smaller: gefapixant 45 mg (63.7%), 15 mg (62.6%) and placebo (55.2%). The estimated difference between the 45 mg and placebo was 8.4 % (95% CI 1.81, 15.02%). In the PP analyses, the 45 mg dose showed an estimated relative difference with placebo from baseline to week 24 of 7.7 % (95% CI 0.66, 14.72).

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.

II Original data: mITT, MI

At week 24, the observed percentage of participants with a ≥1.3-point increase from baseline in LCQ total score was higher in the gefapixant 45 mg (75.67%) compared with the placebo group (68.1%). The estimated difference between the 45 mg and placebo group was 7.63 % (95% CI 1.34, 13.76) with an estimated odds ratio *vs* placebo of 1.46 (95 % CI 1.07, 1.99) p-value=0.016.

≥30% reduction from baseline in 24-h coughs, Study P030

II Original data: mITT, MI

A slight increase in the proportion of participants with ≥30% reduction from baseline in 24-hour coughs per hour at Week 24 was observed in the gefapixant 45 mg group 72.9% compared to the placebo group 66.6%. The estimated difference with placebo was 6.32 % (95% CI not provided). The estimated Odds ratio *versus* placebo was 1.35 (95% CI 0.98, 1.86) p=0.06.

Cough Severity Diary

II Original data: mITT, MI

At week 24, the observed proportion of participants with a ≥1.3-point reduction from baseline in mean weekly CSD total score was higher in the gefapixant 45 mg (77.4%) than in the placebo group (69.3%). The estimated difference between the 45 mg group and placebo was 8.09 % (95% CI not provided). The estimated Odds ratio relative to placebo was 1.52 (95% CI 1.09, 2.12).

At week 24, the observed proportion of participants with a ≥2.7-point reduction from baseline in mean weekly CSD total score was higher in the gefapixant 45 mg (55.0%) than in the placebo group (41.8%). The estimated difference between the 45 mg group and placebo was 13.21% (95% CI not provided). The estimated Odds ratio *versus* placebo was 1.70 (95% CI 1.25, 2.32).

Cough Severity Visual Analog Score (Study P030).

II Original data: mITT, MI

At week 24, the observed percentage of participants with a ≥30 mm reduction from baseline in mean weekly Cough Severity VAS score was higher in the gefapixant 45 mg (51.1%) than in the placebo group (40.3%). The estimated difference between the 45 mg and placebo was 10.81 % (95% CI not provided). The estimated odds ratio *versus* placebo was 1.55 (95% CI 1.16, 2.07).

Ancillary analyses

Subgroup analyses were available for

- The primary efficacy variable i.e., reduction from baseline in 24 cough/h at week 24
- ≥ 1.3 LCQ responder rate (at week 24)

The primary efficacy variable i.e., reduction from baseline in 24 cough/h at week 24

II Original data: mITT, MI + ANCOVA

The subgroup analyses showed a general consistent improvement of gefapixant 45 mg over placebo. in all subgroups for the reduction in 24 h cough/h (Table 33).

Table 33 Analysis of 24-hour coughs per hour by subgroups estimated relative reduction over placebo (%) (95% CI) full analyses set- multiple imputation Study P030- Baseline to week 24

	Gefapixant 45 mg (N)	Placebo (N)	Estimate relative reduction over placebo (95% CI) †
Gender			
Male	110	109	-3.74 (-28.40, 29.40)
Female	329	326	-17.17 (-29.64, -2.50)
Age (years)			
<60	222	205	-11.13 (-28.96, 11.18)
≥ 60	217	230	-14.74 (-28.52, 1.71)
Age (years)			
< 65	293	291	-11.43 (-26.29, 6.43)
≥ 65	146	144	-14.62 (-31.26, 6.05)
Region			
North America	98	97	-30.35 (-46.95, -8.57)
Europe	239	238	-4.29 (-21.49, 16.67)
Duration of cough			
<10 years	258	247	-6.75 (-23.28, 13.34)
≥ 10 years	181	188	-19.15 (-34.09, -0.81)
Baseline mean weekly cough severity VAS category			
<60 mm	135	128	-14.77 (-36.35, 14.11)
≥ 60 mm	309	299	-12.40 (-26.00, 3.70)
Baseline number of coughs/hr			
<20 cough/h	227	210	-0.53 (-17.83, 20.42)
≥ 20 cough /h	207	222	-27.27 (-41.01, -10.32)
Primary diagnosis			
RCC	279	278	-10.44 (-25.35, 7.45)
UCC	160	157	-16.97 (-34.61, 5.42)
Taste related adverse events			
With taste related adverse events	302	38	-15.74 (-41.07, 20.46)
Without taste related adverse event	137	397	0.11 (-19.42, 24.38)

N = Number of participants included in the analysis. CI = Confidence Interval.

†The estimated relative reduction (relative to Placebo) is calculated by 100 (e**DIFF -1). Here DIFF is the treatment difference in change from baseline at Week 24, as provided by the analysis of the log-transformed data.

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 is conducted at the time point of interest, adjusting for covariates of treatment, baseline, region, and gender.

≥ 1.3 LCQ responder rate (at week 24)

II Original data: mITT, MI

The results of the subgroup analyses are provided in Table 34 for the improvement in the LCQ ≥ 1.3 point increase for study P030 at week 24. Most subgroups showed a numerical improvement in the LCQ responder rate at week 24 (Table 34).

Table 34 Analysis of subjects with ⩾1.3 point increase from baseline in LCQ total score at week 24 subgroup P030 - full analyses set multiple imputation

	Gefapixant 45 mg N* (%)*		Placebo N* (%)		Estimated % difference With placebo†	Estimated Odds ratio vs placebo 95% CI
Gender						
Male	110	76.9	109	71.0	4.83	1.36 (0.72, 2.58
Female	329	74.7	326	67.0	7.71	1.46 (1.00, 2.12)
Age (years)						
<60	222	75.9	205	66.7	9.20	1.57 (1.00, 2.47)
≥ 60	217	75.0	230	69.4	5.62	1.33 (0.85, 2.08)
Age (years)						
< 65	293	76.1	291	68.9	7.27	1.44 (0.97, 2.15)
≥ 65	146	74.3	144	67.1	7.25	1.42 (0.82, 2.47)
Region						
North America	98	73.8	97	65.7	8.12	1.48 (0.74, 2.94)
Europe	239	72.0	238	66.9	5.07	1.27 (0.84, 1.92)
Duration of cough						
<10 years	258	80.3	247	72.8	7.49	1.52 (0.97, 2.39)
≥ 10 years	181	68.5	188	62.3	6.24	1.32 (0.83, 2.11)
Baselines mean weekly cough severity VAS category						
<60 mm	128	73.1	135	66.3	6.83	1.39 (0.76, 2.52)
≥ 60 mm	309	75.0	299	68.4	6.57	1.38 (0.94, 2.04)
Baseline number of coughs/hr						
<20 cough/h	227	73.6	210	74.7	-1.04	0.95 (0.60, 1.50)
≥ 20 cough /h	207	78.9	222	63.8	15.11	2.13 (1.33, 2.40)
Primary diagnosis						
RCC	279	76.4	278	72.2	4.21	1.25 (0.83, 1.87)
UCC	160	75.9	157	63.1	12.75	1.84 (1.08, 3.15)
Taste related adverse events						
With taste related AE	301	81.3	38	74.1	7.19	1.52 (0.68, 3.43)
Without taste related AE	138	68.8	397	66.5	2.30	1.11 (0.70, 1.76)

N = Number of subjects included in the analysis. % * = Model-based percent responders at Week 24*
CI = Confidence Interval. LCQ = Leicester Cough Questionnaire.
† Missing baseline values were imputed based on gender and region, followed by multiple imputation of the missing data (m = 50 imputed dataset) for all follow-up visits using treatment arm, study, gender, region, and the other follow-up visits as covariates. Following imputation, logistic regression is conducted on the dichotomised scores at Week 24, adjusting for covariates of treatment, study, baseline underlying continuous score, region, and gender.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial P027 (Original dataset, CHMP requested analyses)

Title: A Phase 3, Randomised, Double-blind, Placebo-controlled, 12-month Study to Evaluate the Efficacy and Safety of MK-7264 in Adult Participants with Chronic Cough (PN027)			
Study identifier	P027 EudraCT: 2017-000537-31 NCT: 03449134		
Design	Multicentre, efficacy, safety, double-blind, placebo-controlled intervention		
	Duration of main phase:		12 weeks
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		40 weeks
Hypothesis	Hypothesis (H1): At least 1 gefapixant dose is superior to placebo in reducing coughs per hour (over 24 hours) at Week 12 Hypothesis (H2): At least 1 gefapixant dose is superior to placebo in reducing coughs per hour (while awake during a 24-hour period) at Week 12 Hypothesis (H3): At least 1 gefapixant dose is superior to placebo with respect to the proportion of participants with a ≥30% reduction from baseline in 24-hour coughs per hour at Week 12		
Treatments groups	MK-7264 45 mg		Main Study Period: 12 weeks Extension Study Period: 40 weeks 244 randomised
	Placebo		Main Study Period: 12 weeks Extension Study Period: 40 weeks 244 randomised
Endpoints and definitions	Primary endpoint	24-hour cough	24-hour coughs per hour at Week 12
	Secondary endpoint	awake cough	Awake coughs per hour at Week 12
	Secondary endpoint	≥30% reduction	Proportion of participants with a ≥30% reduction from baseline in 24-hour coughs per hour at Week 12
	Secondary endpoint	≥1.3 CSD	Proportion of participants with a ≥1.3-point reduction from baseline in mean weekly Cough Severity Diary (CSD) total score at Week 12
	Secondary endpoint	≥2.7 CSD	Proportion of participants with a ≥2.7-point reduction from baseline in mean weekly CSD total score at Week 12

	Secondary endpoint	VAS	Proportion of participants with a ≥30 mm reduction from baseline in Cough Severity Visual Analog Scale (VAS) score at Week 12
	Secondary endpoint	LCQ	Proportion of participants with a ≥1.3-point increase from baseline in Leicester Cough Questionnaire (LCQ) total score at Week 12
Database lock			

Results and Analysis				
Analysis description	Primary analysis, current results are taken from the response to the CHMP's request			
Analysis population and time point description	The primary efficacy analysis was based on the modified ITT population, which considered of all randomised patients who received at least 1 dose of study drug. In Study P027, two patients were randomised and not treated.			
Descriptive statistics and estimate variability	Treatment group	Placebo		MK-7264 45 mg
	Number of subjects (primary endpoint)	243		242
	24-hour cough Model based geometric mean ratio	0.48 (0.42, 0.55)		0.39 (0.34, 0.45)
	95% CI			
	awake cough Model based geometric mean ratio			
	95% CI			
	≥30% reduction Model based % responders	66.5		71.4
	≥1.3 CSD Model based % responders	52.5		60.5
	≥2.7 CSD Model based % responders	28.8		35.8
	VAS Model based % Responders	29.6		39.1
	LCQ Model based % Responders	61.7		66.9

Effect estimates per comparison	Primary endpoint MI + ANCOVA analysis	Comparison groups	MK-7264 45 mg *vs* placebo
		Treatment difference (estimated relative reduction)	-18.52%
		95% CI	(-32.76, -1.28)
		p-Value	0.036
	Secondary	Comparison	MK-7264 45 mg *vs* placebo

	endpoint, awake cough	Treatment difference (estimated relative reduction)	not provided
		95% CI	
		p-Value	
	Secondary endpoint, ≥30% reduction	Comparison groups	MK-7264 45 mg *vs* placebo
		Estimated odds ratio relative to placebo	1.26
		95% CI	0.83, 1.91
		p-Value logistic regression	0.27
	Secondary endpoint, ≥1.3 CSD	Comparison groups	MK-7264 45 mg *vs* placebo
		Estimated odds ratio relative to placebo	1.38
		95% CI	0.25, 2.03
	Secondary endpoint, ≥2.7 CSD	Comparison groups	MK-7264 45 mg *vs* placebo
		estimated odds ratio	1.38
		95% CI	0.95, 203
	Secondary endpoint, VAS	Comparison groups	MK-7264 45 mg *vs* placebo
		Estimated odds ratio relative to placebo	1.53
		95% CI	1.03, 2.27
	Secondary endpoint, LCQ	Comparison groups	MK-7264 45 mg *vs* placebo
		Estimated odds ratio relative to placebo	1.26
		95% CI	0.84, 1.89

Summary of Efficacy for trial P030 (Original data set, CHMP requested analyses)

Title: A Phase 3, Randomised, Double-blind, Placebo-controlled, 12-month Study to Evaluate the Efficacy and Safety of MK-7264 in Adult Participants with Chronic Cough (PN030)		
Study identifier	P030 EudraCT: 2017-003559-49 NCT: 03449147	
Design	Multicentre, efficacy, safety, double-blind, placebo-controlled intervention	
	Duration of main phase:	24 weeks
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	28 weeks

Hypothesis	Hypothesis (H1): At least 1 gefapixant dose is superior to placebo in reducing coughs per hour (over 24 hours) at Week 24 Hypothesis (H2): At least 1 gefapixant dose is superior to placebo in reducing coughs per hour (while awake during a 24-hour period) at Week 24 Hypothesis (H3): At least 1 gefapixant dose is superior to placebo with respect to the proportion of participants with a ≥1.3-point increase from baseline in Leicester Cough Questionnaire (LCQ) total score at Week 24 Hypothesis (H4): At least 1 gefapixant dose is superior to placebo with respect to the proportion of participants with a ≥30% reduction from baseline in 24-hour coughs per hour at Week 24			
Treatments groups	MK-7264 45 mg		Main Study Period: 24 weeks Extension Study Period: 28 weeks 439 randomised	
	MK-7264 15 mg		Main Study Period: 24 weeks Extension Study Period: 28 weeks 442 randomised	
	Placebo		Main Study Period: 24 weeks Extension Study Period: 28 weeks 436 randomised	
Endpoints and definitions	Primary endpoint	24-hour cough	24-hour coughs per hour at Week 24	
	Secondary endpoint	awake cough	Awake coughs per hour at Week 24	
	Secondary endpoint	LCQ	Proportion of participants with a ≥1.3-point increase from baseline in LCQ total score at Week 24	
	Secondary endpoint	≥30% reduction	Proportion of participants with a ≥30% reduction from baseline in 24-hour coughs per hour at Week 24	
	Secondary endpoint	≥1.3 CSD	Proportion of participants with a ≥1.3-point reduction from baseline in mean weekly Cough Severity Diary (CSD) total score at Week 24	
	Secondary endpoint	≥2.7 CSD	Proportion of participants with a ≥2.7-point reduction from baseline in mean weekly CSD total score at Week 24	
	Secondary endpoint	VAS	Proportion of participants with a ≥30 mm reduction from baseline in Cough Severity Visual Analog Scale (VAS) score at Week 24	
Database lock				
Results and Analysis				
Analysis description	Primary Analysis, current results are taken from the response to the CHMP's request			
Analysis population and time point description	The primary efficacy analysis was based on the mITT population, which consisted of all randomised participants who had taken at least 1 dose of study intervention. In Study P030, three patients were randomised and not treated.			
Descriptive statistics and estimate variability	Treatment group	Placebo		MK-7264 45 mg
	Number of subjects (primary endpoint)	434		439

	24-hour cough Model based geometric mean ratio	0.43 (0.39, 0.48)		0.37 (0.34, 0.42)
	95% CI			
	awake cough Model based geometric mean ratio			
	95% CI			
	LCQ Model based % responders	75.7		68.1
	≥30% reduction Model based % responders	66.6		72.9
	≥1.3 CSD Model based % responders	69.3		77.4
	≥2.7 CSD Model based % responders	41.8		55.0
	VAS Model based % responders	40.3		51.1

Effect estimates per comparison	Primary endpoint MI + ANCOVA analysis	Comparison groups	MK-7264 45 mg *vs* placebo
		Treatment difference (estimated relative reduction)	-13.29%
		95% CI	(-24.74, -0.10)
		p-Value	0.048
	Secondary endpoint, awake cough	Comparison groups	MK-7264 45 mg *vs* placebo
		Treatment difference (estimated relative reduction)	
		95% CI	
		p-Value	
	Secondary endpoint, LCQ	Comparison groups	MK-7264 45 mg *vs* placebo
		Estimated odds ratio relative to placebo	1.46
		95% CI	1.05, 2.02
		p-Value logistic regression	0.024
	Secondary endpoint, ≥30% reduction	Comparison groups	MK-7264 45 mg *vs* placebo
		Estimated odds ratio relative to placebo	1.35
		95% CI	
		p-Value logistic regression	
	Secondary	Comparison groups	MK-7264 45 mg *vs* placebo

	endpoint, ≥1.3 CSD	Estimated odds ratio relative to placebo	
		95% CI	
	≥2.7 CSD	Comparison groups	MK-7264 45 mg *vs* placebo
		Estimated odds ratio relative to placebo	1.70
		95% CI	1.25, 2.32
	Secondary endpoint, VAS	Comparison groups	MK-7264 45 mg *vs* placebo
		Estimated odds ratio relative to placebo	1.55
		95% CI	1.66, 2.07

2.5.5.4. Clinical studies in special populations

In clinical studies, patients aged ≥ 65 years might be underrepresented. Table 35 provides an overview of the number of elderly patients included in the clinical trials. The data show that overall, a total of n=1002 (28%) of included study patients were aged ≥ 65 years.

Table 35 The number of patients aged ⩾ 65 years in the clinical trial

	Age 65-74 (n/N)	**Age 75-84 (n/N)**	**Age 85+ (n/N)**
Controlled Trials	828/3568	169/3568	5/3568
Non-Controlled Trials	4/6	Not applicable	Not applicable
n: Number of older subjects in an age group. *N: Total number of subjects.*			

2.5.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Data from Studies P027 and P030 were considered acceptable to pool because the studies had identical entry criteria, dosing regimens, and efficacy endpoints. Participants were pooled across studies by their treatment group at randomisation.

Efficacy analyses of objective cough endpoints and subgroup analyses are provided for Week 12, the timepoint up to which the cough data were available from both studies (see results below).

After week 24, only PRO data was collected. Overall, these PRO showed improved outcomes over placebo which was maintained over time.

Pooled Primary endpoint- 24 h coughs/h at week 12

II Original data: mITT, MI+ANCOVA

At week 12, the pooled analyses showed that the estimated relative reduction in cough rate compared with placebo was -1.87% (95% CI -12.01, 9.43) for the 15 mg dose and -18.27% 95% CI (-27.20, -9.24) for the 45 mg dose (Table 36).

Table 36 Analyses of 24-hour coughs per hour multiple imputation Full analyses set Phase 3 trial pooled across P027 and P030-baseline to week 12

Treatment	N	Estimated Relative Reduction (%)† and (95% CI)
Placebo	678	
MK-7264 15 mg BID	684	-1.87 (-12.01, 9.43)
MK-7264 45 mg BID	682	-18.71 (-27.20, -9.24)

N = Number of participants included in the analysis. CI = Confidence Interval.

†The estimated relative reduction (relative to Placebo) is calculated by 100 (e**DIFF -1). Here DIFF is the treatment difference in change from baseline at Week 12, as provided by the analysis of the log-transformed data.

Differences in LS mean of change from baseline at the time point of interest in the full FAS population. 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 is conducted at the time point of interest, adjusting for covariates of treatment, baseline, region, and gender.

Pooled other outcomes

Pooled *Awake coughs per hour at week 12*

II Original data: mITT, MI+ANCOVA

At week 12, the pooled analyses showed a relative estimated reduction in cough count for the 45 mg gefapixant group compared with placebo (estimated relative reduction of -16, 94 % (955 CI -25.67, -71.9), while the observed improvement with the 15 mg was minimal (estimated relative reduction (-0.36 % (95% CI -10, 79, 11.27) (Table 37).

Table 37 Analysis of awake coughs per hour mITT multiple imputation + ANCOVA

Treatment	N	Estimated Relative Reduction (%)† and (95% CI)	p-Value
Placebo	678		
MK-7264 15 mg BID	684	-0.36 (-10.78, 11.27)	
MK-7264 45 mg BID	682	-16.94 (-25.67, -7.19)	

N = Number of participants included in the analysis. CI = Confidence Interval.
*†The estimated relative reduction (relative to Placebo) is calculated by 100 (e**DIFF -1). Here DIFF is the treatment difference in change from baseline at Week 12 for P027, at Week 24 for p030, and at Week 12 for Pooled, as provided by the analysis of the log-transformed data.*
Differences in LS mean of change from baseline at the time point of interest in the full FAS population. 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 study, treatment arm gender, region and the other
follow-up visits as covariates. Following imputation, ANCOVA model is conducted at the time point of interest, adjusting for covariates of study, treatment, baseline, region, and gender.

Proportion of participants with ≥30%, ≥ or ≥ 70% reduction from baseline in 24 Hour coughs per hour

II Original data: mITT, MI

≥30% reduction in 24 cough counts/h from baseline to week 12

At week 12, the pooled number of patients with ≥30% reduction from baseline in 24-hour coughs were 71.4% with gefapixant 45 mg and 64.7% with placebo. The estimated difference between gefapixant 45 mg and placebo was 6.70 % (95% CI not provided). The estimated odds ratio *vs* placebo was 1.36 (95% CI 1.07, 1.74).

Pooled analyses of subjects with Leicester Cough Questionnaire Score (≥ 1.3) increase from baseline at week 12

II Original data: mITT, MI

At week 12, in the pooled analysis, the estimated difference between gefapixant 45 mg and placebo in the number of Subjects with ≥ 1.3-point increase in LCQ was 7.88 % (95% CI not provided). The estimated odds ratio is 1.44 (95%CI 1.13, 1.83).

Pooled subgroup analyses of study P027 and P030 according to subgroup analyses

Subgroup analyses were available for

- The primary efficacy variable i.e., reduction from baseline in 24 cough/h at week 12
- ≥ 30 % reduction from baseline cough count at week 12

During the assessment, also a post-hoc, post randomisation subgroup was defined according to the presence of taste disorders yes/no. The results for the primary efficacy outcome are also provided below.

Primary efficacy variable: reduction from baseline in 24h cough/h

II Original data: mITT, MI + ANCOVA

The pooled data for the subgroup analyses showed overall a consistent reduction in the number of 24 h cough/h over the predefined subgroups (Table 38). The subgroup with a baseline cough count ≥ 20 coughs /h showed a numerically larger improvement than the complementary group with a baseline cough count < 20 cough/h. The *post-hoc* post-randomisation subgroup without taste disorders showed no numerical improvement.

Table 38 Analysis of 24-hour coughs per hour by subgroups estimated relative reduction over placebo (%) (95% CI) – full analysis set - original data MI + ANCOVA phase 3 trials pooled across P027 and P030 – Baseline to Week 12

	Gefapixant 45 mg (N)	Placebo (N)	Estimate relative reduction over placebo (95% CI) †
Gender			
Male	171	173	-21.99 (-37.83, -2.13)
Female	509	507	-17.35 (-26.96, -6.47)
Age (years)			
<60	334	320	-15.43 (-28.89, 0.58)
≥ 60	348	358	-19.98 (-29.92, -8.63)
Age (years)			
< 65	441	437	-17.82 (-28.88, -5.04)
≥ 65	241	241	-18.17 (-30.67, -3.40)
Region			
North America	154	153	-26.77 (-42.20, -7.22)
Europe	360	359	-18.22 (-29.08, -5.70)
Duration of cough			
<10 years	392	374	-11.46 (-23.53, 2.52)
≥ 10 years	290	304	-25.59 (-36.80, -12.40)

	Gefapixant 45 mg (N)	Placebo (N)	Estimate relative reduction over placebo (95% CI) †
Baseline mean weekly cough severity VAS category			
<60 mm	199	197	-11.93 (-28.80, 8.93)
≥ 60 mm	481	478	-20.22 (-29.72, -9.43)
Baseline number of coughs/hr			
<20 cough/h	348	306	-13.72 (-26.27, 0.98)
≥ 20 cough /h	323	358	-22.96 (-33.42, -10.85)
Primary diagnosis			
RCC	418	426	-16.03 (-26.14, -4.54)
UCC	264	252	-22.00 (-35.60, -5.53)
Taste related adverse events			
With taste related adverse events	446	49	-29.86 (-48.27, -4.89)
Without taste related adverse event	236	629	-9.57 (-22.28, 5.21)

N = Number of participants included in the analysis. CI = Confidence Interval.

†The estimated relative reduction (relative to Placebo) is calculated by 100 (e**DIFF -1). Here DIFF is the treatment difference in change from baseline at Week 12, as provided by the analysis of the log-transformed data.

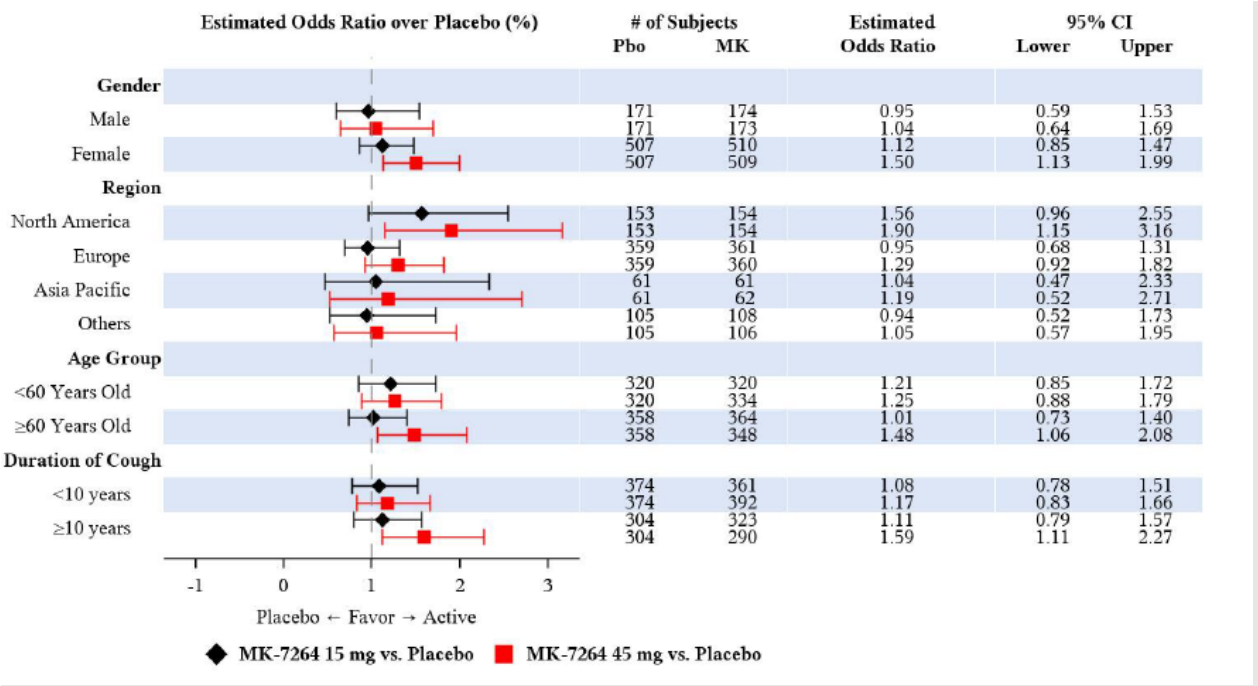
Missing baseline values were imputed based on gender and region, followed by multiple imputation of the missing data (m = 50 imputed datasets) for all follow-up visits using treatment arm gender, region and the other follow-up visits as covariates. Following imputation, ANCOVA model is conducted at the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

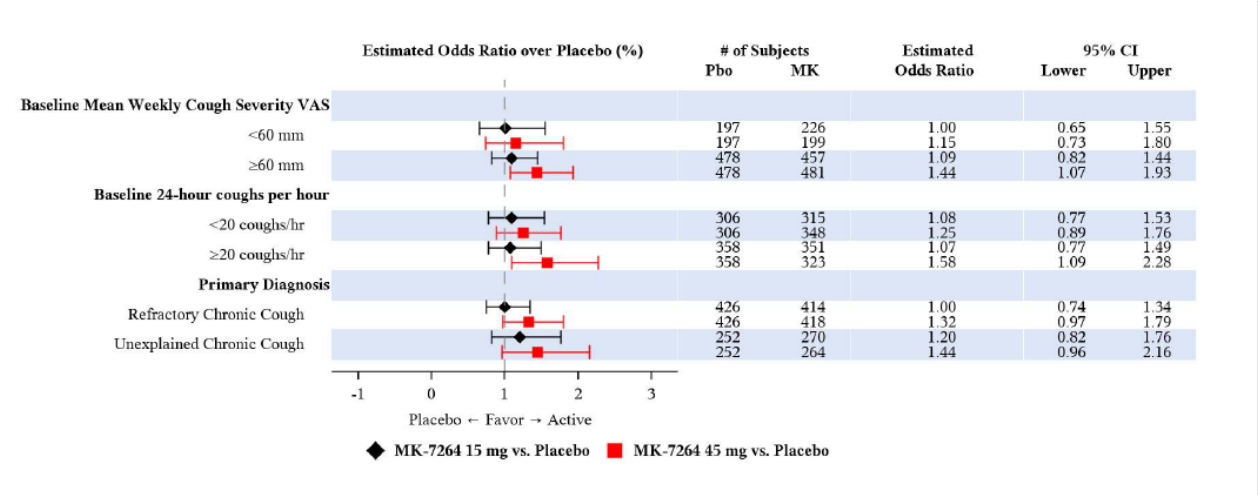
≥ 30% reduction in baseline cough count

II Original data: mITT, MI

Additional subgroup analyses according to the predefined subgroups were provided. The subgroup analyses for the number of responders that showed a ≥ 30% reduction in cough rate revealed that all pre-defined subgroups showed an improvement favouring MK 45 treatment over placebo. (*Figure 20*)

Figure 19 Analysis of subjects with ≥30% reduction from baseline in 24-hour coughs per hour at week 12 by subgroup multiple imputation estimated odds ratio vs. placebo (%) (95% CI) Phase 3 trials pooled across P027 and P030 full analysis set





Additional Post-Hoc defined subgroup according taste disorders

II Original data: mITT, MI

Taste disorders: The subgroup who experienced taste disorders show a numerically larger difference in the responders than the LCQ questionnaire than the subgroup that did not experience taste disorders (Table 39).

Table 39 analysis of subjects with ⩾1.3 point increase from baseline in LCQ total score at week 24 by taste-related adverse events up to week 24 multiple imputation - full analysis set phase 3 trials pooled across P027 and P030

Treatment Difference	N *	% *	Estimated Difference	Estimated Odds Ratio vs. Placebo (95% CI)
Subjects with taste-related adverse events by Week 24				
Placebo, at Week 24	49	70.4		
MK-7264 45 mg, at Week 24	445	78.5	8.13	1.54 (0.77, 3.07)
Subjects without taste-related adverse events by Week 24				
Placebo, at Week 24	629	66.1		
MK-7264 45 mg, at Week 24	237	68.9	2.77	1.14 (0.79, 1.62)

N* = Number of subjects included in the analysis. % * = Model-based percent responders at Week 24
CI = Confidence Interval. LCQ = Leicester Cough Questionnaire.
Missing baseline values were imputed based on gender and region, followed by multiple imputation of the missing data (m = 50 imputed dataset) for all follow-up visits using treatment arm, gender, region, and the other follow-up visits as covariates. Following imputation, logistic regression is conducted on the dichotomized scores at the time point of interest, adjusting for covariates of treatment, baseline underlying continuous score, region, and gender.

2.5.5.6. Supportive studies

After careful consideration of the advice provided by the MWP, the information submitted in the validation studies, and in the context of the results, the CHMP concluded that the original data should remain as the primary data set for the discussion on benefit/risk and reporting of the treatment effect in the SmPC.

Recount data set: After the validation exercise, the applicant provided the results of the recount data set. The recount data may affect the primary, cough related outcome and other cough related outcomes. The subgroup that would be most affected by the recount of the data was the subgroup according baseline cough count (<20 cough/h *vs* ≥ 20 cough/h) because also the baseline grouping of the subjects might be impacted. Table 40 shows the comparison of the main baseline and efficacy data of the recount data set and the original data set. Upon recount of the data, the subgroup of patients with baseline cough count ≥ 20 cough/h included n=20 more patients.

The comparison of the primary, secondary and subgroup analyses according baseline cough show generally comparable results between the original and recount data set. Comparable results were also seen in the subgroup analyses, including the subgroup analyses according baseline cough count (Table 40).

Table 40 Comparison of the baseline and cough related outcomes between the recount data set and original data set (mITT, MI))

	Recount data		***Original data***	
Demographics				
Baseline cough count (median range)				
Study P027	**Patients with data**	**Median range**	**Patients with data**	**Median range**
MK 45 mg (n=243)	234	19.7 (0, 399)	237	19.21 (0.2-286.4)
Placebo (n=243)	232	25.96 (0-1053)	232	25.37 (0.4-1055.5)
Study P030				
MK 45 mg (n=439)	434	19.71 (0-230)	434	19.15 (0-230)
Placebo (n=435)	432	21.17 (1-184)	432	20.53 (1-180)
Pooled analyses				
< 20 cough /h (n)	634		654	
≥ 20 cough/h (n)	701		671	
Results				
MK 45 mg vs placebo				
Study P027				
Reduction in 24 cough/h (%, 95% CI)	-17.10 (-31.22, -0.06) p=0.049		-18.52 (-32.96, -1.28) p=0.03	

Reduction awake cough/h (%, 95% CI)	-17.11 (-31.40, 0.16) P=0.052		-18.33 (-32.65, -0.96) p=0.040	
Study P030				
Reduction in 24 cough/h (%, 95% CI)	-13.13 (-24.45, -0.12) p=0.04 8		-13.29 (-24.74, -1.00) p=0.048	
Reduction awake cough/h (%, 95% CI)	-13.82 (-25.36, -0.49) p=0.043		-14.31 (-25, 95, -0.84) p=0.038	
Pooled analyses				
Pooled Responder rate in reduction in (%) cough from baseline, MK 45 mg vs. placebo	***Estimated difference***	***Odds ratio (95% CI)***	***Estimated difference***	***Odds ratio (95% CI)***
≥ 30%	5.00%	1.24 (0.98, 1.57)	6.70%	1.36 (1.07, 1.74)
≥ 50%	7.62%	1.36 (1.08, 1.70	9.26%	1.45 (1.11, 1.81)
≥ 70%	8.81%	1.40 (1.09, 1.80)	7.52%	1.45 (1.11, 1.81)
Pooled analysis of subgroups according baseline cough count				
< 20 cough/h				
Reduction in baseline cough count at week 12 (%, 95%CI)	-9.39 (-22.57, 6.04)		-13.72 (-26, 27, 0.98)	
Improvement LCQ responder rate at week 24 (estimated odds ratio, 95% CI)	P027 1.03 (0.54, 1.89) P030 0.85 (0.53, 1.36)		0.99 (0.68, 1.45	
≥ 20 cough /h				
Reduction baseline cough count at week 12 (% , 95% CI)	-24.54 (-34.68, -12.83)		-22.96 (-33.42, -10.85)	
Improvement in LCQ responder rate at week 24 (estimated odds ratio, 95% CI)	P027 1.35 (0.77, 2.36) P030 2.25 (1.41, 3.59		1.85 (1.27, 2.69)	

Off -treatment durability study: The off-treatment durability Study was a multicentre, 12-week, noninterventional, observational study conducted at select sites and countries. A total of 163 participants enrolled in the Off-treatment Durability Study; 41 participants enrolled from Study P027-03 and 122 participants enrolled from Study P030-04. Of the participants enrolled, all but 2 participants completed the study. Although participants were no longer receiving study intervention, previous treatment assignments remained blinded. To analyse the exploratory efficacy objectives, participants completed various PRO measures including the Cough Severity VAS, LCQ and CSD.

Efficacy results: After 52 weeks of treatment and through the 12-week off-treatment period (Week 64), the above PROs were relatively stable and did not return to baseline (Week0): mean weekly Cough Severity VAS score, mean LCQ total score, and mean weekly CSD total score. Across the gefapixant and placebo groups, most participants who achieved an on-treatment response at Week 52 were also responders at the end of the 12-week off- treatment period (Week 64) as measured by: Cough Severity VAS score (82% overall), LCQ total score (85% overall), CSD total score with ≥1.3-point reduction from baseline (87% overall), and CSD total score with ≥2.7-point reduction from baseline (79% overall). Across the gefapixant and placebo groups, most participants who achieved a n on-treatment response at Week 52 had a durable off-treatment response over the 12-week off-treatment period (Week 64) as measured by: Cough Severity VAS score, LCQ total score, and CSD total score. For those who lost response, timing to loss of response trended similarly across the gefapixant and placebo groups through the 12-week off- treatment period.

Phase 3 study P042 and P043: Additional supportive top-line results of two, randomised, blinded, placebo-controlled phase 3 studies of 12-week duration were provided (study P042 and study P043).

Study P042 was conducted in patients with stress induced urine incontinence. At week 12, gefapixant 45 mg showed a statistically significant reduction in cough induced stress induced episodes measures as the percentage change from baseline (estimated difference -11.67 % (95% CI -19.67, -3.67), p=0.004.

Study P043 was conducted in patients with recent onset chronic refractory or unexplained cough chronic cough (RCC or UCC) of < 1-year duration. At week 12, gefapixant 45 mg in improved the mean change in LCQ total score, with a statistically significant treatment difference of 0.75 (95% CI: 0.06, 1.44; p=0.034).

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The application for gefapixant was supported by two pivotal Phase 3 studies P027 and P030. Additional evidence was provided from the phase 2 study P012 and the top-line results from the phase 3 studies P042 and P043. The two pivotal phase 3 studies were international randomised, double-blind, placebo-controlled, 12-month studies with near-identical designs, i.e., study MK7264-P027 (P027) and study MK7264-P03 (P030). These studies had similar inclusion and exclusion criteria, and dosing regimens (placebo bid, gefapixant 15 mg bid and gefapixant 45 mg bid) and collected the same primary and secondary endpoints. The study included patients with chronic cough for 1 years a diagnosed as RCC or UCC as defined by the ACCP guidelines.

The differences in trial design between the two trials P027 and P030 refer to the duration of the main study period of collection of the main efficacy outcomes (P027: 12 weeks and P030: 24 weeks), and the hierarchical testing. Only Study P030 included a patient-reported outcome i.e., LCQ responder rate in the hierarchical testing, and will provide the main support for the clinical relevance by a patient-derived outcome. In a limited number of countries, the study was extended with a 3-month off treatment period durability period to explore the impact of withdrawing therapy in patients who had been treated for 1 year. Only high-level data is provided from this study during assessment.

The inclusion and exclusion criteria of the phase 3 studies are almost identical to the phase 2 studies and are considered acceptable to include a heterogenous chronic cough population. Upon inclusion, patients had to be symptomatic as defined by a cough severity VAS score of ≥ 40 mm. All patients had to have a diagnosis of chronic cough defined as RCC or UCC as defined by the ERS guideline and confirmed by the principal investigator or sub-investigator. All investigators were trained on the ACCP guidelines before the startof the Phase 3 programme as well as during subsequent trainings throughout the Phase 3 programme. All exclusion criteria were appropriate for including a broad chronic cough population. Patients with significant, modifiable risk factors such as smoking and taking ACE-inhibitors were excluded, in line with current guidelines.

During the study, patients were treated in a blinded manner with gefapixant 45 mg bid, gefapixant 15 mg bid or placebo. The use of the placebo comparison arm is acceptable because no generalised authorised substance exists for chronic cough in Europe. The study patients were stratified according to gender and region, which is considered adequate. The studies were not stratified according to the underlying disease like RCC or UCC because of the lack of evidence that this factor would influence the treatment outcomes. The pivotal phase 3 clinical studies did not follow the SAWP advice to include two co-primary endpoints representing an objective endpoint in reducing the cough frequency, and a subjective PRO endpoint. Following the SAWP advice, study P030 was sufficiently powered to show a statistically significant improvement in a subjective PRO outcome to support the clinical relevance of the findings.

The primary endpoint was the reduction of cough frequency per hour measured over 24 hours from baseline until the end of the maintenance treatment (12-week study P027, 24-week study P030) compared with placebo. The minimally clinically important difference (MCID) for the reduction in cough

frequency is not well established. On a patient level, a reduction of 30% from baseline can be perceived (and therefore, this 30% reduction might be considered as the MCID. A 20% (15 mg) and 30% reduction (45 mg) from baseline had been used in the sample size calculation.

The key secondary parameter was the number of awake coughs measured over a 24-hour period. This objective secondary parameter has a considerable overlap with the primary outcome. As it is not distinctively different, its values were limited as supportive outcome measure.

The Leicester Cough Questionnaire (LCQ) was used as a secondary outcome in the hierarchical testing of study P030 to support the clinical relevance of the primary outcome. The LCQ is a validated questionnaire of a patient-reported outcome in the quality of life, where a ≥ 1.3 reduction is associated with a minimal clinically relevant improvement in QoL. A statistically significant improvement in the responder rate would support the clinical relevance if a reduction in the cough rate would be observed.

Supportive outcomes included both objective and subjective parameters. Objective supportive measurement was the difference in responders with placebo showing a ≥ 30%, ≥ 50% or ≥70% reduction in cough count which would show the consistency of findings of the primary outcome when more stringent criteria were used. Additional supportive subjective outcome data was provided using the responder rate of 2 additional cough specific PRO measures i.e., the Cough Severity Dairy (CSD) and the Cough Severity Visual analogue scale (VAS).

In the studies P027 and P030, various subgroups were predefined to show the consistency of efficacy. Except for the RCC and UCC, the subgroup analyses were not based on a well-accepted, distinct disease entity or clear pharmacological and /or pathophysiological rational.

Different data sets available for the primary analyses: The new outcome measure, the relative reduction in cough counts measured with the VitaloJAK system initially appeared to be insufficiently validated. During the assessment procedure, the system was re-validated based on the use of one compression algorithm and around 90% of the cough recordings were re-compressed using this algorithm. Results based on the recount data were provided as supportive data. The recount data showed that the overall inferences and conclusions are consistent between the original and recount data, and the point estimates are largely in agreement. The results from the validation studies suggest that there are unlikely to be systematic biases introduced into the cough counts, also using the other two compression algorithms with dual channel processing.

After careful consideration of the advice provided by the MWP (Sept 2022), the information submitted in the validation studies, and in the context of the results, the CHMP concluded that the original data should remain as the primary data set for the discussion on benefit/risk, and reporting of the treatment effect in the SmPC.

Method of analyses: In the SAP, it is stated that the primary analysis approach was to be conducted using the longitudinal ANCOVA model. The use of a longitudinal ANCOVA model was raised as a potential concern in the scientific advice as it does not validly account for the missing data. It was instead suggested that an MMRM be fitted. Based on the SAS code provided in the supplemental SAP, it is understood that for the original analysis, an MMRM was fitted. As stated in the CSRs for studies P027 and P030, the intercurrent events of treatment discontinuation and/or use of prohibited medication were to be handled through a treatment policy estimand strategy, under which, outcome data should continue to be collected and included in the final analysis regardless of discontinuation or use of prohibited medication. It is agreed that a treatment policy strategy is an appropriate approach in this context. However, despite the goal to collect outcome data after treatment discontinuation or use of prohibited medicine, not all participants had data available at all timepoints. Given the initial observations of missing data and the importance of the potential impact on estimating the treatment policy estimand, the CHMP requested the electronic datasets containing the individual patient data for

Studies 027 and 030, which the applicant provided during the assessment. An investigation of these data identified that less than a third of participants in both studies had "off-treatment" data available after discontinuing treatment. Therefore, the current approaches to handling these missing data don't produce an estimate of treatment effect under the treatment policy estimand strategy.

There are two main issues related to the current handling of missing data:

- The treatment policy estimand targets the ITT analysis population. The current definition of the analysis population for the original analyses performed in studies P027 and P030 resulted in the exclusion of participants for whom the baseline, or all post-baseline measurements were missing. The exclusion of these participants was considered likely to result in a biased estimate of the treatment effect for the ITT population.
- Not all patients included in the analysis had data available at all timepoints, including week 12 (in study P027) or week 24 (in study P030). More data are missing on participants in the 45mg treatment arm, primarily as a result of withdrawal following treatment discontinuation.

Additional analyses were requested by the CHMP that sought to address the problem of the missing data in the mITT population and to better target the treatment policy estimand. These included additional J2R approaches, with participants who discontinued treatment but remained in follow up, and approaches that included all participants who received treatment regardless of the extent of their available data. Based on an evaluation of these approaches it was concluded that the primary results should be based on the constrained longitudinal analysis, or the preferred method of a multiple imputation + ANCOVA. Hence, the multiple imputation + ANCOVA approach would be considered the primary analysis method for reporting in the SmPC. The best approach to target the treatment policy estimand remains uncertain, however it is considered that the pre-planned J2R method, with placebo as the reference group is sufficiently consistent with the primary results. The results from the hypothetical estimand strategy (constrained longitudinal analysis and MI + ANCOVA) give an estimate of the treatment effect under the situation where patients continued treatment regardless of having experienced an adverse event, perceived lack of efficacy, or other events that led to treatment discontinuation.

Based on these considerations, the B/R assessment is conducted on the original data set analysis methods applied that intended to include the mITT population.

Efficacy data and additional analyses

Pivotal studies – P027 and P030

Demographic and other baseline characteristics: The baseline characteristics, including smoking status, were generally well balanced across the intervention groups in both phase 3 studies. In both studies, the proportion of females recruited were higher than males (74.2% females in study P027; 74.9% females in study P030), which aligns with the target population. The included patient population had a long history of chronic cough with a median duration of 8-10 years. More patients with RCC (~60%) than UCC (~40%) were included in both trials.

In study P027 (but not in P030), it was noticed that the mean baseline cough counts per hour are much higher in the placebo group. This is likely to be explained by patients with excessive cough frequency, i.e., of over 1000 coughs per hour. The median is more balanced between the groups but still slightly higher in the placebo group. This imbalance is accounted for in the constrained longitudinal analysis, or by adjustment for baseline in an ANCOVA.

Number analysed: The initially provided dataset excluded patients with missing baseline or all missing post baseline data. Using the requested updated analyses, all patients in the mITT population were accounted for in the analyses. This approach is considered to better estimate the treatment effect for

the treatment policy estimand as the exclusion of any patient with missing data is likely to lead to biased estimates of effect.

Missing data methods were used to account for missing follow up data, with the missing data assumptions dependent on the method. More patients discontinued in the active treatment arms compared with placebo. The premature discontinuation rate was highest in the 45 mg group, the difference with the other treatment groups was driven by the adverse events, including taste disorder. Although it was intended to follow up all patients who discontinued, this was not possible. Missing data methods were used to account for the missing follow up data. The primary analysis assumes that the missing data are missing at random, conditional on the available data and thus represents a hybrid treatment policy and hypothetical estimand. Sensitivity analyses that were intended to better target the treatment policy estimand were also performed, as was an analysis that targeted the hypothetical estimand. This analysis only included data that were recorded when patients were on treatment.

Efficacy results: The two pivotal placebo-controlled trial had a large placebo effect (larger than in the phase 2 trial P012). The placebo effect affected both objective and subjective outcome measures, i.e., frequency of cough registration, as well as the patient reported outcomes. Nevertheless, the double-blind, randomised controlled designs made it possible to address a treatment effect on top of placebo (if present). The 15 mg dose did not show superiority over placebo in the primary outcome and most of the secondary outcome measures. As such, the efficacy of the 15 mg dose is insufficiently shown and was not further pursued. Therefore, the results for the 15 mg dose will not be further discussed to focus on the results of the 45 mg dose.

Gefapixant 45 mg dose: summary of results

Primary and secondary outcomes: In line with the two-phase II studies MK7264 -P010 and MK7264-P012, the primary and key secondary cough related outcome measures showed consistent improvements favouring the gefapixant 45 mg. In both studies, the 45 mg dose demonstrated a superior effect over placebo in the primary efficacy outcome, i.e., a relative reduction in the number of coughs per 24/h (Study P027:- 18.52%; (95% CI– 32,76, -1.28) p=0.036; Study P030: -13.3% (95%CI -24.74, -0.10) p=0.048).
In study P030, this primary endpoint was also supported with a statistically significant improvement in the number of awake coughs and the responder rate in the LCQ (absolute difference ~7.32 % (95 % CI not provided) p=0.024); numerical improvements for both parameters were observed in study P027; Study P027 was not designed to show superiority in the LCQ responder rate. Overall, these outcomes show a clinically relevant effect.

Additional supportive outcomes: The objective reduction in cough rate, the primary efficacy variable, was supported with numerical improvements in the responder rate of patients that show a reduction in the baseline cough rate ≥ 30 %, at week 12 (4.91% for study P027) or and 6.32 % at week 24 (study P030) on top of a large placebo response. Exploratory analyses showing somewhat larger differences when more stringent criteria (i.e., ≥ 50% reduction, ≥ 70% reduction) were used, supporting the treatment effect. No data for the objective outcome measures "reduction in cough rate" could be provided beyond the 24-week treatment as this efficacy parameter was no longer measured. The observed improvements in the LCQ score were supported with numerical improvements in the other PRO of the responder rate favouring gefapixant 45 mg dose. These improvements over placebo maintained in the extension period of the study up to 48 weeks show that distinct, yet related, aspects of the impact cough on a patient related outcomes may provide additional support for the subjective improvements as measured by the LCQ.

Subgroup analyses: The results of the subgroup analyses generally supported the primary analyses. The *post-hoc*, post randomisation subgroup of patients according to taste disorders showed larger improvements in the subgroup with taste disorder compared to those without taste disorder.

The results in the subgroup of patients with a baseline cough rate < 20/h were discussed extensively, as the overall improvement in cough/h was numerically smaller than in the complementary group of ≥ 20 cough/h, while no numerical improvement in the LCQ responder rate was shown (on top of a large placebo response. Overall, it was considered that the results of this subgroup finding must be interpreted with caution. This subgroup is based on an arbitrary cut-off value of the baseline cough rate, and not supported by a biological or pharmacological rational. It is also noted that the largest potential for measurement error was observed in the lower cough counts in the validation studies. The baseline 24 h cough count is rarely used as a clinical tool, while the guidelines on RCC and UCC do not mention a threshold for hourly cough counts to define chronic cough. The efficacy result in this subgroup is not extreme which enhances a chance finding. As this product is the first in class for the treatment of chronic cough, replication can also not be shown. Based on these considerations, it cannot be excluded that the results are based on a chance finding. The *post hoc* defined subgroup according to taste disorder showed larger responses than the subgroup without taste disorder. Although this analysis must be interpreted with caution given it is based on a post-randomisation subgroup, it appears that the patients that experience side effects may also have the largest benefit.

Recount data set: Additional supportive analysis was provided based on the data generated after the validation and recount of the cough counts based on compression algorithm WHO3V3.0. A total of about 90% of the originally provided cough count data set was recounted and confirmed the reported results of the primary data set, i.e., a small, but statistically significant improvement in the reduction in coughs per hour on top of a large placebo response, at week 12 (Study P027) or at week 24 weeks (study P030).

Subgroup analyses of the recount data set revealed comparable results and support the primary data set.

Additional expert consultation

Methodology Working Party consultation

During the procedure, the Methodology Working Party (MWP) was consulted on the proposed validation studies. A summary of the questions asked to the MWP and the response as provided to the applicant (through the CHMP) is provided below:

The CHMP comments concern the marketing authorisation application for gefapixant (Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application), which is proposed to be indicated for the treatment of refractory and unexplained chronic cough. During the assessment procedure, it became clear that only the cough recording device of the VitaloJAK system has been validated, but that the full system, including the compression algorithm and manual cough tagging by multiple trained cough analysts, has not been validated against the gold standard for manual cough count which is the count of the uncompressed cough recording. The CHMP considers it critical to resolve the issues related to the validation of the full VitaloJAK system before the assessment of the benefit/risk ratio can be continued. In addition, issues related to the quality controls of the manual cough counts by the cough analyses have been identified. The applicant provided an updated version of the proposed validation and IRR protocols, which were commended by the CHMP.

CHMP MWP comments

- **Acceptability of the 5% Maximal Allowable Difference (MAD) considering the strength of the current treatment effect**

It is agreed that 5% might be an acceptable limit in this specific situation, if conclusions from the primary analysis are understood to be robust against differences below such a patient-level MAD. It will be important to understand whether any systematic errors are associated with the cough frequency as this may lead to overestimation or underestimation of the treatment effect under the alternative hypothesis.

The MAD should reflect clinically irrelevant differences and there should be reassurance that differences below the MAD do not alter the conclusions of the clinical trials. This could be supported by simulation studies. The applicant is invited to reflect this in the protocol.

It seems important to consider the possible technical-physiologic-psychological precision which is achievable by manual raters based on uncompressed recordings as a reference standard.

- **Adequacy of the proposed Bland-Altman methods and supportive analyses given the data will not satisfy the distributional assumptions**

The Bland-Altman method is a standard method to descriptively compare two measures on the same scale and, therefore, is accepted. The use of alternative methods if the assumptions of the Bland-Altman method are not met seems acceptable. However, the decision criteria to use one of these methods and not the other should be clearly pre-specified and the decisions documented.

Results of both the planned method and an alternative, robust method, which does not violate the assumptions (fallback-method), should be provided, and any inconsistencies should be discussed.

- **It is currently proposed to test the variance component of raters to evaluate inter-rater reliability.** Consistent with other measurement evaluation studies, it is recommended to also evaluate inter-rater agreement descriptively by calculating the Intra-Class-Correlation (ICC) coefficient (with a confidence interval). The thresholds need to be pre-specified. In addition, the applicant may consider providing a clinically more interpretable measure of inter-rater agreement, for example the average absolute difference between any rater.

- **It is currently proposed to include only 5 out of the 8 cough analysts included in the IRR study in the analysis, assuming the study already has 95% power with only 5 analysts. This is considered a bit counterintuitive given the objective to evaluate analyst-level variability.**

The rationale to select 5 out of 8 raters seems to be to avoid "overpowering" the study because of the proposed statistical significance testing of the variance component of the raters (analysts). However, by reporting inter-rater reliability descriptively as intra-class correlation coefficient (ICC) (with confidence interval), these concerns do not seem relevant anymore. Therefore, it is recommended to include all available raters in the statistical model to assess inter-rater reliability.

- **Following the validation exercises, it is currently proposed to consider the current results (based on the two compression algorithms) as primary and the results based on the recounts as sensitivity analysis.**

In general, for testing CHMP prefers to use the analysis according to what was prespecified in the protocol. It is therefore agreed to use the current testing results. Sensitivity analysis based on the use of compression algorithm v3.0 are also considered to be important, and any inconsistency between the two proposed analyses would likely raise concerns.

2.5.7. Conclusions on the clinical efficacy

Clinical efficacy data from the studies P027 and P030 showed a large placebo response in both the original cough count set supported by the recount data set. Despite the large placebo response, the clinical benefit was demonstrated by gefapixant 45 mg by showing a significant improvement over placebo in an objective measurement of the (the relative reduction in the cough rate/ 24 h) as well as an improved responder rate in a patient reported quality of life assessment measured by the LCQ. The results of the LCQ responder rate are supported other PRO data with a sustained effect over time, showing the consistency of the findings.

Furthermore, the findings from the pivotal phase III trials are supported by results of two-phase II studies MK7264 -P010 and MK7264-P012 where the primary and key secondary cough-related outcome measures showed consistent improvements favouring the gefapixant 45 mg. The consistency of efficacy is also supported by two additional supportive studies (Study P042 and study P043) showing a significant improvement over placebo in cough-related outcomes.

2.5.8. Clinical safety

The safety and tolerability assessment for the gefapixant chronic cough programme primarily comprises pooled data from the 52-week treatment periods of Studies P027 and P030 (henceforth referred to as the P027/P030 Pool). These studies were double-blind, randomised, placebo-controlled Phase 3 studies. As the studies had identical entry criteria and dosing regimens and collected the same endpoints, it is acceptable to pool the data.

Both studies were designed to collect safety data from the 52-week treatment period and to collect safety data from the ongoing off-treatment Durability Study periods (Study P027 Amendment 03, Study P030 Amendment 04) conducted at select sites, and to explore the impact of withdrawing gefapixant after 52 weeks of treatment in a subset of participants in the latter. Study P030 also includes an ongoing China-specific Extension Study, implemented to extend enrolment in China beyond the global study enrolment period to satisfy local regulatory requirements. Data from the ongoing off-treatment Durability Studies and the China-specific Extension Study are not included.

Of note, safety data for the Phase 1 and Phase 2 studies were not integrated with the P027/P030 Pool or across study phases because of differences in dosing regimens and study populations.

Methods and Pooling Strategy for Safety Analyses: MedDRA version 23.0 was used at the time of data analysis. This version of MedDRA includes the newly added Preferred Term (PT) of taste disorder. As a result of this addition, some Lowest Level Terms (LLTs) previously classified under the PT of dysgeusia were classified under the PT of taste disorder. This reclassification may have impacted the frequency of AEs of dysgeusia reported in earlier Phase 1 and Phase 2 CSRs.

Phase 1 and Phase 2: Across the Phase 1 programme in healthy participants, AEs were summarised 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"). Because of the wide range of doses administered during the Phase 2 programme, Phase 2 AEs were summarised by gefapixant total daily dose (<100 mg TDD or ≥100 mg TDD) and placebo. Phase 2 AEs were further summarised by participants with chronic cough and participants with indications other than chronic cough (including healthy participants) to evaluate the safety profiles of these subsets.

Phase 3 – P027/P030 Pool: Participants were pooled across the P027 and P030 Studies to 1 of the following groups: gefapixant 15 mg BID (referred to as "gefapixant 15 mg"), gefapixant 45 mg BID (referred to as "gefapixant 45 mg"), or "placebo" groups. Additionally, both gefapixant dose groups were pooled across studies and comprised the "gefapixant 15/45 mg BID pooled" group. Safety for the P027/P030 Pool was assessed in the All participants as treated (APaT) population, which included all randomised participants who received at least 1 dose of gefapixant or placebo. Participants were grouped based on the treatment received. Participants who were cross treated (i.e., took 1 or more incorrect dose(s) of study intervention from the randomised assignment of gefapixant or placebo) were counted in the highest dose of gefapixant received.

2.5.8.1. Patient exposure

Across the gefapixant clinical development programme, 2413 participants received at least 1 dose of gefapixant in the completed Phase 1 and Phase 2 clinical studies and in the P027/P030 Pool. The P027/P030 Pool included 2044 participants who were randomised and received at least 1 dose of the study intervention.

Table 41 Participant exposure to gefapixant

	Phase 1	Phase 2	Phase 3	Total
MK-7264	448	596	1369	2413
Phase 1 trials include: P001, P002, P003, P007, P011, P017, P020, P022, P023, P024, P025, P026, P028, P032, P036, P039, P040, and P044. Phase 2 trials include: P004, P005, P006, P009, P010, P012, P013, P014, P015, P016, P019, P021 (an extension study of P010), and P033. Phase 3 trials include: P027 and P030.				

Phase 3 - P027/P030 Pool: A total of 2049 participants were randomised, and 2044 were treated; 82.4% of the participants completed the study, and 72.3% completed the study intervention.

Table 42 Extent of exposure to MK-7264 by dose safety pool across P027 and P030 over the period of 52 weeks all subjects as treated

MK-7264	≤4 wks	> 4 to ≤8 wks	> 8 to ≤12 wks	> 12 to ≤24 wks	> 24 to < 52 wks	≥52 wks	Total Subjects	Duration Range	Mean (SD) Duration	Median Duration
Any 15/45 mg BID	129	61	53	99	394	633	1,369	1 to 388 days	277.2 (131.4) days	358.0 days
15 mg BID	34	24	25	45	206	352	686	1 to 388 days	297.4 (116.1) days	360.0 days
45 mg BID	95	37	28	54	188	281	683	1 to 379 days	256.9 (142.4) days	355.0 days

Each subject who received MK-7264 is counted once on the "Any 15/45 mg BID" row in the column that reflects the total duration of exposure to MK-7264.
Each subject is counted again on one or more specific dose category rows that correspond to the actual dose(s) received. On each applicable specific dose row, the subject is counted once in the column that reflects the duration of exposure to that specific dose.
Duration of exposure is calculated assuming one day of dosing = one day of exposure. One day of dosing means one day with at least one tablet of MK-7264.
Exposure ≤4 wks includes 1 to 28 days of exposure; >4 wks ≤8 wks includes 29 to 56 days of exposure; >8 wks ≤12 wks includes 57 to 84 days of exposure; >12 wks to ≤24 wks includes 85 to 168 days of exposure; >24 wks to < 52 wks includes 169 to 359 days of exposure; ≥52 wks includes 360 and more days of exposure.

Demographics and characteristics

Baseline characteristics were generally balanced across intervention groups. The mean age was 58.4 years, with approximately one-third of the participants aged ≥65 years; 74.7% of the participants were female, and 79.6% were white. The mean BMI was 28.59 kg/m2. More participants had a primary diagnosis of RCC (61.5%) than UCC (38.5%).

Participants had a mean duration of chronic cough of approximately 11 years prior to enrolment, and the mean number of coughs per hour over 24 hours at baseline was slightly higher in the placebo group than in the gefapixant groups. Additional baseline factors were also generally consistent. Baseline smoking status was similar across intervention groups; approximately 74% of participants never smoked, and none were current smokers.

2.5.8.2. Adverse events

Phase 3 – P027/P030 Pool

The overall incidence of AEs was higher in the gefapixant 45 mg group compared with the gefapixant 15 mg and placebo groups. 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; these imbalances across intervention groups were primarily due to taste-related AEs (Table 43).

Table 43 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)

[†] 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'.

Common Adverse Events: The most frequently reported AE in any intervention group was dysgeusia and was higher in the gefapixant 45 mg group than in the gefapixant 15 mg and placebo groups. Other most frequently reported AEs (≥10% of participants) in the gefapixant 45 mg group were nasopharyngitis, ageusia, headache, and hypogeusia. The most frequently reported AEs (≥10% of participants) in the gefapixant 15 mg group were nasopharyngitis, headache, and dysgeusia. The incidence of taste-related AEs was higher in the gefapixant 45 mg group than in the gefapixant 15 mg and placebo groups. The incidences of all other AEs were generally balanced across the gefapixant and placebo groups (Table 44).

Table 44 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)
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)**

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.

Adverse Events Related to Study Intervention

Overall, the incidence of study intervention-related AEs was higher in the gefapixant 45 mg group than in the gefapixant 15 mg and placebo groups. Of the most frequently reported study intervention-

related AEs (≥5% of participants in the gefapixant 45 mg group), most were categorised in the SOC Nervous system disorders, which included the taste-related AEs of dysgeusia, ageusia, hypogeusia, and taste disorder (Table 45).

Table 45 Subjects with drug-related 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 drug-related† adverse events	138	(20.4)	194	(28.3)	470	(68.8)
Gastrointestinal disorders	**54**	**(8.0)**	**57**	**(8.3)**	**139**	**(20.4)**
Dry mouth	15	(2.2)	14	(2.0)	40	(5.9)
Nausea	16	(2.4)	14	(2.0)	37	(5.4)
Nervous system disorders	**63**	**(9.3)**	**134**	**(19.5)**	**433**	**(63.4)**
Ageusia	6	(0.9)	14	(2.0)	98	(14.3)
Dysgeusia	29	(4.3)	73	(10.6)	276	(40.4)
Hypogeusia	3	(0.4)	21	(3.1)	70	(10.2)
Taste disorder	2	(0.3)	10	(1.5)	54	(7.9)
Respiratory, thoracic and mediastinal disorders	**12**	**(1.8)**	**16**	**(2.3)**	**47**	**(6.9)**

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.

† Determined by the investigator to be related to the drug.

Adverse Events by Intensity: The majority of participants reported mild (29.5%) or moderate (42.4%) AEs; 7.1% of participants reported severe AEs. The overall incidences of severe and severe drug-related AEs were higher in gefapixant 45 mg group (8.8% and 3.1%, respectively) compared to gefapixant 15 mg (7.9% and 0.4%, respectively) and placebo (6.4% and 0.3%, respectively) groups. The incidences of severe AEs across the system organ classes (SOCs) by treatment arm were low (<3.5%). The SOCs with an incidence of ≥1% for severe AEs were: Nervous system disorder, Infections and infestations, Injury, poisoning, and procedural complications, Respiratory, thoracic and mediastinal disorder, and Gastrointestinal disorders. The SOC for Nervous system disorder for gefapixant 45 mg, was the only SOC with an incidence ≥1% for both severe (3.1%) and severe drug-related AEs (2.8%), driven by the higher incidences of taste related AEs.

Analysis of Adverse Events by Organ System: Taste-related AEs, including dysgeusia, ageusia, taste disorder, hypogeusia, and hypergeusia, were predefined at the study design stage as safety endpoints of special interest, and AEs of paraesthesia oral and hypoaesthesia oral were prespecified safety endpoints. PTs of loss of appetite, weight loss, and dehydration were evaluated for potential clinical sequelae of taste-related AEs. Renal and urological events, although not prespecified as safety endpoints, were reviewed based on preclinical observations. Clinical evaluation included a review of PTs indicative of haematuria, crystalluria, and urolithiasis. Specialised urine crystal analysis for identifying gefapixant crystals was conducted on urine samples that were confirmed to have crystals or unexplained haematuria. 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. Specific AEs suggestive of hypersensitivity were reviewed, including but not limited to PTs of hypersensitivity, rash, urticaria, dermatitis, lip swelling, and tongue pruritis.

Adverse events of specific interest (AESI) and other prespecified safety endpoints

The adverse event of specific interest are the taste-related AEs, hypoesthesia oral and paraesthesia oral, renal and urinary tract injury, pneumonia and lower respiratory tract infection and hypersensitivity.

Taste-related Adverse Events were defined as AESI in the SAP. The overall incidence of taste-related AEs was higher in the gefapixant 45 mg group than the gefapixant 15 mg and placebo groups. Most participants who experienced a taste-related AE did not discontinue study intervention due to a taste-related AE. Among the participants with taste-related AEs, study intervention discontinuation due to taste-related AEs was higher in the gefapixant 45 mg group compared with the gefapixant 15 mg and placebo groups. The majority of taste-related AEs were of mild or moderate intensity (Table 46).

Dysgeusia was the most frequently reported taste-related AE and was higher in the gefapixant 45 mg group than the gefapixant 15 mg and placebo groups. The individual incidences of ageusia, hypogeusia, and taste disorder, were higher in the gefapixant 45 mg group than the gefapixant 15 mg and placebo groups, while the incidence of hypergeusia was low (<1.0%) across the intervention groups. Most of the taste-related AEs were considered to be related to study intervention by the investigator. No taste-related SAEs were reported.

Table 46 Subjects with taste-related adverse events by maximum intensity (incidence > 0% 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	
	Intensity	n	(%)	n	(%)	n	(%)
Subjects in population		675		686		683	
With one or more taste-related adverse events	Total	47	(7.0)	120	(17.5)	447	(65.4)
	Mild	41	(6.1)	93	(13.6)	289	(42.3)
	Moderate	6	(0.9)	25	(3.6)	141	(20.6)
	Severe	0	(0.0)	2	(0.3)	17	(2.5)
Nervous system disorders							
Ageusia	Total	6	(0.9)	16	(2.3)	100	(14.6)
	Mild	6	(0.9)	13	(1.9)	55	(8.1)
	Moderate	0	(0.0)	3	(0.4)	41	(6.0)
	Severe	0	(0.0)	0	(0.0)	4	(0.6)
Dysgeusia	Total	36	(5.3)	78	(11.4)	281	(41.1)
	Mild	32	(4.7)	56	(8.2)	178	(26.1)
	Moderate	4	(0.6)	20	(2.9)	92	(13.5)
	Severe	0	(0.0)	2	(0.3)	11	(1.6)
Hypergeusia	Total	2	(0.3)	2	(0.3)	5	(0.7)
	Mild	2	(0.3)	1	(0.1)	4	(0.6)
	Moderate	0	(0.0)	1	(0.1)	1	(0.1)
Hypogeusia	Total	4	(0.6)	22	(3.2)	73	(10.7)
	Mild	3	(0.4)	17	(2.5)	53	(7.8)
	Moderate	1	(0.1)	5	(0.7)	19	(2.8)
	Severe	0	(0.0)	0	(0.0)	1	(0.1)
Taste disorder	Total	3	(0.4)	10	(1.5)	61	(8.9)
	Mild	2	(0.3)	10	(1.5)	44	(6.4)
	Moderate	1	(0.1)	0	(0.0)	14	(2.0)
	Severe	0	(0.0)	0	(0.0)	3	(0.4)

Every subject is counted a single time for each applicable specific adverse event, and is classified according to the highest non-missing intensity grading.

Source: [ISS: adam-adsl; adae]

The mean time to onset of any taste-related AE was approximately 9 days in the gefapixant 45 mg group compared with ≥36 days in the gefapixant 15 mg and placebo groups. Within 1 week of receiving study intervention, approximately 50% of participants in the gefapixant 45 mg group had a taste-related AE compared with <8% of participants in the gefapixant 15 mg and placebo groups. The mean duration of any taste-related AE was higher in the gefapixant 45 mg group (203.9 days) compared with the gefapixant 15 mg (178.1 days) and placebo groups (132.6 days).

All taste-related AEs resolved in 96.0% of the participants in the gefapixant 45 mg group who experienced a taste-related AE. In the majority of participants, all taste-related AEs resolved after discontinuation of gefapixant treatment (Table 47).

Table 47 Summary of resolution of taste-related adverse events high level safety pool across P027 and P030 over the period of 52 weeks; all subjects as treated

Category	Placebo n (%)	MK-7264 15 mg BID n (%)	MK-7264 45 mg BID n (%)
Subjects in population	675	686	683
with one or more taste-related adverse events (among all subjects as treated)	47 (7.0)	120 (17.5)	447 (65.4)
discontinued* due to taste-related adverse events (among all subjects as treated)	2 (0.3)	9 (1.3)	95 (13.9)
discontinued* due to taste-related adverse events (among all subjects with one or more taste-related adverse events)	2 (4.3)	9 (7.5)	95 (21.3)
Any taste-related adverse event	**47**	**120**	**447**
Subjects with all taste-related adverse events resolved†	40 (85.1)	109 (90.8)	429 (96.0)
with all taste-related adverse events resolved on or before the last dose	24 (51.1)	51 (42.5)	110 (24.6)
with all taste-related adverse events resolved within treatment period‡ post the last dose	10 (21.3)	35 (29.2)	215 (48.1)
with all taste-related adverse events resolved after treatment period‡	6 (12.8)	14 (11.7)	66 (14.8)
Subjects with all taste-related adverse events ongoing§	6 (12.8)	9 (7.5)	15 (3.4)
Other††	1 (2.1)	2 (1.7)	3 (0.7)

Subjects with multiple taste-related adverse events may be counted in more than one category.
* "Discontinued" means that action taken is listed as 'drug withdrawn'.
† "Resolved" refers to a non-missing adverse event end date. "Subjects with all taste-related adverse events resolved" is an overall count of subjects that had all taste-related AEs resolved (with non-missing adverse event end date). Subjects with taste-related AEs that resolved during more than one of the three breakdowns that follow, are not included in a breakdown, but are included in the overall count.
§ "Ongoing" refers to a missing adverse event end date.
‡ "Treatment period" is defined as the period from the first dose to the last dose + 14 days.
†† None of the above categories.

Source: [ISS: adam-adsl; adae]

As of 02-Nov-2021, a total of 30 participants (placebo group, n=6; gefapixant 15 mg group, n=9; and gefapixant 45 mg group, n=15) had ongoing taste-related AEs. The applicant does not expect to receive additional information on the 2 participants who withdrew consent. Updated safety information as of 14 Dec 2021 revealed that 6 participants in placebo group (0.9%) 5 participants in gefapixant 15 mg group (0.7%), and 7 participants gefapixant 45 mg group (1.0%) had ongoing taste-related AEs. Out of these 18 participants, information was not available for 2 participants in the placebo group, 1 participant in the gefapixant 15 mg group, and 4 participants gefapixant 45 mg group. The course of taste-related AEs is presented in (Table 48).

Table 48 Summary of ongoing taste-related adverse events safety pool across P027 and P030 over the period of 52 weeks; all subjects as treated

Category	**Placebo n (%)**	**Gefapixant 15 mg n (%)**	**Gefapixant 45 mg n (%)**
Subjects in population	**675**	**686**	**683**
Subjects with all taste-related events ongoing at Week 54	6 (0.9%)	9 (1.3%)	15 (2.2%)
Other at Week 54	1 (0.1%)	2 (0.3%)	3 (0.4%)
Subjects with all taste-related events *ongoing* at 2 Nov 2021	6 (0.9%)	9 (1.3%)	15 (2.2%)
Subjects with all taste-related events *ongoing* at 14 DEC 2021	6 (0.95)	5 (0.7%)	7 (1.0)
Subjects with Any taste-related adverse events	**47**	**120**	**447**
Subjects with all taste-related events ongoing at Week 54	6 (12.8)	9 (7.5)	15 (3.4)
Other at Week 54	1 (2.1)	2 (1.7)	3 (0.7)
Subjects with all taste-related events ongoing at 2 Nov 2021	6 (12.8)	9 (7.5%)	15 (3.4)
Subjects with all taste-related events *ongoing* at 14 DEC 2021	6 (12.8)	5 (4.2%)	7 (1.6)

Sequelae of taste-related AEs: 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 (<1.5%) 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.

Characterisation of the patient population with taste disorders

Upon request of CHMP, the applicant provided a post-hoc comparison of the baseline characteristics of the patients who experienced taste disorder and of the of population who discontinued due to taste disorder.

Of the 682 patients treated with gefapixant 45 mg, 447 (66%) subjects experienced a taste related adverse event compared to 47 (6.9%) of the placebo treated patients.
Comparing the gefapixant 45 mg group with and without a taste related adverse event, the analysis showed that the gefapixant treated patients with a taste related adverse events included a higher proportion of UCC patients (41 % *vs* 34%). The patients with a taste related event had also a slightly higher baseline cough count (median 20.7 *vs* 16.21).

Regarding discontinuation, 95 (14%) gefapixant 45 mg treated patients and 2 (0%) of placebo treated discontinued because of taste-related adverse event. A total of 352 gefapixant 45 mg treated patients did not discontinue due to taste related adverse event.
The differences are small, but the data show that slightly higher proportion of UCC than RCC patients treated with gefapixant 45 mg treated experienced a taste disorder and prematurely left the trial (17.4% *vs* 11,2%). The patients that prematurely left had also signs of less severe disease as shown by a lower median cough count (15.33 (1-102) *vs* 21.95 (0-386 coughs/h) and lower proportion of VAS score > 60mm (61 *vs* 71%). No data is provided for the subgroup with a low or high baseline cough count (< 20 cough/h or ≥ 20 cough/h).

The gefapixant 45 mg treated patients who left the study because of taste related adverse events also experienced a more frequently AEs of moderate (n=59 (62%) *vs* n=82 (23%)) or severe intensity (n=10 (10%) *vs* n=7 (2%)) compared to those who remained in the study.

Other prespecified safety endpoints

Hypoaesthesia Oral and Paraesthesia Oral

The overall incidences of hypoaesthesia oral and paraesthesia oral were low (<3.5%) in all intervention groups. The incidence of hypoaesthesia oral in the gefapixant 45 mg group was 3.1% compared with the gefapixant 15 mg group at 0.9% and the placebo group at 0.1%. Similarly, the incidence of paraesthesia oral in the gefapixant 45 mg group was 2.2% compared with the gefapixant 15 mg group at 1.5% and placebo group at 0.3%.

Discontinuation of study intervention due to hypoesthesia oral or paraesthesia oral was low (<0.5%). Most incidences of hypoaesthesia oral and paraesthesia oral were considered to be related to study intervention and none were SAEs.

The participants who presented with an oral paraesthesia/oral hypoaesthesia and a taste-related event are displayed in *Table 49*.

Table 49 Incidence of taste-related AEs in participants with and without AEs of oral paraesthesia/oral hypoaesthesia

	Participants with AEs of Oral paraesthesia/Oral hypoaesthesia				Participants without AEs of Oral paraesthesia/Oral hypoaesthesia			
	Placebo N=3		Gefapixant 45 mg BID N=34		Placebo N=672		Gefapixant 45 mg BID N=649	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants with ≥1 AE	3	(100)	34	(100)	530	(78.9)	573	(88.3)
Dysgeusia	1	(33.3)	23	(67.6)	35	(5.2)	258	(39.8)
Ageusia	0		11	(32.4)	6	(0.9)	89	(13.7)
Hypogeusia	0		1	(8.8)	4	(0.6)	70	(10.8)
Taste disorder	1	(33.3)	4	(11.8)	2	(0.3)	57	(8.8)
Hypergeusia	0		0		2	(0.3)	5	(0.8)
Every subject is counted a single time for each applicable row and column								

Renal and urinary tract injury

The overall incidence of specific renal and urinary AEs potentially associated with renal and urinary tract injury was low (<6.0%) in all intervention groups, and the individual incidences of the haematuria, crystalluria, and urolithiasis PTs were low (<3.0%) in all intervention groups. (Table 50)

Table 50 Subjects with haematuria, crystalluria, and urolithiasis adverse events (incidence >0% 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 renal/urinary adverse events	31	(4.6)	40	(5.8)	33	(4.8)
with no renal/urinary adverse events	644	(95.4)	646	(94.2)	650	(95.2)
Investigations	**15**	**(2.2)**	**13**	**(1.9)**	**8**	**(1.2)**
Crystal urine	1	(0.1)	0	(0.0)	1	(0.1)
Crystal urine present	14	(2.1)	13	(1.9)	7	(1.0)
Renal and urinary disorders	**18**	**(2.7)**	**29**	**(4.2)**	**26**	**(3.8)**
Calculus bladder	0	(0.0)	0	(0.0)	1	(0.1)
Calculus urinary	0	(0.0)	2	(0.3)	2	(0.3)
Crystalluria	2	(0.3)	1	(0.1)	3	(0.4)
Haematuria	13	(1.9)	20	(2.9)	20	(2.9)
Nephrolithiasis	2	(0.3)	6	(0.9)	1	(0.1)
Ureterolithiasis	1	(0.1)	0	(0.0)	0	(0.0)
Every subject is counted a single time for each applicable row and column.						

Source: [ISS: adam-adsl; adae]

Five participants reported SAEs, i.e. 2 participants with nephrolithiasis (1 participant in the gefapixant 45 mg group and 1 participant in the placebo group), 2 participants calculus urinary (1 participant in the gefapixant 45 mg group and 1 participant in the placebo group), and 1 participant with ureterolithiasis in the placebo group.

Renal and urinary AEs that resulted in study intervention discontinuation were haematuria (1 participant in the gefapixant 15 mg and 1 participant in the placebo groups) and the SAE of ureterolithiasis (1 participant in the placebo group). One participant in the gefapixant 45 mg group

tested positive for gefapixant urinary crystals at the last study visit (Week 52); however, the concentration of gefapixant in a simultaneous PK plasma sample was below the limit of quantification. No adverse clinical sequelae attributable to urinary crystals were observed in this participant.

Pneumonia and Lower Respiratory Tract Infections

The potential for protective cough reflex suppression was reviewed by evaluating pneumonia and lower respiratory tract infection AEs. The overall incidence of AEs associated with pneumonia and lower respiratory tract infection was low (≤5%) in all intervention groups. The incidences of individual pneumonia PTs (atypical pneumonia, pneumonia, pneumonia bacterial, pneumonia staphylococcal, and pneumonia streptococcal) were low (≤1.5%) and comparable across the intervention groups. In all intervention groups, the incidences of lower respiratory tract infection and respiratory tract infection were low (<3.0%) and comparable. Pneumonia SAEs were reported by 6 participants in the gefapixant 15 mg group, 1 participant in the gefapixant 45 mg group, and none in the placebo group. Respiratory tract infection SAEs were reported in 1 participant in the gefapixant 15 mg group and 1 participant in the placebo group (Table 51).

Table 51 Subjects with pneumonia and lower respiratory tract infections adverse events (incidence > 0% 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 pneumonia and lower respiratory tract infections	22	(3.3)	34	(5.0)	29	(4.2)
with no pneumonia and lower respiratory tract infections	653	(96.7)	652	(95.0)	654	(95.8)
Infections and infestations*	**22**	**(3.3)**	**34**	**(5.0)**	**29**	**(4.2)**
Atypical pneumonia	0	(0.0)	1	(0.1)	0	(0.0)
Lower respiratory tract infection	9	(1.3)	18	(2.6)	12	(1.8)
Pneumonia	5	(0.7)	6	(0.9)	10	(1.5)
Pneumonia bacterial	0	(0.0)	2	(0.3)	0	(0.0)
Pneumonia staphylococcal	0	(0.0)	1	(0.1)	0	(0.0)
Pneumonia streptococcal	1	(0.1)	0	(0.0)	0	(0.0)
Respiratory tract infection	7	(1.0)	8	(1.2)	8	(1.2)

Every subject is counted a single time for each applicable row and column.
* Preferred terms for Lower respiratory tract infection viral and Respiratory tract infection viral were excluded.

Source: [ISS: adam-adsl; adae]

Hypersensitivity

To minimise the potential for hypersensitivity, participants with a history of anaphylaxis or cutaneous adverse drug reaction to sulphonamide antibiotics or other sulphonamide-containing drugs were excluded from Studies P027 and P030.

The overall incidence of hypersensitivity AEs was low and comparable across intervention groups, 5.6% in the gefapixant 45 mg group, 3.6% in the gefapixant 15 mg group and 5.6% in the placebo group. The individual incidences of these specific AEs suggestive of hypersensitivity were low (<2.5%) and comparable across the intervention groups, except for minor differences in gastro-intestinal events (swollen tongue, lip swelling) and urticaria in disfavour for gefapixant 45 mg. Drug-related events of hypersensitivity occurred at a slightly higher rate in the gefapixant 45 mg group (2.0%) compared to placebo (1.3%). None of the events was reported as severe or serious in the gefapixant group while

one serious/severe event of facial oedema in the placebo group. No events of anaphylaxis/anaphylactic event were reported.

Table 52 Subjects with adverse events suggestive of hypersensitivity (incidence > 0% 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 suggestive of hypersensitivity adverse events	42	(6.2)	25	(3.6)	38	(5.6)
with no suggestive of hypersensitivity adverse events	633	(93.8)	661	(96.4)	645	(94.4)
Gastrointestinal disorders	**0**	**(0.0)**	**1**	**(0.1)**	**4**	**(0.6)**
Lip swelling	0	(0.0)	0	(0.0)	1	(0.1)
Swollen tongue	0	(0.0)	1	(0.1)	2	(0.3)
Tongue pruritus	0	(0.0)	0	(0.0)	1	(0.1)
General disorders and administration site conditions	**1**	**(0.1)**	**1**	**(0.1)**	**0**	**(0.0)**
Face oedema	1	(0.1)	1	(0.1)	0	(0.0)
Immune system disorders	**4**	**(0.6)**	**2**	**(0.3)**	**0**	**(0.0)**
Hypersensitivity	4	(0.6)	2	(0.3)	0	(0.0)
Skin and subcutaneous tissue disorders	**39**	**(5.8)**	**21**	**(3.1)**	**34**	**(5.0)**
Angioedema	1	(0.1)	0	(0.0)	1	(0.1)
Dermatitis	4	(0.6)	0	(0.0)	1	(0.1)
Dermatitis allergic	2	(0.3)	0	(0.0)	3	(0.4)
Drug eruption	0	(0.0)	1	(0.1)	1	(0.1)
Erythema multiforme	1	(0.1)	1	(0.1)	0	(0.0)
Pruritus	15	(2.2)	11	(1.6)	12	(1.8)
Rash	5	(0.7)	4	(0.6)	4	(0.6)
Rash macular	6	(0.9)	1	(0.1)	3	(0.4)
Rash maculo-papular	1	(0.1)	1	(0.1)	0	(0.0)
Rash papular	4	(0.6)	1	(0.1)	4	(0.6)
Rash pruritic	0	(0.0)	0	(0.0)	1	(0.1)
Rash vesicular	1	(0.1)	1	(0.1)	0	(0.0)
Urticaria	3	(0.4)	1	(0.1)	10	(1.5)
Urticaria papular	0	(0.0)	0	(0.0)	1	(0.1)

Every subject is counted a single time for each applicable row and column.

Source: [ISS: adam-adsl; adae]

2.5.8.3. Serious adverse event/deaths/other significant events

Serious adverse events: The overall incidence of SAEs was low (≤6.0% in all intervention groups) and comparable across intervention groups. SAEs reported in ≥2 participants in either the gefapixant group or placebo group are presented in Table 53. There were two SAEs (hypoglycaemia in the gefapixant 45 mg group and ureterolithiasis in the placebo group) considered to be related to study intervention by the investigator.

Table 53. Subjects with serious adverse events (incidence ⩾ 2 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	(%)
Subjects 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)**
Gastritis	2	(0.3)	0	(0.0)	0	(0.0)
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)
Pneumonia bacterial	0	(0.0)	2	(0.3)	0	(0.0)
Urosepsis	2	(0.3)	0	(0.0)	0	(0.0)
Injury, poisoning and procedural complications	**1**	**(0.1)**	**3**	**(0.4)**	**8**	**(1.2)**
Metabolism and nutrition disorders	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.3)**
Musculoskeletal and connective tissue disorders	**3**	**(0.4)**	**6**	**(0.9)**	**5**	**(0.7)**
Osteoarthritis	1	(0.1)	0	(0.0)	2	(0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3**	**(0.4)**	**5**	**(0.7)**	**2**	**(0.3)**
Nervous system disorders	**3**	**(0.4)**	**5**	**(0.7)**	**1**	**(0.1)**
Cerebrovascular accident	0	(0.0)	2	(0.3)	0	(0.0)
Psychiatric disorders	**2**	**(0.3)**	**1**	**(0.1)**	**1**	**(0.1)**
Renal and urinary disorders	**3**	**(0.4)**	**2**	**(0.3)**	**3**	**(0.4)**
Reproductive system and breast disorders	**0**	**(0.0)**	**2**	**(0.3)**	**0**	**(0.0)**
Respiratory, thoracic and mediastinal disorders	**7**	**(1.0)**	**2**	**(0.3)**	**5**	**(0.7)**
Asthma	2	(0.3)	1	(0.1)	1	(0.1)
Cough	0	(0.0)	0	(0.0)	2	(0.3)
Laryngeal stenosis	2	(0.3)	0	(0.0)	0	(0.0)
Vascular disorders	**2**	**(0.3)**	**3**	**(0.4)**	**2**	**(0.3)**

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.

Source: [ISS: adam-adsl; adae]

Deaths: Four deaths occurred in the 2 studies in the P027/P030 Pool. 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 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 was related to study intervention by the investigator.

2.5.8.4. Laboratory findings

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 haematology measurements across intervention groups. Although a small percentage (<1%) of participants tested negative for urinary crystals at baseline and subsequently tested positive at Week 52, there were no clinically important shifts in participants from baseline to Week 52. The incidences of laboratory findings that met predetermined criteria were low (<12%), and individual incidences were generally comparable across intervention groups.

No participant met the criteria of an elevated ALT or AST ≥3x ULN, an elevated total bilirubin ≥2x ULN, and an alkaline phosphatase <2x ULN.

There were no clinically meaningful findings in the P027/P030 Pool in vital sign measurements (blood pressure, temperature, respiratory rate, heart rate) or weight. Observations were comparable across intervention groups.

2.5.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.5.8.6. Safety in special populations

AEs and demographics were summarised for the following subgroups: gender, region (North America, Europe, Asia-Pacific, others), age groups, duration of cough (<10 years, ≥10 years), baseline Cough Severity VAS (<60 mm, ≥60mm), baseline 24-hour coughs per hour (<20 coughs per hour, ≥20 coughs per hour), and primary diagnosis (RCC, UCC). At the request of a health authority, post hoc analyses of AE summaries and corresponding demographics were conducted in additional age groups (≤40 years, 41 to <65 years), additional regions (US, ex-US), race, and BMI (<25 kg/m2, 25 to <30 kg/m2, ≥30 kg/m2). Participants age <65 years account for the majority of the participants in the P027/P030 safety pool. The incidence of AEs in that age group were comparable to or lower than the incidence in younger participants except for AEs leading to discontinuation. The incidence of events leading to discontinuation in adults age 75-84 years (35%) was higher compared to adults age 65-74 years (27.9%) and <65 years (22.6%).

Table 54 Subjects with adverse events by age group MK-7264 45 mg BID safety pool across P027 and P030 over the period of 52 weeks; all subjects as treated

	MK-7264 45 mg BID							
	Age <65		Age 65-74		Age 75-84		Age 85+	
	n	(%)	n	(%)	n	(%)	n	(%)
Total AEs	**393**		**172**		**40**		**2**	
Serious AEs - Total†	**18**	**(4.6)**	**17**	**(9.9)**	**2**	**(5.0)**	**1**	**(50.0)**
- Fatal	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
- Hospitalization/prolong existing hospitalization	17	(4.3)	15	(8.7)	1	(2.5)	1	(50.0)
- Life-threatening	1	(0.3)	4	(2.3)	1	(2.5)	0	(0.0)
- Disability/incapacity	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
- Other (medically significant)	2	(0.5)	1	(0.6)	0	(0.0)	0	(0.0)
AE leading to drop-out‡	**89**	**(22.6)**	**48**	**(27.9)**	**14**	**(35.0)**	**0**	**(0.0)**
Psychiatric disorders	**22**	**(5.6)**	**11**	**(6.4)**	**1**	**(2.5)**	**0**	**(0.0)**
Nervous system disorders	**305**	**(77.6)**	**136**	**(79.1)**	**26**	**(65.0)**	**1**	**(50.0)**
Accidents and injuries††	**52**	**(13.2)**	**24**	**(14.0)**	**3**	**(7.5)**	**0**	**(0.0)**
Cardiac disorders	**8**	**(2.0)**	**5**	**(2.9)**	**0**	**(0.0)**	**0**	**(0.0)**
Vascular disorders	**15**	**(3.8)**	**6**	**(3.5)**	**1**	**(2.5)**	**0**	**(0.0)**
Cerebrovascular disorders‡‡	**0**	**(0.0)**	**1**	**(0.6)**	**0**	**(0.0)**	**0**	**(0.0)**
Infections and infestations	**206**	**(52.4)**	**90**	**(52.3)**	**18**	**(45.0)**	**1**	**(50.0)**
Anti cholinergic syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Quality of life decreased	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	**26**	**(6.6)**	**13**	**(7.6)**	**3**	**(7.5)**	**0**	**(0.0)**
Sum of other AEs appearing more frequently in older patients†	**1**	**(0.3)**	**0**	**(0.0)**	**11**	**(27.5)**	**1**	**(50.0)**
- Actinic keratosis	0	(0.0)	0	(0.0)	1	(2.5)	0	(0.0)
- Blood urine present	0	(0.0)	0	(0.0)	1	(2.5)	0	(0.0)
- Duodenal ulcer haemorrhage	0	(0.0)	0	(0.0)	1	(2.5)	0	(0.0)
- Frequent bowel movements	0	(0.0)	0	(0.0)	1	(2.5)	0	(0.0)
- Haemangioma of skin	0	(0.0)	0	(0.0)	1	(2.5)	0	(0.0)
- Haemorrhagic erosive gastritis	0	(0.0)	0	(0.0)	1	(2.5)	0	(0.0)
- Helicobacter infection	0	(0.0)	0	(0.0)	2	(5.0)	0	(0.0)
- Hypothyroidism	1	(0.3)	0	(0.0)	1	(2.5)	1	(50.0)
- Leukopenia	0	(0.0)	0	(0.0)	0	(0.0)	1	(50.0)
- Mastication disorder	0	(0.0)	0	(0.0)	1	(2.5)	0	(0.0)
- Neutrophil count decreased	0	(0.0)	0	(0.0)	1	(2.5)	0	(0.0)
- Oesophageal candidiasis	0	(0.0)	0	(0.0)	1	(2.5)	0	(0.0)
- Periodontitis	0	(0.0)	0	(0.0)	1	(2.5)	0	(0.0)
- Pulmonary fibrosis	0	(0.0)	0	(0.0)	1	(2.5)	0	(0.0)
- Retinal vein occlusion	0	(0.0)	0	(0.0)	1	(2.5)	0	(0.0)
- Solar lentigo	0	(0.0)	0	(0.0)	1	(2.5)	0	(0.0)
- Urethral polyp	0	(0.0)	0	(0.0)	1	(2.5)	0	(0.0)
- Vaccination complication	0	(0.0)	0	(0.0)	1	(2.5)	0	(0.0)
- Vaccination site reaction	0	(0.0)	0	(0.0)	1	(2.5)	0	(0.0)

Every subject is counted a single time for each applicable row and column.

† Subjects may be counted more than once in any of the sub categories.

‡ AEs leading to drop-out include Abdominal pain, Abdominal pain upper, Ageusia, Arthralgia, Bronchitis, Burning sensation, Chest discomfort, Choking sensation, Chronic gastritis, Cough, Croup infectious, Decreased appetite, Depressed mood, Diarrhoea, Dizziness, Drug intolerance, Dry mouth, Dry throat, Dysarthria, Dysgeusia, Dysphagia, Dyspnoea, Ear discomfort, Feeling abnormal, Gastritis, Gastrooesophageal reflux disease, Headache, Hot flush, Hyperchlorhydria, Hypoacusis, Hypoaesthesia, Hypoaesthesia oral, Hypogeusia, Increased viscosity of bronchial secretion, Insomnia, Malaise, Migraine, Muscle spasms, Musculoskeletal chest pain, Nausea, Neck pain, Neuritis, Oesophageal candidiasis, Pain in extremity, Paraesthesia, Paraesthesia oral, Pertussis, Pharyngeal hypoaesthesia, Pharyngeal paraesthesia, Pharyngeal swelling, Pulmonary fibrosis, Rash, Salivary hypersecretion, Sensation of foreign body, Skin discolouration, Spinal meningioma benign, Taste disorder, Throat irritation, Tinnitus, Tongue coated, Tongue discomfort, Tongue pruritus, Transaminases increased, Urticaria, Vertigo, Vitamin D deficiency, Vomiting, Weight decreased.

†† The system organ class term of Injury, poisoning and procedural complications is used.

‡‡ AEs for cerebrovascular disorders are included under the high level group term of central nervous system vascular disorders.

The incidences of all AE summary measures across intrinsic factor subgroups, including gender, age group, duration of cough, baseline Cough Severity VAS, baseline 24-hour coughs per hour, and primary diagnosis, were generally comparable to the overall study population. In addition, analyses for additional intrinsic factors, including race, BMI, summarised *post hoc* based on a health authority request, were generally comparable to the overall study population.

Use in Pregnancy and Lactation

In the P027/P030 Pool, 2 participants (1 in the gefapixant 45 mg group and 1 in the gefapixant 15 mg group) discontinued study intervention due to pregnancies. Both full-term pregnancies resulted in live births. No congenital or other abnormalities were reported.

2.5.8.7. Immunological events

Not applicable.

2.5.8.8. Safety related to drug-drug interactions and other interactions

In vitro and clinical data indicate a low potential for gefapixant to be a victim or perpetrator of DDIs.

2.5.8.9. Discontinuation due to 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. The most frequently reported AEs leading to discontinuation of study intervention (>3% in any intervention group) were dysgeusia and ageusia. Taste-related AEs are discussed further under AESI. Participants treated with gefapixant 45 mg who discontinued because of an adverse event (n=151 (22%)), had a somewhat longer duration of cough 9 years (2-56 y) *vs* 7 years 2-65y), a lower mean weakly cough severity VAS score < 60mm (38% *vs* 27%) and lower baseline cough values (median 16.71 *vs* 19.88) compared to participants treated with gefapixant 45 mg who did not discontinue due to adverse event (n=532 (88%)).

In the participants with a taste disorder, the data show that a slightly higher proportion of UCC than RCC patients treated with gefapixant 45 mg treated experienced a taste disorder and prematurely left the trial (17.4% *vs* 11,2%). The patients that prematurely left had also signs of less severe disease as shown by a lower median cough count (15.33 (1-102) *vs* 21.95 (0-386 coughs/h) and lower proportion of VAS score > 60mm (61 *vs* 71%). The gefapixant 45 mg treated patients who left the study because of taste related adverse events also experienced a more frequently AEs of moderate (n=59 (62%) *vs* n=82 (23%)) or severe intensity (n=10 (10%) *vs* n=7 (2%)) compared to those who remained in the study.

2.5.8.10. Other important safety aspects

Impact on quality of life

In a 12-week study, Study P012, participants were asked, "How likely would you be to take this medication in reference to each a time frame. Thirty-four of 57 subjects (59.6%) receiving MK-7264 50 mg BI dose were extremely likely to take study treatment for 4 weeks, and 54.4% of the subjects for at least 6 months to 1 year. The incidence of taste-related AEs in P012 participants treated with gefapixant 50 mg was 81%.

In the Phase 3 – P027/P030 Pool, the acceptability questionnaire was not used. Instead, the quality of life of the participants can be assessed through the evaluation of the sequalae of taste disorder in participants with and without taste-related AEs.

The overall incidence of AEs suggestive of weight loss and dehydration in participants with taste-related AEs treated with gefapixant was low (<5%), with the incidence of decreased appetite reported higher in the placebo arm (8.5%) compared to gefapixant 45 mg (4.7%) and gefapixant 15 mg (2.5%). This was supported by quantitative measures of weight, BUN and creatinine. There was no difference between participants with and without taste-related AEs treated with gefapixant.

Participants with taste-related AEs treated with gefapixant remained in the study at rates similar to those without taste-related AEs. The majority of participants with taste-related AEs did not discontinue due to their AE, and participants who did discontinue reported higher intensities of taste-related AEs than those who did not discontinue. Among the participants treated with gefapixant 45 mg, the incidences of study completion for participants with and without taste-related AEs were 79.9% *vs* 77.5%, respectively.

Experience from Phase I and Phase II

Phase I

The overall incidence of AEs in the Phase 1 programme was higher in the gefapixant group (63.1%) compared to the placebo group (44.7%). The most frequently reported AEs (≥5% participants) in the gefapixant group compared with the placebo group, were dysgeusia (34.7% and 1.3%, respectively), headache (12.0% and 3.9%, respectively), dry mouth (7.5% and 1.3%, respectively), paraesthesia oral (7.5% and 0.0%, respectively), hypoaesthesia oral (6.1% and 1.3%, respectively), nausea (5.4% and 1.3%, respectively), and hypogeusia (5.2% and 0.0%, respectively). Three participants in the gefapixant group and 1 participant in the placebo group discontinued study intervention due to an AE. Study intervention-related AEs were higher in the gefapixant group (59.6%) compared with the placebo group (32.9%). The most frequently reported study intervention-related AEs (≥5% participants) in the gefapixant group compared with the placebo group, were dysgeusia (34.5% and 1.3%, respectively), headache (9.6% and 3.9%, respectively), paraesthesia oral (7.5% and 0.0%, respectively), dry mouth (7.3% and 1.3%, respectively), hypoaesthesia oral (5.9% and 0.0%, respectively), and hypogeusia (5.2% and 0.0%, respectively). No deaths or SAEs occurred in the Phase 1 programme.

Specific adverse events: Pollakiuria was observed in 17 subjects (4.0%) in the gefapixant group and in 0 subjects in the placebo group. Events in the SOC eye disorders were higher in gefapixant compared to the other groups, 2.8% 1.9% and 0% for gefapixant, gefapixant + other and placebo, respectively. Within the two groups, the incidences of the adverse events (AEs) of ocular hyperaemia and vision blurred were reported most frequently (0.7% to 0.9%), but in total, only 4 participants per event.

Events in the SOC Respiratory, thoracic and mediastinal, are also higher in the gefapixant group compared to the other groups, 9.9% 3.7% and 6.6% for gefapixant, gefapixant + other and placebo, respectively. Most frequent were cough (3.1), dry throat (2.8) and throat irritation (2.1%).

Chocking sensation occurred in 1 subject in the gefapixant group.

Phase II

The AEs were summarised by gefapixant total daily dose (<100 mg TDD or ≥100 mg TDD) and placebo. Phase 2 AEs were further summarised by participants with chronic cough and participants with indications other than chronic cough (including healthy participants). The incidence of AEs overall was higher in the ≥100 mg TDD group (94.7%) compared with the gefapixant <100 mg TDD (78.2%) and placebo groups (56.4%). Study intervention-related AEs were higher in the ≥ 100 mg TDD group (90.4%) compared with the gefapixant <100 mg TDD (48.2%) and placebo groups (26.5%). Discontinuations due to AEs and discontinuations due to study intervention-related AEs were higher in the ≥100 mg TDD group (16.1% and 14.9%, respectively) compared with the gefapixant <100 mg

TDD (3.6% and 3.0%, respectively) and placebo groups (2.7% and 1.3%, respectively). The incidences of SAEs and study intervention-related SAEs were low and balanced across the intervention groups. There were 2 SAEs with fatal outcomes, both from Study P016, a study in participants with persistent cough due to IPF. One participant in the gefapixant ≥100 mg TDD group with a medical history of chronic respiratory failure, end-stage interstitial pneumonia, and IPF died due to acute respiratory failure; this SAE was considered possibly related to study intervention by the investigator. One participant in the placebo group died due to pneumonia; this SAE was considered not related to study intervention by the investigator.

Specific adverse events: Apart from the adverse events that were already identified in phase I, events that were higher in gefapixant < 100 mg total daily dose and gefapixant ≥ 100 mg total daily dose compared to placebo are urine output decreased, decreased appetite, cough and dry throat/throat irritation.

2.5.8.11. Post marketing experience

Not applicable, since the product has not been authorised in the EU.

2.5.9. Discussion on clinical safety

The gefapixant clinical programme comprised 2413 participants who received at least 1 dose of gefapixant in the completed Phase 1 and Phase 2 clinical studies and in pivotal studies P027 and P030 (P027/P030 Pool). The P027/P030 Pool offers extensive safety pool of 2044 participants who received at least 1 dose of study drug, of which 683 patients received gefapixant 45 mg for ≥ 52 weeks. The safety and tolerability assessment for the gefapixant chronic cough is mainly based on the P027/P030 Pool. The mean and median duration was close to 52 weeks in 2044 participants in the P027/P030 Pool. Sufficient number of patients were included to comply with the requirement of ICH1.

P027/P030 Pool

A substantially higher proportion of participants were female (74.7%). However, the female predominance is consistent with the affected population of RCC and UCC patients in real-world and the safety data are reliable and generalisable given the generally similar safety profile between both genders.

The overall incidence of AEs was higher in the gefapixant 45 mg group than the gefapixant 15 mg and placebo groups. The majority of the AEs were mild or moderate; the frequency of severe AEs was highest in the gefapixant 45 mg group (8.1%). The incidences of severe AEs across the system organ classes (SOCs) by treatment arm were low (<3.5%). The SOC for Nervous system disorder for gefapixant 45 mg was the only SOC with an incidence ≥1% for both severe (3.1%) and severe drug-related AEs (2.8%). Within that SOC, taste-related AEs were the primary driver for the higher incidences in the gefapixant groups. The imbalances in TEAEs are caused by the differences in dry mouth and nausea the SOCs Gastrointestinal disorders and ageusia, dysgeusia, hypogeusia and taste disorders in the SOC Nervous system disorders. Other frequently reported AEs in the gefapixant 45 mg group were nasopharyngitis and headache, but without a difference between the groups. However, in the phase 1 pool, intervention-related headache was higher.

A small, but stable trend of higher incidence of AEs in the SOC of Psychiatric disorders has been demonstrated for gefapixant exposed patients across all studies. Even if psychiatric disorders are mostly consequences of impaired QoL because of chronic cough, it does not explain the disbalance between the gefapixant group and the placebo group. Insomnia was the only preferred term with an incidence >1%. Also, insomnia was considered as related in the gefapixant group.

For the related TEAEs, the imbalance between groups was substantial, i.e., 68.8% for gefapixant 45 mg compared to 28.3% and 20.4% for gefapixant 15 mg and placebo, respectively. The drug-related adverse events that occurred more frequently in gefapixant 45 mg treated patients were ageusia, dysgeusia, hypogeusia and taste disorder, dry mouth, and nausea.

Taste disorder: Taste-related AEs were predefined as safety endpoints of special interest (AESI) based on the alleged mechanism of action of gefapixant. Overall, there was a consistent, dose-proportional increase in all events of taste-related items i.e., overall incidence, intensity, time to onset, time of duration, sequelae and discontinuation. Many taste-related AEs were mild or moderate; 2.5% of taste-related AEs were severe. Within 1 week of receiving study intervention, approximately 50% of participants in the gefapixant 45 mg group had a taste-related AE with a median time of onset of 2 days. The mean duration of any taste-related AE was longer in the gefapixant 45 mg group, i.e., 203.9 days. The highest percentage of taste-related AEs was reached at > 4 to ≤ 8 weeks.

In 96.0% of the participants in the gefapixant 45 mg group who experienced taste-related AEs resolved during treatment or after discontinuation of treatment, while in 2.2% of the subjects in population (3.4% of the patients with a taste disorder), the event was ongoing (unresolved).Even more taste-related AEs were resolved per 14 Dec 2021, i.e. 6 participants in placebo group (0.9%), 5 participants in gefapixant 15 mg group (0.7%), and 7 participants gefapixant 45 mg group (1.0%) had ongoing taste-related AEs. Thus, the resolving of taste related AEs can take quite a while after discontinuation of the treatment. The prolonged duration of the taste disorder might be of concern, as it may impact the quality of life. However, no clear difference between the treatment groups could be observed in the potential sequelae of taste-related AEs (weight decreased, abnormal weight loss, dehydration thirst). Furthermore, the impact of taste-related AEs on quality of life was not assessed in the studies P027 and P030. However, the acceptability of the drug was measured in the 12-week acceptability study (study P012) in subjects with RCC. The results suggested that the taste-related events did not negatively affect the acceptability of the drug.
Furthermore, it is considered important to be informed whether a specific patient group can be identified that is more at risk to develop a persistent taste disorder. When comparing the baseline characteristics of participants with long-lasting taste disorder, females, participants with UCC and patients with VAS ≥ 60 treated with gefapixant appeared to be more likely to have a long-lasting taste disorder. However, the small numbers of participants with ongoing taste-related AE make it difficult to draw meaningful conclusions.

It was not possible to give a recommendation on discontinuation and restarting of treatment, as there is no experience in the clinical programme with intermittent or temporary discontinuation or dose reduction. Therefore, this is up to the opinion of the health professionals as part of their clinical care. However, a warning in section 4.4 of the SmPC and description in 4.8 of the SmPC are warranted to inform the healthcare professional and the patient about the possibility of a long-lasting taste disorder. Further follow-up of these patients is also considered necessary (recommendation).

A comparison for participant with a positive effect, defined as ≥30% reduction from baseline in 24-hour coughs per hour or ≥1.3 point increase from baseline in LCQ Total Score according to presence or absence of taste disorder, revealed an association between the efficacy and the presence of a taste disorder. This occurs also in the subgroup with baseline cough count < 20 cough/h. However, all the analyses used the data of subjects who had an efficacy value thus missing out the subject who discontinued early. These subjects could have experienced an AE but could not experience (yet) a benefit. Thus, the results should be interpreted with caution because they may overestimate the difference between the patients with and without AE.

When regarding the severity of the disease, as defined by cough count and VAS, subgroup analyses showed that subjects with a lower cough count (< 20 cough/h) or VAS score (< 60 mm) had a higher

discontinuation rate and a higher discontinuation rate due to taste related adverse events compared to their complementary subgroups of patients with cough count ≥ 20 cough/h or VAS ≥ 60 mm. This suggests that subjects with more severe disease tolerate the taste related side effects better. However, the differences between complementary subgroups are too small to be conclusive.

The incidences of AEs representing potential clinical sequelae of taste-related AEs, including weight decreased, abnormal loss of weight, dehydration, and thirst, were low (<1.5%) across the intervention groups but highest in gefapixant 45 mg. Deceased appetite was somewhat higher with 1.7% in the gefapixant 45 mg group. Blood urea increased was reported only in the gefapixant 15 mg group (0.1%). In addition, patients with and without a taste disorder in the P027/P030 pool were analysed for measures of sequelae, such as decreased appetite, weight decreased, dehydration, or thirst. However, these parameters are only a very indirect measure of the quality of life by a taste disorder. There was not a clear trend shown in these expected sequelae. However, in the group of participants with a taste disorder, the incidence of discontinuation was higher in the gefapixant 45 mg than in placebo.

In the off-treatment Durability Studies, only three subjects with ongoing taste-related AEs were included. However, no additional information is available on these subjects.
Altogether, it would have been helpful to identify patients who will likely develop a taste disorder or a persistent taste disorder or who will discontinue.

Oral paraesthesia and hypoaesthesia: As one of the prespecified safety endpoints, frequencies of paraesthesia oral and hypoaesthesia oral were low, with the highest frequency in the gefapixant 45 mg, i.e., for hypoaesthesia oral and for paraesthesia oral 2.2%. The taste disorders occurred concomitantly with oral paraesthesia/hypoaesthesia and appeared to be associated.

Renal and urological events: These events were reviewed based on preclinical observations that gefapixant can cause damage to the kidney, ureter and bladder. Crystalluria was more frequently observed in female than in male animals, and a risk on stones was observed. The precipitation of crystals was explained by the applicant as likely due to a combination of minimal solubility of gefapixant at physiological urine pH, the primary excretion of gefapixant in the kidney and the fact that chemical structure contains sulphonamide moiety.

In the P027/P030 pool, the incidence of specific renal and urinary AEs was 4.8% in the gefapixant 45 mg group, 5.8% in the gefapixant 15 mg group and 4.6% in the placebo group. The individual incidences of haematuria, crystalluria and urolithiasis PTs were low (<3.0%) in all intervention groups. Haematuria was higher in the gefapixant groups (2.9%) than in the placebo group (1.9%). The pattern for calculi is diverse, but the total number appears to be increased for gefapixant compared to placebo. A total of 5 participants reported SAEs, nephrolithiasis, and calculus urinary each in 1 participant in the gefapixant 45 mg, calculus urinary in 1 participant in the gefapixant 15 mg groups, and nephrolithiasis and ureterolithiasis each in 1 participant in the placebo group.
Specialised urine crystal analysis for the identification of MK-7264 crystals was positive in one participant in the gefapixant 45 mg group on one occasion without any reported AEs potentially attributable to urinary crystals. The frequency of the stones was not higher than in the general population (5%). However, the study population is not considered fully representative for the occurrence of crystalluria and nephrolithiasis because of the higher number of females (74.7%), as the incidence of nephrolithiasis is higher in males than females above 40 years. Altogether, there were no clear signals for the presence of specific renal and urinary AEs but given the higher number of stones for gefapixant compared to placebo and the risk of severe clinical sequela of stones, the inclusion of these adverse reactions in the SmPC is warranted.

Protective cough reflex suppression: The cough reflex is necessary as protection against infections, and suppression may cause serious health risks. The mode of action is not fully explained, and a negative effect on the bronchial drainage and cough cannot be excluded in patients with an acute respiratory tract infection. The potential for protective cough reflex suppression was reviewed by evaluating pneumonia and lower respiratory tract infection AEs.

The incidence of pneumonia and lower respiratory tract infection AEs was considered slightly increased in the gefapixant 45 mg group (4.2%), and in the gefapixant 15 mg group (5.0%) compared to the placebo group (3.3%). Moreover, pneumonia as a SAE was reported in 6 participants in the gefapixant 15 mg group compared to 1 participant in the gefapixant 45 mg group and none in the placebo group Further analyses could not identify a specific patient group that was more at risk to develop pneumonia and URTI during the use of gefapixant. As most of the events of pneumonia and LRTI occurred within the first 24 weeks, this is rather a general risk than a risk that can be prevented by limiting the duration of treatment. Against this background, a warning that the treatment regimen should be evaluated and should be individualised for each patient with an acute respiratory infection is proposed to be included in section 4.4. of the SmPC.
As an unexpected finding, cough as an AE, was highest in the MK-7264 45 mg. For inclusion of cough as an AE in the trials, the reported event of cough as an AE had to have included one of the terms 'worsening', exacerbation', 'increase' or 'increased' in the narrative indicative for a change in cough. Given the presence of these adverse events in the Phase I studies in healthy volunteers, it is accepted that cough is an adverse event of gefapixant.

Hypersensitivity and anaphylaxis: Gefapixant contains a sulfonamide moiety, although it is considered to be a non sulfonylarylamine. Specific attention was given to AEs of hypersensitivity because of potential cross-reactivity with sulfonamide-containing drugs. Based on the current understanding of the pathogenesis of sulfonylarylamine adverse reactions, non-sulfonylarylamines and other sulfonamide moiety–containing drugs do not share the same risk on a chemical or metabolic basis even though the clinical presentation may appear to be similar. Nevertheless, participants 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 because of the risk of an allergic reaction based on cross-reactivity between gefapixant and sulfonamide antibiotics. The individual incidences of specific AEs suggestive of hypersensitivity were low (<2.5%) and comparable across the intervention groups, except for minor differences. No events of anaphylaxis/anaphylactic event were reported. However, as participants with sulfonamide allergy were excluded in the phase III trials, the hypersensitive reaction caused by gefapixant in the trials are not representative for patients with sulfonamide allergy.

SAEs and deaths: Four deaths occurred in the 2 studies in the P027/P030 Pool. None of the deaths was considered to be related to study intervention by the investigator. The overall incidence of SAEs was low (≤6.0% in all intervention groups) and comparable across intervention groups. Two SAEs were considered to be related to study intervention by the investigator, i.e., hypoglycaemia in the gefapixant 45 mg group and ureterolithiasis in the placebo group.

Discontinuation: 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. Adverse events by treatment arm with an incidence of ⩾ 1% leading to discontinuation were dysgeusia, ageusia, taste disorder, cough, and nausea. The comparison of the baseline characteristics of the gefapixant treated patient who prematurely left because of a taste related adverse event compared to those who remained in the trial despite a taste related event showed that a slightly higher proportion of patients UCC than RCC prematurely left the trial because of adverse event (48% *vs* 40%).

Laboratory results: Overall, there were no notable differences in mean changes over time in chemistry and haematology measurements across intervention groups. In the additional shift tables, there were no relevant differences between the groups, except for haematocrit, i.e., an increase in both gefapixant groups (13.8% and 11.2%) compared to placebo (9.5%). Furthermore, 'Haematocrit increased' was more often reported as an AE, i.e., for gefapixant twice (0.3%), while for placebo none. Although other parameters indicative for the presence of dehydration did not show any sign of dehydration, the haematocrit is a sensitive and early parameter.

Safety in special populations

Participant's age <65 years account for the majority of the participants in the P027/P030 safety pool. The incidence of AEs in that age group were comparable to or lower than the incidence in younger participants except for AEs leading to discontinuation, that was highest in adults age 75-84 years (35%). This could imply that the participant in this age group was rather less willing to accept the adverse event than that the events were more serious, as the incidence of serious events was quite similar with the age group > 65 years. In the age group 65-74 years, hospitalisations were more frequent. It is not likely, that these events were related.

Phase I: In the phase I study, 19 patients with moderate to severe OSA who were not using PAP, gefapixant 180 mg QHS compared to placebo was associated with a lower mean SaO2 and a higher proportion of time with SaO2 <90% across all sleep stages, but no difference in the Apnea/Hypopnea Index (AHI), which was the primary endpoint. Approximately 6% of participants within the P027/P030 Pool reported a medical history of sleep apnoea syndrome or apnoea. As the effects of gefapixant on SaO_2 have not been evaluated in the Phase 3 programme, a warning is included in section 4.4 of the SmPC that gefapixant should be used with caution in patients with RCC or UCC with untreated comorbid OSA.

From the safety database all adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.5.10. Conclusions on the clinical safety

Gefapixant administered at 15 mg BID and 45 mg BID in adults with RCC or UCC has a generally acceptable safety profile. There were no clear signals that suppression of the cough by gefapixant in patients with chronic cough is accompanied by suppression of natural airway protection against infections, while the clinical studies were long enough to detect such signals. As most of these events occurred within the first 24 weeks, it is acceptable to allow the use for an unlimited period of time at the decision of the prescriber, but additional warnings are included in the SmPC.

Taste-related AEs are the most frequently reported AEs in participants who receive gefapixant 45 mg BID and are dose-related. Within the taste-related AEs, ageusia and dysgeusia are the most important as it can be expected that they would affect the quality of life. However, *post-hoc* efficacy analyses indicated that patients with a taste related disorders experience a larger treatment effect, generally alleviating the concern of the impact on the quality of life by the taste disorder. No clear trend could be detected in the expected sequelae of a taste disorder, The taste-related AEs did not (yet) resolve in all subjects even after more than a year, which is a concern that these taste-related AEs are not 100% reversible. Follow-up information from patients with persistent taste disorders will be reported within PSURs in the post-authorisation phase.

Close review of renal and urological events, or hypersensitivity, did not show significant imbalances between treatment groups.

2.6. Risk Management Plan

2.6.1. Safety concerns

Summary of safety concerns

The applicant proposed the following summary of safety concerns in version 1.0 of the RMP:

Table 55 Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Progression of respiratory tract infections and risk of development of pneumonia
Missing information	Use in pregnancy and lactation Use in patients with comorbid obstructive sleep apnoea

Taste-related AEs are the most frequently reported AEs in participants who receive gefapixant 45 mg BID and are dose-related. Within the taste-related AEs, ageusia and dysgeusia are the most important as it can be expected that they would affect the quality of life. Although most events were mild or moderate, in a small proportion of the patients, i.e., 2.2% of the subjects in population (3.4% of the patients with a taste disorder), the event of taste disorder was ongoing (unresolved) even after more than a year. However, as this risk is already sufficiently characterised within the clinical trials and can be sufficiently minimised with routine risk minimisation measures it is accepted that this risk does not qualify for inclusion in the summary of safety concerns according to the principles outlined in GVP V rev 2.

In preclinical studies, it was observed that gefapixant can cause damage to the kidney, ureter and bladder, and urolithiasis. The individual incidences of the haematuria, crystalluria and urolithiasis PTs were low (<3.0%) in all intervention groups. In the safety pool of P027/P030, no specific risk for stones could be detected, as the frequency is not higher than in the general population (5%). It is accepted that urolithiasis is not included in the summary of safety concerns. Missing information included in the RMP refers to gaps in knowledge about the safety of a medicinal product for certainly anticipated utilisation or for use in particular patient populations. There is insufficient knowledge to determine whether the safety profile differs from that characterised so far.

As there are no data from the use of gefapixant in pregnant women and toxicological data in animals, have shown the excretion of gefapixant in breast milk, the safety profile of use in pregnancy and lactation cannot fully be established at this moment. The safety profile of gefapixant within these populations will be further characterised by routine pharmacovigilance activities. It is accepted that use in pregnancy and lactation is included as missing information.

'Patients with comorbid obstructive sleep apnoea' was included as missing information in the safety specifications. The relevance of higher proportion of time with SaO_2 <90% across all sleep stages in the 19 patients with moderate to severe OSA who were not using PAP is not clear but could be of importance. Effects of gefapixant on SaO_2 have not been evaluated in the Phase 3 programme.

It is agreed that 'severe renal impairment' is left out of the safety specifications. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2 OR eGFR ≥30 mL/min/1.73 m2 and <50 mL/min/1.73 m2 with unstable renal function were excluded. Elimination of gefapixant is primarily through renal

excretion. A Phase 1 study in 6 participants with severe renal impairment and 6 participants with end-stage renal disease (ESRD) confirmed that participants would be expected to have higher drug exposure, to the extent that might be clinically meaningful. Modelling of the effect of renal impairment on gefapixant PK, support the dosing recommendations for severe renal impairment.

Patients with a history of anaphylaxis or cutaneous adverse drug reaction to sulphonamide antibiotics or other sulphonamide containing drugs were excluded to avoid factors that may confound the evaluation of safety and efficacy in the trial. As a result, the safety profile of use in patients with an allergy to sulphonamide containing drugs cannot fully be established at this moment. However, the likelihood of a hypersensitivity reaction is considered low. The warnings and precautions section of the label includes information stating that gefapixant should be used with caution in patients with known hypersensitivity to sulphonamides is sufficient. No additional risk minimisation measures are warranted.

Gefapixant suppresses the cough reflex, but complete suppression of the cough reflex is dangerous as the lung is then deprived of an essential defence mechanism in case of respiratory tract infection. Overall, the frequency of pneumonia or lower respiratory tract infection was considered slightly increased compared to placebo. As gefapixant will be used chronically, (mild) respiratory tract infections might be missed, or symptoms might progress due to the suppression of the cough reflex. As this is a first in class molecule and the mechanism of action is not fully explained, the potential risk of progression of respiratory tract infections (incl. development of pneumonia) due to suppression of the cough reflex by gefapixant is not fully characterised and can have an impact on the risk benefit balance of the product if confirmed. This risk should be monitored *via* routine pharmacovigilance activities and cases of respiratory tract infections and pneumonia discussed in the PSURs. In line with GVP V rev 2, the CHMP considers that progression of respiratory tract infections and risk of development of pneumonia qualifies for inclusion in the summary of safety concerns as an important potential risk.

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities are proposed at the moment. The PRAC, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product. The PRAC also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

2.6.3. Risk minimisation measures

The SmPC submitted as part of the MAA already reflects the lack of data for "Use in pregnancy and lactation" in the relevant sections 4.6 and 5.3. Furthermore, gefapxiant will be a prescription only medicine. No further risk minimisation measures beyond routine are deemed necessary for the time being.

2.6.4. Conclusion

Currently, only routine risk minimisation measures are proposed by the applicant. If the post-marketing data should reveal any signals indicating the need for more information, appropriate additional measures will be requested. The PRAC considers that the risk management plan version 1.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list, and a new entry will be required. The new EURD list entry uses the IBD to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant requested an alignment of the PSUR cycle with the international birth date (IBD) of 20 January (first approval date in Japan in 2022).

2.8. Non-Conformity of paediatric studies

Not applicable.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Lyfnua (gefapixant) is included in the additional monitoring list as it contains a new active substance which was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

In the past, cough was only perceived as a clinical entity. Cough was considered only as a symptom from other respiratory disease. Nowadays, chronic cough is recognised as a specific disease entity.

Cough is a protective reflex to prevent aspiration into the lung and to enhance airway clearance. Cough can be voluntarily inducted, but also various peripheral mechanisms may be involved for eliciting chronic cough. However, 5-10% of the adult population has a pathologically excessive and protracted cough.

A cough that pertains for longer than 8 weeks in adults is considered being chronic cough. The evaluation of chronic cough starts with searching for a treatable disease. If these co-morbidities are treated, cough disappears in many patients The following comorbidities are associated with chronic cough: Asthmatic cough/eosinophilic cough, Reflux cough, Postnasal drip syndrome/upper airways cough syndrome or iatrogenic cough (use of ACE-inhibitors). However, a proportion of patients have a persistent cough despite thorough investigation and treatment according to the published practice guidelines. These patients have a:

1. Refractory Chronic Cough (RCC): if they have a cough-associated condition, but the conventional treatments do not work

2. Unexplained Chronic Cough (UCC): when no diagnosable cause for the cough has been found (despite extensive assessment for common and uncommon cases)

RCC and UCC may have a major effect on the quality of life as cough may interfere with social life. RCC and UCC may lead to in social isolation, interference with speech and depression. Such a risk will be increased if RCC and UCC are associated with co-morbidities such as incontinence, cough syncope and dysphonia.

3.1.2. Available therapies and unmet medical need

Currently, no authorised treatments exist for the treatment of RCC or UCC in the EU. When the initial treatment according to published practice guidelines (stop risk factors, start corticosteroids, leukotriene receptor antagonist (LTRA), proton pump inhibitors (PPI) does not result in improvement, other off-label treatment can be used, such as gabapentin, dextromethorphan, low-dose morphine and codeine or speech and language therapy (SLT). These off-label treatments are either associated with considerable side effects and/or have limited data to support their use.

3.1.3. Main clinical studies

The main evidence of gefapixant's efficacy derived from two almost identical phase 3 trials. Study P027 (n=732, main study 12 weeks) and P030 (n=1317, main study 24 weeks) were multicentre, double-blind, placebo-controlled parallel assignment intervention study evaluating the efficacy and safety of gefapixant 15 mg bid and 45 mg bid in adults with refractory chronic cough or unexplained chronic cough:

- Refractory chronic cough was defined as participants who have had a clinical evaluation that suggested a comorbid condition that may be related to cough (e.g., gastroesophageal reflux disease [GERD], asthma, or upper airway cough syndrome), the participant has received appropriate diagnostic work-up and therapy according to ACCP (American College of Chest Physicians guidelines), and the participant continues to cough.

- Unexplained chronic cough was defined as participants who have had a clinical evaluation of their cough per ACCP guidelines, and this evaluation has not suggested a comorbid condition that may be related to cough.

The main efficacy outcome was a change from baseline in (log-transformed) 24-hour coughs per hour (i.e., average hourly cough frequency based on 24-hour sound recordings) at Week 12 (P027) or week

24 (P030). Secondary outcomes include several patient-reported outcomes, such as the Cough Severity Diary (CSD), Cough Severity VAS and Leicester Cough Questionnaire. Study P030 includes identical objectives as for study P027, but the main efficacy treatment period is prolonged to 24 weeks to show durability of response. The study also included the PRO LCQ in the multiplicity testing hierarchy to support the clinical relevance of the reduction in cough frequency, and Study P030 was powered for the LCQ endpoint analysis.

Unlike the 45 mg dose, the 15 mg bid dose failed to show superiority over placebo over the primary efficacy parameter in both studies. Therefore, the efficacy appears to be insufficiently demonstrated for the low dose and the applicant applies for an indication for the high dose 45 mg only.

The cough count data set is provided with the integrated Vitalo JAK recording system using three different versions of compression algorithms to remove non-cough sounds from the recordings; a supportive cough count data set has also been provided based on one compression algorithm WHO3v3.0 i.e., the recount data set (see sections above).

3.2. Favourable effects

Pivotal studies

Primary outcome
In both pivotal studies, based on results from the MI + ANCOVA including the mITT population of treated patients, the 45 mg dose showed superiority over placebo in the estimated relative reduction in the number of coughs per 24 hours.

- In study P030, the estimated relative reduction at week 24 was -13.29 % (95% CI -24.74, -0.10); p = 0.048
- In study P027, the estimated relative reduction at week 12 was -18.52 % (95% CI -32.76, -1.28); p = 0.036

Secondary outcomes
Based on results from the MI+ANCOVA approach including the mITT population of treated patients, the 45 mg doses also showed a showed superiority over placebo in the estimated relative reduction of number of awake coughs at week 24 (study P30), and at week 12 for study P027

- In study P030, the treatment difference (estimated relative reduction) was -14.31 % (95% CI -25.95, -0.84), p=0.038
- In study P027, the treatment difference (estimated relative reduction) -18.33 % (95% CI -32, 95, -0.96) p=0.040

The 45 mg dose showed statistically significant improvements compared with placebo in the responder rate in the Leicester Cough Questionnaire (LCQ). In study P030, the difference reached statistical significance.

- In Study P030, this response rates for the LCQ were 75.7% and 68.1% respectively, the estimated absolute difference with placebo is 7.63% (95% CI 1.34, 13.76); the estimated odd ratio is 1.46 (1.07, 1.99) p=0.016
- In study P027, this response rate for the LCQ were 66.9 *vs* 61.7% respectively, with an estimated treatment difference with placebo of 5.25 % (95% CI not provided) at week 12. The estimated odds *vs* placebo ratio is 1.26 (95% CI 0.84, 1.89)

Additional supportive outcomes were provided by the increase in number of MK-45 mg patients compared to placebo showing an improvement in at least the minimal clinically relevant improvement

in the reduction of baseline cough rate (≥ 30%, ≥ 50% or ≥ 70%) or an improvement ≥ minimal clinically important difference in the Cough Symptom dairy or Cough severity VAS. After stopping, no rebound effect occurred. The use of gefapixant is not associated with abuse related signals such as reported for some other applied cough treatments.

All treatment analyses on both the original data and recount data show comparable outcome measures for the primary and key secondary outcome measures.

Supportive data for a treatment effect of gefapixant 50 mg are also shown by the two randomised, placebo-controlled studies phase II study MK7264-P010 and MK7264-P012, and the top-line results in two short term studies MK7264-P042 and MK 7264-P043 for 45mg BID.

3.3. Uncertainties and limitations about favourable effects

Methodological/ statistical

Despite the goal to collect outcome data after treatment discontinuation or use of prohibited medicine (for the treatment policy estimand strategy), not all participants had data available at all time points. Less than a third of participants in both studies had "off-treatment" data available after discontinuing treatment for the primary endpoint. Therefore, the initially provided analyses were not able to estimate the treatment effect under the pre-planned treatment policy estimand strategy. Analyses that account for all treated participants in the mITT population, and sensitivity analyses for the treatment policy estimand support a conclusion of a treatment effect. Analyses that target the hypothetical estimand strategy also suggest a stronger treatment effect under the (hypothetical) scenario where participants remained on allocated treatment.

The study did not include two co-primary endpoints for both an objective and subjective improvement in cough score. Only one pivotal trial was sufficiently powered to provide type I protected data for a subjective improvement, i.e., the difference in the responder rate in the LCQ ≥ 1.3. However, no clinically relevant difference with placebo was defined beforehand.

Methodological/statistical/ clinical

Concerns were raised by the CHMP during the assessment about the validation of the full VitaloJAK cough counting system. Although the VitaloJAK audio recording device has been FDA cleared as an audio-recording system, the overall integrated system of VitaloJAK audio recording, Web Portal, compression algorithm and cough count analyses is not. Upon request of the CHMP, the applicant provided results from 1) a study focused on the validation of the compression algorithm, 2) an Inter-rater reliability study of cough count analysts. These studies were performed using only one of the algorithms that was used in the two clinical studies: i.e., v3.0 compression algorithm with single channel processing. Based on the results from these studies, it was concluded that the full VitaloJAK cough counting system was valid for use in the clinical studies.

Just over 90% of the coughs in the original data were compressed using the two algorithms with dual channel processing, these cough recordings were re-compressed using WHO3.v3.0 compression algorithm with single channel processing. The recount data were analysed, and the set of results from these data are considered as supportive to the original data.

Although the two compression algorithms with dual channel processing were not part of the validation study, the results are considered to be sufficiently similar to support a decision to maintain the original data as the primary data source.

The currently provided subgroup analyses for the primary outcome of the original data set are not analysed according to the mITT (MI+NCOCA, but according to the longitudinal data for the full

analyses set; while for the LCQ subgroup analyses, invertedly adjusting is missed for the treatment status during the MI step.

More patients in the active treatment arm prematurely discontinued the trial than the placebo group. The difference with placebo in discontinuation rate was about 13% in the main phase and 15% for the total trial duration.

Unlike the phase II studies, both pivotal phase III studies showed a large and continuing placebo effect in both the objective and subjective outcome measures. The observed placebo effect exceeded the differences between treatment and placebo. The included patient population is heterogeneous and not selected on a reduced threshold during the ATP cough challenge test.

Except for RCC and UCC, the subgroups were not based on a distinct pathophysiological or pharmacological rationale, or distinct well-recognised distinct disease entities. No baseline characteristics could be identified to select a population that would most likely benefit.

Post-hoc provided subgroup analyses of the original data set suggested an association between the taste effects and the reduction in coughs and response to the LCQ, including the subgroup of patients with a baseline cough count< 20 cough/h.

3.4. Unfavourable effects

In the clinical development programme, 2,413 participants received at least 1 dose of gefapixant. In the pivotal studies (P027/P030 Pool) that included 2,044 participants, 683 patients received gefapixant 45 mg for ≥ 52 weeks. In this P027/P030 Pool, the overall incidence of the AEs was higher in the gefapixant 45 mg group compared to the gefapixant 15 mg and placebo groups. While the majority of the AEs were mild or moderate, the frequency of severe AEs was highest in the gefapixant 45 mg group (8.1%).

The imbalances in TEAEs are caused by the differences in AEs ageusia, dysgeusia, hypogeusia and taste disorder in the SOC Nervous system disorders, and dry mouth and nausea in the SOCs gastrointestinal disorders. Other frequently reported AEs (≥10% of participants) in the gefapixant 45 mg group were nasopharyngitis and headache, but without a difference between the groups. The incidences of all other AEs were generally balanced across both gefapixant groups and placebo groups. Similarly, for the related TEAEs, the imbalance between groups was substantial, i.e., 68.8% for gefapixant 45 mg compared to 28.3% and 20.4% for gefapixant 15 mg and placebo, respectively. The imbalance is mainly driven by an imbalance in taste disorders. The incidence of severe taste-related AEs was low (2.5%).

Taste related AE: There was a consistent, dose-proportional increase in all events of the taste-related AEs in overall incidence, intensity, time to onset, time of duration, sequelae and discontinuation. The onset of the event was fast and the duration longer: within 1 week approximately 50% of participants in the gefapixant 45 mg group had a taste-related AE, and the mean duration was longer in the gefapixant 45 mg group 203.9 days. All taste-related AEs resolved in 96.0% of the participants in the gefapixant 45 mg group, during treatment or after discontinuation of treatment. The incidences of AEs representing potential clinical sequelae of taste-related AEs, e.g., decreased appetite and thirst, were low (<1.5%) across the intervention groups but highest in gefapixant 45 mg.

Paraesthesia oral and hypoaesthesia oral: The frequencies of paraesthesia oral and hypoaesthesia oral were low but highest in the gefapixant 45 mg, i.e., for hypoaesthesia oral and for paraesthesia oral, 2.2%.

Renal and urological events: In preclinical studies, it was observed that gefapixant can cause damage to the kidney, ureter and bladder, and urolithiasis. The individual incidences of the haematuria, crystalluria and urolithiasis PTs were low (<3.0%) in all intervention groups; Specialised urine crystal analysis were identified in 1 participant in the gefapixant 45 mg group on one occasion.

Pneumonia and URTI: The incidence of pneumonia and lower respiratory tract infection AEs was balanced between treatments (4.2%). Serious events of pneumonia were higher in the gefapixant 45 mg group.

Hypersensitivity: The incidence of AEs suggestive of hypersensitivity was Comparable between the intervention groups. The individual incidences of these specific AEs suggestive of hypersensitivity were low (<2.5%) and generally comparable across the intervention groups. None were SAEs.

Cough: Cough as an AE was higher reported in the gefapixant 45 mg group than in the gefapixant 15 mg and placebo group.

Deaths and other SAE: Four deaths occurred in the P027/P030 Pool, of which two deaths occurred in the gefapixant 15 mg group and two deaths in the placebo group. None of the deaths was considered to be related to study intervention by the investigator. The overall incidence of SAEs was low (≤6.0% in all intervention groups) and comparable across intervention groups. Only a case of hypoglycaemia in the gefapixant 45 mg group and ureterolithiasis in the placebo group were related to study intervention by the investigator.

Discontinuation: Discontinuation because of an AE was higher in the gefapixant 45 mg group (22.1%) compared with the gefapixant 15 mg (8.0%) and placebo (5.8%) groups. Adverse events by treatment arm with an incidence of ≥ 1% leading to discontinuation were dysgeusia, ageusia, taste disorder, cough, and nausea. The gefapixant 45 mg treated patients that discontinue because of taste related adverse appeared to have a somewhat longer duration of cough (median 10 years *vs* 7 years), lower baseline cough count (<20 coughs/h) and lower baseline and VAS score (< 60) compared to the gefapixant treated patients that did not discontinue because of taste related adverse event. The proportion of UCC patients was also slightly higher. The gefapixant 45 mg treated patients that prematurely discontinued because of taste related adverse event, experienced more AEs of moderate (62% *vs* 23%) and severe intensity (10% *vs* 2%) compared to those who remained in the study.

Safety in special populations: Generally, the incidences of all AE summary measures were reasonably balanced between subgroups, including gender. Only AEs leading to discontinuation was higher in adults aged 75-84 years compared to other age groups (> 65, 65-74, 75-84, ≤ 85 years).

3.5. Uncertainties and limitations about unfavourable effects

Gefapixant suppresses the cough reflex, but complete suppression of the cough reflex is dangerous as the lung will be deprived of an essential defence mechanism in case of respiratory tract infection. Overall, the frequency of pneumonia or lower respiratory tract infection could be considered slightly increased compared to placebo, as most of these events occurred within the first 24 weeks, which cannot be prevented by limiting the duration of treatment. Further analyses could not identify a specific patient group that was more at risk to develop pneumonia and URTI during the use of gefapixant.

Taste disorders occurred frequently (65.4%). The quality of life is recognised to be affected by taste disorders like ageusia or dysgeusia, that can be seriously important. The impact on the quality of life of ageusia or dysgeusia by gefapixant is not measured in the pivotal 027 and 030 studies, but an acceptability assessment in the 12-week Study P012 did not show a difference between the patients

treated with gefapixant 50 mg BID and the placebo-treated patient. Furthermore, there was no difference between participants with and without taste-related AEs treated with gefapixant in the incidence of AEs suggestive of consequences of taste-related AE. In the P027/P030 pool, although the continuation of treatment seems reasonably re-assuring in the studies, it remains unsure how this effect on taste will impact the quality of life in real life. This adverse event will be monitored in the PSURs.

In some patients, 2.2% of the subjects in population (3.4% of the patients with a taste disorder), the event of taste disorder was ongoing (unresolved) even after more than a year. Hence, ongoing taste-related AEs could resolve during the or after the treatment discontinuation, still leaving 7 participants gefapixant 45 mg group (1.0%) with ongoing taste-related AEs per 14 DEC 2021 which was comparable to the placebo group (0.9%).

The frequencies of paraesthesia oral and hypoaesthesia oral were low. They appear to be associated with taste disorders. Although no serious crystalluria and nephrolithiasis related events were reported, the representativeness of these results can be questioned as the study population is not considered fully representative. The results of hypersensitivity reaction may be underrepresented, because participants 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. A small, but stable trend of higher incidence of AEs in the SOC of psychiatric disorders has been demonstrated for gefapixant exposed patients across all studies, which cannot be fully explained by impaired QoL. Insomnia was the only preferred term with an incidence >1% (and more frequently in the gefapixant treatment groups.

In the phase I study P039, in patients with moderate to severe OSA who were not using PAP, gefapixant 180 mg QHS compared to placebo was associated with a lower mean SaO2 and a higher proportion of time with SaO2 <90% across all sleep stages.

3.6. Effects Table

Table 56 Effects Table for gefapixant in the treatment of refractory and unexplained chronic cough (data cut-off: 17-SEP-2020, for the P027/P030 pool); data on the original data set, mITT population

Effect	Short Description	Unit	Gefapixant 45 mg	Gefapixant 15 mg	Placebo	Uncertainties/ Strength of evidence	Ref.
Favourable Effects							
Study P027			n = 242		n = 243		
Primary endpoint Coughs/Hour	Geometric Mean Ratio Wk 12/ Baseline		0.39 (0.34, 0.45)		0.48 (0.42, 0.55)	**SoE:** Results from MI + ANCOVA analysis The estimated relative reduction of 45 mg *vs* placebo: -18.52 % (95% CI (-32.96, -1.28), p=0.036; similar effect in Study 030 and Pool P027/P030. **Unc**: Not all participants continued to provide data after treatment discontinuation. Therefore, the extent to which this analysis approach estimates the treatment effect under the treatment policy estimand strategy remains uncertain. Sensitivity analyses support evidence of an effect.	P027
LCQ	Subjects with ≥ 1.3 points increase	%	66.9		61.7	Gefapixant 45 mg *vs* placebo: the estimated treatment difference is 5.25% (95% CI not provided) Estimated odds ratio *vs* placebo is 1.26 (0.84, 1.89)	
Study P030			n =439		n = 434		

Effect	Short Description	Unit	Gefapixant 45 mg	Gefapixant 15 mg	Placebo	Uncertainties/ Strength of evidence	Ref.
Primary endpoint Coughs/Hour	Geometric Mean Ratio Wk 24/ Baseline		0.37 (0.34, 0.42)		0.43 (0.39, 0.48)	**SoE:** estimated relative reduction of 45mg *vs* placebo: -13.29 (-24.74, -0.10); p = 0.048. **Unc**: Not all participants continued to provide data after treatment discontinuation. Therefore, the extent to which this analysis approach estimates the treatment effect under the treatment policy estimand strategy remains uncertain. Sensitivity analyses support evidence of an effect.	P030
LCQ	Subjects with ≥ 1.3 points increase	%	75.7		68.1	Gefapixant 45 mg *vs* placebo: the estimated treatment difference is 7.63% (95% CI 1.34, 13.76); the estimated odd ratio is 1.46 (1.07, 1.99) p=0.016.	
Unfavourable Effects							
Pooled P027/P030			n = 682	n = 686	n = 678		
Total taste related disorders			65.4%	17.5%	7%	Discontinued due to taste-related AE: 45mg: 95 (14%) 15mg: 9 (1%) Placebo: 2 (0.3%) Number of participants with ongoing taste disorders: 45mg: n=17 ; 15mg: n=7; Placebo: n=2	Pooled P027/P030
Persistent taste disorder	incidence	%	1.0%	0.73%	0.9%	Per 14 Dec 2021	
Nausea	Incidence	%	9.4	5.0	6.7		
Cough	Incidence	%	7.2	6.4	4.1		
Oropharyngeal pain	Incidence	%	5.4	3.8	4.3		

Effect	Short Description	Unit	Gefapixant 45 mg	Gefapixant 15 mg	Placebo	Uncertainties/ Strength of evidence	Ref.
Pneumonia/LRTI	Incidence	%	3.3	5.0	3.3		
Urolithiasis	Incidence	%	0.6	1.1	0.4	**Unc**: the population is not fully representative of real world	

Abbreviations: LRTI = lower respiratory tract infection, CSD = cough severity diary, LCQ = Leicester cough Questionnaire, VAS = visual analogue scale

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

During the assessment, two different sets of data (originally provided and recount validated cough count data set) and results based on different methods of analyses were provided. The results provide a consistent signal of a modest treatment effect on top of a large placebo response in a population with a long history of chronic cough, i.e., > 10 years in both the original and recount data set.

Favourable effects

Both studies met their objective primary endpoint, the reduction in the cough/h during 24 h, in a patient population with cough duration of chronic cough > 10 years in both studies. The clinical relevance of the reduction in cough rate was demonstrated by a statistically significant increase in the number of patients that experienced a clinically relevant improvement in the quality of life as measured by the LCQ at week 24 in study 030, while supportive effects were observed in the study P027 of shorter duration (12 weeks). In both studies, the additional secondary patient-reported outcome measures supported these outcomes, including when more stringent criteria for the definition of responder were applied, for both the objective outcomes (i.e., % reduction in cough count) and PRO related criteria.

The maintenance of efficacy over time was supported with the maintenance of the improvements in the patient reported outcomes when measured in the extension study. Thus, the data suggest a modest but clinically relevant effect of gefapixant.

Subgroup analyses: These generally showed the consistency of the efficacy in both the primary data set and the recount data set with improvements in both the reduction in cough rate and LCQ responder rate. The subgroup with a baseline cough count < 20 cough/h showed a reduction in cough rate, but no improvement in the LCQ responder rate on top of a large placebo response. However, the results of this exploratory subgroup must be interpreted with caution, despite the large numbers included. In clinical practice, the baseline cough count is hardly objectivated as the 24 h cough monitoring is rarely used as a clinical tool. The subgroup with a baseline cough count is based on an arbitrary cut off value and is not supported with a biological or pharmacological rational, nor a well-recognised disease entity. The reported efficacy result is not extreme.

Based on these considerations, it cannot be excluded that the limited efficacy results in this subgroup is due to a chance finding (see EMA/CHMP/539146/2013 31 Jan 2019: Guideline on the investigation of subgroups in confirmatory clinical trials). As the overall efficacy is shown, this subgroup will also likely receive benefit from the treatment.

Unfavourable effects

Compared with patients in the placebo group, more patients in the gefapixant 45 mg-treated patient group discontinued prematurely, a difference which was driven by taste related adverse events. Taste-related AEs were the most important, dose dependent AEs, with dysgeusia, as most frequently reported AE up to 65%.

Although most events were mild or moderate, in a small proportion of the patients, i.e., 2.2% of the subjects in population (3.4% of the patients with a taste disorder), the event of taste disorder was ongoing (unresolved) even after more than a year that is considered important, as this is associated with a loss of quality of life. Thus, in general, ongoing taste-related AEs could resolved after treatment discontinuation, leaving a comparable and low incidence between gefapixant 45 mg group and placebo

group. Unwarranted cough reflex suppression as a loss of protective mechanisms against infections is considered potentially important as complete suppression of the cough reflex is dangerous as the lung is then deprived of an essential defence mechanism. Small differences in pneumonia or LRTI, mostly occurring within the first 24 weeks, were observed, which cannot be prevented by limiting the duration of treatment. Additional warnings in the SmPC have been warranted to limit the risks. The observed association between efficacy and taste disorder, including the subgroup of subjects with cough count >20/h, alleviates the concern that these patients might be exposed to the prolonged side effects of the treatment or a detrimental effect on quality of their life.

Impact of uncertainties and limitations of the data on the importance of the unfavourable effects: The effect on the quality of life of taste disorders has not been investigated, thus the impact on quality of life is not quantified. However, it is known from other diseases, e.g., COVID-19 and treatments that affect the taste, that the impact can be high. Indirect measures impacted by a taste disorder did not reveal a difference between participants with and without a taste disorder. However, it is unclear how patients would have assessed the effect on the quality of life in real life.

It is not possible to give a recommendation on discontinuation and restarting of treatment, as there is no experience in the clinical programme with intermittent or temporary discontinuation or dose reduction. A warning in section 4.4 of the SmPC and description in 4.8 of the SmPC are warranted to inform the healthcare professional as part of their clinical care and the patient about the possibility of a long-lasting taste disorder.

Additional *post-hoc* analyses were provided to identify the baseline characteristics of the gefapixant 45 mg treated patients who prematurely left because a taste related adverse event. The patients who discontinued had a somewhat lower disease burden and experienced more moderate to severe taste disorders compared to those who remained in the study.

Based on the animal studies, crystalluria and urolithiasis were of concern as these events could lead to kidney damage and ultimately to renal impairment. Although no evidence was found in the clinical studies, the study population was not fully representative. Therefore, the significance is still unknown. The results of a phase I study in patients with moderate to severe OSA who were not using PAP, showed that a high dose of gefapixant (180 mg QHS) had a negative impact on mean SaO2 and the proportion of time with SaO2 <90%. The significance of these findings is unknow for the proposed lower posology (gefapixant 45 mg BID) is unknown. A warning in the SmPC was included to limit the risk. For patients with OSA, appropriate treatment for OSA should be considered prior to initiating treatment with gefapixant.

3.7.2. Balance of benefits and risks

The results based on the original and recount data set show a modest, clinically relevant effect in reducing the relative cough rate and difference in the LCQ responder rate for gefapixant 45 mg in the presence of a large placebo response. The results of the LCQ responder rate are supported with the outcomes of other Patient reported outcomes showing consistency of findings with improvement that are maintained overtime, providing further support for the benefit of gefapixant.

Treatment is generally well tolerated, and only a low number of SAEs are reported. The most frequently reported adverse events are taste-related adverse events, which are likely to be associated with efficacy. Most taste disorders resolved upon treatment discontinuation, and only in a minority of cases the taste disorder remained, with an incidence comparable to placebo. Both chronic cough and taste disorders affect the quality of life.

Of concern is the possible impairment of the physiological defence mechanism against pathogens, foreign objects or endogenous secretions. During the trial, a slightly higher incidence of pneumonia was observed within the first 24 weeks of treatment in the gefapixant 45 mg group compared to placebo. This suggests that the use of the treatment should be limited during a period of respiratory infection and a warning in section 4.4. is included in order to minimise this risk.

3.7.3. Additional considerations on the benefit-risk balance

None.

3.8. Conclusions

The overall benefit/risk balance of Lyfnua is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Lyfnua is favourable in the following indication(s):

Lyfnua is indicated in adults for the treatment of refractory or unexplained chronic cough.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being

reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that gefapixant is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.