Report on the Deliberation Results

December 8, 2021
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Lyfnua Tablets 45 mg
Non-proprietary Name	Gefapixant Citrate (JAN*)
Applicant	MSD K.K.
Date of Application	February 26, 2021

Results of Deliberation

In its meeting held on December 2, 2021, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

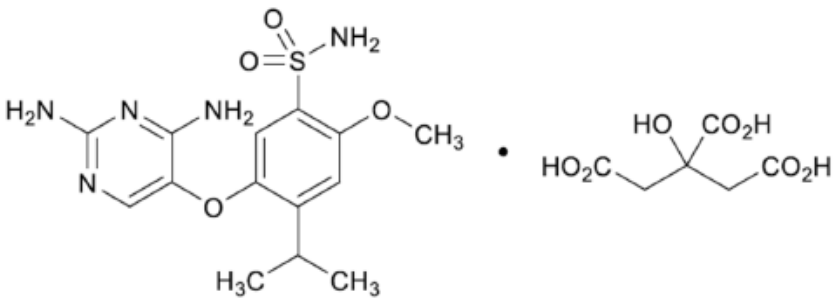
Review Report

November 22, 2021
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Lyfnua Tablets 45 mg
Non-proprietary Name	Gefapixant Citrate
Applicant	MSD K.K.
Date of Application	February 26, 2021
Dosage Form/Strength	Tablets, each containing 69.48 mg of Gefapixant Citrate (45 mg as gefapixant)
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{14}H_{19}N_5O_4S \cdot C_6H_8O_7$
Molecular weight: 545.52
Chemical name:
5-[(2,4-Diaminopyrimidin-5-yl)oxy]-2-methoxy-4-(propan-2-yl)benzene-1-sulfonamide monocitrate

Reviewing Office Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of refractory chronic cough, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition. The safety etc. of the product in clinical practice,

including the incidence of taste-related events, should be further investigated via post-marketing surveillance etc., and the obtained information should be provided to healthcare providers and patients.

Indication

Refractory chronic cough

Dosage and Administration

The usual adult dosage is 45 mg of gefapixant administered orally twice daily.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

November 2, 2021

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Lyfnua Tablets 45 mg
Non-proprietary Name	Gefapixant Citrate
Applicant	MSD K.K.
Date of Application	February 26, 2021
Dosage Form/Strength	Film-coated tablets, each containing 69.48 mg of Gefapixant Citrate (45 mg as gefapixant)
Proposed Indication	Refractory or unexplained chronic cough
Proposed Dosage and Administration	The usual adult dosage is 45 mg of gefapixant administered orally twice daily.

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List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

The active substance of "Lyfnua Tablets 45 mg," Gefapixant Citrate is a selective P2X3 receptor antagonist discovered by Roche Pharmaceuticals. Gefapixant Citrate antagonizes the P2X2/3 receptor as well.

Cough is basically a defense mechanism that clears excess secretions and inhaled foreign materials from the airways. When sensory nerve endings distributed in the submucosa of the airway wall, e.g., within or beneath the bronchial epithelium (cough receptors: myelinated Aδ-fibers and unmyelinated C-fibers) are overstimulated mechanically or chemically, impulses are transmitted to the cough center in the solitary tract nucleus of the medulla oblongata via the vagal afferent nerves, and the cough center generates an efferent signal that travels to the intercostal muscles and diaphragm to produce the cough.

Coughs are categorized by their duration: acute cough is one lasting <3 weeks, prolonged cough lasts 3 to <8 weeks, and chronic cough lasts ≥8 weeks. The predominant cause of acute cough is respiratory tract infections including common cold, while the causes of chronic cough include cough variant asthma, atopic cough/pharyngeal allergy, and gastroesophageal reflux disease. Although patients with cough receive specific therapy for associated conditions based on their medical history and test results, not a few patients have no identifiable conditions associated with cough or are refractory to treatment of associated conditions. In Japan, the prevalence of chronic cough has been reported to be approximately 2% (*Allergology International.* 2012; 61: 573-81), and approximately 20% of patients on treatment for cough at the cough clinic have been reported to be non-responders (*Allergology International*. 2019; 68: 478-85).

As non-specific antitussives for any condition associated with cough, centrally-acting antitussives (narcotic [codeine] and non-narcotic antitussives [dextromethorphan, etc.]) and peripherally-acting antitussives (Chinese herbal medicines, etc.) exist. However, the use of centrally-acting antitussives suppresses cough as a defense mechanism as well, and adverse events such as constipation and sleepiness occur frequently. Due to these problems, the clinical practice guidelines recommend that its use should be minimized, and there is still an unmet need for a drug that treats cough.

The P2X3 receptor is an ATP-gated ion channel expressed mainly on Aδ- and C-fibers. Aδ-fibers distributed in the submucosa of the airway wall are sensitive to mechanical or acid stimulation and protect the lower airway from excess secretions and aspiration. C-fibers terminate in the airway mucosal epithelium and have been suggested to be activated by ATP released from mucosal cells in the airway due to inflammation or a chemical stimulant, evoking cough (*Physiol Rev*. 2016; 96: 975-1024). Since gefapixant selectively binds to and antagonizes the P2X3 receptor, the clinical development of gefapixant as a drug for the treatment of refractory or unexplained chronic cough was initiated.

The clinical development of Gefapixant Citrate (hereinafter referred to as gefapixant) began in [redacted] 20[redacted], and a marketing application has been submitted based on the results from a global study involving Japan, etc. Outside Japan, US, [redacted], [redacted], and [redacted] applications are under review as of October 2021.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to pale yellow powder. Its appearance, thermal analysis (differential scanning calorimetry, thermogravimetric analysis), solubility, hygroscopicity, partition coefficient, pH, and dissociation constant (the pyrimidinium group and the sulfonamide group) have been determined. Although 5 crystalline forms of the drug substance ([redacted]) occur, the commercial synthesis yields the crystalline form [redacted] only, which has been demonstrated to be stable at room temperature. In order to improve the relative bioavailability of gefapixant when coadministered with a proton pump inhibitor (PPI), the anhydrous citrate of gefapixant, which was thermodynamically stable, was defined as the drug substance [see Sections 6.1.2 and 6.1.3].

Its chemical structure has been elucidated by ultraviolet-visible spectroscopy, infrared spectrophotometry (IR), nuclear magnetic resonance spectrometry (NMR) (^{1}H- and ^{13}C-NMR), mass spectrometry, and single crystal X-ray crystallography.

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted] as starting materials.

A Quality by Design (QbD) approach was used. A quality control strategy was established based on the following, etc.

- Identification of [redacted] as critical quality attributes (CQAs)
- Development of the method of control of the quality attributes through the manufacturing process and the specification
- Identification of critical process parameters (CPPs) through quality risk assessment, design of experiments, and one-factor-at-a-time approach

[redacted] have been defined as critical steps. [redacted] are controlled as critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance consist of content, appearance, identity (IR), purity [related substances (high performance liquid chromatography [HPLC]), residual solvents (gas chromatography [GC]), [redacted] (HPLC)], water content, particle size, [redacted] (potentiometric titration), and assay (HPLC).

2.1.4 Stability of drug substance

The primary stability studies on the drug substance are shown in Table 1. The stability results indicated that the drug substance is stable. Photostability data showed that the drug substance is photostable.

Table 1. Stability studies on drug substance

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 production batches	25℃	60%RH	double low-density polyethylene bags + fiber drum	24 months
Accelerated	3 production batches	40℃	75%RH		6 months

Based on the above, a re-test period of [redacted] months was proposed for the drug substance when stored in double low-density polyethylene bags within a fiber drum at room temperature, in accordance with "Guideline on Evaluation of Stability Data" (PMSB/ELD Notification No. 0603004 dated June 3, 2003). The long-term testing will be continued up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an immediate-release film-coated tablet containing 69.48 mg of Gefapixant Citrate (45 mg as gefapixant) and the following excipients: microcrystalline cellulose, D-mannitol, hypromellose, crospovidone, colloidal silicon dioxide, sodium stearyl fumarate, magnesium stearate, Opadry Pink ([redacted]), and carnauba wax.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of blending, lubrication blending, tablet compression, film-coating, and packaging/labeling. [redacted] has been defined as a critical step, and process control items and values have been established.

A QbD approach was used. A quality control strategy was established based on the following etc. (Table 2).

- Identification of CQAs
- Identification of CPPs through quality risk assessment

Table 2. Overview of drug product control strategy

CQA	Method of control
[redacted]	Manufacturing process, Specification
[redacted]	Manufacturing process, Specification
[redacted]	Manufacturing process, Specification
[redacted]	Manufacturing process
[redacted]	Manufacturing process, Specification
[redacted]	Specification
[redacted]	Manufacturing process, Specification

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, appearance, identity (HPLC), purity [related substances (HPLC)], uniformity of dosage units [content uniformity testing (HPLC)], dissolution (HPLC), and assay (HPLC).

Real time release testing (RTRT), performed as in-process testing by using near-infrared spectrophotometry, has been proposed for [redacted] to make release decisions of the drug product. If RTRT cannot be used for batch release, the specification tests will be performed in accordance with the pre-defined acceptance criteria and procedures to make batch release decisions.

2.2.4 Stability of drug product

The primary stability studies on the drug product are shown in Table 3. The stability results indicated that the drug product is stable. Photostability data showed that the drug product is photostable.

Table 3. Stability studies on drug product

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 production batches	25℃	60%RH	Blister pack	24 months
Accelerated	3 production batches	40℃	75%RH		6 months

Based on the above, a shelf-life of 36 months was proposed for the drug product when packaged in blister packs (films made from polyvinyl chloride and polyvinylidene chloride/aluminum foils) and stored at room temperature, in accordance with "Guideline on Evaluation of Stability Data" (PMSB/ELD Notification No. 0603004 dated June 3, 2003). The long-term testing will be continued up to [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The applicant submitted the results from the following primary pharmacodynamic studies: *in vitro* studies that evaluated the binding affinity for the P2X3 receptor, the antagonism of the P2X3 and P2X2/3 receptors, etc. and *in vivo* studies that determined efficacy in various models of sensitization, etc. The applicant submitted the results from secondary pharmacodynamic studies that evaluated the inhibitory activity against various receptors, etc. and the results from safety pharmacology studies that assessed the effects on the central nervous, respiratory, cardiovascular, urinary, and gastrointestinal systems. Pharmacologic parameters are expressed as the mean.

3.1 Primary pharmacodynamics

3.1.1 Antagonism of P2X3 and P2X2/3 receptors (CTD 4.2.1.1.1 to 4.2.1.1.3)

In Chinese hamster ovary-K1 (CHO-K1) or 1321N1 cells expressing various P2X receptors, the IC_{50} values of gefapixant for agonist (α,β-MeATP, etc.)-evoked intracellular calcium flux are shown in Table 4.

Table 4. Inhibitory activity of gefapixant against various P2X receptors (IC_{50}, nmol/L)

	Rat P2X3[a)]	Human P2X3[a)]	Human P2X2/3[b)]	Human P2X1[c)]	Human P2X2[d)]	Human P2X4[d)]	Rat P2X5[d)]	Human P2X7[e)]
Gefapixant free-base	68	—	83	—	—	—	—	—
Gefapixant hydrochloride salt	79	28	257	>10,000	>10,000	>10,000	>10,000	>10,000

—: Not determined
a) In the presence of α,β-MeATP 1 μmol/L, b) In the presence of α,β-MeATP 5 μmol/L, c) In the presence of α,β-MeATP 0.5 μmol/L,
d) In the presence of ATP 1 μmol/L, e) In the presence of benzoylbenzoyl ATP 300 μmol/L

In a study using a voltage clamp technique, gefapixant inhibited α,β-MeATP (10 μmol/L)-induced P2X3-mediated transient currents and P2X2/3-mediated sustained currents in isolated rat dorsal root and nodose ganglion neurons. The p*K*i value for the inhibition of P2X3 currents in isolated rat dorsal root ganglion neurons was 8.3, and the p*K*i value for the inhibition of P2X2/3 currents in isolated rat nodose ganglion neurons was 6.9.

In electrophysiological studies using recombinant human P2X3 and P2X2/3 receptors expressed in human embryonic kidney cells (HEK-293 cells), gefapixant inhibited α,β-MeATP-induced membrane currents, and the K_D values for the P2X3 receptor (α,β-MeATP 10 μmol/L) and the P2X2/3 receptor (α,β-MeATP 100 μmol/L) were approximately 140 and 250 nmol/L, respectively.

3.1.2 Effects on complete Freund's adjuvant-induced mechanical hyperalgesia (CTD 4.2.1.1.6)

The effects of gefapixant on complete Freund's adjuvant-induced chronic inflammation and mechanical hyperalgesia in male SD rats were assessed by the Randall-Selitto test.

Gefapixant (1, 3, 10, or 30 mg/kg) or a positive control, rofecoxib (5 mg/kg) was administered subcutaneously. Compared with vehicle, gefapixant 30 mg/kg and rofecoxib reduced mechanical hyperalgesia by 83% and 97%, respectively.

Gefapixant (3, 10, 30, or 100 mg/kg) was administered orally, or rofecoxib (5 mg/kg) was administered subcutaneously. Compared with vehicle, gefapixant dose-dependently reduced mechanical hyperalgesia (reduced by 52% at 30 mg/kg and by 84% at 100 mg/kg), and rofecoxib reduced mechanical hyperalgesia by 72%.

3.1.3 Effects in chronic constriction injury model (CTD 4.2.1.1.9)

Gefapixant (90 mg/kg) or a positive control, gabapentin (60 mg/kg) was administered orally twice daily for 7 days in female SD rats. At 14 hours following the last dose, cold allodynia (assessed by the number of withdrawal responses [paw withdrawal from cold water] per minute) induced by the sciatic nerve ligation was reduced by 32.4% in the gefapixant group and by 47.4% in the gabapentin group, compared with the vehicle group. Subsequently, a subcutaneous dose of gefapixant (30 mg/kg) or gabapentin (60 mg/kg) was administered 1 hour later, and cold allodynia was reduced by 49.6% and 42.3%, respectively, at 30 minutes post-dose.

Gefapixant (90 mg/kg) or gabapentin (60 mg/kg) was administered orally twice daily for 7 days, and the duration of action was evaluated. Cold allodynia at 14, 20, and 38 hours following the last dose was reduced

by 34.5%, 25.9%, and 19.8%, respectively, in the gefapixant group and by 40.5%, 37.1%, and 8.0%, respectively, in the gabapentin group, compared with the vehicle group.

3.1.4 Effects on the micturition reflex in the refill anesthetized rat model (CTD 4.2.1.1.12)

In the refill model of bladder sensory function in which the urinary muscle contractions of the micturition reflex were induced by intravesical infusion of saline in female SD rats, the intravenous administration of gefapixant 10 mg/kg and 30 mg/kg increased the threshold volume by 15.2% and 36.4%, respectively, compared to vehicle treatment (a positive control, WAY100635 [5-HT_{1A} antagonist], a ≥67% increase).

3.2 Secondary pharmacodynamics

3.2.1 Effects on various receptors, ion channels, transporters, and enzymes (CTD 4.2.1.2.2 and 4.2.1.2.6)

Gefapixant (10 μmol/L) did not cause ≥50% inhibition of any of 73 receptors, ion channels, transporters, and enzymes.

3.2.2 Effects on a panel of kinases (CTD 4.2.1.2.3)

Gefapixant was screened for activity against a panel of 121 kinases. Gefapixant (10 μmol/L) caused 84% inhibition of v-abl Abelson murine leukemia viral oncogene homolog 1 (ABL1) only. On the other hand, as gefapixant was reported as an inhibitor of ABL1 in a panel of kinases, gefapixant concentrations up to 40 μmol/L were tested in an additional assay to estimate the IC_{50}, but no inhibition of activity was observed.

3.2.3 Effect on locomotor activity in rats (CTD 4.2.1.2.1)

Gefapixant (30, 100, and 300 mg/kg) or a positive control, desipramine (30 mg/kg) was orally administered to male SD rats. Gefapixant at all dose levels had no effect on ambulation, and desipramine reduced ambulation as compared to vehicle treated animals.

3.3 Safety pharmacology

Table 5 shows the results of safety pharmacology studies of gefapixant.

Table 5. Overview of safety pharmacology studies

Organ systems evaluated	Test system	Endpoints/Method of assessment, etc.	Doses	Route of administration	Findings	CTD
Cardiovascular	hERG-transfected CHO-K1 cells	hERG current	1, 10, 100 μmol/L	*In vitro*	Gefapixant blocked outward and inward tail hERG potassium currents with an IC_{20} and IC_{50} of >100 μmol/L (35.4 μg/mL).	Reference data 4.2.1.3.1
	Beagle dog (4 males and 4 females)	ECG, heart rate, blood pressure, body temperature	15, 70, 200 mg/kg	Oral	8%-9% lower heart rate at ≥70 mg/kg and 2%-7% lower blood pressure at all dose levels [a)]	4.2.1.3.3
Respiratory	Wistar rat (8 males)	respiratory rate, tidal volume	100, 500, 1,680 mg/kg	Oral	Approximately 20% decrease in tidal volume at 1,680 mg/kg	4.2.1.3.4
CNS	Wistar rat (6 males)	Irwin test	100, 500, 2,000 mg/kg	Oral	No effects	4.2.1.3.5
Renal/Urinary	Wistar rat (10 males)	urine volume, urine electrolyte concentration	100, 500, 2,000 mg/kg	Oral	transient increase in total urinary excretion of sodium/chloride at 2,000 mg/kg, transient decrease in urinary potassium excretion	Reference data 4.2.1.3.6
Gastrointestinal	Wistar rat (10 males)	gastric emptying, intestinal motility	100, 500, 2,000 mg/kg	Oral	Decrease in gastric emptying at ≥500 mg/kg Decreased intestinal motility at 2,000 mg/kg	Reference data 4.2.1.3.7

a) These changes were not considered adverse because these were minimal and reversible and were not dose-related.

3.R Outline of the review conducted by PMDA

The applicant's explanation about the pharmacological effects of gefapixant:

The P2X3 and P2X2/3 receptors are expressed mainly on C- and Aδ-fiber sensory neurons, and these fibers are activated by ATP released in response to stimulation, upon binding to these receptors, leading to cough (*J Physiol*. 2012; 590: 4109-20, *Physiol Rev*. 2016; 96: 975-1024).

In *in vitro* studies, gefapixant antagonized the P2X3 and P2X2/3 receptors, but did not antagonize other P2X channels at the concentrations tested (up to 10 μmol/L). Cough induced in animal models is far from natural cough present in human disease, and there is a possibility that the effects of the drug in animal models cannot directly be translated to a clinical outcome in humans (*Respir Physiol Neurobiol*. 2021; 290: 103656). Thus, the effects of gefapixant were not evaluated in animal models of cough in the present application. Meanwhile, studies in multiple animal models of inflammatory and chronic neuropathic pain and bladder sensory function showed that gefapixant reduced nocifensive responses and modulated the micturition reflex, etc., which were considered to be mediated by the P2X3 and P2X2/3 receptors.

On the basis of the data submitted, PMDA concluded that gefapixant has been suggested to inhibit biological activity via the P2X3 and P2X2/3 receptors, and that the efficacy of gefapixant in the treatment of cough is expected from a pharmacological point of view if the P2X3 and P2X2/3 receptors are considered to be involved in its pathogenesis.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The applicant submitted the data on the absorption, distribution, metabolism, and excretion of gefapixant, in the form of the results from oral or intravenous studies in mice, rats, dogs, and rabbits. Plasma and milk concentrations of gefapixant were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (lower limit of quantitation [LLOQ], 5 ng/mL in mouse and rat plasma, 200 ng/mL in dog plasma, 50 ng/mL in rabbit plasma, 10 ng/mL in rat milk), and radioactivity concentrations in samples were determined by liquid scintillation counter. Unless otherwise specified, doses are expressed in terms of gefapixant, and pharmacokinetic parameters are expressed as the mean or the mean ± standard deviation (SD).

4.1 Absorption

4.1.1 Single-dose studies (Reference data CTD 4.2.2.2.1, 4.2.2.2.2, 4.2.2.2.4, and 4.2.2.2.8)

Table 6 shows the pharmacokinetic parameters of gefapixant following a single oral or intravenous dose of gefapixant in rats and dogs. The absolute oral bioavailability of gefapixant was 38.3% in rats and 81.5% in dogs.

Table 6. Pharmacokinetic parameters of gefapixant following a single dose of gefapixant

Species	Route of administration/ Feeding condition		Dose (mg/kg)	No. of animals	C_{max} (µg/mL)	$AUC_{0\text{-}24\,h}$ (µg·h/mL)	t_{max} (h)	CL (mL/min/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)
Rat	Fasted	IV	2	3F	—	1.25	—	29.5	4.22	4.38
		P.O.	2	3F	0.156	0.478	1.5	—	—	1.5
	Fed	P.O.	100	10F	3.85	9.06	—	—	—	—
			250	10F	9.15	24.6	—	—	—	—
			500	10F	14.6	40.4	—	—	—	—
			1,000[a)]	10F	21.0	117	—	—	—	—
			2,000[a)]	10F	17.3	162	—	—	—	—
			3,000[a)]	10F	16.0	180	—	—	—	—
			500	10M	9.08	27.6	—	—	—	—
			2,000	10M	9.44	45.8	—	—	—	—
Dog	Fasted	IV	0.5	4F	—	3.22 ± 0.33	—	2.40 ± 0.25	0.64 ± 0.21	4.17 ± 1.88
		P.O.	0.5	4F	0.535 ± 0.153	2.60 ± 0.33	1.00 [0.500, 2.00]	—	—	3.75 ± 0.63
	Fed	P.O.	25[a)]	2F3M	12.8 ± 1.71	162 ± 18.4	—	—	—	—
			300[a)]	3M3F	84.9 ± 38.0	1,128 ± 473	—	—	—	—

Mean or Mean ± SD; Median or Median [Min., Max.] for t_{max}; —, Not applicable or not calculated
a) BID dosing

4.1.2 Repeated-dose studies (CTD 4.2.3.2.4, 4.2.3.2.10, and 4.2.3.2.16)

Table 7 shows the pharmacokinetic parameters of gefapixant following repeated oral administration of gefapixant in mice, rats, and dogs. In all animal species, increases in gefapixant exposure tended to be less than dose-proportional, and there were no consistent gender-related differences. In rats and dogs, there was no accumulation of gefapixant following repeated dosing.

Table 7. Pharmacokinetic parameters of gefapixant following repeated oral administration of gefapixant

Species	Sampling time point	No. of animals	Dose[a)] (mg/kg/day)	C_{max} (µg/mL)		$AUC_{0\text{-}24\,h}$ (µg·h/mL)	
				M	F	M	F
Mouse	Week 13	3/sex/time point	150	7.10	4.78	29.5	23.0
			500	12.3	9.08	48.8	47.1
			1,500	16.7	25.5	76.3	82.7
Rat	Day 1	3/sex/time point	75	2.63	1.95	18.6	17.6
			225	5.34	7.29	37.6	41.8
			450	7.48	8.06	72.6	68.1
	Week 26	3/sex/time point	75	1.48	1.78	15.7	16.2
			225	2.97	4.84	28.9	38.7
			450	4.09	8.34	63.8	78.7
Dog	Day 1	4/sex	25	8.87 ± 0.978	9.98 ± 1.37	123 ± 9.63	129 ± 8.49
		6/sex	50	20.2 ± 4.08	18.2 ± 4.95	250 ± 45.8	232 ± 41.2
		6/sex	100	24.5 ± 6.39	27.7 ± 6.85	307 ± 79.7	348 ± 75.1
	Week 27	4/sex	25	7.85 ± 1.76	7.80 ± 0.730	105 ± 12.3	112 ± 13.0
		5M6F	50	14.5 ± 4.88	14.4 ± 1.26	191 ± 42.9	200 ± 21.9
		5M6F	100	20.9 ± 3.39	27.4 ± 7.06	309 ± 59.7	343 ± 85.5
	Week 39	3M4F	25	6.78 ± 0.919	7.64 ± 1.03	101 ± 18.8	108 ± 13.4
		5M6F	50	11.8 ± 2.02	15.1 ± 3.22	188 ± 44.4	215 ± 38.3
		6/sex	100	18.3 ± 2.05	20.2 ± 3.83	283 ± 48.9	301 ± 63.6

Mean or Mean ± SD
a) BID dosing in mice and dogs, TID dosing in rats

4.1.3 *In vitro* cell permeability (Reference data CTD 4.2.2.2.10 and 4.2.2.6.9 to 4.2.2.6.10)

The apparent permeability coefficients of gefapixant in the apical to basolateral direction ($P_{app\ A \rightarrow B}$) across colorectal adenocarcinoma (Caco-2) cells, Madin-Darby canine kidney II (MDCKII) cells, and Lilly laboratory cell-porcine renal epithelial (LLC-PK1) cells were 0.63×10^{-6}, 2.2 to 2.4×10^{-6}, and 0.99×10^{-6} cm/s, respectively (the concentrations tested were 100, 0.1-1, and 5 μmol/L, respectively), suggesting that gefapixant is poorly permeable.

4.2 Distribution

4.2.1 Tissue distribution (Reference data CTD 4.2.2.3.1 to 4.2.2.3.3)

Following a single oral dose of ^{14}C-gefapixant 20 mg/kg in male albino and pigmented rats, the tissue distribution of radioactivity[1)] was evaluated by quantitative whole-body autoradiography.

The highest levels of radioactivity occurred at 2 or 6 hours post-dose in most tissues, and then radioactivity was eliminated rapidly. At 168 hours post-dose, radioactivity was below the detection limit in all tissues except for the eyes and uveal tract of pigmented rats.

Although the tissue to plasma ratio of radioactivity at 2 hours post-dose was similar between albino and pigmented rats, the uveal tract to plasma ratio of radioactivity was approximately 3-fold higher in pigmented rats than in albino rats, suggesting that gefapixant binds to melanin.

Following a single oral dose of gefapixant 90 mg/kg, a single subcutaneous dose of gefapixant 30 mg/kg, or a single intravenous dose of gefapixant 62.3 mg/kg in rats, its distribution into the CNS was evaluated. Regardless of route or dose, the brain to plasma ratio was approximately 0.05, and the cerebrospinal fluid to unbound plasma concentration ratio was approximately 0.1 or less than 0.1, suggesting little distribution of gefapixant into the CNS.

4.2.2 Plasma protein binding and distribution in blood cells (Reference data CTD 4.2.2.3.5 to 4.2.2.3.8)

The plasma protein binding of gefapixant as determined by an equilibrium dialysis method was 65.1% to 67.2% in mice, 51.2% to 53.0% in rats, 47.4% to 48.9% in rabbits, 58.1% to 59.2% in dogs, and 51.0% to 56.8% in humans over the concentration range tested (1-50 μmol/L in non-humans, 0.1-10 μmol/L in humans). The binding of gefapixant to human serum albumin and α_1-acid glycoprotein (0.5-5 μmol/L) was 68.4% to 87.3% and 10.5% to 26.5%, respectively.

The blood to plasma concentration ratio of gefapixant (0.3 μmol/L) was 1.26 in rats and 0.83 in dogs. The blood to plasma concentration ratio of gefapixant (0.1-5 μmol/L) was 1.06 to 1.18 in humans.

[1)] Samples were collected at 2-672 hours post-dose in pigmented rats and at 2 and 168 hours post-dose in albino rats. The plasma, blood, aorta, blood (cardiac), brain (whole), cerebellum, cerebrum, medulla oblongata, spinal cord, eye, lens, uveal tract, non-pigmented skin, pigmented skin, adrenal cortex, adrenal gland, adrenal medulla, pituitary gland, thyroid gland, abdominal fat, brown fat, cecum mucosa, esophagus wall, large intestine wall, oral mucosa, small intestine wall, stomach wall, cecum contents, large intestine contents, small intestine contents, stomach contents, urinary bladder contents, bone marrow (femur), lymph node (cervical), spleen, thymus, kidney, kidney cortex, kidney medulla, liver, urinary bladder wall, diaphragm, heart, muscle (femoral), epididymis, prostate, seminal vesicle, testis, lung, nasal turbinates, trachea, exorbital lacrimal gland, Harderian gland, intraorbital lacrimal gland, pancreas, salivary gland, and bone (femur) were evaluated.

4.2.3 Placental transfer to fetus (CTD 4.2.2.3.4 and 4.2.2.5.1)

Gefapixant 300 or 675 mg/kg/day was administered orally to pregnant rats from gestation day 6 through gestation day 18. The fetal plasma concentrations of gefapixant at 30 minutes and 1 hour post-dose on gestation day 18 were 0.865 and 0.798 μg/mL, respectively, at 300 mg/kg/day and 1.04 and 1.51 μg/mL, respectively, at 675 mg/kg/day. The fetal to maternal plasma gefapixant concentration ratio was 0.151 to 0.206.

Gefapixant 400 or 1,500 mg/kg/day was administered orally to pregnant rabbits from gestation day 7 through gestation day 20. The fetal plasma concentrations of gefapixant at 1 and 2 hours post-dose on gestation day 20 were 3.81 and 5.39 μg/mL, respectively, at 400 mg/kg/day and 3.23 and 5.30 μg/mL, respectively, at 1,500 mg/kg/day. The fetal to maternal plasma gefapixant concentration ratio was 0.182 to 0.248.

The above results suggested that gefapixant crosses the placenta.

4.3 Metabolism

4.3.1 *In vitro* studies (Reference data CTD 4.2.2.4.2, 4.2.2.4.3, and 4.2.2.4.5)

When gefapixant (1 μmol/L) was incubated with rat, rabbit, dog, and human live microsomes for 30 minutes in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), the intrinsic clearance values were 4.51, 7.88, 2.24, and 0.04 μL/min/mg, respectively,[2)] suggesting slow metabolism in liver microsomes.

When ^{14}C-gefapixant (10 μmol/L) was incubated with mouse, rat, rabbit, dog, and human cryopreserved hepatocytes for 48 hours, oxidative metabolites (M6, M8, M9, M11, M12, M13), glucuronide conjugates (M5 and M7), and a glucuronide conjugate of M6 (M1) were identified, and no metabolites unique to humans were identified.

4.3.2 *In vivo* studies (Reference data CTD 4.2.2.5.2)

Table 8 shows metabolites in different samples following a single intravenous or oral dose of ^{14}C-gefapixant in rats and dogs. In a foreign mass balance study [see Section 6.2.1.3], no metabolites unique to humans were identified.

[2)] Propranolol, diaminodiphenyl sulfone, and verapamil were used as positive controls, and the intrinsic clearance values were 44.3-1,322, 18.6, and 431-695 μL/min/mg, respectively.

Table 8. Metabolite profiles in different animal species

Species	Dosing regimen	No. of animals	Plasma	Bile	Feces	Urine
Rat	20 mg/kg Single oral dose	3M	Up to 24 hours post-dose unchanged drug, M4, M6, M9, M13			
	20 mg/kg Single oral dose	3M		Up to 8 hours post-dose unchanged drug, M1, M2, M3, M4, M5, M6, M7, M9	Up to 48 hours post-dose unchanged drug, M6, M9, M10, M13	Up to 24 hours post-dose unchanged drug, M1, M4, M6, M7, M8, M9, M10, M11, M13
	2 mg/kg Single IV dose	3M		Up to 8 hours post-dose unchanged drug, M2, M3, M6, M9	Up to 24 hours post-dose unchanged drug, M6	Up to 24 hours post-dose unchanged drug, M4, M6, M9, M11, M13
Dog	1 mg/kg Single oral dose	3M	Up to 8 hours post-dose unchanged drug, M8, M11, M13	Up to 24 hours post-dose unchanged drug, M6	Up to 24 hours post-dose unchanged drug, M13	Up to 24 hours post-dose unchanged drug, M4, M7, M11, M13

Based on the above metabolism studies, the proposed metabolic pathway of gefapixant is shown in Figure 1.

Figure 1. Proposed metabolic pathway of gefapixant in rats, dogs, and humans

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion (Reference data CTD 4.2.2.5.2)

Following a single intravenous dose of ^{14}C-gefapixant (2 mg/kg) in bile duct cannulated rats (3 males), the mean total recovery of radioactivity up to 72 hours post-dose was 97.0%, and urinary, fecal, and biliary

recoveries of radioactivity were 67.9%, 17.2%, and 9.7%, respectively. The unchanged drug (96.2%), M9 (2.8%), and M11 (1.0%) were detected in the urine up to 24 hours post-dose. The unchanged drug (95.5%) and M6 (4.5%) were detected in the feces up to 24 hours post-dose, and the unchanged drug (54.3%), M2/M3 (38.3%), and M9 (7.4%) in the bile up to 8 hours post-dose.

Following a single oral dose of ^{14}C-gefapixant (20 mg/kg) in bile duct cannulated rats (3 males), the mean total recovery of radioactivity up to 72 hours post-dose was 99.9%, and fecal, urinary, and biliary recoveries of radioactivity were 62.8%, 30.9%, and 5.73%, respectively. The unchanged drug (98.7%) and M6 (1.3%) were detected in the feces up to 48 hours post-dose. The unchanged drug (93.2%), M9 (5.4%), and M11 (1.4%) were detected in the urine up to 24 hours post-dose, and the unchanged drug (51.9%), M2 (28.6%), M9 (10.9%), M3 (5.1%), and M1 (3.5%) in the bile up to 8 hours post-dose.

Following a single oral dose of ^{14}C-gefapixant (1 mg/kg) in bile duct cannulated dogs (3 males), the mean total recovery of radioactivity up to 96 hours post-dose was 98.5%, and urinary, fecal, and biliary recoveries of radioactivity were 71.9%, 15.6%, and 5.57%, respectively. The unchanged drug (91.2%) and M11 (8.8%) were detected in the urine up to 24 hours post-dose. The unchanged drug (100%) was detected in the feces up to 24 hours post-dose, and the unchanged drug (100%) in the bile up to 24 hours post-dose.

The above results suggested that renal excretion contributes significantly to the clearance of gefapixant.

4.4.2 Excretion into milk (CTD 4.2.2.5.1)

Gefapixant 300 or 675 mg/kg/day was administered orally to pregnant rats (n = 4) from gestation day 6 through lactation day 10. The milk concentrations of gefapixant at 1 hour post-dose on lactation day 10 were 17.2 and 31.1 μg/mL, respectively, and the milk to plasma gefapixant concentration ratios were 3.65 and 4.05, respectively.

The above results suggested that gefapixant is excreted in milk.

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition or induction (Reference data CTD 4.2.2.6.3 and 4.2.2.6.6 to 4.2.2.6.8)

Using human liver microsomes, gefapixant was evaluated as inhibitors of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5).[3)] The IC_{50} values of gefapixant were >100 μmol/L (except for CYP2D6) or 56 μmol/L (CYP2D6). Gefapixant was not a time-dependent inhibitor of the CYP isoforms.

Using human hepatocytes, the potential of gefapixant (0.1-20 μmol/L) to induce the mRNA expression of CYP isoforms (CYP1A2, CYP2B6, CYP2C9, CYP3A4) and uridine 5'-diphospho-glucuronosyl transferase 1 (UGT1) was evaluated. Gefapixant induced a 2.3- to 2.9-fold increase in the mRNA of CYP2B6 in hepatocytes

[3)] The following compounds were used as substrates of CYP isoforms: phenacetin for CYP1A2, efavirenz for CYP2B6, amodiaquine for CYP2C8, diclofenac for CYP2C9, *S*-mephenytoin for CYP2C19, dextromethorphan for CYP2D6, chlorzoxazone for CYP2E1, testosterone and midazolam for CYP3A4/5

from 2 out of 3 donors and a 2.7- to 5-fold increase in the mRNA of CYP3A4 in hepatocytes from all 3 donors. Gefapixant induced a 2.2- to 3.3-fold increase in CYP3A4 activity.

The applicant's explanation:
Based on the results of evaluation using the correlation method,[4] gefapixant at the clinical dose[5] is unlikely to cause clinically relevant induction of CYP3A4 and CYP2B6.

4.5.2 Transporter substrate assessment (Reference data CTD 4.2.2.2.10 and 4.2.2.6.9 to 4.2.2.6.12)

The results of assays using Caco-2 cells, MDCKII cells, or LLC-PK1 cells expressing human P-glycoprotein (P-gp) and membrane vesicles or MDCKII cells expressing human breast cancer resistance protein (BCRP)[6] suggested that gefapixant may be a substrate for P-gp and BCRP.

The results of assays using MDCKII cells expressing human organic anion transporter 1 (OAT1), OAT3, organic cation transporter 2 (OCT2), or multidrug and toxin extrusion protein 2-K (MATE2-K) and CHO-K1 cells expressing human OCT2 or MATE1[7] suggested that gefapixant may be a substrate for MATE1 and MATE2-K.

4.5.3 Transporter inhibition (Reference data CTD 4.2.2.6.13 and 4.2.2.6.14)

Using LCC-PK1 cells expressing human P-gp, HEK-293 cells expressing human organic anion transporting polypeptide 1B1 (OATP1B1) or OATP1B3, CHO-K1 cells expressing OCT1, OCT2, or MATE1, MDCKII cells expressing human OAT1, OAT3, or MATE2-K, and membrane vesicles expressing human BCRP or bile salt export pump (BSEP), gefapixant (the concentrations tested, 1-100 μmol/L [except for BCRP] or 10-600 μmol/L [BCRP]) was evaluated as inhibitors of the drug transporters.[8] The results are shown in Table 9. The applicant explained that gefapixant at the clinical dose[5] is unlikely to cause clinically relevant inhibition of the transporters.

Table 9. Inhibition of drug transporters by gefapixant

Transporter	IC_{50} (μmol/L) (% inhibition at highest concentration tested)	Transporter	IC_{50} (μmol/L) (% inhibition at highest concentration tested)
P-gp	>100 (4%)	OCT1	17.2 (84.2%)
BCRP	>600 (48.6%)	OCT2	94.7 (55.2%)
OATP1B1	35 (79.4%)	MATE1	34.7 (75.6%)
OATP1B3	97 (51.2%)	MATE2-K	31.5 (69.5%)
OAT1	>100 (－)	BSEP	>100 (7.2%)
OAT3	>100 (27.1%)	－: No inhibition	

4.R Outline of the review conducted by PMDA

Crystals of gefapixant were found in the urine in toxicity studies [see Section 5.R.1].

[4] CYP3A4 induction potential of gefapixant was evaluated in human hepatocytes calibrated for Relative Induction Score (RIS) assessment. No change in the AUC of midazolam was predicted at the clinical dose of 45 mg of gefapixant.
[5] The C_{max} of gefapixant after oral administration of gefapixant 45 mg BID in patients with chronic cough was 1.5 μmol/L.
[6] Elacridar, ketoconazole, and cyclosporine A were used as inhibitors of P-gp, and Ko143 was used as an inhibitor of BCRP.
[7] The following compounds were used as inhibitors of transporters: probenecid for OAT1/OAT3, quinidine for MATE1/OCT2, pyrimethamine for MATE2-K
[8] The following compounds were used as substrates of transporters: digoxin for P-gp, methotrexate for BCRP, pitavastatin for OATP1B1, sulfobromophthalein for OATP1B3, cidofovir for OAT1, estrone-3-sulfate for OAT3, metformin for OCT1/OCT2/MATE1/MATE2-K, taurocholic acid for BSEP

The applicant's explanation about the solubility of gefapixant in human urine:
Crystals of gefapixant were detected in the urine in rat and dog toxicity studies [see Section 5.7.4]. In Study 036 in humans [see Section 6.2.3], the urine gefapixant concentrations at the 45 mg dose of gefapixant (0.005-0.084 mg/mL) were lower than the solubility of gefapixant in water at pH 5 to 7, i.e., the normal pH range of human urine (approximately 0.13 mg/mL).[9)]

PMDA accepted the above explanation and concluded that the submitted study results gave a grasp of the body's handling of gefapixant to a certain extent.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted the results from the following toxicity studies of gefapixant: single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and local tolerance studies and other toxicity studies (a skin sensitization study, a study on impurities, a phototoxicity study, crystalluria evaluation studies).

5.1 Single-dose toxicity

In single-dose studies of oral gefapixant in mice, rats, and dogs, the approximate lethal dose and acute toxicity of gefapixant were assessed (Table 10). There was no mortality in mice, rats, and dogs, and the approximate lethal doses were determined to be >2,000 mg/kg, >2,000 mg/kg, and >1,000 mg/kg, respectively. As acute symptoms, emesis was observed in dogs. However, as there is little expression of the P2X3 receptor in the brain stem (*Pharmacol Rev.* 2006; 58: 58-86) and the distribution of gefapixant into the CNS is very limited [see Section 4.2.1], emesis was not a CNS effect and was considered of little toxicological significance.

Table 10. Overview of single-dose toxicity studies

Test system	Route of administration	Doses (mg/kg)	Noteworthy findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male and female mice (CD-1)	Oral	0,[a)] 100, 500, 2,000	2,000: white feces [c)] (male and female), decreased body weight (female)	>2,000	4.2.3.1.1
Male and female rats (Wistar)	Oral	0,[a)] 100, 500, 2,000	≥500: white feces [c)] (male and female) 2,000: calculus within the urinary bladder, hyperplasia/suppurative inflammation/crystals/superficial necrosis of the transitional epithelium and necrosis of the smooth muscle in the urinary bladder (female)	>2,000	4.2.3.1.2
Male and female dogs (Beagle)	Oral	0, [b)] 30, 100, 300, 1,000	300：soft feces, mucoid feces (male), emesis (male and female) 1,000: decreased food consumption, no feces (male), emesis (male and female)	>1,000	4.2.3.7.7.11

a) [redacted]
b) [redacted]
c) White feces were associated with unabsorbed gefapixant and were not considered adverse.

[9)] In clinical studies in healthy adult subjects, crystalluria was not found in all 8 subjects at the mean urine gefapixant concentration of 0.03 mg/mL (Study 022, 50 mg BID), and crystalluria was present in 4 of 25 subjects at 0.14 mg/mL (Study 007, 600 mg BID) and in all 8 subjects at 0.59 mg/mL (Study 003, 1,800 mg BID).

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies of oral gefapixant were conducted in rats (Table 11). The noteworthy systemic toxicities or abnormal findings of gefapixant were crystal formation in the urine and kidney, injurious changes in the urinary system leading to death and abnormalities in blood renal function parameters associated with crystal formation, and the findings or abnormal clinical parameters suggestive of inflammatory responses associated with injurious changes. Myocardial degeneration/necrosis etc. observed in rats that died or were sacrificed moribund were considered secondary to deterioration in clinical signs associated with kidney injuries. The main component of crystalluria or calculus observed in the urinary system was gefapixant [see Section 5.7.4], and crystalluria without injurious changes in the urinary system was considered less adverse. Blood exposures ($AUC_{0\text{-}24h}$ and C_{max}) at the no-observed-adverse-effect level (NOAEL) in a 26-week repeated-dose toxicity study in rats (225 mg/kg/day) at Week 26 were 33,800 ng·h/mL and 3,910 ng/mL (the mean of males and females), respectively, which were approximately 4-fold and approximately 7-fold the blood exposures at the recommended clinical dose of gefapixant (45 mg BID orally) in Japanese patients with unexplained chronic cough (the $AUC_{0\text{-}24h}$ of 7,664 ng·h/mL and the C_{max} of 538 ng/mL [the human exposures]).

Table 11. Overview of repeated-dose toxicity studies in rats

Test system	Route of administration	Duration of dosing	Doses (mg/kg/day)	Noteworthy findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (Wistar)	Oral	29 days (TID) + 14-day recovery period	0,[a] 300, 500, 675, 900	[Death][b] 900: moribund sacrifice (1 of 17 females), decreases in body weight/food consumption, hunched posture, irregular respiration, dilated pupils, hypoactivity, few feces, thin appearance, increases in blood leukocyte/neutrophil counts, increases in blood BUN/creatinine, discolored kidney, hypertrophy of the ureter, crystals in the kidney/basophilic tubules/lymphocytic infiltrate/fibrosis of the interstitium/renal pelvis dilatation/pyelonephritis/dilatation of the tubules/casts in the tubules, urothelium hyperplasia, ureteral dilatation/serosa fibrosis/chronic inflammation of the serosa, hemorrhage/chronic inflammation in the urinary bladder wall [Surviving animals] ≥300: crystalluria (male and female) ≥675: hunched posture, few feces, decreased body weight, increases in blood BUN/creatinine, increased relative kidney weight, large kidney/crystals in the kidney/basophilic tubules/dilatation of the renal pelvis/dilatation of the tubules, fibrosis of the interstitium/pyelonephritis/lymphocytic infiltrate in the kidney, urothelium hyperplasia, ureteral dilatation/chronic inflammation of the serosa/serosa fibrosis (female) 900: discolored kidney, chronic inflammation/fibrosis/hemorrhage/thrombosis in the capsule, hemorrhage in the renal pelvis, urothelium hyperplasia/muscularis hypertrophy in the ureter, chronic inflammation/hemorrhage in the urinary bladder wall (female) These findings were reversible.	Males: 900 Females: 500	4.2.3.2.8
Male and female rats (Wistar)	Oral	12 weeks (TID) + 4-week recovery period	0,[a] 225, 450, 675 (females), 1,200 (males)	[Death][b] 1,200: unscheduled death (2 of 12 animals), moribund sacrifice (2 of 12 animals), hypoactivity, pale feet and ears, ataxia, irregular respiration, piloerection, myocardial degeneration/necrosis, crystals in the kidney, tubular degeneration, chronic inflammation/papilla necrosis in the kidney, renal pelvis dilatation, lymphoid depletion in the spleen, inflammation/atrophy in the prostate gland, thymic atrophy, ureteral dilatation/transitional cell hyperplasia in the ureter, dilatation of the urinary bladder and hemorrhage/transitional cell hyperplasia in the urinary bladder [Surviving animals] ≥225: crystalluria (male and female), decreased blood lymphocyte count[c] (male) ≥450: increased mandibular salivary gland weight[c] (male and female) 675: calculus in the kidney, urinary occult blood, red blood cells in the urine, increased kidney weight, vacuolation in the mandibular salivary gland [2] 1,200: increases in blood leukocyte/neutrophil/monocyte counts, increases in blood BUN/creatinine, decreases in body weight/body weight gain, increased kidney weight, urinary occult blood, red blood cells in the urine, vacuolation in the salivary gland,[c] calculus in the kidney/large kidney/discolored kidney/rough surface of the kidney, calculus in the ureter/large ureter, calculus in the urinary bladder/large urinary bladder, crystals in the kidney and tubular degeneration/inflammation/papilla necrosis/renal pelvis dilatation in the kidney, ureteral dilatation/transitional cell hyperplasia in the ureter, crystals in the urinary bladder/dilatation of the urinary bladder and transitional cell hyperplasia/hemorrhage/ulcer in the urinary bladder	450	4.2.3.2.9
				Recovery period 1,200: moribund sacrifice (1 of 5 animals), myocardial degeneration/necrosis, toxicity findings related to kidney injuries[d]		

Male and female rats (Wistar)	Oral	26 weeks (TID) + 8-week recovery period	0,[a] 75, 225, 450	≥75: crystalluria (male and female) ≥225: increased salivary gland weight[c] (male and female), increased blood triglycerides[c] (male) ≥450: vacuolation of acinar cells of the salivary gland,[c] crystals in the renal papillary tubule, inflammatory dilatation of the tubule, increases in blood leukocyte/neutrophil/monocyte/large unstained cell counts, increases in blood alkaline phosphatase[c]/albumin, decreased blood A/G ratio, increased urine specific gravity, increases in urine white blood cells/red blood cells, interstitium inflammation in the kidney, tubular crystals/degeneration, ureteral dilatation/inflammation, transitional cell hyperplasia in the urinary bladder (male and female), increased blood triglycerides,[c] urinary occult blood/protein positive (female) These findings were reversible.	225	4.2.3.2.10

a) [redacted]
b) Only the noteworthy toxicity findings related to gefapixant are listed.
c) The finding was considered of little toxicological significance due to the absence of associated changes, etc.
d) Toxicity findings similar to kidney injuries observed in animals that were sacrificed moribund during the dosing period or surviving animals

Repeated-dose toxicity studies of oral gefapixant were conducted in dogs (Table 12). The noteworthy systemic toxicities or abnormal findings of gefapixant were emesis, crystals and calculi in the renal pelvis and urinary bladder, and inflammatory changes in the urinary bladder and renal pelvis. The main component of crystalluria or calculus observed in the urinary system was gefapixant [see Section 5.7.4], and crystalluria without injurious changes in the urinary system was considered less adverse.

Blood exposures ($AUC_{0\text{-}24h}$ and C_{max}) at the NOAEL (50 mg/kg/day) in a 39-week repeated-dose toxicity study in dogs were 203,000 ng·h/mL and 13,600 ng/mL (the mean of males and females), respectively, which were approximately 26-fold and approximately 25-fold the human exposures (the $AUC_{0\text{-}24h}$ of 7,664 ng·h/mL, the C_{max} of 538 ng/mL), respectively.

Table 12. Overview of repeated-dose toxicity studies in dogs

Test system	Route of administration	Duration of dosing	Doses (mg/kg/day)	Noteworthy findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female dogs (Beagle)	Oral	4 weeks (QD) + 4-week recovery period	0,[a] 15, 70, 300	300: emesis, white feces,[c] yellow feces[c] (male and female) These findings were reversible.	300	4.2.3.2.14
Male and female dogs (Beagle)	Oral	12 weeks (BID) + 4-week recovery period	0,[b] 40, 100, 200	≥100: chronic inflammation in the urinary bladder (male), renal pelvis inflammation (female) 200: swelling of the face (male), calculus in the kidney/ureter/urinary bladder, chronic active inflammation in the kidney, chronic inflammation in the urinary bladder, transitional cell hyperplasia in the urinary bladder, calculus in the renal pelvis (female) These findings were reversible.	40	4.2.3.2.15
Male and female dogs (Beagle)	Oral	39 weeks (BID) + 8-week recovery period	0,[b] 25, 50, 100	≥25: prism-shaped crystals in the urine, turbid urine (male and female) 100: increase in urine red blood cells, focal degeneration of the cortical tubule of the kidney (male) These findings were reversible.	50	4.2.3.2.16

a) [redacted]
b) [redacted]
c) The finding was associated with gefapixant that was excreted unabsorbed and considered of little toxicological significance.

5.3 Genotoxicity

An *in vitro* bacterial reverse mutation assay (Ames assay), an *in vitro* chromosomal aberration assay in cultured mammalian cells, and an *in vivo* micronucleus assay in rat bone marrow were conducted (Table 13). Gefapixant was considered negative for genotoxicity.

Table 13. Overview of genotoxicity studies

Type of study		Test system	Metabolic activation (Treatment time)	Concentrations or doses	Test result	Attached document CTD
In vitro	Ames assay	*Salmonella typhimurium*: TA1535, TA97, TA98, TA100, TA102	S9−/+	0,[a] 50, 158, 500, 1,580, 5,000 µg/plate	Negative	4.2.3.3.1.2
	Chromosomal aberration assay in cultured mammalian cells	Cultured human peripheral blood lymphocytes	S9− (24 hours)	0,[a] 80, 180, 250 µg/mL	Negative	4.2.3.3.1.4
			S9− (3 hours)	0,[a] 450, 640, 1,000 µg/mL		
			S9+ (5 hours)	0,[a] 400, 800, 1,600 µg/mL		
			S9+ (3 hours)	0,[a] 450, 640, 1,000 µg/mL		
In vivo	Rat micronucleus assay	Male and female rat (Wistar) bone marrow		0,[b] 100, 500, 2,000 mg/kg/day (administered orally once daily for 2 days)	Negative	4.2.3.3.2.1

a) DMSO
b) [redacted]

5.4 Carcinogenicity

A 26-week carcinogenicity study of oral gefapixant was conducted in Tg rasH2 hemizygous (tg/wt) (Tg rasH2) mice (Table 14), and no evidence for carcinogenicity was found. The incidences of neoplastic lesions presented in Table 14 tended to be higher in the gefapixant group than in the control group, but fell within the historical control ranges of the test facility. Thus, these neoplastic lesions are unlikely related to gefapixant.

The $AUC_{0\text{-}24h}$ at the no-observed-effect level (NOEL) for carcinogenicity (500 mg/kg/day) was 33,500 ng·h/mL, which was approximately 4-fold the human exposure ($AUC_{0\text{-}24h}$, 7,664 ng·h/mL).

Table 14. Overview of carcinogenicity study in Tg rasH2 mice

Test system	Route of administration	Duration of dosing	Major lesions	Sex	Doses (mg/kg/day)					NOEL for carcinogenicity (mg/kg/day)	Attached document CTD
					Control I	Control II	Gefapixant				
					0[a]	0[a]	30	100	500		
				N	30/sex	30/sex	30/sex	30/sex	30/sex		
Male and female mice (Tg rasH2)	Oral	26 weeks	Neoplastic lesions							500	4.2.3.4.1.1
			Whole body/ Lymphoma	M	0	0	0	0	1		
				F	0	0	0	0	0		
			Lung/ Adenocarcinoma	M	0	0	0	0	1		
				F	0	0	1	0	0		
			Whole body/ Hemangiosarcoma	M	2	7	2	2	4		
				F	0	1	1	4	1		
			Other findings								
			Survival rate	M	97	93	97	100	93		
				F	100	100	97	93	97		

a) [redacted]

A 2-year carcinogenicity study of oral gefapixant was conducted in rats (Table 15), and no evidence for carcinogenicity was found. The incidences of neoplastic lesions presented in Table 15 tended to be higher in

the gefapixant group than in the vehicle control group. These neoplastic lesions are unlikely related to gefapixant because the incidences fell within the historical control ranges, were not statistically significant, and were not dose-related., etc. The major non-neoplastic lesions were chronic nephropathy, crystals in the tubules, hyperplasia of the transitional epithelium in the kidney, crystals in the urinary bladder and ureter, ureteral dilatation, and inflammation/hyperplasia of the transitional epithelium in the urinary bladder and ureter.

The $AUC_{0\text{-}24h}$ at the NOEL for carcinogenicity (300 mg/kg/day) was 71,900 ng·h/mL (the mean of males and females), which was approximately 9-fold the human exposure ($AUC_{0\text{-}24h}$, 7,664 ng·h/mL).

Table 15. Overview of carcinogenicity study in rats

Test system	Route of administration	Duration of dosing	Major lesions	Sex	Doses (mg/kg/day)					NOEL for carcinogenicity (mg/kg/day)	Attached document CTD
					Control I	Control II	Gefapixant				
					0[a)]	0[b)]	30	100	300		
				N	60/sex	60/sex	60/ sex	60/ sex	60/ sex		
Male and female rats (Wistar)	Oral	104 weeks	Neoplastic lesions							300	4.2.3.4.1.2
			Skin/ Malignant schwannoma	M	1	0	1	4	1		
				F	1	0	0	0	0		
			Whole body/ Lymphoma	M	1	2	0	1	4		
				F	2	3	2	5	0		
			Adrenal gland/ Pheochromocytoma[c)]	M	3	4	4	6	4		
				F	0	1	2	3	0		
			Skin/ Benign keratoacanthoma	M	0	0	3	0	2		
				F	1	0	0	0	0		
			Small intestine/ Adenocarcinoma	M	0	0	1	2	0		
				F	0	0	1	0	0		
			Pancreas/ Islet cell adenoma	M	2	0	1	3	1		
				F	1	0	2	0	1		
			Mammary gland/ Adenocarcinoma	M	0	0	0	0	0		
				F	14	2	5	9	4		
			Mammary gland/ Fibroadenoma	M	0	0	1	0	0		
				F	15	21	9	15	8		
			Other findings								
			Survival rate (%)	M	60	75	60	65	37		
				F	62	55	67	70	30		
			300: chronic nephropathy, crystals/hyperplasia of the transitional epithelium in the tubules, crystals/inflammation/hyperplasia of the transitional epithelium in the urinary bladder, crystals in the ureter/ureteral dilatation and inflammation/hyperplasia of the transitional epithelium in the ureter, crystals in the urethra/urethral dilatation and inflammation/hyperplasia of the transitional epithelium in the urethra, diffuse hyperplasia in the parathyroid gland, fibrous osteodystrophy in the sternum/femur, hypertrophy of the adrenal zona glomerulosa, mineralization in the aorta/soft tissues, polyarteritis (male and female)								

a) [redacted]
b) [redacted]
c) The sum of rats with benign or malignant pheochromocytoma

5.5 Reproductive and developmental toxicity

A study of fertility and early embryonic development to implantation was conducted in male and female rats (Table 16). Gefapixant had no effects on fertility and early embryonic development. Embryo-fetal development studies were conducted in rats and rabbits, and there was no evidence of teratogenicity. As other fetal effects, decreased fetal weight was observed in rats. A rabbit aborted, which was considered secondary to maternal systemic toxicity, e.g., decreases in body weight and food consumption. Gefapixant blood exposure ($AUC_{0\text{-}24h}$) at the NOAEL for embryo-fetal development in rats (300 mg/kg/day) was 53,000 ng·h/mL (gestation day 17), which was approximately 7-fold the human exposure ($AUC_{0\text{-}24h}$, 7,664 ng·h/mL). A study for effects on pre- and postnatal development, including maternal function, was conducted in rats (Table 16), and gefapixant

had no effects on maternal reproductive performance and pups. Total litter loss in the gefapixant-treated group was attributed to poor maternal care due to a gefapixant-related maternal systemic toxicity and not an effect of gefapixant on the reproductive performance of the dam or pup viability.

Table 16. Overview of reproductive and developmental toxicity studies

Type of study	Test system	Route of administration	Duration of dosing	Doses (mg/kg/day)	Noteworthy findings	NOAEL (mg/kg/day)	Attached document CTD
Fertility and early embryonic development to implantation	Male rat (SD)	Oral	from 28 days before cohabitation through the day before necropsy (TID)	0,[a] 120, 300, 675	Paternal animals: None	Paternal general toxicity: 675 Male fertility: 675	4.2.3.5.1.1
	Female rat (SD)	Oral	from 14 days before cohabitation through gestation day 7 (TID)	0,[a] 120, 300, 675	Maternal animals: 675: mild dehydration, hunched posture, renal pelvis dilatation Early embryonic development: None	Maternal general toxicity: 300 Female fertility: 675 Early embryonic development: 675	4.2.3.5.1.1
Embryo-fetal development	Female rat (SD)	Oral	Gestation day 7 through gestation day 17 (TID) Caesarean section: gestation day 21	0,[a] 120, 300, 675	Dams: 675: decreased body weight gain, decreased food consumption Fetuses: 675: decreased body weight	Maternal toxicity: 300 Embryo-fetal development: 300	4.2.3.5.2.2
	Female rabbit (NZW)	Oral	Gestation day 7 through gestation day 19 (QD) Caesarean section: gestation day 29	0,[a] 100, 400, 1,500	Dams: 1,500: abortion, decreases in body weight/food consumption Fetuses: No effects	Maternal toxicity: 400 Embryo-fetal development: 1,500	4.2.3.5.2.5
Pre- and postnatal development, including maternal function	Female rat (SD)	Oral	Dams: Gestation day 6 through lactation day 20 (TID)	0,[a] 120, 300, 675	Dams: 300: decreased body weight 675: mortality (2 of 24 animals), moribund sacrifice (2 of 24 animals), hunched posture, dehydration, piloerection, decreased motor activity, decreased body weight, decreased food consumption, renal pelvis dilatation, mottled tan and red on the interior and exterior surface of the kidney, distended ureter with calculi present, calculi in the urinary bladder, distended urinary bladder F1 pups: 675: total litter loss[b]	Maternal general toxicity: 120 Maternal reproductive toxicity: 675 F1 generation: 675	4.2.3.5.3.1

a) [redacted]

b) Total litter loss was attributed to poor maternal care due to a gefapixant-related maternal toxicity and not an effect of gefapixant on the reproductive performance of the dam or pup viability.

5.6 Local tolerance

Bovine corneal opacity and permeability test (BCOP) and skin corrosion test were conducted. In both tests, gefapixant was classified as a non-irritant (Table 17).

Table 17. Overview of local tolerance studies

Type of study	Test system	Test method	Noteworthy findings	Attached document CTD
BCOP	Isolated bovine corneas	A 20% gefapixant formulation was applied to the bovine corneal epithelium for 4 hours at 32℃ to assess corneal opacity and permeability.	Irritation score: −0.14 Gefapixant was classified as a non-irritant.	4.2.3.6.1
Skin corrosion test	MatTek EpiDerm™	Tissues were exposed with gefapixant 100 mg for 1, 4, and 24 hours, and cell viability was assessed.	MTT Effective Time−50: >24 hours Gefapixant was classified as a non-irritant.	4.2.3.6.2

5.7 Other studies

5.7.1 Skin sensitization study

A murine local lymph node assay (LLNA) was performed, and gefapixant was not considered a dermal sensitizer (Table 18).

Table 18. Overview of skin sensitization study

Type of study	Test system	Test method	Noteworthy findings	Attached document CTD
LLNA	Female mouse (CBA/J)	Mice were treated with 5%, 10%, or 25% gefapixant in N,N-dimethylformamide (DMF), positive control [25% (v/v) hexyl cinnamaldehyde], or vehicle control (DMF) once daily by topical application at the dorsum of each ear for 3 days.	None Gefapixant was not considered a dermal sensitizer.	4.2.3.7.2.1

5.7.2 Toxicologic evaluation of impurities

Impurities in the drug substance and drug product of gefapixant (Impurity A, Impurity B, Impurity C, Impurity D, Impurity E, Impurity F) were considered nonmutagenic when assessed using Derek Nexus, Sarah Nexus, and Case Ultra. A repeated oral dose toxicity study with these impurities was conducted in rats, and no toxicity findings were observed (Table 19).

Table 19. Study on impurities

Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Noteworthy findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (Wistar)	Oral	4 or 13 weeks (QD)	0,[a] 50[b]	None	50	4.2.3.7.6.1

a) [redacted]

b) Margins were calculated based on comparison of rat and human doses of impurities in the drug substance (Qualified level/Upper specification limit): Impurity A, 5-fold; Impurity B, 3.5-fold; Impurity C and Impurity D, 2.2-fold; Impurity E, 2-fold; Impurity F, 6.4-fold

5.7.3 Phototoxicity

Since gefapixant exhibits absorption in the ultraviolet wavelength region (240-340 nm), an *in vitro* phototoxicity study of gefapixant was conducted. Gefapixant was considered negative for phototoxicity (Table 20). No adverse events suggestive of phototoxicity have been reported in humans treated with gefapixant [see Section 7.R.3].

Table 20. Overview of phototoxicity study

Type of study	Test system	Test method	Noteworthy findings	Attached document CTD
Phototoxicity	Mouse fibroblast (Balb/c 3T3)	0,[a] 0.49, 1.23, 3.07, 7.68, 19.20, 48, 120, 300 μg/mL, irradiation with UVA 5 J/cm^2	No phototoxicity	Reference data 4.2.3.7.7.1

a) 3% DMSO-containing PBS

5.7.4 Crystalluria evaluation studies

Crystalluria was observed in rat and dog repeated-dose toxicity studies [see Section 5.2] and a rat carcinogenicity study [see Section 5.4]. Repeated-dose toxicity studies (rats [CTD 4.2.3.2.8][10)] and dogs [CTD4.2.3.2.12][11)]) and studies presented in Table 21 showed that the main component of crystalluria was gefapixant.

Table 21. Overview of crystalluria evaluation studies

Type of study	Test system	Test method	Noteworthy findings	Attached document CTD
A single oral dose study	Male and female rats (Wistar)	Following administration of gefapixant 2,000 mg/kg, urine samples were collected during 0-6 hours and 6-24 hours post-dose. Crystals in the urine samples were analyzed by Raman microspectroscopy.	Crystals in the urine had spectral consistent with gefapixant.	Reference data 4.2.3.7.7.4
A single oral dose study to evaluate crystalluria	Male and female dogs (Beagle)	Vehicle[a] was administered on Day 0 and a single dose of gefapixant 70 mg/kg was administered on Day 1. Urine samples were collected during 0-6 hours and 6-24 hours post-dose. Crystals in the urine samples were analyzed by Raman microspectroscopy.	Crystals in the urine had spectra consistent with gefapixant.	Reference data 4.2.3.7.7.8

a) [redacted]

5.R Outline of the review conducted by PMDA

5.R.1 Effects of crystalluria on renal function

The applicant's explanation:

Urinary organ injuries associated with crystals derived from gefapixant in the kidney, ureter, and urinary bladder were observed in both rodent and non-rodent. Given the gefapixant concentrations in human urine at the clinical dosage and the solubility of gefapixant in the urine [see Section 4.R], administration of gefapixant at the recommended clinical dose is unlikely to result in crystals in human urine, and there is little concern about effects on the renal function in clinical use of gefapixant.

PMDA's view:

Taking account of the applicant's explanation and given that gefapixant blood concentration-dependent injuries in the urinary system considered associated with crystalluria observed in animals have acceptable safety margins [see Section 5.2], gefapixant is unlikely to affect the human renal function. Meanwhile, the effects of gefapixant on the human renal function need to be assessed, taking also account of changes in renal function parameters etc. noted in clinical studies [see Section 7.R.3.2].

10) Calculi collected from the urinary bladder were analyzed by Fourier-transform infrared spectroscopy. Calculi were composed of gefapixant.
11) Calculi collected from the urinary bladder were analyzed by Fourier transform infrared spectroscopy. Calculi were composed of a mixture of gefapixant and urine matrix (high molecular weight components and cellular fragments).

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

The applicant submitted the following biopharmaceutic studies: a bioequivalence study, relative bioavailability studies, etc.

Formulations used in the clinical development of gefapixant are shown in Table 22. Study 040 assessed the bioequivalence between the phase III formulation and the proposed commercial formulation [see Section 6.1.1]. The phase III formulation resulted from formulation changes of [redacted], and an *in vitro* dissolution test [12)] demonstrated the comparability of dissolution profiles of the formulations.

Table 22. Formulations used in clinical development

	Dosage form	Active substance	[redacted]	Clinical studies
[redacted] formulation 1	[redacted]	gefapixant citrate	[redacted]	Phase I (Study 001)
[redacted] formulation 2	7.5-, 30-, 50-, 100-, and 300-mg tablets	[redacted]	[redacted]	Phase I (Studies 001, 007, and 020) Phase II (Study 010)
[redacted] formulation 3	7.5-, 20-, and 50-mg tablets		[redacted]	Phase I (Studies 020, 022, 024, 025, and 026) Phase II (Studies 010 and 012)
[redacted] formulation	50-mg tablets		[redacted]	Phase I (Studies 024 and 025)
Phase III formulation	15- and 45-mg tablets		[redacted]	Phase I (Studies 036, 040, and 044) Phase II (Study 033) Phase III (Studies 027, 030, and 038)
Proposed commercial formulation	15- and 45-mg tablets		[redacted]	Phase I (Study 040)

Gefapixant concentrations in human plasma, urine, and dialysate were determined by LC-MS/MS (LLOQ, [1.00 or 10.0 ng/mL] in plasma, [10.0 ng/mL or 1.00 μg/mL] in urine, [100 pg/mL] in dialysate). Unless otherwise specified, doses are expressed in terms of gefapixant, and pharmacokinetic parameters and the data are expressed as the mean ± SD.

6.1.1 Bioequivalence study (CTD 5.3.1.2.7, Study 040 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, open-label, 2-treatment, 2-period crossover study was conducted in non-Japanese healthy adult subjects to determine the bioequivalence between the phase III formulation and the proposed commercial formulation. Subjects were to receive a single oral dose of 45 or 15 mg of gefapixant under fasting conditions. The results are shown in Table 23. The 90% confidence intervals (CIs) for the C_{max}, AUC_{last}, and AUC_{inf} geometric mean ratios for the proposed commercial formulation vs. the phase III formulation were all within the predefined bioequivalence range of 0.80 to 1.25.

[12)] Dissolution test was performed according to [redacted] [[redacted] revolutions/minute, dissolution medium (900 mL) ([redacted] and [redacted] 12 tablets each)] using dissolution media (1st fluid for dissolution test [JP], diluted McIlvaine buffer [pH [redacted]], 2nd fluid for dissolution test [JP], water).

Table 23. Pharmacokinetic parameters of gefapixant following a single oral dose

Formulation		Dose (mg)	N	C_{max} (ng/mL)	AUC_{last} (μg·h/mL)	AUC_{inf} (μg·h/mL)	t_{max} (h)	Geometric mean ratio vs. phase III formulation [90% CI]		
								C_{max}	AUC_{last}	AUC_{inf}
45-mg tablet	Phase III formulation	45	19	463 ± 136	3.41 ± 0.672	3.57 ± 0.684	2.00 [1.00, 3.00]			
	Proposed commercial formulation	45	20	431 ± 127	3.28 ± 0.781	3.43 ± 0.797	1.77 [1.00, 4.01]	0.95 [0.86, 1.04]	0.97 [0.93, 1.01]	0.97 [0.93, 1.01]
15-mg tablet	Phase III formulation	15	20	139 ± 32	0.988 ± 0.204	1.10 ± 0.220	1.51 [1.02, 3.00]			
	Proposed commercial formulation	15	19	142 ± 33.5	0.996 ± 0.175	1.11 ± 0.186	2.00 [1.07, 3.00]	1.02 [0.96, 1.08]	1.02 [0.97, 1.06]	1.01 [0.98, 1.06]

Mean ± SD, Median [Range] for t_{max}

6.1.2 Relative bioavailability study (Reference data CTD 5.3.1.2.3, Study 020 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A partially randomized, open-label, 6-treatment, 6-period crossover study was conducted in non-Japanese healthy adult subjects to assess the relative bioavailability of 50 mg of [redacted] formulation 2 vs. 25[13] or 50 mg of [redacted] formulation 3, administered orally twice daily after a moderate-fat meal for 2 days and the effect of an acid reducer[14] on the pharmacokinetics of gefapixant. The results are shown in Table 24 and Table 25. Gefapixant exposure following administration of gefapixant alone was similar between the different formulations. Coadministration of [redacted] formulation 2 that does not contain [redacted] with an acid reducer resulted in decreased gefapixant exposure, whereas there was no clinically relevant effect of an acid reducer when administered with [redacted] formulation 3 that contains [redacted].

Table 24. Pharmacokinetic parameters of gefapixant following multiple-dose administration of [redacted] formulations

Group	Formulation (Dosing condition)	Dose (mg)	N	C_{max} (ng/mL)	AUC_{tau} (μg·h/mL)	t_{max} (h)	C_{min} (ng/mL)
A	Formulation 3 (after a moderate-fat meal)	25	13	257 ± 42.9	1.72 ± 0.276	2.00 [1.00, 3.00]	70.7 ± 15.9
B	Formulation 3 (after a moderate-fat meal)	50	13	510 ± 51.2	3.58 ± 0.498	2.00 [2.00, 5.00]	145 ± 32.4
C	Formulation 2 (after a moderate-fat meal)	50	13	519 ± 92.0	3.61 ± 0.555	2.00 [2.00, 3.00]	150 ± 29.1
D	Formulation 3 (after a moderate-fat meal, concomitant acid reducer)	25	13	231 ± 40.5	1.78 ± 0.277	3.00 [1.01, 5.01]	76.5 ± 17.9
E	Formulation 3 (after a moderate-fat meal, concomitant acid reducer)	50	13	577 ± 125	3.88 ± 0.571	2.00 [1.00, 5.00]	160 ± 32.9
F	Formulation 2 (after a moderate-fat meal, concomitant acid reducer)	50	13	329 ± 124	2.66 ± 1.04	3.00 [2.00, 8.00]	126 ± 55.0

Mean ± SD, Median [Range] for t_{max}

Table 25. Comparisons of pharmacokinetic parameters of gefapixant across different dosing conditions

Items assessed		Test group	Control group	Geometric mean ratio for test group vs. control group [90% CI]	
				C_{max}	AUC_{tau}
Relative bioavailability of Formulation 3 vs. Formulation 2		B	C	0.992 [0.902, 1.09]	0.993 [0.906, 1.09]
Effect of acid reducer on Formulation 2		F	C	0.602 [0.547, 0.662]	0.692 [0.631, 0.759]
Effect of acid reducer on Formulation 3	25 mg	D	A	0.898 [0.817, 0.987]	1.03 [0.943, 1.13]
	50 mg	E	B	1.11 [1.01, 1.22]	1.08 [0.987, 1.19]

6.1.3 Relative bioavailability study (Reference data CTD 5.3.1.2.5, Study 025 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, 5-treatment, 5-period, fixed treatment sequence study was conducted in non-Japanese healthy adult subjects to assess the relative bioavailability of a single oral dose of 50 mg of [redacted] formulation 3 vs. [redacted] formulation and the effect of food,[15] the effect of an acid reducer,[16] etc., on the pharmacokinetics of gefapixant. The results are shown in Table 26 and Table 27. Although gefapixant exposure following

[13] The 50-mg tablet was split into half for administration.
[14] The effect of acid reducer was assessed by pretreatment with omeprazole 20 mg QD.
[15] The effect of food was assessed using a high-fat meal (919 kcal, approximately 57% fat).
[16] The effect of acid reducer was assessed by pretreatment with omeprazole 40 mg QD.

administration of gefapixant alone after a high-fat meal was similar between the two formulations, gefapixant exposure tended to be higher with [redacted] formulation compared with [redacted] formulation 3 under fasting conditions. Following administration of [redacted] formulation, there were no effects of food or an acid reducer on the pharmacokinetics of gefapixant.

Table 26. Pharmacokinetic parameters of gefapixant following a single dose

Group	Formulation (Dosing condition)	N	C_{max} (ng/mL)	AUC_{last} (μg·h/mL)	AUC_{inf} (μg·h/mL)	t_{max} (h)
A	[redacted] formulation 3 (fasted)	14	351 ± 152	3.18 ± 1.12	3.47 ± 0.976[a)]	3.00 [2.00, 3.00]
B	[redacted] formulation (fasted)	13	417 ± 95.1	3.78 ± 0.666	3.98 ± 0.661	2.00 [1.00, 4.00]
C	[redacted] formulation (after a high-fat meal)	13	383 ± 68.0	3.62 ± 0.470	3.82 ± 0.434	2.00 [1.00, 4.00]
D	[redacted] formulation (fasted, concomitant acid reducer)	11	377 ± 62.3	3.58 ± 0.511	3.80 ± 0.507	3.00 [1.00, 4.00]
E	[redacted] formulation 3 (after a high-fat meal)	10	379 ± 52.2	3.66 ± 0.473	3.85 ± 0.455	3.00 [2.00, 4.00]

Mean ± SD, Median [Range] for t_{max}
a) N = 12

Table 27. Comparisons of pharmacokinetic parameters of gefapixant across different dosing conditions

Items assessed		Test group	Control group	Geometric mean ratio for test group vs. control group [90% CI]		
				C_{max}	AUC_{last}	AUC_{inf}
Relative bioavailability of [redacted] formulation vs. [redacted] formulation 3	Fasted	B	A	1.32 [1.00, 1.76]	1.26 [1.02, 1.57]	1.16 [0.99, 1.35]
	After a high-fat meal	C	E	1.00 [0.91, 1.09]	0.98 [0.92, 1.05]	0.98 [0.93, 1.04]
Effect of food on [redacted] formulation 3		E	A	1.23 [0.92, 1.65]	1.24 [0.99, 1.55]	1.14 [0.97, 1.34]
Effect of food on [redacted] formulation		C	B	0.93 [0.83, 1.04]	0.96 [0.89, 1.04]	0.96 [0.90, 1.04]
Effect of acid reducer on [redacted] formulation		D	B	0.91 [0.82, 1.02]	0.96 [0.88, 1.04]	0.97 [0.90, 1.05]

6.2 Clinical pharmacology

The applicant submitted clinical pharmacology data, in the form of the results from studies in healthy adult subjects, subjects with renal impairment, or elderly subjects and pharmacokinetic interaction studies, the results of a population pharmacokinetic analysis, etc. *In vitro* studies using human biomaterials are described in Sections 4.1, 4.2, 4.3, and 4.5. Unless otherwise specified, doses are expressed in terms of gefapixant, and pharmacokinetic parameters and the data are expressed as the mean ± SD.

6.2.1 Studies in healthy adult subjects

6.2.1.1 Foreign phase I study (Reference data CTD 5.3.3.1.1, Study 001 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Table 28 shows the pharmacokinetic parameters of gefapixant following a single oral dose of 10 to 1,800 mg of [redacted] formulation 1 or placebo in non-Japanese healthy adult subjects under fasting conditions. Gefapixant exposure was almost dose-proportional over the dose range of 10 to 450 mg, but less than dose-proportional over the dose range of 900 to 1,800 mg.

Table 28. Pharmacokinetic parameters of gefapixant following a single dose

Dose (mg)	N	C_{max} (μg/mL)	AUC_{last} (μg·h/mL)	AUC_{inf} (μg·h/mL)	$t_{1/2}$ (h)	t_{max} (h)	CL_r (L/h)	F_e (%)
10	8	0.0715 ± 0.0181	0.590 ± 0.141	0.607 ± 0.138	6.94 ± 1.22	1.50 [1.00, 2.00]	9.75 ± 1.88	53.1 ± 8.92
30	8	0.274 ± 0.0811	1.94 ± 0.256	1.97 ± 0.248	8.09 ± 1.32	1.50 [1.00, 2.00]	6.95 ± 1.05	40.9 ± 6.67
100	8	0.652 ± 0.208	5.27 ± 1.30	5.37 ± 1.29	9.18 ± 1.94	1.25 [1.00, 2.00]	8.74 ± 2.27	40.4 ± 9.31
200	8	1.32 ± 0.348	10.3 ± 2.80	10.5 ± 2.85	8.56 ± 1.19	1.00 [1.00, 2.00]	10.2 ± 1.25 [a)]	46.6 ± 11.9 [a)]
300	8	2.15 ± 0.706	15.3 ± 4.52	15.6 ± 4.55	9.27 ± 1.59	1.50 [1.00, 1.50]	8.34 ± 1.62	38.1 ± 8.25
450	8	3.89 ± 1.27	23.4 ± 5.27	23.7 ± 5.47	8.23 ± 1.50	1.50 [1.00, 3.00]	9.28 ± 3.88	45.0 ± 23.7
900	8	5.76 ± 0.452	35.7 ± 6.86	36.1 ± 6.85	8.09 ± 0.891	1.00 [0.500, 1.50]	8.75 ± 3.48	31.0 ± 8.56
1,800	8	8.70 ± 2.45	48.7 ± 13.5	49.3 ± 13.6	8.44 ± 1.07	1.00 [0.500, 2.00]	8.23 ± 4.66	20.3 ± 11.1

Mean ± SD, Median [Range] for t_{max}
a) N = 7

6.2.1.2 Foreign phase I study (Reference data CTD 5.3.3.1.4, Study 022 [[redacted] to [redacted]])

Table 29 shows the pharmacokinetic parameters of gefapixant in non-Japanese healthy adult subjects following multiple-dose administration. Subjects received 7.5 to 50 mg of [redacted] formulation 3 or placebo orally twice daily after a meal for 14 days. Gefapixant exposure was almost dose-proportional over the dose range tested, and gefapixant exposure on Day 7 was similar to that on Day 14.

Table 29. Pharmacokinetic parameters of gefapixant following multiple-dose administration

Dose (mg)	Sampling day	N	C_{max} (ng/mL)	$AUC_{0\text{-}12\ h}$ (μg·h/mL)	t_{max} (h)	CL_r (L/h)	F_e (%)
7.5	Day 1	8	60.3 ± 14.8	0.361 ± 0.0741	2.50 [1.50, 3.01]	—	—
	Day 7	8	74.5 ± 11.5	0.519 ± 0.0805	2.00 [1.50, 3.00]	—	—
	Day 14	8	73.7 ± 12.7	0.511 ± 0.106 [a)]	2.51 [1.50, 5.00]	8.69 ± 1.54	59.9 ± 13.6
15	Day 1	8	124 ± 20.6	0.859 ± 0.0870 [b)]	3.00 [2.00, 5.00]	—	—
	Day 7	8	173 ± 23.7	1.21 ± 0.159	2.46 [1.69, 3.02]	—	—
	Day 14	8	171 ± 27.4	1.22 ± 0.201 [a)]	2.00 [1.99, 5.01]	8.29 ± 1.97	65.5 ± 6.04
30	Day 1	8	238 ± 22.8	1.54 ± 0.156	2.00 [1.50, 3.02]	—	—
	Day 7	8	317 ± 44.3	2.16 ± 0.348	2.00 [1.50, 3.00]	—	—
	Day 14	8	322 ± 40.4	2.17 ± 0.335	2.03 [1.50, 3.00]	8.39 ± 1.55	59.6 ± 6.37
50	Day 1	8	383 ± 68.6	2.54 ± 0.412 [a)]	3.00 [2.00, 5.00]	—	—
	Day 7	8	511 ± 91.7	3.81 ± 0.607	3.00 [2.00, 3.00]	—	—
	Day 14	8	488 ± 83.6	3.76 ± 0.558 [a)]	3.00 [3.00, 5.00]	8.31 ± 2.22	61.4 ± 14.5

Mean ± SD; Median [Range] for t_{max}; —, not calculated
a) N = 7, b) N = 6

6.2.1.3 Mass balance study (Reference data CTD 5.3.3.1.5, Study 028 [[redacted] to [redacted]])

Following a single oral dose of ^{14}C-gefapixant 50 mg in non-Japanese healthy adult subjects (N = 6) under fasting conditions, the t_{max} values of plasma radioactivity and gefapixant (median [range]) were both 1.5 [1.0, 4.0] hours, and gefapixant accounted for 88 ± 3% of plasma radioactivity based on the AUC_{last}. The total recovery of radioactivity up to 120 hours post-dose was 98.9%, and urinary and fecal recoveries of radioactivity were 76.4% and 22.6%, respectively. In the urine (up to 48 hours post-dose), 64% of the dose was excreted unchanged, and M5 (4.2%), M13 (4.0%), M11 (1.8%), M1 (1.6%), and M8 (0.5%) were also detected. In the feces (up to 168 hours post-dose), 20% of the dose was excreted unchanged, and M13 (0.8%), M5 (0.7%), M6 (0.5%), and M11 (0.3%) were also detected. Approximately 14% of the dose was excreted as metabolites in the urine and feces.

6.2.1.4 Japanese phase I study (CTD 5.3.3.1.6, Study 024 [[redacted] to [redacted]])

Japanese healthy adult subjects received a single oral dose of 15, 30, 50, or 100 mg of [redacted] formulation 3 or placebo under fasting conditions or multiple oral doses of [redacted] formulation 3 or placebo twice daily after a meal for 15 days, and the pharmacokinetics of gefapixant were evaluated. The pharmacokinetic parameters of gefapixant are shown in Table 30 and Table 31. Following a single dose administration under fasting conditions, gefapixant exposure was less than dose-proportional over the dose range tested. Following multiple-dose administration after a meal, gefapixant exposure was almost dose-proportional over the dose range tested.

Table 30. Pharmacokinetic parameters of gefapixant following a single dose administration

Dose (mg)	N	C_{max} (ng/mL)	AUC_{last} (μg·h/mL)	AUC_{inf} (μg·h/mL)	$t_{1/2}$ (h)	t_{max} (h)	CL/F (L/h)	V_z/F (L)
15	6	181 ± 36.2	1.11 ± 0.251	1.25 ± 0.278	5.84 ± 1.42	1.75 [1.00, 2.00]	12.5 ± 2.71	102 ± 17.3
30	6	313 ± 62.1	2.25 ± 0.229	2.49 ± 0.300	7.75 ± 1.60	1.50 [1.00, 3.00]	12.2 ± 1.55	135 ± 24.1
50	6	224 ± 105	1.70 ± 0.739	1.93 ± 0.777	8.46 ± 2.26	2.00 [1.00, 3.00]	30.7 ± 15.8	350 ± 133
100	6	363 ± 238	2.71 ± 1.61	3.02 ± 1.69	8.95 ± 1.96	2.00 [2.00, 4.00]	41.8 ± 19.1	564 ± 321

Mean ± SD, Median [Range] for t_{max}

Table 31. Pharmacokinetic parameters of gefapixant following multiple-dose administration

Dose (mg)	Sampling day	N	C_{max} (ng/mL)	$AUC_{0\text{-}12\ h}$ (μg·h/mL)	t_{max} (h)	CL_r (L/h)	F_e (%)
15	Day 1	6	128 ± 25.0	0.841 ± 0.0904	3.00 [1.50, 4.00]	—	—
	Day 15	6	167 ± 26.0	1.23 ± 0.170	2.50 [1.50, 3.00]	7.93 ± 1.24	85.1 ± 8.95
30	Day 1	6	273 ± 59.4	1.73 ± 0.229	3.00 [1.50, 3.00]	—	—
	Day 15	6	360 ± 34.8	2.43 ± 0.182	1.75 [1.00, 3.00]	7.93 ± 0.735	86.3 ± 8.36
50	Day 1	6	465 ± 73.2	2.66 ± 0.374	3.50 [1.50, 4.00]	—	—
	Day 15	5	572 ± 56.0	4.02 ± 0.407	4.00 [3.00, 4.00]	7.79 ± 0.754	88.0 ± 6.96

Mean ± SD; Median [Range] for t_{max}; —, not calculated

The effect of food on the pharmacokinetics of gefapixant was assessed following a single oral dose of 50 mg of [redacted] formulation. The results are shown in Table 32.

Table 32. Pharmacokinetic parameters of gefapixant following a single oral dose

Dosing condition	N	C_{max} (ng/mL)	AUC_{last} (μg·h/mL)	AUC_{inf} (μg·h/mL)	t_{max} (h)	Geometric mean ratio vs. fasted administration [90% CI]		
						C_{max}	AUC_{last}	AUC_{inf}
Fasted	14	498 ± 104	4.14 ± 0.934	4.34 ± 0.925	1.50 [1.50, 4.00]			
After a high-fat meal	14	436 ± 65.5	3.76 ± 0.716	3.96 ± 0.675	2.50 [1.50, 4.00]	0.88 [0.82, 0.95]	0.91 [0.86, 0.97]	0.92 [0.87, 0.97]

Mean ± SD, Median [Range] for t_{max}

6.2.2 Intrinsic factor pharmacokinetic studies

6.2.2.1 Study in elderly subjects (Reference data CTD 5.3.3.3.1, Study 007 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Using [redacted] formulation 2, the effects of age and gender on the pharmacokinetics of gefapixant were investigated in non-Japanese healthy adult and elderly subjects. When gefapixant 300 mg was administered orally twice daily after a meal for 7 days, and then gefapixant 600 mg was administered orally twice daily after a meal for 14 days, the steady-state pharmacokinetic parameters of gefapixant are shown in Table 33. Although gefapixant exposure tended to be higher in elderly subjects (65-80 years) than in non-elderly subjects (18-55 years) and in women than in men, the results of a regression analysis showed no effects of age or gender on gefapixant exposure when eGFR was included in the model.

Table 33. Steady-state pharmacokinetic parameters of gefapixant following multiple-dose administration

Age	Gender	Sampling day	N	C_{max} (μg/mL)	$AUC_{0\text{-}12\ h}$ (μg·h/mL)	t_{max} (h)
18-55 years	Male	Day 7	8	2.37 ± 0.367	17.6 ± 3.30	3.00 [2.00, 5.00]
		Day 21	7	3.89 ± 0.876	29.4 ± 8.20	3.00 [2.00, 5.00]
	Female	Day 7	8	2.45 ± 0.573	19.7 ± 5.18	5.00 [2.00, 5.00]
		Day 21	8	4.65 ± 1.50	34.0 ± 10.8	3.00 [2.00, 5.00]
65-80 years	Male	Day 7	6	2.81 ± 0.282	22.8 ± 2.57[a)]	3.00 [3.00, 5.00]
		Day 21	5	3.64 ± 0.844	31.1 ± 4.88	4.99 [3.00, 8.00]
	Female	Day 7	5	3.16 ± 0.542	24.4 ± 2.71	3.00 [3.00, 3.10]
		Day 21	5	5.59 ± 0.444	38.8 ± 3.98	3.00 [3.00, 3.00]

Mean ± SD, Median [Range] for t_{max}
a) N = 5

6.2.2.2 Study in subjects with renal impairment (Reference data CTD 5.3.3.3.2, Study 026 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Table 34 shows the pharmacokinetic parameters of gefapixant following a single oral dose of 50 mg of [redacted] formulation 3 in non-Japanese subjects with renal impairment under fasting conditions, which suggested an increase in gefapixant exposure with decreasing renal function and removal of gefapixant by hemodialysis.

Table 34. Pharmacokinetic parameters of gefapixant following a single dose

Degree of renal impairment[a]		N	C_{max} (ng/mL)	AUC_{last} (μg·h/mL)	AUC_{inf} (μg·h/mL)	CL/F (L/hr)	$t_{1/2}$ (h)	Geometric mean ratio [90% CI][b]		
								C_{max}	AUC_{last}	AUC_{inf}
Normal		6	173 ± 95.7	2.00 ± 1.23	2.28 ± 1.16	25.7 ± 9.42	13.9 ± 5.30			
Moderate		6	338 ± 127	5.93 ± 1.95	6.45 ± 1.91	8.30 ± 2.25	18.6 ± 3.62	2.09 [1.22, 3.56]	3.23 [2.01, 5.20]	2.98 [2.01, 4.41]
Severe		6	311 ± 137	7.63 ± 3.08	9.97 ± 4.08	5.81 ± 2.47	39.2 ± 29.4	1.89 [1.10, 3.25]	4.08 [2.49, 6.70]	4.43 [2.82, 6.96]
End stage renal disease	Not requiring dialysis	6	281 ± 92.5	7.79 ± 2.74	9.99 ± 3.61	5.67 ± 2.28	33.3 ± 5.68	1.76 [1.06, 2.94]	4.21 [2.58, 6.86]	4.50 [2.91, 6.95]
	Requiring hemodialysis	6	228 ± 87.1	6.46 ± 2.64	8.59 ± 4.19	7.00 ± 3.09	33.9 ± 7.95	0.80 [0.56, 1.15]	0.82 [0.59, 1.13]	0.83 [0.57, 1.21]

Mean ± SD

a) Normal, eGFR ≥90 mL/min/1.73 m^2; moderate, eGFR 30-59 mL/min/1.73 m^2; severe, eGFR <30 mL/min/1.73 m^2; end stage renal disease, requiring hemodialysis 3 times a week

b) Ratios for moderate and severe renal impairment and end stage renal disease (not requiring dialysis) vs. normal renal function
Ratio for end stage renal disease (requiring hemodialysis) vs. end stage renal disease (not requiring dialysis)

6.2.3 Pharmacokinetic interaction studies

Two studies[17] were conducted to evaluate the potential for drug-drug interactions between gefapixant and a MATE1/2-K inhibitor, pyrimethamine or a substrate for OATP1B, pitavastatin. The pharmacokinetic parameters of gefapixant or pitavastatin are shown in Table 35 and Table 36. The applicant explained that there is little concern about drug interactions via MATE1/2-K inhibition by pyrimethamine or OATP1B inhibition by gefapixant, and that no dose adjustment of gefapixant or concomitant drugs is needed in clinical use of gefapixant.

Table 35. Effects of pyrimethamine on pharmacokinetic parameters of gefapixant (Study 036)

Dose[a]		N	C_{max} (ng/mL)	AUC_{last} (μg·h/mL)	AUC_{inf} (μg·h/mL)	CL/F (L/hr)	$t_{1/2}$ (h)	CL_r (L/hr)	Geometric mean ratio vs. without pyrimethamine [90% CI]		
Pyrimethamine	Gefapixant								C_{max}	AUC_{last}	AUC_{inf}
−	45 mg	12	434 ± 168	3.44 ± 0.546	3.63 ± 0.564	12.6 ± 1.70	7.90 ± 2.52	8.25 ± 1.34			
50 mg	45 mg	12	429 ± 156	4.32 ± 0.783	4.52 ± 0.749	10.2 ± 1.66	10.6 ± 2.24	5.86 ± 1.31	0.99 [0.90, 1.08]	1.25 [1.19, 1.31]	1.24 [1.19, 1.30]

Mean ± SD

a) A single oral dose regimen was used.

Table 36. Effects of gefapixant on pharmacokinetic parameters of pitavastatin (Study 044)

Dose[a]		N	C_{max} (ng/mL)	AUC_{last} (ng·h/mL)	AUC_{inf} (ng·h/mL)	CL/F (L/hr)	$t_{1/2}$ (h)	Geometric mean ratio vs. without gefapixant [90% CI]		
Gefapixant	Pitavastatin							C_{max}	AUC_{last}	AUC_{inf}
−	1 mg	20	19.3 ± 7.63	45.2 ± 21.0	48.5 ± 22.2	24.6 ± 10.2	15.1 ± 4.59			
45 mg	1 mg	20	18.6 ± 6.93	44.3 ± 20.6	47.0 ± 21.1	25.1 ± 9.70	13.1 ± 4.16	0.98 [0.90, 1.07]	0.98 [0.94, 1.03]	0.97 [0.93, 1.02]

Mean ± SD

a) Gefapixant BID orally, a single oral dose of pitavastatin

6.2.4 Evaluation of risk of QT interval prolongation by plasma drug concentration-response modeling (Reference data CTD 5.3.5.3.1 and 5.3.5.3.2)

Based on the data from 2 phase I studies in non-Japanese healthy adult subjects (Studies 001 and 007), a plasma drug concentration-response analysis was performed using a linear mixed-effects model. According to this

[17] Reference data CTD 5.3.3.4.1, Study 036 [March 2019 to April 2019]; Reference data CTD 5.3.3.4.2, Study 044 [July 2019 to September 2019]

analysis, the upper limits of the 90% confidence intervals for the model-based ΔΔQTcP and ΔΔQTcF (7.66 and 6.63 ms, respectively) at the geometric mean C_{max} after a single oral dose of gefapixant 1,800 mg in Study 001 (8,168 ng/mL) were below 10 ms. The upper limit of the 90% confidence interval for the model-based ΔΔQTcF (0.68 ms) at the geometric mean C_{max} after 14-day oral administration of gefapixant 600 mg BID in Study 007 (3,481 ng/mL) was below 10 ms.

Based on the above results, the applicant explained that the risk of QT interval prolongation is low at the clinical dose of gefapixant.

6.3 Population pharmacokinetic analysis (Reference data CTD 5.3.3.5.1)

Using the data from 9 Japanese or foreign clinical studies in healthy adult subjects or patients with chronic cough[18)] (1,618 subjects, 8,886 sampling points), a population pharmacokinetic analysis (NONMEM version 7.3) was performed.

The pharmacokinetics of gefapixant were described by a 2-compartment model with lagged first order absorption. eGFR, age, body weight, and gender were chosen as covariates on CL/F, age, gender, and body weight as covariates on Vc/F, and food intake (only administration of [redacted] formulation 3) as a covariate on k_a (absorption rate constant) and incorporated in the final model.[19)]

Table 37 shows the final model-predicted pharmacokinetic parameters of gefapixant at steady state after oral administration of gefapixant 15 or 45 mg BID in Japanese and non-Japanese patients with chronic cough enrolled in Study 027. Among the incorporated covariates, severe renal impairment had a clinically meaningful effect on the pharmacokinetic of gefapixant.

Table 37. Pharmacokinetic parameters of gefapixant at steady state in Japanese and non-Japanese patients with chronic cough enrolled in Study 027 (*Post hoc* estimates)

Dosing regimen	Race	N	AUC_{tau} (μg·h/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)
15 mg BID orally	Japanese	6	1.36 ± 0.276	180 ± 29.4	63.8 ± 18.2
	Non-Japanese	238	1.46 ± 0.418	185 ± 38.9	73.3 ± 30.8
45 mg BID orally	Japanese	14	3.91 ± 0.771	544 ± 83.8	170 ± 52.6
	Non-Japanese	229	4.41 ± 1.27	559 ± 122	220 ± 90.4

Mean ± SD

6.4 Exposure-response analysis (Reference data CTD 5.3.5.3.3)

Using efficacy data obtained from Study 027 [see Section 7.2.1] and Study 030 [see Section 7.2.2] in patients with chronic cough and individual AUC_{tau} values estimated from the population pharmacokinetic analysis [see Section 6.3], an exposure-response analysis was performed. Cough frequency was described by a maximal effect (E_{max}) model that took into account a time-dependent decrease in the placebo effect, and the AUC_{tau} associated with 50% of the maximal effect ($EAUC_{50}$) was estimated at 2.65 μg·h/mL.

[18)] Phase I studies (011, 020, 022, 024, 025, 026), a phase II study (012), and phase III studies (027 and 030)

[19)] The potential covariates tested were eGFR, age, body weight, gender, race (Caucasian/Asian/Black/others), and ethnicity (Hispanic/non-Hispanic/others) for CL/F, age, body weight, gender, race, and ethnicity for V_c/F, and food intake, concomitant use of PPI, and formulation for absorption lag time and k_a.

6.R Outline of the review conducted by PMDA

6.R.1 Ethnic differences in the pharmacokinetics of gefapixant

The applicant's explanation about ethnic differences in the pharmacokinetics of gefapixant:

In Study 024 in Japanese healthy adult subjects [see Section 6.2.1.4] and Study 025 in non-Japanese healthy adult subjects [see Section 6.1.3], the pharmacokinetics of gefapixant following a single oral dose of 50 mg of [redacted] formulation 3 or [redacted] formulation were similar between Japanese and non-Japanese subjects, either under fasting conditions or after a high-fat meal.

According to the population pharmacokinetic analysis based on the data from Japanese and foreign clinical studies [see Section 6.3], there were no marked differences in the final model-predicted steady-state pharmacokinetic parameters following multiple dosing of gefapixant 15 or 45 mg between Japanese and non-Japanese patients with chronic cough (Table 37).

Based on the above, there were no clinically relevant differences in the pharmacokinetics of gefapixant between Japanese and non-Japanese subjects.

PMDA accepted the above explanation.

6.R.2 Dose adjustment of gefapixant in patients with hepatic or renal impairment

The applicant's explanation about the need for dose adjustment of gefapixant in patients with hepatic or renal impairment:

Although no clinical pharmacology study in subjects with hepatic impairment has been conducted, as hepatic metabolism or excretion accounts for <20% of the clearance of gefapixant [see Section 6.2.1.3], hepatic impairment should have no impact on gefapixant exposure. Thus, no dose adjustment of gefapixant is required in patients with hepatic impairment.

Renal excretion has been suggested to contribute significantly to the clearance of gefapixant [see Section 4.4.1], and a clinical pharmacology study in subjects with renal impairment [see Section 6.2.2.2] showed that gefapixant exposure tended to increase according to the degree of renal impairment. Table 38 shows the pharmacokinetic parameters of gefapixant by severity of renal impairment based on the population pharmacokinetic analysis [see Section 6.3].

Based on the above, no dose adjustment of gefapixant is required in patients with mild or moderate renal impairment because no clinically important increases in gefapixant exposure are expected. On the other hand, an increase in gefapixant exposure in patients with severe renal impairment is close to the upper clinical bound of exposure to gefapixant (the AUC of gefapixant, 2.0-fold)[20] as the range of the relative changes that are

[20] Although adverse findings associated with crystallization of the drug in the urinary tract were noted in non-clinical studies [see Section 5.R.1], no crystals similar to triple phosphate were observed in urine at exposure levels up to 5-fold the AUC at 45 mg BID in Study 007 [see Section 6.2.2.1]. However, as there is no clinical experience with long-term administration of gefapixant at those exposure levels, the upper clinical bound was established conservatively at 2-fold (corresponding to the AUC of 8.29 μg·hr/mL).

clinically unimportant for the efficacy and safety of gefapixant in patients with chronic cough. Thus, the 45 mg QD regimen of gefapixant should be used in patients with severe renal impairment.

Table 38. Pharmacokinetic parameters of gefapixant at steady state following multiple oral doses of gefapixant 45 mg by severity of renal impairment

Regimen	Severity of renal impairment[a)]	N	AUC_{tau} (μg·h/mL)	C_{max} (ng/mL)	Geometric mean ratio [90% CI] (Renal impairment/normal renal function)	
					$AUC_{0\text{-}24\ h}$	C_{max}
BID	Normal	670	3.82 [3.73, 3.91]	508 [498, 519]		
	Mild	817	4.47 [4.37, 4.58]	554 [543, 565]	1.17 [1.14, 1.20]	1.09 [1.06, 1.12]
	Moderate	2246	5.57 [5.44, 5.71]	644 [631, 657]	1.46 [1.42, 1.50]	1.27 [1.24, 1.30]
	Severe	126	7.22 [7.05, 7.39]	785 [769, 802]	1.89 [1.84, 1.94]	1.54 [1.5, 1.58]
QD	Severe	126	7.29 [7.12, 7.47]	524 [515, 534]	0.954 [0.93, 0.98]	1.03 [1.0, 1.06]

Geometric mean [95% CI]
a) Normal, eGFR ≥90 mL/min/1.73m^2; mild, eGFR ≥60 mL/min/1.73m^2 and <90 mL/min/1.73m^2;
moderate, eGFR ≥30 mL/min/1.73m^2 and <60 mL/min/1.73m^2; severe, eGFR ≥15 mL/min/1.73m^2 and <30 mL/min/1.73m^2

In patients with end stage renal disease requiring dialysis, as urine volume and dialysis treatment regimen change over time and vary from patient to patient, it is difficult to predict gefapixant exposure. Although there are currently no sufficient data to select the optimal dosing regimen for these patients, Study 026 [see Section 6.2.2.2] raised no safety concerns.

PMDA accepted the above explanation.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted the efficacy and safety evaluation data, in the form of the results from studies presented in Table 39.

Table 39. Listing of efficacy and safety clinical studies

Geographical location	Study ID	Phase	Study population	No. of subjects	Dosing regimen	Main endpoints [Primary endpoint]
Foreign	010	II	Chronic cough	Cohort 1 29 Cohort 2 30	Gefapixant[a)] or placebo BID orally in a crossover fashion in treatment periods 1 and 2	Efficacy [Awake objective cough frequency] Safety
Foreign	012	II	Chronic cough	(1) 64 (2) 63 (3) 63 (4) 63	(1) Gefapixant 7.5 mg (2) Gefapixant 20 mg (3) Gefapixant 50 mg (4) Placebo BID orally for 12 weeks	Efficacy [Change from baseline in awake cough frequency at Week 12] Safety
Japan	033	II	Chronic cough	(1) 11 (2) 12	(1) Gefapixant 45 mg (2) Placebo BID orally for 4 weeks	Safety Efficacy
Global	027	III	Chronic cough	(1) 244 (2) 244 (3) 244	(1) Gefapixant 15 mg (2) Gefapixant 45 mg (3) Placebo BID orally for 52 weeks	Efficacy [24-hour cough frequency (coughs/hour) at Week 12] Safety
Foreign	030	III	Chronic cough	(1) 442 (2) 439 (3) 436	(1) Gefapixant 15 mg (2) Gefapixant 45 mg (3) Placebo BID orally for 52 weeks	Efficacy [24-hour cough frequency (coughs/hour) at Week 24] Safety
Japan	038	III	Chronic cough	(1) 84 (2) 85	(1) Gefapixant 15 mg (2) Gefapixant 45 mg BID orally for 52 weeks	Safety Efficacy

a) The doses of gefapixant in each cohort are as follows: Cohort 1, 50, 100, 150, or 200 mg; Cohort 2, 7.5, 15, 30, or 50 mg

7.1 Phase II studies

7.1.1 Foreign study in patients with chronic cough (CTD 5.3.5.1.1, Study 010 [March 2015 to February 2016])

A placebo-controlled, randomized, double-blind, 2-treatment, 2-period crossover, dose-escalation study was conducted in the US to assess the efficacy and safety of gefapixant in patients with chronic cough (Table 40) (target sample size, 60 subjects [30 per cohort]).

Table 40. Key inclusion/exclusion criteria

Key inclusion criteria
(1) Refractory chronic cough[21)] for ≥1 year
(2) Chest radiograph or computed tomography scan of the thorax within 12 months of screening not demonstrating any abnormality considered to be significantly contributing to the chronic cough or any other clinically significant lung disease
(3) A score of ≥40 mm on cough severity VAS at screening
(4) 18-80 years of age
Key exclusion criteria
(1) Individuals who had given up smoking within 6 months of screening, or those with >20 pack-year smoking history
(2) FEV_1/FVC <60%
(3) History of upper or lower respiratory tract infection or recent clinically significant change in pulmonary status within 4 weeks of baseline visit
(4) Individuals who had taken an angiotensin converting enzyme inhibitor within 4 weeks prior to baseline visit
(5) eGFR <60 mL/min/1.73 m^2 at screening
(6) History of renal disease
(7) History of kidney/bladder stones within 5 years of screening
(8) History of conditions or disorders that predisposed to nephrolithiasis
(9) Systolic blood pressure >160 mmHg or diastolic blood pressure >90 mmHg at screening

The study included 2 cohorts. Subjects in each cohort were to receive gefapixant or placebo in Period 1 and then crossed-over to the alternative treatment in Period 2 following the washout period. Gefapixant or placebo was to be administered orally twice daily. Subjects in cohort 1 were to receive ascending doses of gefapixant 50, 100, 150, and 200 mg for 4 days each, and the washout period was 3 to 7 days. Subjects in cohort 2 were to receive ascending doses of gefapixant 7.5, 15, 30, and 50 mg for 4 days each, and the washout period was 14 to 21 days.

All of 59 randomized subjects (29 in Cohort 1, 30 in Cohort 2) received at least 1 dose of study drug and were included in the safety set. Of whom, those who provided at least one baseline and one post-baseline endpoint observations were included in the full analysis set (FAS) (29 in Cohort 1, 30 in Cohort 2), and the FAS was used as the efficacy analysis population.

The discontinuation rates were 10.3% (3 of 29 subjects) in Cohort 1 and 3.3% (1 of 30 subjects) in Cohort 2, and the reasons for discontinuations were all adverse events.

The results of the primary efficacy endpoint of awake objective cough frequency are shown in Table 41.

[21)] A cough that was unresponsive to at least 8 weeks of targeted treatment for identified underlying triggers including reflux disease, asthma, and post-nasal drip, or unexplained cough (a cough for which no objective evidence of an underlying trigger could be determined after investigation)

Table 41. Awake cough frequency (coughs/hour) (FAS)

			Gefapixant	Placebo
Cohort 1	Baseline		54.5 ± 41.1 (28)	52.8 ± 40.4 (26)
			37.0 [7.1, 155.1] 25.2, 70.8	43.3 [8.0, 139.8] 16.7, 84.0
	50 mg	End of treatment	29.9 ± 22.5 (26)	51.1 ± 39.5 (27)
			23.1 [3.7, 101.7] 16.6, 37.7	38.2 [5.7, 129.4] 15.5, 78.6
		Ratio of end of treatment vs. baseline in cough frequency [95% CI][a),c)]	0.56 [0.43, 0.72]	0.95 [0.73, 1.23]
		Relative reduction vs. placebo [95% CI] (%)[a),b),c)]	−41.2 [−59.3, −15.1]	
	100 mg	End of treatment	25.7 ± 19.1 (24)	51.0 ± 39.1 (26)
			22.1 [1.9, 68.0] 10.3, 35.7	40.9 [3.3, 144.3] 16.6, 69.7
		Ratio of end of treatment vs. baseline in cough frequency [95% CI][a),c)]	0.46 [0.34, 0.61]	0.95 [0.71, 1.28]
		Relative reduction vs. placebo [95% CI] (%)[a),b),c)]	−52.0 [−68.2, −27.4]	
	150 mg	End of treatment	26.0 ± 17.9 (23)	56.0 ± 48.7 (24)
			26.8 [2.2, 60.5] 9.9, 43.4	41.4 [4.1, 169.5] 16.4, 87.5
		Ratio of end of treatment vs. baseline in cough frequency [95% CI][a),c)]	0.48 [0.35, 0.65]	0.90 [0.65, 1.24]
		Relative reduction vs. placebo [95% CI] (%)[a),b),c)]	−46.9 [−66.3, −16.2]	
	200 mg	End of treatment	28.0 ± 23.8 (25)	54.0 ± 39.3 (27)
			21.2 [1.1, 105.1] 9.9, 43.7	51.1 [4.4, 161.8] 20.4, 77.7
		Ratio of end of treatment vs. baseline in cough frequency [95% CI][a),c)]	0.45 [0.33, 0.63]	1.06 [0.75, 1.48]
		Relative reduction vs. placebo [95% CI] (%)[a),b),c)]	−57.1 [−73.4, −30.8]	
Cohort 2	Baseline		49.6 ± 44.0 (30)	46.1 ± 39.8 (29)
			35.7 [0.1, 169.5] 18.1, 76.4	32.9 [0.7, 147.3] 14.4, 59.8
	7.5 mg	End of treatment	39.3 ± 36.0 (29)	44.8 ± 34.9 (28)
			35.9 [0.4, 164.4] 16.8, 55.1	39.5 [0, 139.0] 18.4, 62.7
		Ratio of end of treatment vs. baseline in cough frequency [95% CI][a),c)]	0.80 [0.66, 0.96]	0.93 [0.77, 1.13]
		Relative reduction vs. placebo [95% CI] (%)[a),b),c)]	−14.7 [−35.3, 12.5]	
	15 mg	End of treatment	34.8 ± 31.4 (30)	41.4 ± 33.3 (29)
			19.7 [0.1, 103.2] 14.0, 51.2	42.6 [0.8, 119.5] 12.9, 56.8
		Ratio of end of treatment vs. baseline in cough frequency [95% CI][a),c)]	0.67 [0.57, 0.80]	0.90 [0.75, 1.08]
		Relative reduction vs. placebo [95% CI] (%)[a),b),c)]	−25.2 [−42.0, −3.4]	
	30 mg	End of treatment	26.8 ± 26.3 (29)	48.2 ± 42.4 (29)
			20.4 [0.1, 101.4] 10.2, 32.4	38.4 [0.1, 145.5] 10.4, 66.1
		Ratio of end of treatment vs. baseline in cough frequency [95% CI][a),c)]	0.53 [0.40, 0.69]	0.84 [0.64, 1.10]
		Relative reduction vs. placebo [95% CI] (%)[a),b),c)]	−37.1 [−57.3, −7.4]	
	50 mg	End of treatment	27.0 ± 27.4 (29)	50.6 ± 34.4 (27)
			26.0 [0.1, 96.8] 5.3, 41.2	49.1 [3.5, 138.7] 22.7, 74.9
		Ratio of end of treatment vs. baseline in cough frequency [95% CI][a),c)]	0.44 [0.32, 0.60]	1.00 [0.72, 1.38]
		Relative reduction vs. placebo [95% CI] (%)[a),b),c)]	−55.9 [−71.9, −30.8]	

Mean ± SD (N); Upper shaded row, Median [Min., Max.,]; Lower shaded row, 1st quartile, 3rd quartile

a) The least squares estimate of the geometric mean

b) {(Ratio of end of treatment vs. baseline in cough frequency in the gefapixant group)/(Ratio of end of treatment vs. baseline in cough frequency in the placebo group) − 1} ×100

c) Change from baseline in awake cough frequency at the end of treatment was analyzed using a mixed effect repeated measures (MMRM) model with period, treatment, dose, the interaction of period by treatment, the interaction of period by dose, the interaction of treatment by dose, and the interaction of period by treatment by dose as fixed effects and the mean baseline value of period 1 and the relevant period and the baseline value of the relevant period as covariates. A heterogeneous compound symmetry covariance matrix was used to model the correlation between different treatment measurements within the same subject.

In cohort 1, the incidences of adverse events were 60.7% (17 of 28 subjects) in the 50 mg dosing period, 81.5% (22 of 27 subjects) in the 100 mg dosing period, 88.5% (23 of 26 subjects) in the 150 mg dosing period, 92.3% (24 of 26 subjects) in the 200 mg dosing period, and 50.0% (14 of 28 subjects) in the placebo dosing period. In

cohort 2, the incidences of adverse events were 26.7% (8 of 30 subjects) in the 7.5 mg dosing period, 33.3% (10 of 30 subjects) in the 15 mg dosing period, 66.7% (20 of 30 subjects) in the 30 mg dosing period, 76.7% (23 of 30 subjects) in the 50 mg dosing period, and 31.0% (9 of 29 subjects) in the placebo dosing period. The main events are shown in Table 42.

No deaths were reported.

In cohort 1, the incidences of serious adverse events were 3.7% (1 of 30 subjects) (vasovagal reflex, dehydration, and serum creatinine increased) in the 100 mg dosing period and 3.6% (1 of 28 subjects) (invasive ductal breast carcinoma) in the placebo dosing period. In cohort 2, the incidence of serious adverse events was 3.3% (1 of 30 subjects) (cerebrovascular accident) in the 50 mg dosing period. A causal relationship to study drug could not be ruled out for 1 case (serum creatinine increased) in the 100 mg dosing period in cohort 1.

The incidences of adverse events leading to discontinuation were 3.6% (1 of 28 subjects) in the 50 mg dosing period, 3.7% (1 of 27 subjects) in the 100 mg dosing period, and 3.6% (1 of 28 subjects) in the placebo dosing period in cohort 1 and 3.3% (1 of 30 subjects) in the 50 mg dosing period in cohort 2.

In cohort 1, the incidences of adverse drug reactions were 60.7% (17 of 28 subjects) in the 50 mg dosing period, 81.5% (22 of 27 subjects) in the 100 mg dosing period, 88.5% (23 of 26 subjects) in the 150 mg dosing period, 92.3% (24 of 26 subjects) in the 200 mg dosing period, and 14.3% (4 of 28 subjects) in the placebo dosing period. In cohort 2, the incidences of adverse drug reactions were 13.3% (4 of 30 subjects) in the 7.5 mg dosing period, 16.7% (5 of 30 subjects) in the 15 mg dosing period, 53.3% (16 of 30 subjects) in the 30 mg dosing period, 63.3% (19/30 subjects) in the 50 mg dosing period, and 6.9% (2 of 29 subjects) in the placebo dosing period.

Table 42. Adverse events reported by ≥5.0% of subjects in any dosing period (Safety set)

Event term	Cohort 1					Cohort 2				
	50 mg (N = 28)	100 mg (N = 27)	150 mg (N = 26)	200 mg (N = 26)	Placebo (N = 28)	7.5 mg (N = 30)	15 mg (N = 30)	30 mg (N = 30)	50 mg (N = 30)	Placebo (N = 29)
Dysgeusia	13 (46.4)	19 (70.4)	21 (80.8)	21 (80.8)	1 (3.6)	2 (6.7)	2 (6.7)	14 (46.7)	16 (53.3)	0
Hypogeusia	2 (7.1)	4 (14.8)	4 (15.4)	4 (15.4)	0	0	0	0	0	0
Paraesthesia oral	2 (7.1)	2 (7.4)	2 (7.7)	3 (11.5)	0	0	0	2 (6.7)	2 (6.7)	0
Urine output decreased	2 (7.1)	2 (7.4)	2 (7.7)	1 (3.8)	0	0	0	0	0	0
Ageusia	2 (7.1)	1 (3.7)	1 (3.8)	1 (3.8)	0	0	0	0	2 (6.7)	0
Hypoaesthesia oral	1 (3.6)	3 (11.1)	2 (7.7)	3 (11.5)	0	0	0	1 (3.3)	1 (3.3)	0
Dry mouth	1 (3.6)	1 (3.7)	1 (3.8)	1 (3.8)	0	0	0	1 (3.3)	1 (3.3)	2 (6.9)
Flank pain	1 (3.6)	1 (3.7)	0	2 (7.7)	0	0	0	0	0	0
Cough	0	1 (3.7)	2 (7.7)	1 (3.8)	0	0	0	0	0	0
Viral upper respiratory tract infection	0	0	0	0	2 (7.1)	0	0	0	0	0
Rhinitis	0	0	0	0	1 (3.6)	2 (6.7)	2 (6.7)	2 (6.7)	0	0
Upper respiratory tract infection	0	0	0	0	1 (3.6)	0	0	0	4 (13.3)	0
Nasal dryness	0	0	0	0	0	2 (6.7)	2 (6.7)	2 (6.7)	2 (6.7)	0

n (%)

7.1.2 Foreign study in patients with chronic cough (CTD 5.3.5.1.2, Study 012 [December 2015 to November 2016])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in the US and the UK to assess the efficacy and safety of gefapixant in patients with chronic cough (Table 43) (target sample size, 200 subjects [50 per group][22)]).

Table 43. Key inclusion/exclusion criteria

Key inclusion criteria
(1) Refractory or unexplained chronic cough for ≥1 year
(2) Chest radiograph or computed tomography scan of the thorax within 5 years of screening not demonstrating any abnormality considered to be significantly contributing to the chronic cough or any other clinically significant lung disease
(3) A score of ≥40 mm on cough severity VAS at screening
(4) 18-80 years of age
Key exclusion criteria
(1) Individuals who had given up smoking within 6 months of screening
(2) FEV_1/FVC <60%
(3) History of upper or lower respiratory tract infection or recent clinically significant change in pulmonary status within 4 weeks of baseline visit
(4) Individuals who had taken an angiotensin converting enzyme inhibitor within 4 weeks prior to baseline visit
(5) eGFR <60 mL/min/1.73 m^2 at screening
(6) History of cystic fibrosis or bronchiectasis
(7) History of renal disease
(8) History of kidney/bladder stones within 5 years of screening
(9) History of conditions or disorders that predisposed to nephrolithiasis
(10) Systolic blood pressure >160 mmHg or diastolic blood pressure >90 mmHg at screening

Gefapixant 7.5, 20, or 50 mg, or placebo was to be administered orally twice daily for 12 weeks.

Among 253 randomized subjects (64 in the 7.5 mg group, 63 in the 20 mg group, 63 in the 50 mg group, 63 in the placebo group), 252 subjects (63 per group) after excluding 1 subject who did not receive study drug were included in the safety set. Of whom, those who provided at least one baseline and one post-baseline primary endpoint observations were included in the FAS (59 in the 7.5 mg group, 59 in the 20 mg group, 57 in the 50 mg group, 61 in the placebo group), and the FAS was used as the efficacy analysis population.

The discontinuation rates were 12.5% (8 of 64 subjects) in the 7.5 mg group, 7.9% (5 of 63 subjects) in the 20 mg group, 20.6% (13 of 63 subjects) in the 50 mg group, and 7.9% (5 of 63 subjects) in the placebo group. The main reason for discontinuations was adverse events (3.1% [2 of 64 subjects] in the 7.5 mg group, 4.8% [3 of 63 subjects] in the 20 mg group, 15.9% [10 of 63 subjects] in the 50 mg group, 3.2% [2 of 63 subjects] in the placebo group).

The results of the primary efficacy endpoint of the change from baseline in awake cough frequency at Week 12 are shown in Table 44.

[22)] Assuming an expected difference of 25 for each dose of gefapixant vs. placebo for the primary endpoint of the change from baseline in awake cough frequency (coughs/hour) at Week 12 and a standard deviation of 38 in each group, 43 patients per group were required to achieve 85% power at a two-sided significance level of 5%. Allowing for a dropout rate of 13%, a sample size of 50 patients per group (200 patients to be randomized into 4 groups) was chosen.

Table 44. Awake cough frequency at Week 12 (coughs/hour) (FAS)

Treatment group	7.5 mg	20 mg	50 mg	Placebo
Baseline	48.3 ± 95.8 (59)	37.0 ± 32.3 (59)	39.8 ± 40.6 (57)	36.4 ± 26.2 (61)
	27.5 [1.3, 733.5] 14.4, 48.2	28.2 [0.4, 171.8] 14.1, 53.4	28.0 [2.7, 268.2] 18.2, 49.6	31.7 [1.9, 116.9] 15.8, 49.4
Week 12	37.7 ± 85.9 (56)	23.0 ± 18.9 (56)	16.7 ± 12.7 (51)	29.6 ± 25.4 (57)
	13.9 [0.5, 511.3] 6.5, 34.8	19.8 [0, 70.3] 6.6, 34.9	12.5 [0.4, 47.8] 6.0, 24.3	21.6 [1.3, 104.1] 7.7, 44.2
Ratio of Week 12 to baseline cough frequency [95% CI][a),c)]	0.53 [0.43, 0.65]	0.52 [0.42, 0.65]	0.42 [0.34, 0.53]	0.67 [0.55, 0.83]
Relative reduction vs. placebo [95% CI] (%)[a),b),c)]	−22.0 [−41.8, 4.6]	−22.2 [−42.0, 4.3]	−37.0 [−53.3, −14.9]	
P-value[c),d)]	—	0.0928	0.0027	

Mean ± SD (N); Upper shaded row, Median [Min., Max.]; Lower shaded row, 1st quartile, 3rd quartile

a) The least squares estimate of the geometric mean

b) ｛(Ratio of Week 12 to baseline cough frequency in gefapixant group)/(Ratio of Week 12 to baseline cough frequency in placebo group) − 1｝ × 100

c) Change from baseline in log-transformed awake cough frequency at each time point was analyzed using a MMRM model that included fixed effects for treatment group, visit, country, and the treatment-by-visit interaction, and the log-transformed baseline value as a covariate. An unstructured covariance matrix was used to model the correlation among repeated measurements.

d) Two-sided significance level of 5%, A closed testing procedure (sequentially from a comparison between the highest dose and placebo groups) was used to adjust for the multiplicity of hypothesis tests.

The incidences of adverse events were 69.8% (44 of 63 subjects) in the 7.5 mg group, 85.7% (54 of 63 subjects) in the 20 mg group, 92.1% (58 of 63 subjects) in the 50 mg group, and 61.9% (39 of 63 subjects) in the placebo group. The main events are shown in Table 45.

No deaths were reported.

A serious adverse event occurred in 1.6% (1 of 63) of subjects in the 50 mg group (frostbite), and its causal relationship to study drug could not be ruled out.

The incidences of adverse events leading to discontinuation were 3.2% (2 of 63 subjects) in the 7.5 mg group, 4.8% (3 of 63 subjects) in the 20 mg group, 15.9% (10 of 63 subjects) in the 50 mg group, and 3.2% (2 of 63 subjects) in the placebo group.

The incidences of adverse drug reactions were 30.2% (19 of 63 subjects) in the 7.5 mg group, 68.3% (43 of 63 subjects) in the 20 mg group, 87.3% (55 of 63 subjects) in the 50 mg group, and 34.9% (22 of 63 subjects) in the placebo group.

Table 45. Adverse events reported by ≥5.0% of subjects in any group (Safety set)

Event term	7.5 mg (N = 63)	20 mg (N = 63)	50 mg (N = 63)	Placebo (N = 63)
Dysgeusia	6 (9.5)	21 (33.3)	30 (47.6)	3 (4.8)
Upper respiratory tract infection	5 (7.9)	9 (14.3)	6 (9.5)	2 (3.2)
Blood creatine phosphokinase increased	5 (7.9)	2 (3.2)	0	0
Headache	4 (6.3)	12 (19.0)	4 (6.3)	3 (4.8)
Paraesthesia oral	4 (6.3)	5 (7.9)	4 (6.3)	5 (7.9)
Urinary tract infection	3 (4.8)	5 (7.9)	2 (3.2)	2 (3.2)
Cough	2 (3.2)	5 (7.9)	5 (7.9)	2 (3.2)
Hypoaesthesia oral	2 (3.2)	4 (6.3)	5 (7.9)	3 (4.8)
Dry mouth	2 (3.2)	3 (4.8)	3 (4.8)	6 (9.5)
Oropharyngeal pain	1 (1.6)	0	4 (6.3)	2 (3.2)
Hypogeusia	0	11 (17.5)	15 (23.8)	1 (1.6)
Nausea	0	4 (6.3)	6 (9.5)	0
Nasopharyngitis	0	4 (6.3)	0	2 (3.2)
Ageusia	0	3 (4.8)	13 (20.6)	1 (1.6)

n (%)

7.1.3 Japanese study in patients with chronic cough (CTD 5.3.5.1.3, Study 033 [March 2018 to June 2018])

An exploratory, placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the safety and efficacy of gefapixant in Japanese patients with chronic cough (Table 46) (target sample size, 20 subjects [10 per group]).

Table 46. Key inclusion/exclusion criteria

Key inclusion criteria
(1) Refractory[23] or unexplained[24] chronic cough for ≥1 year
(2) Chest radiograph or computed tomography scan of the thorax within 5 years of screening not demonstrating any abnormality considered to be significantly contributing to the chronic cough or any other clinically significant lung disease
(3) A score of ≥40 mm on cough severity VAS at screening and baseline visit
(4) ≥20 years of age
Key exclusion criteria
(1) Individuals who had given up smoking within 12 months of screening or former smokers with a pack-year history greater than 20 pack-years
(2) FEV_1/FVC <60%
(3) History of upper or lower respiratory tract infection or recent clinically significant change in pulmonary status within 4 weeks of screening
(4) History of chronic bronchitis (a cough that produced a clinically significant amount of sputum [greater than approximately 1 tablespoon of phlegm] that occurred every day for at least 3 months in a row, with those periods occurring at least 2 years in a row)
(5) Individuals who had taken an angiotensin converting enzyme inhibitor within 3 months of screening
(6) eGFR <50 mL/min/1.73 m^2 at screening
(7) Systolic blood pressure >160 mmHg or diastolic blood pressure >90 mmHg at screening

Gefapixant 45 mg or placebo was to be administered orally twice daily for 28 days.

All of 23 randomized subjects (11 in the 45 mg group, 12 in the placebo group) who received at least 1 dose of study drug were included in the safety set. Of whom, those who provided at least one baseline and one post-baseline endpoint observations were included in the FAS (11 in the 45 mg group, 12 in the placebo group), and the FAS was used as the efficacy analysis population

The discontinuation rate was 9.1% (1 of 11 subjects) in the 45 mg group, and the reason for discontinuation was an adverse event.

The incidences of adverse events were 81.8% (9 of 11 subjects) in the 45 mg group and 16.7% (2 of 12 subjects) in the placebo group, and the main event was dysgeusia (7 subjects in the 45 mg group).

There were no deaths or serious adverse events.

An adverse event leading to discontinuation occurred in 9.1% (1 of 11) of subjects in the 45 mg group (drug eruption).

Adverse drug reactions occurred in 72.7% (8 of 11) of subjects in the 45 mg group.

[23] Patients who continued to cough despite receiving appropriate diagnostic workup and therapy for comorbid conditions that may be related to cough (GERD, asthma, upper airway cough syndrome, etc.) according to ACCP guidelines

[24] Patients who had a clinical evaluation of their cough per ACCP guidelines and this evaluation did not suggest a comorbid condition that may be related to cough.

The results of efficacy endpoints of 24-hour and awake cough frequency (coughs/hour) at Week 4 are shown in Table 47.

Table 47. Cough frequency (coughs/hour) (FAS)

		45 mg	Placebo
24-hour	Baseline	12.4 ± 21.2 (11)	15.4 ± 15.4 (12)
		11.9 [0.2, 300.3] 7.9, 23.0	17.7 [2.8, 73.3] 8.6, 30.6
	Week 4	10.6 ± 12.4 (11)	5.2 ± 8.5 (12)
		11.9 [1.6, 120.7] 4.3, 18.1	5.3 [0.1, 37.1] 2.7, 20.0
	Ratio of Week 4 to baseline cough frequency [95% CI][a),c)]	0.80 [0.35, 1.81]	0.36 [0.16, 0.79]
	Relative reduction vs. placebo [95% CI] (%)[a),b),c)]	121.3 [−29.1, 590.8]	
Awake	Baseline	15.2 ± 26.2 (11)	19.6 ± 18.3 (12)
		14.1 [0.3, 357.4] 10.6, 32.4	22.4 [3.6, 66.9] 10.7, 39.6
	Week 4	13.6 ± 15.2 (11)	6.9 ± 10.9 (12)
		13.8 [2.6, 179.6] 6.5, 22.4	6.9 [0.1, 42.1] 3.5, 27.9
	Ratio of Week 4 to baseline cough frequency [95% CI][a),c)]	0.82 [0.37, 1.82]	0.38 [0.18, 0.82]
	Relative reduction vs. placebo [95% CI] (%)[a),b),c)]	114.7 [−29.3, 552.3]	

Mean ± SD (N); Upper shaded row, Median [Min., Max.]; Lower shaded row, 1st quartile, 3rd quartile
a) The least squares estimate of the geometric mean
b) {(Ratio of Week 4 to baseline cough frequency in gefapixant group)/(Ratio of Week 4 to baseline cough frequency in placebo group) − 1} × 100
c) Log-transformed cough frequency was analyzed using an ANCOVA model with treatment and gender as fixed effects and the log-transformed baseline value as a covariate.

7.2 Phase III studies

7.2.1 Global study in patients with chronic cough (CTD 5.3.5.1.4, Study 027 [March 2018 to June 2020])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in 17 countries or regions including Japan, the US, the UK, and Korea to evaluate the superiority and safety of gefapixant vs. placebo in patients with chronic cough (Table 48) (target sample size, 720 subjects [240 per group][25)]).

Table 48. Key inclusion/exclusion criteria

Key inclusion criteria
(1) Chronic cough ≥1 year with a diagnosis of RCC[26)] or UCC[24)]
(2) Chest radiograph or computed tomography scan of the thorax within 5 years of screening not demonstrating any abnormality considered to be significantly contributing to the chronic cough or any other clinically significant lung disease
(3) A score of ≥40 mm on cough severity VAS at screening and baseline visit
(4) ≥18 years of age
Key exclusion criteria
(1) Individuals who had given up smoking within 12 months of screening or former smokers with a pack-year history greater than 20 pack-years
(2) FEV_1/FVC <60%
(3) History of upper or lower respiratory tract infection or recent clinically significant change in pulmonary status within 4 weeks of screening
(4) History of chronic bronchitis (a cough that produced a clinically significant amount of sputum [greater than approximately 1 tablespoon of phlegm] that occurred every day for at least 3 months in a row, with those periods occurring at least 2 years in a row)
(5) Individuals who had taken an angiotensin converting enzyme inhibitor within 3 months of screening
(6) eGFR <30 mL/min/1.73 m^2 at screening, or eGFR ≥30 mL/min/1.73 m^2 and <50 mL/min/1.73 m^2 at screening with a ≥50% increase of serum creatinine compared to a value obtained at least 6 months prior to screening
(7) Systolic blood pressure >160 mmHg or diastolic blood pressure >90 mmHg at screening

Gefapixant 15 or 45 mg, or placebo was to be administered orally twice daily for 52 weeks.

[25)] Assuming expected relative reductions of −[redacted]% and −[redacted]% vs. placebo for gefapixant 15 or 45 mg, respectively, for the primary endpoint of 24-hour cough frequency (coughs/hour) at Week 12, 240 patients per group (720 patients to be randomized into 3 groups) were required to achieve ≥[redacted]% power at a two-sided significance level of 4.99%.

[26)] Patients who had received appropriate diagnostic workup and at least 2 months of therapy for underlying diseases that may be associated with cough (GERD, asthma, upper airway cough syndrome, etc.), prior to screening, according to ACCP guidelines, but continued to cough despite being on therapy.

Among 732 randomized subjects (244 per group), 730 subjects after excluding 2 subjects who did not receive study drug (1 in the 45 mg group, 1 in the placebo group) were included in the safety set (244 in the 15 mg group, 243 in the 45 mg group, 243 in the placebo group). Of whom, those who provided at least one baseline and one post-baseline endpoint observations[27)] were included in the FAS (244 in the 15 mg group, 243 in the 45 mg group, 243 in the placebo group), and the FAS was used as the efficacy analysis population.

The discontinuation rates were 18.0% (44 of 244 subjects) in the 15 mg group, 24.6% (60 of 244 subjects) in the 45 mg group, and 18.4% (45 of 244 subjects) in the placebo group. The main reason for discontinuations was consent withdrawal (16.0% [39 of 244 subjects] in the 15 mg group, 22.5% [55 of 244 subjects] in the 45 mg group, 15.2% [37 of 244 subjects] in the placebo group).

The results of the primary efficacy endpoint of 24-hour cough frequency (coughs/hour) at Week 12 are shown in Table 49. A pairwise comparison between 45 mg and placebo showed a statistically significant difference. A pairwise comparison between 15 mg and placebo did not show a statistically significant difference. Table 50 shows the results from the Japanese subgroup.

Table 49. 24-hour cough frequency (coughs/hour) (FAS)

	15 mg	45 mg	Placebo
Baseline	26.8 ± 21.1 (235)	28.5 ± 37.1 (237)	38.1 ± 79.4 (232)
	21.1 [0.8, 131.3] 12.5, 35.5	19.2 [0.2, 386.4] 11.6, 33.9	25.4 [0.4, 1055.5] 12.3, 42.6
Week 12	15.5 ± 14.8 (218)	14.4 ± 19.2 (199)	20.8 ± 45.9 (216)
	10.8 [0.1, 100.4] 5.3, 21.1	8.5 [0, 174.3] 3.5, 18.6	11.2 [0.2, 562.7] 4.9, 25.3
Ratio of Week 12 to baseline cough frequency [95% CI][a),c)]	0.48 [0.41, 0.55]	0.38 [0.33, 0.44]	0.47 [0.41, 0.54]
Relative reduction vs. placebo [95% CI] (%)[a),b),c)]	1.6 [−16.1, 23.0]	−18.5 [−32.9, −0.9]	
P-value[c),d)]	0.874	0.041	

Mean ± SD (N); Upper shaded row, Median [Min., Max.]; Lower shaded row, 1st quartile, 3rd quartile
Seventeen subjects in the 15 mg group, 26 subjects in the 45 mg group, and 21 subjects in the placebo group with missing baseline or post-baseline values were excluded from the analysis using a model.
a) The least squares estimate of the geometric mean
b) {(Ratio of Week 12 to baseline cough frequency in gefapixant group)/(Ratio of Week 12 to baseline cough frequency in placebo group) − 1} × 100
c) The change from baseline in log-transformed 24-hour coughs per hour at each time point was analyzed using a repeated measures ANCOVA model with treatment, visit, the interaction of treatment by visit, gender, and region as fixed effects and the log-transformed baseline value and the interaction of log-transformed baseline value by visit as covariates. An unstructured covariance matrix was used to model the correlation among repeated measurements.
d) Two-sided significance level of 4.99%. In order to adjust for the multiplicity of hypothesis tests, if the comparison of 45 mg vs. placebo was statistically significant, the comparison of 15 mg vs. placebo was to be made.

27) Including 9 patients with RCC who had received <2 months of therapy for the cause of cough (5 in the 15 mg group, 2 in the 45 mg group, 2 in the placebo group).

Table 50. 24-hour cough frequency (coughs/hour) (FAS, Japanese subgroup)

	15 mg	45 mg	Placebo
Baseline	31.5 ± 38.9 (6)	63.9 ± 96.4 (14)	109.9 ± 273.0 (14)
	15.4 [9.5, 110.4] 14.6, 24.0	31.6 [9.5, 386.4] 20.9, 64.0	39.0 [4.5, 1055.5] 21.5, 52.9
Week 12	18.1 ± 23.2 (6)	20.3 ± 35.0 (14)	47.3 ± 88.1 (14)
	7.0 [3.9, 63.5] 4.9, 22.5	8.4 [1.1, 132.5] 2.8, 14.3	23.0 [0.9, 340.5] 6.1, 33.9
Ratio of Week 12 to baseline cough frequency [95% CI][a),c)]	0.52 [0.22, 1.27]	0.24 [0.13, 0.43]	0.44 [0.23, 0.84]
Relative reduction vs. placebo [95% CI] (%)[a),b),c)]	19.0 [−56.8, 228.1]	−46.2 [−75.3, 17.1]	

Upper row, Mean ± SD (N); Upper shaded row, Median [Min., Max.]; Lower shaded row, 1st quartile, 3rd quartile

a) The least squares estimate of the geometric mean

b) {(Ratio of Week 12 to baseline cough frequency in gefapixant group)/(Ratio of Week 12 to baseline cough frequency in placebo group) − 1} × 100

c) The change from baseline in log-transformed 24-hour coughs per hour at each time point was analyzed using a repeated measures ANCOVA model with treatment, visit, the interaction of treatment by visit, and gender as fixed effects and the log-transformed baseline value and the interaction of log-transformed baseline value by visit as covariates. An unstructured covariance matrix was used to model the correlation among repeated measurements.

The incidences of adverse events were 76.2% (186 of 244 subjects) in the 15 mg group, 85.6% (208 of 243 subjects) in the 45 mg group, and 75.7% (184 of 243 subjects) in the placebo group. The main events are shown in Table 51.

There were 1 death in the 15 mg group (respiratory tract infection) and 2 deaths in the placebo group (death; and accidental death [1 subject each]), but a causal relationship to study drug was denied for all cases.

The incidences of serious adverse events were 7.0% (17 of 244 subjects) in the 15 mg group, 5.3% (13 of 243 subjects) in the 45 mg group, and 5.8% (14 of 243 subjects) in the placebo group, and a causal relationship to study drug could not be ruled out for 1 case in the placebo group (ureterolithiasis).

The incidences of adverse events leading to discontinuation were 6.1% (15 of 244 subjects) in the 15 mg group, 21.0% (51 of 243 subjects) in the 45 mg group, and 5.8% (14 of 243 subjects) in the placebo group.

The incidences of adverse drug reactions were 20.1% (49 of 244 subjects) in the 15 mg group, 65.0% (158 of 243 subjects) in the 45 mg group, and 19.3% (47 of 243 subjects) in the placebo group.

Table 51. Adverse events reported by ≥5% of subjects in any group (Safety set)

Event term	15 mg (N = 244)	45 mg (N = 243)	Placebo (N = 243)	Event term	15 mg (N = 244)	45 mg (N = 243)	Placebo (N = 243)
Dysgeusia	22 (9.0)	88 (36.2)	8 (3.3)	Upper respiratory tract infection	18 (7.4)	13 (5.3)	9 (3.7)
Nasopharyngitis	47 (19.3)	50 (20.6)	51 (21.0)	Dry mouth	7 (2.9)	13 (5.3)	6 (2.5)
Ageusia	3 (1.2)	33 (13.6)	0	Hypogeusia	5 (2.0)	13 (5.3)	1 (0.4)
Headache	34 (13.9)	29 (11.9)	31 (12.8)	Diarrhoea	15 (6.1)	12 (4.9)	14 (5.8)
Taste disorder	2 (0.8)	24 (9.9)	2 (0.8)	Bronchitis	20 (8.2)	11 (4.5)	11 (4.5)
Back pain	14 (5.7)	20 (8.2)	19 (7.8)	Asthma	9 (3.7)	11 (4.5)	17 (7.0)
Cough	14 (5.7)	17 (7.0)	10 (4.1)	Urinary tract infection	14 (5.7)	9 (3.7)	11 (4.5)
Nausea	8 (3.3)	17 (7.0)	13 (5.3)	Arthralgia	13 (5.3)	9 (3.7)	8 (3.3)
Oropharyngeal pain	13 (5.3)	14 (5.8)	10 (4.1)				

n (%)

In the Japanese subgroup, the incidences of adverse events were 100% (6 of 6 subjects) in the 15 mg group, 100% (14 of 14 subjects) in the 45 mg group, and 100% (14 of 14 subjects) in the placebo group. The main events are shown in Table 52.

No deaths were reported.

The incidences of serious adverse events were 16.7% (1 of 6 subjects) (bronchopulmonary aspergillosis and staphylococcal pneumonia) in the 15 mg group, 7.1% (1 of 14 subjects) (traumatic haemothorax) in the 45 mg group, and 7.1% (1 of 14 subjects) (lacunar infarction) in the placebo group, but a causal relationship to study drug was denied for all those events.

No adverse events leading to discontinuation were reported.

The incidences of adverse drug reactions were 33.3% (2 of 6 subjects) in the 15 mg group, 100% (14 of 14 subjects) in the 45 mg group, and 42.9% (6 of 14 subjects) in the placebo group.

Table 52. Adverse events reported by ≥2 subjects in any group (Safety set, Japanese subgroup)

Event term	15 mg (N = 6)	45 mg (N = 14)	Placebo (N = 14)	Event term	15 mg (N = 6)	45 mg (N = 14)	Placebo (N = 14)
Dysgeusia	1 (16.7)	8 (57.1)	0	Stomatitis	0	2 (14.3)	1 (7.1)
Nasopharyngitis	2 (33.3)	7 (50.0)	7 (50.0)	Rash papular	0	2 (14.3)	1 (7.1)
Asthma	1 (16.7)	4 (28.6)	4 (28.6)	Acute sinusitis	0	2 (14.3)	0
Taste disorder	0	4 (28.6)	1 (7.1)	Herpes simplex	0	2 (14.3)	0
Urticaria	0	4 (28.6)	1 (7.1)	Influenza	0	2 (14.3)	0
Bronchitis	2 (33.3)	3 (21.4)	2 (14.3)	Rib fracture	0	2 (14.3)	0
Headache	0	3 (21.4)	4 (28.6)	Cough	0	2 (14.3)	0
Dizziness	0	3 (21.4)	0	Pharyngitis	0	1 (7.1)	2 (14.3)
Cystitis	2 (33.3)	2 (14.3)	0	Oral discomfort	0	1 (7.1)	2 (14.3)
Back pain	1 (16.7)	2 (14.3)	1 (7.1)	Accidental overdose	2 (33.3)	1 (7.1)	1 (7.1)
Rhinitis allergic	1 (16.7)	2 (14.3)	1 (7.1)	Dysphonia	2 (33.3)	0	0

n (%)

7.2.2 Foreign study in patients with chronic cough (CTD 5.3.5.1.5, Study 030 [March 2018 to August 2020])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in 20 countries or regions including the US, the UK, and Ukraine to evaluate the superiority and safety of gefapixant vs. placebo in patients with chronic cough (Table 48) (target sample size, 1,290 subjects [430 per group][28]).

Gefapixant 15 or 45 mg, or placebo was to be administered orally twice daily for 52 weeks.

Among 1,317 randomized subjects (442 in the 15 mg group, 439 in the 45 mg group, 436 in the placebo group), 1,314 subjects[29] (442 in the 15 mg group, 440 in the 45 mg group, 432 in the placebo group) after excluding 3 subjects who did not receive study drug (2 in the 15 mg group, 1 in the placebo group) were included in the

[28] Assuming expected relative reductions of −[redacted]% and −[redacted]% vs. placebo for gefapixant 15 or 45 mg, respectively, for the primary endpoint of 24-hour cough frequency (coughs/hour) at Week 24, 430 patients per group (1,290 patients to be randomized into 3 groups) were required to achieve ≥[redacted]% power at a two-sided significance level of 4.99%.

[29] Three subjects were assigned to the placebo group, but mistakenly received gefapixant 15 mg (1 subject) or 45 mg (2 subjects). Thus, these subjects were included in the 15 mg or 45 mg group, respectively, for the safety analysis.

safety set. Of whom, those who provided at least one baseline and one post-baseline endpoint observations[30] were included in the FAS (440 in the 15 mg group, 439 in the 45 mg group, 435 in the placebo group), and the FAS was used as the efficacy analysis population.

The discontinuation rates were 16.7% (74 of 442 subjects) in the 15 mg group, 19.1% (84 of 439 subjects) in the 45 mg group, and 12.4% (54 of 436 subjects) in the placebo group. The main reason for discontinuations was consent withdrawal (15.4% [68 of 442 subjects] in the 15 mg group, 16.9% [74 of 439 subjects] in the 45 mg group, 10.6% [46 of 436 subjects] in the placebo group).

The results of the primary efficacy endpoint of 24-hour cough frequency (coughs/hour) at Week 24 are shown in Table 53. A pairwise comparison between 45 mg and placebo showed a statistically significant difference. A pairwise comparison between 15 mg and placebo did not show a statistically significant difference.

Table 53. 24-hour cough frequency (coughs/hour) (FAS)

	15 mg	45 mg	Placebo
Baseline	26.8 ± 21.3 (431)	26.8 ± 27.0 (434)	27.4 ± 24.4 (432)
	21.4 [0.8, 151.6] 10.6, 38.9	19.1 [0.2, 230.1] 10.2, 35.6	20.5 [0.7, 179.8] 11.3, 36.3
Week 24	15.1 ± 19.1 (370)	12.1 ± 16.1 (352)	14.8 ± 15.3 (369)
	9.3 [0, 213.2] 3.5, 19.2	7.2 [0, 132.3] 3.3, 14.7	10.7 [0, 93.9] 3.9, 19.5
Ratio of Week 24 to baseline cough frequency [95% CI][a),c)]	0.43 [0.38, 0.47]	0.37 [0.33, 0.41]	0.43 [0.39, 0.48]
Relative reduction vs. placebo [95% CI] (%)[a),b),c)]	−1.14 [−14.3, 14.0]	−14.6 [−26.1, −1.43]	
P-value[c),d)]	0.875	0.031	

Upper row, Mean ± SD (N); Upper shaded row, Median [Min., Max.]; Lower shaded row, 1st quartile, 3rd quartile
Twenty-five subjects in the 15 mg group, 30 subjects in the 45 mg group, and 16 subjects in the placebo group with missing baseline or post-baseline values were excluded from the analysis using a model.
a) The least squares estimate of the geometric mean
b) {(Ratio of Week 24 to baseline cough frequency in gefapixant group)/(Ratio of Week 24 to baseline cough frequency in placebo group) − 1} × 100
c) The change from baseline in log-transformed 24-hour coughs per hour at each time point was analyzed using a repeated measures ANCOVA model with treatment, visit, the interaction of treatment by visit, gender, and region as fixed effects and the log-transformed baseline value and the interaction of log-transformed baseline value by visit as covariates. An unstructured covariance matrix was used to model the correlation among repeated measurements.
d) Two-sided significance level of 4.99%. A closed testing procedure was used to adjust for the multiplicity of hypothesis tests. The procedure was to start with the comparison of 45 mg to placebo, and if this test was statistically significant, multiple comparisons between 45 mg and placebo for the secondary endpoints were to be made in a pre-specified order. If all of these multiple comparisons of 45 mg vs. placebo were statistically significant, comparisons of 15 mg vs. placebo were to be made.

The incidences of adverse events were 84.4% (373 of 442 subjects) in the 15 mg group, 90.7% (399 of 440 subjects) in the 45 mg group, and 80.8% (349 of 432 subjects) in the placebo group. The main events are shown in Table 54.

There was 1 death in the 15 mg group (cardiopulmonary failure), but its causal relationship to study drug was denied.

The incidences of serious adverse events were 5.4% (24 of 442 subjects) in the 15 mg group, 5.7% (25 of 440 subjects) in the 45 mg group, and 5.8% (25 of 432 subjects) in the placebo group. A causal relationship to study drug was denied for all those events, except for 1 case (hypoglycaemia) in the 45 mg group.

[30] Including 2 patients with RCC who had received <2 months of therapy for the cause of cough (both in the 15 mg group).

The incidences of adverse events leading to discontinuation were 9.0% (40 of 442 subjects) in the 15 mg group, 22.7% (100 of 440 subjects) in the 45 mg group, and 5.8% (25 of 432 subjects) in the placebo group.

The incidences of adverse drug reactions were 32.8% (145 of 442 subjects) in the 15 mg group, 70.9% (312 of 440 subjects) in the 45 mg group, and 21.1% (91 of 432 subjects) in the placebo group.

Table 54. Adverse events reported by ≥5.0% of subjects in any group (Safety set)

Event term	15 mg (N = 442)	45 mg (N = 440)	Placebo (N = 432)	Event term	15 mg (N = 442)	45 mg (N = 440)	Placebo (N = 432)
Dysgeusia	56 (12.7)	193 (43.9)	28 (6.5)	Upper respiratory tract infection	38 (8.6)	30 (6.8)	27 (6.3)
Nasopharyngitis	93 (21.0)	70 (15.9)	70 (16.2)	Diarrhoea	27 (6.1)	27 (6.1)	18 (4.2)
Headache	74 (16.7)	70 (15.9)	67 (15.5)	Influenza	30 (6.8)	24 (5.5)	35 (8.1)
Ageusia	13 (2.9)	67 (15.2)	6 (1.4)	Oropharyngeal pain	13 (2.9)	23 (5.2)	19 (4.4)
Hypogeusia	17 (3.8)	60 (13.6)	3 (0.7)	Arthralgia	22 (5.0)	21 (4.8)	30 (6.9)
Nausea	26 (5.9)	47 (10.7)	32 (7.4)	Urinary tract infection	34 (7.7)	19 (4.3)	23 (5.3)
Taste disorder	8 (1.8)	37 (8.4)	1 (0.2)	Bronchitis	20 (4.5)	18 (4.1)	24 (5.6)
Cough	30 (6.8)	32 (7.3)	18 (4.2)	Back pain	30 (6.8)	17 (3.9)	25 (5.8)
Dry mouth	15 (3.4)	32 (7.3)	11 (2.5)	Sinusitis	23 (5.2)	14 (3.2)	18 (4.2)

n (%)

7.2.3 Japanese study in patients with chronic cough (CTD 5.3.5.2.1, Study 038 [October 2018 to October 2020])

A randomized, double-blind, parallel-group study was conducted to evaluate the long-term safety and efficacy of gefapixant in Japanese patients with chronic cough (Table 55) (target sample size, 160 subjects [80 per group]).

Table 55. Key inclusion/exclusion criteria

Key inclusion criteria
(1) Chronic cough for ≥4 months at signing informed consent and a diagnosis of refractory[31] or unexplained[32] chronic cough
(2) Chest radiograph or computed tomography scan of the thorax within 5 years of screening not demonstrating any abnormality considered to be significantly contributing to the chronic cough or any other clinically significant lung disease
(3) Persistent cough, despite treatment in accordance with the clinical practice guidelines, needed further treatment.
(4) ≥20 years of age
Key exclusion criteria
(1) Individuals who had given up smoking within 12 months of screening
(2) FEV_1/FVC <60%
(3) History of upper or lower respiratory tract infection or recent clinically significant change in pulmonary status within 4 weeks of screening
(4) History of chronic bronchitis (a cough that produced a clinically significant amount of sputum [greater than approximately 1 tablespoon of phlegm] that occurred every day for at least 3 months in a row, with those periods occurring at least 2 years in a row)
(5) Individuals who had taken an angiotensin converting enzyme inhibitor within 3 months of screening
(6) eGFR <30 mL/min/1.73 m^2 at screening, or eGFR ≥30 mL/min/1.73 m^2 and <50 mL/min/1.73 m^2 at screening with a ≥50% increase of serum creatinine compared to a value obtained at least 6 months prior to screening
(7) Systolic blood pressure >160 mmHg or diastolic blood pressure >90 mmHg at screening

Gefapixant 15 or 45 mg was to be administered orally twice daily for 52 weeks.

Among 175 randomized subjects (88 in the 15 mg group, 87 in the 45 mg group), 169 subjects (84 in the 15 mg group, 85 in the 45 mg group) after excluding 6 subjects from 1 study site with GCP non-compliance were included in the safety set. Of whom, those who provided at least one baseline and one post-baseline

[31] Patients who continued to cough despite receiving appropriate diagnostic workup and therapy for comorbid conditions that may be related to cough (GERD, asthma, upper airway cough syndrome, etc.) according to the clinical practice guidelines

[32] Patients had a clinical evaluation of their cough per clinical practice guidelines, and this evaluation did not suggest a comorbid condition that may be related to cough.

endpoint observations were included in the FAS (84 in the 15 mg group, 85 in the 45 mg group), and the FAS was used as the efficacy analysis population.

The discontinuation rates were 4.8% (4 of 84 subjects) in the 15 mg group and 7.1% (6 of 85 subjects) in the 45 mg group. The main reason for discontinuations was consent withdrawal (3.6% [3 of 84 subjects] in the 15 mg group, 7.1% [6 of 85 subjects] in the 45 mg group).

The incidences of adverse events were 94.0% (79 of 84 subjects) in the 15 mg group and 96.5% (82 of 85 subjects) in the 45 mg group. The main events are shown in Table 56.

No deaths were reported.

The incidences of serious adverse events were 2.4% (2 of 84 subjects) in the 15 mg group and 11.8% (10 of 85 subjects) in the 45 mg group, but a causal relationship to study drug was denied for all those events.

The incidences of adverse events leading to discontinuation were 7.1% (6 of 84 subjects) in the 15 mg group and 20.0% (17 of 85 subjects) in the 45 mg group.

The incidences of adverse drug reactions were 39.3% (33 of 84 subjects) in the 15 mg group and 76.5% (65 of 85 subjects) in the 45 mg group.

Table 56. Adverse events reported by ≥5.0% of subjects in either group (Safety set)

Event term	15 mg (N = 84)	45 mg (N = 85)	Event term	15 mg (N = 84)	45 mg (N = 85)
Dysgeusia	14 (16.7)	40 (47.1)	Insomnia	1 (1.2)	5 (5.9)
Nasopharyngitis	25 (29.8)	33 (38.8)	Ageusia	0	5 (5.9)
Hypogeusia	9 (10.7)	14 (16.5)	Pharyngitis	8 (9.5)	4 (4.7)
Cough	19 (22.6)	11 (12.9)	Bronchitis	10 (11.9)	3 (3.5)
Taste disorder	6 (7.1)	10 (11.8)	Headache	9 (10.7)	3 (3.5)
Asthma	11 (13.1)	6 (7.1)	Accidental overdose	5 (6.0)	3 (3.5)
Pyrexia	5 (6.0)	6 (7.1)	Diarrhoea	7 (8.3)	2 (2.4)
Gastroenteritis	2 (2.4)	6 (7.1)	Constipation	6 (7.1)	2 (2.4)
Paraesthesia oral	1 (1.2)	5 (5.9)	Gastrooesophageal reflux disease	6 (7.1)	1 (1.2)

n (%)

The results of the efficacy endpoint of the change from baseline in the Leicester Cough Questionnaire (LCQ) total score at Week 12 are shown in Table 57.

Table 57. Change from baseline in LCQ total score at Week 12 (FAS)

	Week 12	
	15 mg	45 mg
Baseline	13.8 ± 3.6 (84)	14.1 ± 3.3 (85)
Week 12	15.2 ± 3.8 (83)	14.9 ± 3.6 (81)
Change from baseline[a)]	1.4 ± 3.3 *1.4 [0.7, 2.0]*	0.9 ± 3.5 *0.9 [0.3, 1.6]*

Mean ± SD (N); Italics, Least-squares mean [95% CI]
a) A repeated measures ANCOVA model with treatment, visit, and the interaction of treatment by visit as fixed effects and baseline value as a covariate. An unstructured covariance matrix was used to model the correlation among repeated measurements.

7.R Outline of the review conducted by PMDA

7.R.1 Development plan

The applicant's explanation about the development plan of gefapixant:

In a global phase III study (Study 027), subjects who had received diagnostic workup and therapy for comorbid conditions associated with cough according to the American College of Chest Physicians (ACCP) guidelines were to be screened for their eligibility. The ACCP guidelines recommend that coughs should be categorized by their duration, the cause of cough should be identified, and specific therapy for the cause of cough should be given. Since the diagnosis of and specific therapies for medical conditions associated with chronic cough in the ACCP guidelines are largely similar to those in the Japanese guidelines, there seem no major differences in the diagnosis of and treatment paradigm for chronic cough between Japan and overseas. While many patients find relief with treatment according to the guidelines, some patients do not respond despite thorough diagnostic workup and treatment. In Japan and overseas, most of such patients with refractory chronic cough (RCC) or unexplained chronic cough (UCC) have been reported to be females and at older age (*Allergol Int*. 2019; 68: 478-85, *Eur Respir J*. 2014; 44: 1149-55). As there are no substantial differences in the diagnosis of and treatment paradigm for chronic cough between Japan and overseas, and no clinically relevant differences in the pharmacokinetics of gefapixant between Japanese and non-Japanese populations have been observed [see Section 6.R.1], the efficacy and safety of gefapixant in Japanese patients can be evaluated by conducting a global phase III study involving Japan (Study 027) and a foreign phase III study (Study 030) and constructing a clinical data package.

Target population

Gefapixant is a P2X3 receptor antagonist. P2X3 receptors on C-fibers are the therapeutic target for cough. Though gefapixant is a peripherally-acting, non-specific antitussive, given that the clinical practice guidelines preferentially recommend specific therapies according to the underlying disease and pathological condition of cough over non-specific antitussives, patients with RCC or UCC were chosen as the target population because no effective treatment for cough has been established for these patients.

Although the clinical practice guidelines define chronic cough as cough lasting for ≥8 weeks, considering that the cough status of patients with a longer duration of cough would not change easily, patients with chronic cough ≥1 year at study entry were enrolled in Studies 027 and 030. For enrollment of patients with RCC or UCC who needed treatment, patients were required to have a score of ≥40 mm on the cough severity visual analogue scale (VAS) (0-100 mm) (self-rated cough severity) at the screening and baseline visits. Patients were considered to have RCC if they continued to cough despite receiving at least 2 months of therapy for the comorbid conditions that may be associated with cough.

Dosage and administration

In Study 012, gefapixant 7.5 to 50 mg BID resulted in dose-dependent improvements in cough frequency and self-rated cough severity and QOL, whereas the incidence of taste-related adverse events also increased in a dose-dependent manner [see Section 7.1.2]. Simulations were performed with exposure–response models to evaluate the dose–response profiles for cough reduction, the incidence of taste-related events, and the

discontinuation rate for a dose range of 0 to 50 mg in steps of 2.5 mg. According to the simulation results, a dose of 15 mg was predicted to provide a clinically meaningful reduction in cough frequency (an approximately 20% reduction in cough frequency relative to placebo) and was not expected to cause taste-related events in approximately 80% of patients, and a dose of 45 mg was predicted to achieve nearly maximal reduction in cough frequency (an approximately 30% reduction in cough frequency relative to placebo) with an acceptable rate of discontinuation (the predicted median of 16.2%). Based on the above, in order to evaluate the appropriate doses of gefapixant from an efficacy and safety point of view, the dose of 15 or 45 mg was selected for phase III studies, and a twice-daily dosing regimen was selected because orally administered gefapixant is absorbed rapidly with an elimination half-life of approximately 6 to 10 hours.

Treatments for conditions associated with chronic cough, such as gastroesophageal reflux disease (GERD), asthma, upper airway cough syndrome, or non-asthmatic eosinophilic bronchitis, were permitted, provided that participants were receiving a stable treatment regimen for at least 2 weeks prior to screening and were likely to remain on the stable treatment regimen through completion of the study.

Efficacy endpoint and timing of endpoint

The primary endpoint for Studies 027 and 030 was an objective endpoint, i.e., 24-hour cough frequency (coughs/hour), calculated from cough counts measured using a digital cough recording device. The results of Study 012 indicated that the efficacy of gefapixant can be assessed more accurately with this endpoint. Since assessment of awake cough frequency was considered meaningful for patients with RCC or UCC, awake cough frequency (coughs/hour) was also measured. In addition, the LCQ total score (a cough-specific QOL measure) and self-rated cough severity (the CSD total score and cough severity VAS) were selected as endpoints.

As there is no consensus about the clinical evaluation period for cough treatments, referring to [redacted] for the development of drugs for the treatment of [redacted], a similar chronic respiratory disease, Week 12 was selected as the timing of the primary endpoint for Study 027. Then, based on [redacted], Week 24 was selected for Study 030 to assess the durability of its effects.

PMDA accepted the above explanation and concluded that the efficacy and safety of gefapixant in patients with refractory or unexplained chronic cough can be evaluated based on the submitted clinical data package, focusing on the results from Study 027 in which Japanese patients participated.

7.R.2 Efficacy

The applicant's explanation about the efficacy of gefapixant:

In Studies 027 and 030 in patients with RCC or UCC, a pairwise comparison showed a statistically significant difference in the primary endpoint of 24-hour cough frequency (coughs/hour) only between 45 mg and placebo, demonstrating the superiority of 45 mg to placebo (Table 49 and Table 53). At the primary time points in Studies 027 and 030 (Week 12 in Study 027, Week 24 in Study 030), the relative reductions in 24-hour cough

frequency vs. placebo for 45 mg were −18.5% (95% CI, −32.9, −0.86) and −14.6% (95% CI, −26.1, −1.43), respectively, which were smaller than the expected value (−[redacted]%) based on the data from Study 012, which served as the basis for sample size determination. This was considered due to a greater placebo response in Studies 027 and 030 than in Study 012, and the ratio of Week 12 to baseline 24-hour cough frequency in the 45 mg group of Study 027 and the ratio of Week 24 to baseline 24-hour cough frequency in the 45 mg group of Study 030 were similar to the ratio of Week 12 to baseline cough frequency in Study 012 (Table 44 and Table 58). With regard to the placebo effect in patients with cough, a great placebo effect has often been observed in clinical studies in cough. For instance, also in a placebo-controlled, randomized, double-blind, parallel-group study of NK-1 receptor antagonist (orvepitant) in 315 patients with refractory chronic cough, the percent change from baseline in awake cough frequency in the placebo group increased over time, i.e. approximately −15% at Week 2 and −30% at Week 12 (*Eur Respir J*. 2019; 54: Suppl 63, PA600). The placebo effect in clinical studies in refractory or unexplained chronic cough for new drug development has been taken up also at an international conference (*American Cough Conference*. 2021 Jun 11-12).

Table 58 shows the results of the main efficacy endpoints. The results of all endpoints favored gefapixant 45 mg over placebo, and its effects were sustained for the subjective endpoints evaluated up to Week 52. On the whole, a similar trend was observed in the Japanese subgroup as in the overall population.

Table 58. Results of main efficacy endpoints (Studies 027 and 030, Overall population)

		Study 027			Study 030		
		15 mg	45 mg	Placebo	15 mg	45 mg	Placebo
Ratio of 24-hour cough frequency (post-baseline/baseline) [95% CI][a),b)]	Week 4	0.57 [0.50, 0.64]	0.43 [0.38, 0.49]	0.64 [0.57, 0.73]	0.57 [0.52, 0.62]	0.46 [0.42, 0.50]	0.63 [0.58, 0.68]
	Week 8	0.48 [0.42, 0.55]	0.40 [0.35, 0.46]	0.52 [0.45, 0.59]	0.48 [0.44, 0.53]	0.42 [0.38, 0.46]	0.53 [0.48, 0.59]
	Week 12	0.48 [0.41, 0.55]	0.38 [0.33, 0.44]	0.47 [0.41, 0.54]	0.47 [0.43, 0.52]	0.39 [0.36, 0.44]	0.48 [0.44, 0.54]
	Week 24				0.43 [0.38, 0.47]	0.37 [0.33, 0.41]	0.43 [0.39, 0.48]
Proportion of patients with ≥30% reduction from baseline in 24-hour cough frequency (coughs/hour)	Week 4	124/224 (55.4)	141/207 (68.1)	105/217 (48.4)	239/409 (58.4)	276/403 (68.5)	208/412 (50.5)
	Week 8	141/218 (64.7)	132/199 (66.3)	123/208 (59.1)	261/389 (67.1)	261/377 (69.2)	239/398 (60.1)
	Week 12	135/210 (64.3)	134/194 (69.1)	136/205 (66.3)	245/373 (65.7)	256/363 (70.5)	238/383 (62.1)
	Week 24				248/363 (68.3)	252/347 (72.6)	244/368 (66.3)
Ratio of awake cough frequency (post-baseline/baseline) [95% CI][a),b)]	Week 4	0.55 [0.49, 0.63]	0.42 [0.37, 0.48]	0.64 [0.57, 0.73]	0.56 [0.52, 0.62]	0.45 [0.41, 0.49]	0.62 [0.57, 0.67]
	Week 8	0.47 [0.41, 0.55]	0.39 [0.34, 0.45]	0.50 [0.44, 0.58]	0.47 [0.43, 0.52]	0.41 [0.37, 0.45]	0.52 [0.47, 0.58]
	Week 12	0.47 [0.41, 0.55]	0.38 [0.33, 0.44]	0.46 [0.40, 0.53]	0.46 [0.42, 0.51]	0.39 [0.35, 0.43]	0.47 [0.42, 0.52]
	Week 24				0.41 [0.37, 0.46]	0.36 [0.32, 0.40]	0.42 [0.38, 0.47]
Proportion of patients with ≥30% reduction from baseline in awake cough frequency (coughs/hour)	Week 4	131/224 (58.5)	137/207 (66.2)	106/217 (48.8)	239/409 (58.4)	277/403 (68.7)	207/412 (50.2)
	Week 8	144/218 (66.1)	125/199 (62.8)	119/208 (57.2)	258/389 (66.3)	264/377 (70.0)	235/398 (59.0)
	Week 12	131/210 (62.4)	133/194 (68.6)	134/204 (65.4)	242/373 (64.9)	256/363 (70.5)	241/383 (62.9)
	Week 24				253/363 (69.7)	258/347 (74.4)	242/368 (65.8)
Proportion of patients with ≥1.3-point[c)] increase from baseline in LCQ total score	Week 4	137/210 (65.2)	129/190 (67.9)	118/203 (58.1)	232/382 (60.7)	242/368 (65.8)	226/386 (58.5)
	Week 8	150/212 (70.8)	138/194 (71.1)	117/199 (58.8)	247/368 (67.1)	251/360 (69.7)	250/381 (65.6)
	Week 12	139/200 (69.5)	134/194 (69.1)	123/196 (62.8)	257/362 (71.0)	257/352 (73.0)	235/372 (63.2)
	Week 24	145/204 (71.1)	129/185 (69.7)	124/193 (64.2)	264/352 (75.0)	262/342 (76.6)	245/355 (69.0)
	Week 52	148/184 (80.4)	116/163 (71.2)	122/180 (67.8)	261/300 (79.1)	267/322 (82.9)	229/334 (68.6)

Proportion of patients with ≥1.3-point[d] reduction from baseline in mean weekly CSD total score	Week 4	118/237 (49.8)	119/226 (52.7)	93/235 (39.6)	215/417 (51.6)	233/418 (55.7)	174/420 (41.4)
	Week 8	134/229 (58.5)	128/210 (61.0)	112/220 (50.9)	246/409 (60.1)	244/387 (63.0)	225/410 (54.9)
	Week 12	137/217 (63.1)	129/204 (63.2)	112/211 (53.1)	259/386 (67.1)	249/374 (66.6)	238/397 (59.9)
	Week 24	140/189 (74.1)	131/181 (72.4)	114/181 (63.0)	253/336 (75.3)	253/331 (76.4)	237/346 (68.5)
	Week 52	123/169 (72.8)	118/156 (75.6)	102/157 (65.0)	222/291 (76.3)	217/271 (80.1)	206/302 (68.2)
Proportion of patients with ≥30 mm[e] reduction from baseline in mean weekly cough severity VAS score	Week 4	43/237 (18.1)	63/226 (27.9)	31/235 (13.2)	92/417 (22.1)	130/418 (31.1)	63/420 (15.0)
	Week 8	69/229 (30.1)	75/210 (35.7)	52/220 (23.6)	130/409 (31.8)	155/387 (40.1)	112/410 (27.3)
	Week 12	79/217 (36.4)	87/204 (42.6)	63/211 (29.9)	157/386 (40.7)	174/374 (46.5)	145/397 (36.5)
	Week 24	80/189 (42.3)	92/181 (50.8)	61/181 (33.7)	178/336 (53.0)	178/331 (53.8)	150/346 (43.4)
	Week 52	85/169 (50.3)	84/156 (53.8)	65/157 (41.4)	168/291 (57.7)	172/271 (63.5)	165/302 (54.6)

a) The least squares estimate of the geometric mean

b) A repeated measures ANCOVA model with the change from baseline in log-transformed cough frequency at each time point as the response variable, treatment group, visit, the interaction of treatment group by visit, gender, and region as fixed effects, and the log-transformed baseline value and the interaction of log-transformed baseline value by visit as covariates. An unstructured covariance matrix was used to model the correlation among repeated measurements.

c) Defined as its threshold for clinically meaningful improvements based on the published data concerning LCQ (*Handb Exp Pharmacol*. 2009; 187: 311-20) and the data from Study 012.

d) Results of distribution-based analyses combined with anchor-based analyses using the PGIC as part of the psychometric assessment of the CSD (*Ther Adv Respir Dis*. 2020; 14: 1–15) indicated that a reduction of 1.3 to 2.7 points (on the 0 to 10-point scale) was appropriate to define clinically meaningful improvements.

e) Results of distribution-based analyses combined with anchor-based analyses using the PGIC as part of the psychometric assessment of cough severity VAS indicated that a reduction of ≥30 mm was appropriate to define clinically meaningful improvements.

Table 59. Results of main efficacy endpoints (Study 027, Japanese subgroup)

		15 mg	45 mg	Placebo
Ratio of 24-hour cough frequency (post-baseline/baseline) [95% CI] [a),b)]	Week 4	0.87 [0.40, 1.91]	0.39 [0.25, 0.63]	0.76 [0.45, 1.31]
	Week 8	0.40 [0.13, 1.17]	0.34 [0.17, 0.69]	0.42 [0.20, 0.89]
	Week 12	0.52 [0.22, 1.27]	0.24 [0.13, 0.43]	0.44 [0.23, 0.84]
Proportion of patients with ≥30% reduction from baseline in 24-hour cough frequency (coughs/hour)	Week 4	3/5 (60.0)	13/14 (92.9)	6/14 (42.9)
	Week 8	6/6 (100)	11/14 (78.6)	10/14 (71.4)
	Week 12	5/6 (83.3)	13/14 (92.9)	10/14 (71.4)
Ratio of awake cough frequency (post-baseline/baseline) [95% CI][a),b)]	Week 4	0.86 [0.39, 1.90]	0.37 [0.23, 0.60]	0.73 [0.42, 1.26]
	Week 8	0.40 [0.14, 1.18]	0.32 [0.16, 0.66]	0.39 [0.18, 0.83]
	Week 12	0.54 [0.23, 1.29]	0.22 [0.12, 0.39]	0.41 [0.22, 0.78]
Proportion of patients with ≥30% reduction from baseline in awake cough frequency (coughs/hour)	Week 4	3/5 (60.0)	13/14 (92.9)	6/14 (42.9)
	Week 8	5/6 (83.3)	11/14 (78.6)	10/14 (71.4)
	Week 12	5/6 (83.3)	13/14 (92.9)	10/14 (71.4)
Proportion of patients with ≥1.3-point[c)] increase from baseline in LCQ total score	Week 4	3/6 (50.0)	12/14 (85.7)	9/13 (69.2)
	Week 8	5/6 (83.3)	12/13 (92.3)	9/13 (69.2)
	Week 12	6/6 (100)	11/14 (78.6)	11/13 (84.6)
	Week 24	5/6 (83.3)	10/14 (71.4)	9/13 (69.2)
	Week 52	5/6 (83.3)	11/14 (78.6)	10/13 (76.9)
Proportion of patients with ≥1.3-point[d)] reduction from baseline in mean weekly CSD total score	Week 4	3/6 (50.0)	6/14 (42.9)	6/14 (42.9)
	Week 8	5/6 (83.3)	10/14 (71.4)	9/14 (64.3)
	Week 12	5/6 (83.3)	10/14 (71.4)	9/13 (69.2)
	Week 24	5/6 (83.3)	11/14 (78.6)	9/14 (64.3)
	Week 52	5/6 (83.3)	10/14 (71.4)	10/14 (71.4)
Proportion of patients with ≥30 mm [e)] reduction from baseline in mean weekly cough severity VAS score	Week 4	1/6 (16.7)	4/14 (28.6)	2/14 (14.3)
	Week 8	2/6 (33.3)	5/14 (35.7)	3/14 (21.4)
	Week 12	3/6 (50.0)	6/14 (42.9)	5/13 (38.5)
	Week 24	4/6 (66.7)	6/14 (42.9)	4/14 (28.6)
	Week 52	5/6 (83.3)	6/14 (42.9)	7/14 (50.0)

a) The least squares estimate of the geometric mean

b) A repeated measures ANCOVA model with the change from baseline in log-transformed cough frequency at each time point (Weeks 4, 8, and 12) as the response variable, treatment group, visit, the interaction of treatment group by visit, gender, and region as fixed effects, and the log-transformed baseline value and the interaction of log-transformed baseline value by visit as covariates. An unstructured covariance matrix was used to model the correlation among repeated measurements.

c) Defined as its threshold for clinically meaningful improvements based on the published data concerning LCQ (*Handb Exp Pharmacol.* 2009; 187: 311-20) and the data from Study 012.

d) Results of distribution-based analyses combined with anchor-based analyses using the PGIC as part of the psychometric assessment of the CSD (*Ther Adv Respir Dis*. 2020; 14: 1–15) indicated that a reduction of 1.3 to 2.7 points (on the 0 to 10-point scale) was appropriate to define clinically meaningful improvements.

e) Results of distribution-based analyses combined with anchor-based analyses using the PGIC as part of the psychometric assessment of cough severity VAS score indicated that a reduction of ≥30 mm was appropriate to define clinically meaningful improvements.

Table 60 shows the ratio of Week 12 to baseline 24-hour cough frequency (coughs/hour) by patient characteristics based on the pooled data from Studies 027 and 030.

Table 60. Ratio of Week 12 to baseline 24-hour cough frequency by patient characteristics (Pooled Studies 027 and 030, FAS)

Patient characteristics			15 mg	45 mg	Placebo
Age	<65 years		0.45 [0.40, 0.50] (419)	0.37 [0.33, 0.42] (405)	0.46 [0.41, 0.51] (415)
	≥65 years		0.52 [0.45, 0.59] (223)	0.42 [0.37, 0.48] (221)	0.52 [0.46, 0.59] (226)
Gender	Male		0.43 [0.36, 0.50] (160)	0.37 [0.31, 0.44] (156)	0.47 [0.40, 0.55] (161)
	Female		0.50 [0.46, 0.55] (482)	0.41[0.37, 0.45] (470)	0.49 [0.45, 0.54] (480)
BMI	<25 kg/m^2		0.47 [0.41, 0.55] (180)	0.39 [0.33, 0.45] (182)	0.50 [0.43, 0.59] (182)
	≥25 kg/m^2 and <30 kg/m^2		0.45 [0.39, 0.51] (230)	0.44 [0.38, 0.51] (234)	0.49 [0.43, 0.56] (235)
	≥30 kg/m^2		0.49 [0.42, 0.56] (232)	0.33 [0.29, 0.39] (209)	0.43 [0.37, 0.50] (224)
Smoking history	No		0.47 [0.43, 0.52] (472)	0.39 [0.35, 0.43] (456)	0.46 [0.42, 0.51] (468)
	Yes		0.47 [0.40, 0.54] (170)	0.38 [0.33, 0.45] (170)	0.51 [0.44, 0.59] (173)
Primary diagnosis	RCC		0.48 [0.44, 0.53] (388)	0.39 [0.36, 0.44] (390)	0.47 [0.42, 0.52] (404)
	UCC		0.46 [0.40, 0.54] (254)	0.39 [0.33, 0.45] (236)	0.50 [0.43, 0.58] (237)
Duration of chronic cough	1 to <5 years		0.44 [0.37, 0.51] (180)	0.38 [0.33, 0.45] (195)	0.38 [0.32, 0.45] (172)
	5 to <10 years		0.44 [0.37, 0.52] (155)	0.38 [0.32, 0.45] (165)	0.47 [0.40, 0.56] (176)
	≥10 years		0.52 [0.46, 0.58] (307)	0.40 [0.35, 0.46] (266)	0.55 [0.48, 0.62] (293)
Baseline 24-hour cough frequency (coughs/hour)	<20		0.55 [0.48, 0.62] (303)	0.47 [0.41, 0.53] (317)	0.54 [0.48, 0.61] (295)
	≥20		0.41 [0.37, 0.46] (339)	0.33 [0.29, 0.37] (309)	0.42 [0.38, 0.47] (346)
Baseline cough severity VAS	<60 mm		0.46 [0.39, 0.53] (209)	0.42 [0.36, 0.50] (178)	0.48 [0.41, 0.56] (191)
	≥60 mm		0.48 [0.43, 0.53] (432)	0.37 [0.34, 0.41] (446)	0.47 [0.43, 0.52] (448)
Comorbid conditions associated with chronic cough	Gastrooesophageal reflux disease		0.53 [0.46, 0.61] (208)	0.44 [0.38, 0.50] (197)	0.52 [0.46, 0.60] (213)
	Asthma		0.49 [0.43, 0.56] (211)	0.42 [0.37, 0.48] (241)	0.50 [0.44, 0.57] (228)
	Upper airway cough syndrome		0.53 [0.36, 0.78] (30)	0.33 [0.22, 0.50] (31)	0.46 [0.31, 0.67] (30)
	Others		0.32 [0.24, 0.43] (49)	0.25 [0.18, 0.34] (42)	0.38 [0.28, 0.52] (47)
Prior medications	Treatments for obstructive airways disease	Yes	0.47 [0.42, 0.51] (467)	0.40 [0.36, 0.44] (467)	0.47 [0.43, 0.52] (480)
		No	0.48 [0.40, 0.57] (175)	0.35 [0.29, 0.41] (159)	0.47 [0.39, 0.56] (161)
	Treatments for gastric acid-related disorders	Yes	0.49 [0.44, 0.54] (396)	0.39 [0.35, 0.44] (372)	0.46 [0.41, 0.51] (387)
		No	0.44 [0.38, 0.51] (246)	0.37 [0.32, 0.43] (254)	0.50 [0.43, 0.58] (254)
	Otolaryngology drugs	Yes	0.48 [0.43, 0.53] (378)	0.40 [0.36, 0.45] (369)	0.49 [0.44, 0.54] (403)
		No	0.46 [0.40, 0.53] (264)	0.37 [0.32, 0.42] (257)	0.45 [0.39, 0.52] (238)
	Systemic antihistamines	Yes	0.46 [0.41, 0.53] (269)	0.36 [0.32, 0.41] (267)	0.46 [0.41, 0.53] (283)
		No	0.47 [0.42, 0.53] (373)	0.41 [0.37, 0.46] (359)	0.48 [0.43, 0.54] (358)
	Treatments for cough and cold	Yes	0.46 [0.41, 0.53] (269)	0.36 [0.32, 0.41] (267)	0.46 [0.41, 0.53] (283)
		No	0.47 [0.42, 0.53] (373)	0.41 [0.37, 0.46] (359)	0.48 [0.43, 0.54] (358)

Least-squares mean [95% CI] (N)
A repeated measures ANCOVA model with the change from baseline in log-transformed cough frequency at each time point as the response variable, treatment group, visit, the interaction of treatment group by visit, gender, and region as fixed effects, and the log-transformed baseline value and the interaction of log-transformed baseline value by visit as covariates. An unstructured covariance matrix was used to model the correlation among repeated measurements.

The applicant's explanation about the efficacy of gefapixant by patient characteristics:
Due to post-hoc analyses of a limited number of patients, the results of the analyses should be interpreted with care. Gefapixant 45 mg failed to show higher efficacy over placebo in the subgroup of patients with a duration of chronic cough of 1 to <5 years, which is considered attributable to a lower-than-expected ratio of Week 12 to baseline 24-hour cough frequency in the placebo group. However, regardless of duration of chronic cough, gefapixant 45 mg showed similar efficacy for the ratio of Week 12 to baseline 24-hour cough frequency (Table 60) and the proportion of patients with a ≥1.3-point increase from baseline in LCQ total score (a

subjective patient-reported endpoint, LCQ) at Week 24 (pooled Studies 027 and 030, a duration of chronic cough of 1 to <5 years, 77.5%; ≥5 years, 72.8%). The durations of chronic cough had no major impact on the efficacy of gefapixant 45 mg, and a certain level of efficacy is expected, regardless of duration of chronic cough.

PMDA's view:
In the 2 phase III studies, a great placebo effect was observed, and the difference in the primary endpoint of 24-hour cough frequency (coughs/hour) between the gefapixant and placebo groups tended to be smaller over time. While the relative reduction vs. placebo for gefapixant 45 mg at the primary time point was −18% to −14%, both studies demonstrated the superiority of gefapixant 45 mg over placebo, and there was a trend towards a greater percent reduction in the gefapixant 45 mg group than in the placebo group throughout the evaluation period. Thus, gefapixant has been shown to have a certain level of efficacy in the treatment of cough. The trend favored gefapixant compared to placebo also in other objective endpoints including the responder rate and subjective endpoints related to QOL etc. with thresholds established for certain clinical significance, and the subjective endpoints tended to favor gefapixant vs. placebo through Week 52. Furthermore, taking also into account that there are limited therapies for RCC and UCC at present, the clinical usefulness of gefapixant in patients with RCC or UCC can be recognized.

On the whole, a similar trend was observed in the Japanese subgroup as in the overall population of Study 027. Thus, a certain level of efficacy of gefapixant is expected in Japanese patients with RCC or UCC. The applicant's explanation about the duration of chronic cough and efficacy is understandable, and the duration of chronic cough should have little impact on the efficacy of gefapixant.

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.3 Safety

The applicant's explanation about the safety of gefapixant based on the results of analyses of the pooled data from Studies 027 and 030 in patients with chronic cough (the pooled Studies 027/030) and the results of analyses of the pooled data from Studies 027, 030, 033, and 038 in patients with chronic cough (the pooled 4 studies), etc.:
Table 61 shows a summary of safety data from the pooled studies. Table 62 and Table 63 show the main adverse events reported in the pooled Studies 027/030 and the pooled 4 studies, respectively.

Table 61. Summary of safety data (Safety set)

	Pooled Studies 027/030			Pooled 4 studies		
Overall population						
Treatment group	15 mg (N = 686)	45 mg (N = 683)	Placebo (N = 675)	15 mg (N = 770)	45 mg (N = 779)	Placebo (N = 687)
Total exposure (patient-years)	596.57	517.16	597.69	675.72	585.50	599.09
All adverse events	559 (81.5) 93.70	607 (88.9) 117.37	533 (79.0) 89.18	638 (82.9) 94.42	698 (89.6) 119.21	535 (77.9) 89.30
Serious adverse events	41 (6.0) 6.87	38 (5.6) 7.35	39 (5.8) 6.53	43 (5.6) 6.36	48 (6.2) 8.20	39 (5.7) 6.51
Death	2 (0.3) 0.34	0	2 (0.3) 0.33	2 (0.3) 0.30	0	2 (0.3) 0.33
Adverse events leading to discontinuation	55 (8.0) 9.22	151 (22.1) 29.20	39 (5.8) 6.53	61 (7.9) 9.03	169 (21.7) 28.86	39 (5.7) 6.51
Adverse drug reactions	194 (28.3) 32.52	470 (68.8) 90.88	138 (20.4) 23.09	227 (29.5) 33.59	543 (69.7) 92.74	138 (20.1) 23.04
Adverse events of special interest						
Taste-related events[a)]	120 (17.5) 20.11	447 (65.4) 86.43	47 (7.0) 7.86	147 (19.1) 21.75	520 (66.8) 88.81	47 (6.8) 7.85
Paraesthesia oral	10 (1.5) 1.68	15 (2.2) 2.90	2 (0.3) 0.33	11 (1.4) 1.63	21 (2.7) 3.59	2 (0.3) 0.33
Hypoaesthesia oral	6 (0.9) 1.01	21 (3.1) 4.06	1 (0.1) 0.17	9 (1.2) 1.33	21 (2.7) 3.59	1 (0.1) 0.17
Haematuria, crystalluria, and urolithiasis [b)]	40 (5.8) 6.70	33 (4.8) 6.38	31 (4.6) 5.19	41 (5.3) 6.07	35 (4.5) 5.98	31 (4.5) 5.17
Pneumonia and lower respiratory tract infection[c)]	34 (5.0) 5.70	29 (4.2) 5.61	22 (3.3) 3.68	38 (4.9) 5.62	35 (4.5) 5.98	22 (3.2) 3.67
Hypersensitivity[d)]	25 (3.6) 4.19	38 (5.6) 7.35	42 (6.2) 7.03	30 (3.9) 4.44	42 (5.4) 7.17	42 (6.1) 7.01
Japanese subgroup						
Treatment group	15 mg (N = 6)	45 mg (N = 14)	Placebo (N = 14)	15 mg (N = 90)	45 mg (N = 110)	Placebo (N = 26)
Total exposure (patient-years)	6.20	14.50	14.20	85.35	82.84	15.60
All adverse events	6 (100) 96.75	14 (100) 96.55	14 (100) 98.56	85 (94.4) 99.59	105 (95.5) 126.75	16 (61.5) 102.58
Serious adverse events	1 (16.7) 16.13	1 (7.1) 6.90	1 (7.1) 7.04	3 (3.3) 3.51	11 (10.0) 13.28	1 (3.8) 6.41
Death	0	0	0	0	0	0
Adverse events leading to discontinuation	0	0	0	6 (6.7) 7.03	18 (16.4) 21.73	0
Adverse drug reactions	2 (33.3) 32.25	14 (100) 96.55	6 (42.9) 42.24	35 (38.9) 41.01	87 (79.1) 105.02	6 (23.1) 38.47
Adverse events of special interest						
Taste-related events[a)]	2 (33.3) 32.25	14 (100) 96.55	1 (7.1) 7.04	29 (32.2) 33.98	87 (79.1) 105.02	1 (3.8) 6.41
Paraesthesia oral	0	1 (7.1) 6.90	1 (7.1) 7.04	1 (1.1) 1.17	7 (6.4) 8.45	1 (3.8) 6.41
Hypoaesthesia oral	1 (16.7) 16.13	1 (7.1) 6.90	0	4 (4.4) 4.69	1 (0.9) 1.21	0
Haematuria, crystalluria, and urolithiasis [b)]	0	1 (7.1) 6.90	0	1 (1.1) 1.17	3 (2.7) 3.62	0
Pneumonia and lower respiratory tract infection[c)]	1 (16.7) 16.13	0	0	5 (5.6) 5.86	6 (5.5) 7.24	0
Hypersensitivity[d)]	1 (16.7) 16.13	6 (42.9) 41.38	3 (21.4) 21.12	6 (6.7) 7.03	10 (9.1) 12.07	3 (11.5) 19.23

Upper row, n (%); Lower row, Incidence rate adjusted for total exposure (Number of patients with an event per 100 patient-years)

a) Ageusia, dysgeusia, hypogeusia, taste disorder, and hypergeusia (all PTs) were counted.

b) Crystal urine, crystal urine present, calculus bladder, calculus urinary, crystalluria, haematuria, nephrolithiasis, and ureterolithiasis (all PTs) were counted.

c) Atypical pneumonia, lower respiratory tract infection, pneumonia, bacterial pneumonia, staphylococcal pneumonia, pneumonia streptococcal, and respiratory tract infection (all PTs) were counted.

d) Lip swelling, swollen tongue, tongue pruritus, face oedema, hypersensitivity, angioedema, dermatitis allergic, dermatitis, drug eruption, erythema multiforme, pruritus, rash, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular, urticaria, and urticaria papular (all PTs) were counted.

Table 62. Adverse events reported by ≥5% of subjects in either gefapixant group of the overall population or adverse events reported by ≥3 subjects in either gefapixant group of the Japanese subgroup (Pooled Studies 027/030, Safety set)

Event term	Overall population			Japanese subgroup		
	15 mg (N = 686)	45 mg (N = 683)	Placebo (N = 675)	15 mg (N = 6)	45 mg (N = 14)	Placebo (N = 14)
Dysgeusia	78 (11.4)	281 (41.1)	36 (5.3)	1 (16.7)	8 (57.1)	0
Nasopharyngitis	140 (20.4)	120 (17.6)	121 (17.9)	2 (33.3)	7 (50.0)	7 (50.0)
Ageusia	16 (2.3)	100 (14.6)	6 (0.9)	0	1 (7.1)	0
Headache	108 (15.7)	99 (14.5)	98 (14.5)	0	3 (21.4)	4 (28.6)
Hypogeusia	22 (3.2)	73 (10.7)	4 (0.6)	1 (16.7)	1 (7.1)	0
Nausea	34 (5.0)	64 (9.4)	45 (6.7)	0	1 (7.1)	1 (7.1)
Taste disorder	10 (1.5)	61 (8.9)	3 (0.4)	0	4 (28.6)	1 (7.1)
Cough	44 (6.4)	49 (7.2)	28 (4.1)	0	2 (14.3)	0
Dry mouth	22 (3.2)	45 (6.6)	17 (2.5)	1 (16.7)	0	1 (7.1)
Upper respiratory tract infection	56 (8.2)	43 (6.3)	36 (5.3)	0	1 (7.1)	0
Diarrhoea	42 (6.1)	39 (5.7)	32 (4.7)	1 (16.7)	1 (7.1)	1 (7.1)
Back pain	44 (6.4)	37 (5.4)	44 (6.5)	1 (16.7)	2 (14.3)	1 (7.1)
Oropharyngeal pain	26 (3.8)	37 (5.4)	29 (4.3)	1 (16.7)	1 (7.1)	0
Influenza	38 (5.5)	35 (5.1)	43 (6.4)	0	2 (14.3)	0
Arthralgia	35 (5.1)	30 (4.4)	38 (5.6)	1 (16.7)	0	0
Asthma	22 (3.2)	30 (4.4)	29 (4.3)	1 (16.7)	4 (28.6)	4 (28.6)
Bronchitis	40 (5.8)	29 (4.2)	35 (5.2)	2 (33.3)	3 (21.4)	2 (14.3)
Dizziness	22 (3.2)	29 (4.2)	15 (2.2)	0	3 (21.4)	0
Urinary tract infection	48 (7.0)	28 (4.1)	34 (5.0)	0	0	1 (7.1)
Urticaria	1 (0.1)	10 (1.5)	3 (0.4)	0	4 (28.6)	1 (7.1)

n (%)

Table 63. Adverse events reported by ≥5% of subjects in either gefapixant group (Pooled 4 studies, Safety set)

Event term	Overall population			Japanese subgroup		
	15 mg (N = 770)	45 mg (N = 779)	Placebo (N = 687)	15 mg (N = 90)	45 mg (N = 110)	Placebo (N = 26)
Dysgeusia	92 (11.9)	327 (42.0)	36 (5.2)	15 (16.7)	54 (49.1)	0
Nasopharyngitis	165 (21.4)	154 (19.8)	121 (17.6)	27 (30.0)	41 (37.3)	7 (26.9)
Ageusia	16 (2.1)	105 (13.5)	6 (0.9)	0	6 (5.5)	0
Headache	117 (15.2)	102 (13.1)	98 (14.3)	9 (10.0)	6 (5.5)	4 (15.4)
Hypogeusia	31 (4.0)	87 (11.2)	4 (0.6)	10 (11.1)	15 (13.6)	0
Taste disorder	16 (2.1)	72 (9.2)	3 (0.4)	6 (6.7)	15 (13.6)	1 (3.8)
Nausea	35 (4.5)	68 (8.7)	45 (6.6)	1 (1.1)	5 (4.5)	1 (3.8)
Cough	63 (8.2)	60 (7.7)	28 (4.1)	19 (21.1)	13 (11.8)	0
Dry mouth	24 (3.1)	49 (6.3)	17 (2.5)	3 (3.3)	4 (3.6)	1 (3.8)
Upper respiratory tract infection	58 (7.5)	43 (5.5)	36 (5.2)	2 (2.2)	1 (0.9)	0
Back pain	47 (6.1)	41 (5.3)	44 (6.4)	4 (4.4)	6 (5.5)	1 (3.8)
Diarrhoea	49 (6.4)	41 (5.3)	32 (4.7)	8 (8.9)	3 (2.7)	1 (3.8)
Oropharyngeal pain	30 (3.9)	39 (5.0)	29 (4.2)	5 (5.6)	3 (2.7)	0
Asthma	33 (4.3)	36 (4.6)	29 (4.2)	12 (13.3)	10 (9.1)	4 (15.4)
Influenza	41 (5.3)	36 (4.6)	43 (6.3)	3 (3.3)	3 (2.7)	0
Bronchitis	50 (6.5)	32 (4.1)	35 (5.1)	12 (13.3)	6 (5.5)	2 (7.7)
Accidental overdose	34 (4.4)	32 (4.1)	28 (4.1)	7 (7.8)	4 (3.6)	1 (3.8)
Urinary tract infection	48 (6.2)	28 (3.6)	34 (4.9)	0	0	1 (3.8)
Paraesthesia oral	11 (1.4)	21 (2.7)	2 (0.3)	1 (1.1)	7 (6.4)	1 (3.8)
Gastroenteritis	22 (2.9)	20 (2.6)	12 (1.7)	3 (3.3)	6 (5.5)	1 (3.8)
Cystitis	20 (2.6)	20 (2.6)	17 (2.5)	6 (6.7)	2 (1.8)	0
Pyrexia	8 (1.0)	18 (2.3)	7 (1.0)	5 (5.6)	6 (5.5)	0
Constipation	15 (1.9)	18 (2.3)	13 (1.9)	6 (6.7)	2 (1.8)	0
Insomnia	15 (1.9)	17 (2.2)	6 (0.9)	2 (2.2)	6 (5.5)	0
Pharyngitis	24 (3.1)	16 (2.1)	16 (2.3)	8 (8.9)	5 (4.5)	2 (7.7)
Gastrooesophageal reflux disease	22 (2.9)	14 (1.8)	14 (2.0)	6 (6.7)	1 (0.9)	0
Stomatitis	4 (0.5)	7 (0.9)	1 (0.1)	3 (3.3)	6 (5.5)	1 (3.8)

n (%)

In the pooled 4 studies, there were 2 deaths in the 15 mg group (cardiopulmonary failure; and respiratory tract infection [1 subject each]) and 2 deaths in the placebo group (death; and accidental death [1 subject each]), and a causal relationship to study drug was denied for all those cases. The incidences of serious adverse events

were 5.6% (43 of 770 subjects) in the 15 mg group, 6.2% (48 of 779 subjects) in the 45 mg group, and 5.7% (39 of 687 subjects) in the placebo group, and a causal relationship to study drug could not be ruled out for 1 case in the 45 mg group (hypoglycaemia) and 1 case in the placebo group (ureterolithiasis). In the Japanese subgroup in the pooled 4 studies, no deaths were reported. The incidences of serious adverse events were 3.3% (3 of 90 subjects) in the 15 mg group, 10.0% (11 of 110 subjects) in the 45 mg group, and 3.8% (1 of 26 subjects) in the placebo group, and a causal relationship to study drug was denied for all those events.

PMDA reviewed the incidences of adverse events of special interest, taking account of the incidences of adverse events in clinical studies, the pharmacological effects of gefapixant, and disease characteristics etc. of patients with RCC or UCC (Table 61) and then focused on the following events.

7.R.3.1 Taste-related events

The applicant's explanation about taste-related events (ageusia, dysgeusia, hypogeusia, taste disorder, hypergeusia):

Non-clinical studies indicated that the absence or functional inhibition of P2X2/3 ion channels leads to altered taste perception (*J Physiol*. 2005; 567: 621-39, *J Physiol*. 2015; 593: 1113-25, *Chem Senses*. 2009; 34:789-97), suggesting that taste-related events reported in clinical studies of gefapixant also occurred via a similar mechanism.

Table 64 shows the incidence of taste-related events in the pooled Studies 027/030. The incidence of taste-related adverse events was higher in the 45 mg group than in the 15 mg and placebo groups. Although a causal relationship to study drug could not be ruled out for the majority of taste-related adverse events, most events were mild or moderate in severity, and there were no serious taste-related adverse events. An investigation was conducted to identify the characteristics etc. of patients who are susceptible to serious taste-related events or taste-related events leading to discontinuation,[33)] but there was no particular trend.

In the pooled Studies 027/030, taste-related adverse events resolved during treatment or following treatment discontinuation in 96.0% of patients with taste-related adverse events in the 45 mg group. Thus, discontinuation or interruption of gefapixant can be a way of managing those adverse events. According to a survey by interviews with all patients with taste-related adverse events in Study 033, many of these patients responded that taste abnormality occurred several hours after taking the drug, especially while eating and drinking.

[33)] The occurrence of those events was analyzed according to gender, age, race, region, BMI, the primary disease, cough duration, and baseline cough severity VAS score and 24-hour cough frequency.

Table 64. Incidence of taste-related events (Pooled Studies 027/030, Safety set)

			Overall population			Japanese subgroup		
			15 mg (N = 686)	45 mg (N = 683)	Placebo (N = 675)	15 mg (N = 6)	45 mg (N = 14)	Placebo (N = 14)
Taste-related adverse events /Taste-related adverse drug reactions			120 (17.5) /112 (16.3)	447 (65.4) /432 (63.3)	47 (7.0) /38 (5.6)	2 (33.3) /2 (33.3)	14 (100) /14 (100)	1 (7.1) /1 (7.1)
	Dysgeusia (PT)		78 (11.4) /73 (10.6)	281 (41.1) /276 (40.4)	36 (5.3) /29 (4.3)	1 (16.7) /1 (16.7)	8 (57.1) /8 (57.1)	0
		Dysgeusia (LLT)	23 (3.4) /22 (3.2)	120 (17.6) /118 (17.3)	12 (1.8) /9 (1.3)	0	0	0
		Taste metallic	24 (3.5) /22 (3.2)	57 (8.3) /56 (8.2)	13 (1.9) /11 (1.6)	0	0	0
		Taste salty	7 (1.0) /7 (1.0)	38 (5.6) /37 (5.4)	2 (0.3) /2 (0.3)	0	3 (21.4) /3 (21.4)	0
		Taste bitter	11 (1.6) /9 (1.3)	34 (5.0) /33 (4.8)	7 (1.0) /6 (0.9)	1 (16.7) /1 (16.7)	3 (21.4) /3 (21.4)	0
		Taste perversion	5 (0.7) /5 (0.7)	13 (1.9) /13 (1.9)	1 (0.1) /1 (0.1)	0	0	0
		Taste peculiar	3 (0.4) /3 (0.4)	8 (1.2) /8 (1.2)	2 (0.3) /1 (0.1)	0	0	0
		Taste sweet	5 (0.7) /5 (0.7)	6 (0.9) /6 (0.9)	0	0	0	0
		Cacogeusia	1 (0.1) /1 (0.1)	6 (0.9) /6 (0.9)	0	0	1 (7.1) /1 (7.1)	0
		Phantom taste perception	1 (0.1) /1 (0.1)	5 (0.7) /5 (0.7)	0	0	2 (14.3) /2 (14.3)	0
		Taste sour	0	4 (0.6) /4 (0.6)	0	0	1 (7.1) /1 (7.1)	0
		Taste bitter-salty	0	4 (0.6) /4 (0.6)	0	0	0	0
		Taste chemical	0	2 (0.3) /2 (0.3)	0	0	0	0
		Chalky taste	0	2 (0.3) /2 (0.3)	0	0	0	0
		Medication after taste	1 (0.1) /1 (0.1)	0	0	0	0	0
	Ageusia		16 (2.3) /14 (2.0)	100 (14.6) /98 (14.3)	6 (0.9) /6 (0.9)	0	1 (7.1) /1 (7.1)	0
	Hypogeusia		22 (3.2) /21 (3.1)	73 (10.7) /70 (10.2)	4 (0.6) /3 (0.4)	1 (16.7) /1 (16.7)	1 (7.1) /1 (7.1)	0
	Taste disorder		10 (1.5) /10 (1.5)	61 (8.9) /54 (7.9)	3 (0.4) /2 (0.3)	0	4 (28.6) /4 (28.6)	1 (7.1) /1 (7.1)
	Hypergeusia		2 (0.3) /2 (0.3)	5 (0.7) /5 (0.7)	2 (0.3) /2 (0.3)	0	0	0
Taste-related events leading to treatment discontinuation			9 (1.3) [7.5]	95 (13.9) [21.3]	2 (0.3) [4.3]	0	0	0
Severity[a)]	Mild		93 (13.6) [77.5]	289 (42.3) [64.7]	41 (6.1) [87.2]	2 (33.3) [100]	12 (85.7) [85.7]	1 (7.1) [100]
	Moderate		25 (3.6) [20.8]	141 (20.6) [31.5]	6 (0.9) [12.8]	0	2 (14.3) [14.3]	0
	Severe		2 (0.3) [1.7]	17 (2.5) [3.8]	0	0	0	0
Outcome[b)]	Resolved		109 [90.8]	429 [96.0]	40 [85.1]	2 [100]	14 [100]	1 [100]
		During treatment	51 [42.5]	110 [24.6]	24 [51.1]	2 [100]	1 [7.1]	0
		Within 14 days after last dose	42 [35.0]	244 [54.6]	10 [21.3]	0	7 [50.0]	0
		≥14 days after last dose	16 [13.3]	75 [16.8]	6 [12.8]	0	6 [42.9]	1 [100]
	Ongoing		9 [7.5]	15 [3.4]	6 [12.8]	0	0	0
	Others		2 [1.7]	3 [0.7]	1 [2.1]	0	0	0
Time to onset (days)			36.4 ± 55.9 [1, 313]	9.1 ± 22.3 [1, 169]	43.1 ± 41.8 [1, 138]	1.5 ± 0.7 [1, 2]	1.4 ± 0.6 [1, 3]	43
Mean duration[c)] (days)			178.1 ± 143.4 [1, 391]	203.9 ± 153.8 [1, 555]	132.6 ± 143.5 [1, 510]	222.5 ± 156.3 [112, 333]	366.9 ± 32.6 [261, 402]	381

n (%), [Proportion among patients with taste-related adverse events (%)], Mean ± SD [Max., Min.] for time to onset and mean duration

a) Mild, easily-tolerated/does not interfere with routine activities; moderate, interferes with routine activities; severe, unable to perform routine activities

b) For subjects with more than one event, the event that resolved later was counted. If not all taste-related events resolved, those cases were categorized as "others."

c) Information on duration was available for 111 subjects in the 15 mg group, 432 subjects in the 45 mg group, and 41 subjects in the placebo group. These subjects were included in the analysis.

PMDA's view:

Although the majority of taste-related events associated with gefapixant observed in clinical studies were mild or moderate in severity, and some events resolved during treatment, taste-related events may drive discontinuations. Thus, after the market launch, how to manage those events should be determined, and the information should be provided to healthcare professionals in clinical practice.

7.R.3.2 Renal dysfunction

The applicant's explanation:

Since injurious changes in kidney tissues associated with crystalluria were observed in repeated-dose toxicity studies [see Section 5.R.1], the following investigations were conducted regarding the occurrence of renal dysfunction in clinical studies, etc. Based on the results, no particular precaution information regarding renal dysfunction associated with gefapixant is necessary.

● In clinical studies in which high-dose gefapixant was administered to healthy adult subjects, urinary crystals of gefapixant were observed in the following subjects, but none of those subjects had signs or symptoms of urinary tract injuries.

· One of 8 subjects treated with gefapixant 300 mg BID for 14 days and 5 of 8 subjects treated with gefapixant 900 mg BID (Study 002)

· All of 8 subjects treated with gefapixant 1,800 mg BID for up to 14 days (Study 003)

· Four of 25 subjects treated with gefapixant 300 mg (Days 1-7) and 600 mg (Days 8-21) BID (Study 007)

● The following relevant findings were observed in clinical studies in patients with chronic cough.

· Urinalysis was performed at Weeks 4, 8, and 12 in Study 012. None of 189 subjects treated with gefapixant 7.5 to 50 mg BID had an adverse event of urinary crystals of gefapixant or haematuria.

· Urinalysis was performed at baseline and Months 3, 6, and 12 in Studies 027, 030, and 038. Only 1 subject in the 45 mg group of Study 030 had crystalluria at Month 12. Though gefapixant was detected in this crystalluria, no adverse events associated with crystalluria were reported.

· In the pooled Studies 027/030, the incidence of adverse events of haematuria, crystalluria, and urolithiasis was low in all treatment groups and similar among the treatment groups (Table 65). Across the treatment groups, the mean changes from baseline in eGFR, urea nitrogen, and creatinine were −1.2 to 0.3 mL/min/1.73m^2, 0 to 0.5 mg/dL, and 0 mg/dL, respectively, which were not clinically relevant.

Table 65. Incidence of haematuria, crystalluria, and urolithiasis (Pooled Studies 027/030)

	Overall population			Japanese subgroup		
	15 mg (N = 686)	45 mg (N = 683)	Placebo (N = 675)	15 mg (N = 6)	45 mg (N = 14)	Placebo (N = 14)
Haematuria, crystalluria, and urolithiasis	40 (5.8)	33 (4.8)	31 (4.6)	0	0	0
Crystal urine	0	1 (0.1)	1 (0.1)	0	0	0
Crystal urine present	13 (1.9)	7 (1.0)	14 (2.1)	0	0	0
Bladder calculus	0	1 (0.1)	0	0	0	0
Urinary calculus	2 (0.3)	2 (0.3)	0	0	0	0
Crystalluria	1 (0.1)	3 (0.4)	2 (0.3)	0	0	0
Haematuria	20 (2.9)	20 (2.9)	13 (1.9)	0	1 (7.1)	0
Nephrolithiasis	6 (0.9)	1 (0.1)	2 (0.3)	0	0	0
Ureterolithiasis	0	0	1 (0.1)	0	0	0

n (%)

PMDA's view:
Although no findings suggestive of effects on the renal function were observed in clinical studies, renal excretion is the primary pathway for clearance of gefapixant, and patients with renal function below a certain level were excluded from phase III studies. Thus, it is necessary to watch for the occurrence of renal dysfunction associated with gefapixant, etc. via post-marketing surveillance etc.

PMDA's view on the safety of gefapixant based on the considerations in Sections 7.R.3.1 and 7.R.3.2:
On the basis of the submitted clinical study results, gefapixant has acceptable safety, provided that the package insert includes a precaution about taste-related events, which may drive discontinuations. Given that the number of Japanese patients with RCC or UCC in clinical studies was limited etc., it is necessary to collect gefapixant safety information via post-marketing surveillance etc. and provide the obtained information to healthcare professionals in clinical practice as appropriate.

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.4 Clinical positioning and indication

The applicant's explanation about the clinical positioning of gefapixant in the treatment of RCC and UCC:
At present, in addition to specific therapies for underlying diseases associated with cough, centrally-acting antitussives, which directly act on the cough center of the brain (codeine, dextromethorphan, etc.), as non-specific therapies for cough, are available for the treatment of chronic cough. However, the clinical practice guidelines recommend that the use of centrally-acting antitussives should be minimized because centrally-acting antitussives suppress cough as a defense mechanism and cause adverse reactions such as constipation and sleepiness. Dependence and abuse of codeine have been a social problem, and codeine is contraindicated in patients with serious respiratory depression etc. due to the risk of serious respiratory depression including death. As described above, effective treatment for RCC and UCC is a significant unmet need, and persistent cough decreases the physical, social, and psychological quality of life. Thus, there is a very high unmet medical need for a drug that treats chronic cough worldwide.

Studies 027 and 030 were conducted in patients with RCC or UCC, i.e. patients who continued to cough despite receiving diagnostic workup and therapy according to the ACCP guidelines, and cough was a burden to them. Since both objective and subjective endpoints demonstrated the efficacy of gefapixant, and no safety issues were identified, gefapixant as a peripherally-acting antitussive with a novel mechanism of action can offer a new treatment option for patients with a diagnosis of RCC or UCC.

For the proper use of gefapixant, gefapixant should be used when patients continue to cough despite receiving diagnostic workup and therapy according to the latest cough guidelines, and cough is a burden to them, in order to ensure that patients are not diagnosed as having UCC as a result of inadequate diagnostic workup and failure to identify the cause of chronic cough, and that patients who do not find relief with inappropriate treatment for the cause of chronic cough are not diagnosed with RCC.

PMDA's view:
Based on the applicant's explanation, the submitted data, and the considerations in Sections 7.R.1 and 7.R.2, since gefapixant is used in patients with chronic cough who continue to cough despite a proper diagnosis of associated conditions and disease-specific therapy according to the latest clinical practice guidelines, the use of centrally-acting antitussives should be minimized, and there are currently limited treatment options, gefapixant can offer a new treatment option for these patients.

In addition, the Japanese or foreign guidelines etc. do not provide clear diagnostic criteria for refractory and unexplained cough, and the clinical practice guidelines recommend that post-treatment diagnosis of cough should be made, based on specific therapy for pre-treatment diagnosis. Since both patients with RCC or UCC are considered to have failed to respond to the above-mentioned existing cough medications, the INDICATION section should explicitly state that gefapixant is indicated for patients refractory to specific therapy for underlying conditions, e.g., refractory chronic cough and chronic cough with an inadequate response to conventional treatments, and advise that prior to the use of gefapixant, patients should receive appropriate diagnostic workup and therapy according to the latest clinical practice guidelines.

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.5 Dosage and administration

PMDA's conclusion:
Based on the submitted data and the considerations in Sections 7.R.2 and 7.R.3, among the dosing regimens selected for Studies 027 and 030, gefapixant 45 mg administered orally twice daily was shown to be superior to placebo, and the efficacy and safety of gefapixant in patients with chronic cough were demonstrated. Thus, the proposed dosage and administration of "The usual adult dosage is 45 mg of gefapixant administered orally twice daily." is acceptable. Based on the considerations in Section 6.R.2, the package insert should advise that gefapixant 45 mg should be administered once daily in patients with severe renal impairment not requiring dialysis, and that there are no sufficient data to select the optimal dosing regimen for patients with end stage renal disease requiring dialysis.

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.6 Post-marketing safety measures

The applicant's explanation about post-marketing safety measures:
In the Japanese subgroup of Study 027 and in Study 038, there were no safety concerns unique to the Japanese population, and the safety profile of gefapixant was similar to that in the overall populations of Studies 027 and 030. However, as there is limited clinical experience with long-term administration of gefapixant in Japanese patients, a post-marketing specified use-results survey to assess the long-term safety of gefapixant in clinical practice is planned to be conducted.

PMDA's view:

As discussed in Section 7.R.3, on the basis of the clinical study results, gefapixant has acceptable safety. Meanwhile, after the market launch, it is necessary to determine how to manage taste-related events, etc., provide the information to healthcare professionals in clinical practice, and watch for the occurrence of renal dysfunction as well. Prior to the use of gefapixant, appropriate diagnostic workup and therapy according to the latest guidelines etc. are important, and it is necessary to appropriately provide information to healthcare providers so as to promote such proper use of gefapixant.

The above conclusion by PMDA will be discussed at the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.4) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that gefapixant has efficacy in the treatment of chronic cough refractory to specific therapy for associated conditions, and that gefapixant has acceptable safety in view of its benefits. Gefapixant is clinically meaningful because it offers a new treatment option for patients with chronic cough refractory to specific therapy for associated conditions.

PMDA has concluded that gefapixant may be approved if gefapixant is not considered to have any particular problems based on comments from the Expert Discussion.

10. Others

The method of efficacy assessment and the definitions of endpoints in clinical studies of gefapixant are shown below.

Endpoint	Definition
CSD	A 7-item, disease-specific patient reported outcome measure, with a recall period of "today." The measure evaluates cough frequency (3 items), intensity (2 items), and disruption (2 items); each item is rated on an 11-point scale ranging from 0 to 10 with higher scores indicating greater severity.
LCQ	A 19-item cough-specific health-related quality of life (HRQoL) questionnaire which contains 3 domains (physical, psychological, and social), and each item on the LCQ assesses symptoms over the past 2 weeks using a 7-point scale ranging from 1 to 7. Higher scores indicate better HRQoL.
Cough frequency	Cough counts were measured using a digital recording device,[34)] and average hourly cough frequency based on 24-hour sound recordings was calculated.
Cough severity VAS	Patients' assessment of the severity of their cough over the past 24 hours using a 100 mm VAS anchored with "No Cough" at 0 and "Extremely Severe Cough" at 100

[34)] The device was worn by the patient, and its chest sensor and microphone recorded sounds from the lungs and trachea and ambient (lapel) sounds for 24 hours. Based on the recording data, an analyst at the central reading center identified and quantified cough.

Review Report (2)

November 22, 2021

Product Submitted for Approval

Brand Name	Lyfnua Tablets 45 mg
Non-proprietary Name	Gefapixant Citrate
Applicant	MSD K.K.
Date of Application	February 26, 2021

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy, clinical positioning, indication, and dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusions concerning the efficacy, clinical positioning, indication, and dosage and administration of gefapixant presented in the Review Report (1) and made the following comments.

- The target population for gefapixant should be patients with a diagnosis of RCC despite continuous necessary and sufficient treatment of the primary disease and patients with a diagnosis of UCC despite adequate workup for differential diagnosis and attempted therapeutic diagnosis.
- The efficacy of gefapixant is clear in the early phase of treatment. Nevertheless, given the efficacy parameters improved over time after Week 12 even in the placebo group and the above-mentioned target population, the physicians should be cautious about prolonged aimless use of gefapixant as a first-line drug for chronic cough.

Based on the above, PMDA concluded that the indication should be "refractory chronic cough" and that the following cautionary notes should be presented in the package insert, and instructed the applicant to provide these precautions. The applicant agreed to respond appropriately.

- The use of gefapixant should be considered for persistent cough despite adequate treatment according to the latest guidelines, etc. based on a comprehensive diagnosis, including medical history, occupation, environmental factors, and laboratory test results that may be associated with chronic cough.
- Do not continue gefapixant therapy aimlessly in view of its symptomatic, non-causal nature.

1.2 Safety and risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusions concerning the safety of gefapixant and post-marketing safety measures presented in the Review Report (1), and made the following comments.

- Taste-related adverse events may decrease QOL, which can drive treatment interruptions frequently.
- Adverse drug reactions of taste-related events were dose-dependent, and crystalline foreign matters in urine derived from gefapixant can cause renal impairment. Given these findings etc., gefapixant should be used more carefully in patients with renal impairment.
- Because of the difficulty in detecting adverse events related to renal impairment attributable to crystalline foreign matters in urine based on the patient's subjective symptoms, regular renal function test, urinalysis, etc. are recommended.

Based on the considerations in Section "7.R.6 Post-marketing safety measures" in the Review Report (1) and the comments from the Expert Discussion, PMDA has concluded that the risk management plan (draft) for gefapixant should include the safety and efficacy specifications presented in Table 66, and that the applicant should conduct additional pharmacovigilance activities, efficacy survey/studies, and additional risk minimization activities presented in Table 67 and a general use-results survey presented in Table 68.

Table 66. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
· Taste abnormality	· Renal impairment attributable to crystalline foreign matters in urine	· None
Efficacy specification		
· None		

Table 67. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
· Early post-marketing phase vigilance · General use-results survey	· None	· Provision of information based on early post-marketing phase vigilance

Table 68. Outline of general use-results survey (draft)

Objective	To assess the safety of gefapixant in patients with refractory chronic cough in clinical practice.
Survey method	Central registry system
Population	Patients with refractory chronic cough
Observation period	6 months
Planned sample size	250 patients for the safety analysis population
Main survey items	· Safety specification: Taste abnormality, renal dysfunction associated with crystalluria · Patient characteristics (the date of diagnosis of cough, the reason for diagnosis, severity of cough, medical history, comorbid condition, etc.) · Use of gefapixant · Prior medications for the treatment of chronic cough · Concomitant medications/therapies · Adverse events

PMDA accepted these measures and considers that it is necessary to appropriately and promptly provide the collected information to healthcare providers etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and dosage and administration as shown below, with the following condition. As the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Indication

Refractory ~~or unexplained~~ chronic cough

(Strikethrough denotes deletions.)

Dosage and Administration

The usual adult dosage is 45 mg of gefapixant administered orally twice daily.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

ACCP	American College of Chest Physicians
A/G	Albumin/globulin ratio
ATP	Adenosine triphosphate
AUC	Area under the concentration-time curve
$AUC_{0\text{-}t}$	Area under the concentration-time curve from zero to t hours
AUC_{inf}	Area under the concentration-time curve from time zero to infinity
AUC_{last}	Area under the concentration-time curve from zero to time of last quantifiable concentration
AUC_{tau}	Area under the concentration-time curve from zero to time of the dosing interval
BCRP	Breast cancer resistance protein
BMI	Body mass index
BSEP	Bile salt export pump
BUN	Blood urea nitrogen
Caco-2	Colorectal adenocarcinoma
CHO-K1	Chinese hamster ovary-K1
CI	Confidence interval
CL	Clearance
CL/F	Apparent clearance
CL_r	Renal clearance
Clinical practice guidelines	Guidelines for the Management of Cough and Sputum 2019, edited by Drafting Committee for the Guidelines for the Management of Cough and Sputum 2019, the Japanese Respiratory Society
C_{max}	Maximum observed plasma concentration
CSD	Cough severity diary
C_{trough}	Trough plasma concentration
CYP	Cytochrome P450
DMSO	Dimethyl sulfoxide
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
FAS	Full Analysis Set
F_e	Fraction of drug excreted unchanged in urine
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in one second
FTIR	Fourier Transform Infrared Spectroscopy
FVC	Forced vital capacity
GC	Gas chromatography
GCP	Good Clinical Practice
GERD	Gastroesophageal Reflux Disease
HEK-293	Human embryonic kidney cells
hERG	Human *ether-à-go-go related gene*
HPLC	High performance liquid chromatography
[redacted]	[redacted]
$IC_{20,\ 50}$	20%, 50% inhibitory concentration
IR	Infrared absorption spectrum
JP	The Japanese Pharmacopoeia
K_D	Equilibrium dissociation constant
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LCQ	Leicester Cough Questionnaire
LLC-PK1	Lilly laboratory cell-porcine renal epithelial
LLT	Lowest level term
MATE	Multidrug and toxin extrusion protein

MeATP	Methyleneadenosine 5'-triphosphate trisodium salt
MDCKII	Madin-Darby canine kidney
MMRM	Mixed model repeated measures
mRNA	Messenger ribonucleic acid
MTT	Methyl thiazole tetrazolium
NADPH	Nicotinamide adenine dinucleotide phosphate hydrogen
NMR	Nuclear magnetic resonance spectrum
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PBS	Phosphate-buffered saline
PGIC	Patient's Global Impression of Change
P-gp	P-glycoprotein
p*K*i	Negative log of the pharmacodynamics equilibrium dissociation constant
PMDA	Pharmaceuticals and Medical Devices Agency
PPI	Proton pomp inhibitor
PT	Preferred term
PTP	Press through packaging
P2X2/3	Purinergic heteromeric receptor P2X2/3
P2X3	Purinergic homomeric receptor P2X3
QbD	Quality by Design
QOL	Quality of life
RCC	Refractory chronic cough
RH	Relative humidity
RTRT	Real time release testing
$t_{1/2}$	Terminal elimination half-life
The product	Lyfnua Tablets
t_{max}	Time at maximum plasma concentration
UCC	Unexplained chronic cough
UGT	Uridine 5'-diphospho-glucuronosyl transferase
VAS	Visual analogue scale
$V_{c/F}$	Apparent central volume of distribution
V_{ss}	Distribution volume at steady state
$V_{z/F}$	Apparent volume of distribution during terminal phase