Report on the Deliberation Results

December 3, 2025
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Avarept Ophthalmic Suspension 0.3%
Non-proprietary Name	Motugivatrep (JAN*)
Applicant	Senju Pharmaceutical Co., Ltd.
Date of Application	January 17, 2025

Results of Deliberation

In its meeting held on November 27, 2025, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. The drug product is not classified as a poisonous drug or a powerful drug, and its drug substance is classified as a powerful drug.

Approval Condition

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

**Japanese Accepted Name (modified INN)*

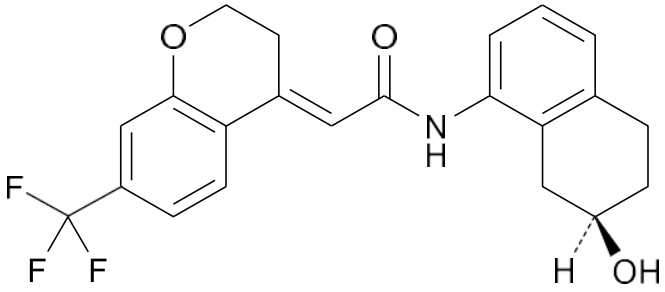
Review Report

November 18, 2025
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	Avarept Ophthalmic Suspension 0.3%
Non-proprietary Name	Motugivatrep
Applicant	Senju Pharmaceutical Co., Ltd.
Date of Application	January 17, 2025
Dosage Form/Strength	An ophthalmic suspension containing 3 mg of Motugivatrep per mL
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{22}H_{20}F_3NO_3$
Molecular weight: 403.39
Chemical name:
(2*E*)-*N*-[(7*R*)-7-Hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]-2-[7-(trifluoromethyl)-2,3-dihydro-4*H*-1-benzopyran-4-ylidene]acetamide

Items Warranting Special Mention None
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 dry eye disease, 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 product is not classified as a biological product or a specified biological product. The drug product is not classified as a poisonous drug or a powerful drug, and its drug substance is classified as a powerful drug.

The long-term safety of the product in pediatric patients, in clinical practice, should be further investigated via post-marketing surveillance etc.

Indication

Dry eye disease

Dosage and Administration

The usual dose is one drop instilled into the eye 4 times daily.

Approval Condition

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

Attachment

Review Report (1)

October 23, 2025

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	Avarept Ophthalmic Suspension 0.3%
Non-proprietary Name	Motugivatrep
Applicant	Senju Pharmaceutical Co., Ltd.
Date of Application	January 17, 2025
Dosage Form/Strength	An ophthalmic suspension containing 3 mg of Motugivatrep per mL

Proposed Indication Dry eye disease

Proposed Dosage and Administration

The usual dose is one drop instilled into the eye 4 times daily.

Table of Contents

List of Abbreviations

See Appendix.

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

"Avarept Ophthalmic Suspension 0.3%" (the product) contains the active substance Motugivatrep (motugivatrep). Motugivatrep is a small molecule discovered by Mochida Pharmaceutical Co., Ltd. It is an antagonist of the transient receptor potential cation channel subfamily V member 1 (TRPV1). TRPV1 is a typical cation channel that is expressed by primary sensory neurons, activated by thermal, inflammatory, and osmotic stimuli, etc., and involved in pain sensation.

Dry eye is a disease characterized by tear film instability, causing subjective symptoms such as ocular discomfort and visual disturbance, and may be accompanied by ocular surface damage. The presumed factors contributing to unstable tear film are reduced lacrimal secretion, decreased wettability of the corneal epithelium, and increased tear evaporation (Clinical practice guidelines). Patients with dry eye disease are known to have tear hyperosmolarity and elevated levels of inflammatory mediators in tears (*Ocul Surf*. 2017; 15: 276-83, *Invest Ophthalmol Vis Sci*. 2011; 52: 7725-30, etc.), and these stimuli are thought to activate TRPV1, lowering the activation threshold of corneal sensory nerves and inducing further production of inflammatory mediators (Clinical practice guidelines, *Invest Ophthalmol Vis Sci*. 2011; 52: 485-93).

According to the clinical practice guidelines, some patients receive surgical treatment for dry eye disease, but eye drops are the mainstay of treatment. As eye drop treatment options, sodium hyaluronate, diquafosol sodium, and rebamipide are recommended, and then artificial tears and topical corticosteroids are suggested. However, cases of persistent subjective symptoms such as ocular discomfort despite the normalization of the tear film and the resolution of keratoconjunctival epithelial disorders by conventional treatments have also been reported. The discrepancy between subjective symptoms and objective findings is often observed (*Journal of the Eye*. 2019; 36: 719-24, Clinical practice guidelines), which is considered due to abnormal corneal sensation.

Motugivatrep was developed with an expectation of its therapeutic effects of normalizing corneal sensation and improving subjective symptoms through TRPV1 inhibition. In Japan, the clinical development of motugivatrep began in December 2020, and a marketing application has now been submitted based on the results from a Japanese phase III study etc. As of October 2025, motugivatrep has not been approved in any country or region.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white powder. Its appearance, solubility, hygroscopicity, melting point, acid dissociation constant (pKa), and specific rotation have been determined. Although 12 crystalline forms of the drug substance occur, Form A* only is produced by the commercial-scale manufacturing process and has been demonstrated to be stable at room temperature.

Its chemical structure has been elucidated by mass spectrometry, elemental analysis, ultraviolet-visible spectroscopy (UV/VIS), infrared absorption spectroscopy (IR), nuclear magnetic resonance spectroscopy

(NMR) (^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR), two-dimensional NMR (^{1}H-^{1}H correlation spectroscopy [COSY]-NMR, ^{1}H-^{13}C heteronuclear single quantum coherence spectroscopy [HSQC]-NMR, ^{1}H-^{13}C heteronuclear multiple bond correlation [HMBC]-NMR, ^{1}H-^{1}H rotating frame nuclear Overhauser effect spectroscopy [ROESY]-NMR), and single-crystal X-ray crystallography.

2.1.2 Manufacturing process

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

A quality control strategy was established based on the following etc. (Table 1)

- Identification of critical quality attributes (CQAs)
- Identification of critical process parameters (CPPs) through design of experiments

Table 1. Overview of drug substance control strategy

CQA	Method of control
Appearance	Manufacturing process, Specification
[redacted]	Manufacturing process, Specification
Related substances	Manufacturing process, Specification
Residual solvents	Manufacturing process
Elemental impurities	Manufacturing process
Residue on ignition	Manufacturing process, Specification
[redacted]	Manufacturing process, Specification
Content	Manufacturing process, Specification
Water content	Manufacturing process, Specification
Polymorphism	Manufacturing process, Specification
Particle size	Specification
Microbial limits	Specification

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

2.1.3 Control of drug substance

The proposed specifications for the drug substance consist of content, appearance, identification (high performance liquid chromatography [HPLC], IR, X-ray powder diffraction), purity (related substances [HPLC], [redacted] [HPLC]), water content, residue on ignition, microbial limits, particle size, and assay (HPLC).

2.1.4 Stability of drug substance

The primary stability studies on the drug substance are shown in Table 2. The stability results indicated that the drug substance is stable. Photostability data showed that the drug substance is photostable.

Table 2. Stability studies on drug substance

Study	Primary batches	Temperature	Relative humidity	Storage package	Storage period
Long-term	3 [redacted] batches	25°C	60%	[redacted]-layer [redacted] bag [redacted] drum	36 months
Accelerated	3 [redacted] batches	40°C	75%		6 months

Based on the above, a re-test period of 36 months was proposed for the drug substance when stored in [redacted]-layer [redacted] bag [redacted] within [redacted] drum at room temperature.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an aqueous ophthalmic suspension containing 3 mg of motugivatrep per mL. It contains the following excipients: tyloxapol, methylcellulose, boric acid, zinc chloride, borax, and purified water.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of testing for acceptance, formulation, filling/capping, and packaging/labeling/storage/testing. [redacted] and [redacted] have been defined as critical steps, and process control items and values have been established for these steps.

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, appearance, identification (HPLC), pH, osmolar ratio, purity ([redacted] [HPLC]), insoluble particulate matter, sterility, particle size, and assay (HPLC).

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	Relative humidity	Storage package	Storage period
Long-term	3 [redacted] batches	25°C	40%	polypropylene container, a shrink sleeve label, carton	[redacted] months
Accelerated	3 [redacted] batches	40°C	20%		6 months

Based on the above, in accordance with the International council for harmonisation of technical requirements of pharmaceuticals for human use (ICH) Q1E guideline, a shelf-life of 36 months was proposed for the drug product when filled into a polypropylene container and wrapped with a shrink sleeve label and then stored in a carton at room temperature. 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 and the following considerations etc., PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

2.R.1 Novel excipients

The drug product contains tyloxapol in an amount higher than the amounts present in existing ophthalmic formulations. Based on the submitted data, PMDA concluded that there are no problems with the specification, stability, and safety.

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

The applicant submitted the results from the following primary pharmacodynamic studies: studies that evaluated the antagonistic activity of motugivatrep against TRPV1 etc., the effects of motugivatrep on trigeminal ganglion cells, corneal epithelial cells, and activated T cells, and its effects in a rat model of dry eye. The applicant submitted the results from secondary pharmacodynamic studies that evaluated the effect of motugivatrep on the corneal sensitivity threshold and its effects on various enzymes, receptors, etc. The applicant submitted the results from safety pharmacology studies that evaluated the effects of motugivatrep on the central nervous system, body temperature, motor coordination, and cardiovascular and respiratory systems. No pharmacodynamic interaction studies were conducted.

Unless otherwise specified, pharmacologic parameters are expressed as the mean, and doses or concentrations are expressed in terms of motugivatrep.

3.1 Primary pharmacodynamics

3.1.1 Antagonistic activity against TRPV1 etc. (CTD 4.2.1.1-1, 4.2.1.1-2 [Reference data])

Using Chinese hamster ovary (CHO) cells expressing human and rat TRPV1 and human embryonic kidney 293 (HEK293) cells expressing mouse, dog, and monkey TRPV1, the antagonistic activity of motugivatrep against capsaicin-induced activation of human, rat, mouse, dog, and monkey TRPV1 was determined based on intracellular calcium concentrations. The IC_{50} values were 0.66 nmol/L, 0.46 nmol/L, 2.1 nmol/L, 1.2 nmol/L, and 0.57 nmol/L, respectively.

Similarly, using CHO cells expressing various transient receptor potential (TRP) cation channels other than TRPV1, the antagonistic activity of motugivatrep (1-10 μmol/L) against allyl isothiocyanate-induced activation of human transient receptor potential cation channel subfamily A member 1 (TRPA1), menthol-induced activation of human transient receptor potential cation channel subfamily M member 8 (TRPM8), 2-aminoethoxydiphenylborate- or camphor-induced activation of human TRPV3, and 4α-Phorbol 12,13-didecanoate-induced activation of human TRPV4 was determined. Although motugivatrep at a concentration of 10 μmol/L exhibited antagonistic activity against TRPV4, motugivatrep showed no antagonistic activity against TRPA1, TRPM8, or TRPV3 even at a concentration of 10 μmol/L.

3.1.2 Effect on trigeminal ganglion cells (CTD 4.2.1.1-6)

Using rat trigeminal ganglion cells, the effect of motugivatrep (0.1-100 nmol/L) on substance P release induced by TRPV1 stimulation by capsaicin was evaluated by an enzyme-linked immunosorbent assay (ELISA). Motugivatrep at concentrations of ≥1 nmol/L suppressed substance P release.

3.1.3 Effect on corneal epithelial cells (CTD 4.2.1.1-7)

Using human corneal epithelial cell line (HCE-T), the effect of motugivatrep (0.1-10 μmol/L) on the upregulation of CC-chemokine ligand 5 (CCL5) mRNA expression induced by TRPV1 stimulation by hyperosmolarity was evaluated by quantitative polymerase chain reaction (qPCR). Motugivatrep suppressed the upregulation of CCL5 mRNA expression at the concentrations tested.

3.1.4 Effect on activated T cell (CTD 4.2.1.1-8)

Using murine spleen CD4+ T cells activated by anti-CD3 and anti-CD28 antibodies, the effect of motugivatrep (1 or 10 nmol/L) on interferon gamma (IFNγ) production via TRPV1 was evaluated by an ELISA. Motugivatrep suppressed IFNγ production at the concentrations tested.

3.1.5 Effect on blink rate in rat model of dry eye (CTD 4.2.1.1-3, 4.2.1.1-4)

Dry eye was induced in male rats (Sprague-Dawley [SD]) by scopolamine administered by surgically implanted osmotic pumps. When the rats were housed in a low-humidity environment, the effect of a single ocular instillation of motugivatrep (0.1%, 0.3%, or 1.0% suspension) or formulation vehicle[1)] on an increased blink rate was evaluated. The blink rate is commonly used as a behavioral readout indicating the eye's dryness and uncomfortableness to the animal (*Comp Med.* 2016; 66: 112-8, *Mol Vis*. 2024; 30: 150-9). An increase in the blink rate was inhibited by 0.3% motugivatrep suspension and 1.0% motugivatrep suspension compared with formulation vehicle.

The duration of inhibition of an increase in the blink rate by 1.0% motugivatrep suspension was determined. Inhibition of an increase in the blink rate was maintained up to 4 hours after a single instillation of motugivatrep.

3.1.6 Effect on corneal epithelial disorder in rat model of dry eye (CTD 4.2.1.1-5)

In a rat model of dry eye as described in Section 3.1.5, the effect of 0.3% motugivatrep suspension or formulation vehicle,[2)] instilled into the eye 4 times daily for 14 days, on an increase in superficial punctate keratopathy (SPK) score[3)] (the SPK score indicates the severity of superficial punctate keratopathy, a corneal epithelial disorder), was evaluated. An increase in the SPK score was inhibited by 0.3% motugivatrep suspension compared with formulation vehicle.

[1)] Vehicle for non-clinical formulations (containing [redacted]mg, [redacted]mg, and [redacted]mg per mL)
[2)] Dulbecco's Phosphate-Buffered Saline containing 0.1% polysorbate 80
[3)] Each cornea was divided into 3 zones. Each zone was graded from 0 to 3 (0: no punctate staining, 1: sparse density of punctate staining [punctate staining was separated], 2: moderate density of punctate staining [between 1 to 3 points], 3: high density of punctate staining [punctate staining was nearly adjacent]). The SPK score was the sum of all zones (a maximum score of 9).

3.2 Secondary pharmacodynamics

3.2.1 Effect on corneal sensitivity threshold in rat model of dry eye (CTD 4.2.1.2-1)

In a rat model of dry eye as described in Section 3.1.5, the effect of 0.3% motugivatrep suspension or formulation vehicle,[2)] instilled into the eye 4 times daily for 14 days, on the mechanical corneal sensitivity threshold, was evaluated. There were no differences in the corneal sensitivity threshold between the formulation vehicle and 0.3% motugivatrep groups.

3.2.2 Off-target profiling (CTD 4.2.1.2-2 [Reference data])

Motugivatrep [redacted]μmol/L was screened for its activity against the major ion channels, receptors, transporters, and enzymes, using radioligand binding assays and enzyme assays. Motugivatrep did not cause ≥[redacted]% inhibition, except for 5-hydroxytryptamine receptor 2A (5-HT_{2A}) ([redacted]%) and 5-HT_{2B} ([redacted]%).

3.3 Safety pharmacology

Table 4 shows the results of safety pharmacology studies.

Table 4. Overview of safety pharmacology studies

Organ systems evaluated	Test system	No. of animals	Endpoints/ Method of assessment, etc.	Doses (Route of administration)	Findings	Attached document CTD
CNS	Rat (Han Wistar)	6M/group	Sensory, motor, and behavioral function, body temperature, clinical signs	0, 4, 40, 400 mg/kg (Oral)	• 4 mg/kg: increased touch response and increased vocalization during handling at 1 hour post-dose, increased body temperature (a 2.1°C rise) at 1 hour post-dose • 40 mg/kg: proptosis and increased touch response at 1 hour post-dose, increased vocalization during handling at 1-8 hours post-dose, increased body temperature (a 1.0°C rise) at 4 hours post-dose • 400 mg/kg: increased vocalization during handling and increased body temperature (2.0°C and 0.8°C rises) at 1 and 4 hours post-dose, dispersion within the cage at 4 hours post-dose	4.2.1.3-1
Body temperature	Rat (SD)	5M/group	Rectal temperature	0, 3 mg/kg/day (Oral)	• Day 1: An approximately 1°C rise in rectal temperature at 0.5 hours post-dose • Days 3 and 4: An approximately 0.2°C rise in rectal temperature at 0.5 hours post-dose	4.2.1.3-7 (Reference data)
	Dog (Beagle)	3M	Body temperature, general behavior	0, 10 mg/kg (Oral)	• Compared with vehicle (corn oil) (38.4°C), increased body temperature (39.6°C-40.2°C) at 1-8 hours post-dose. Body temperature was still higher at 24 hours post-dose (vehicle, 38.3°C; motugivatrep, 39.3°C)	4.2.1.3-8 (Reference data)
	Monkey (Cynomolgus monkey)	3M	Body temperature, general behavior	0, 3 mg/kg (Oral)	• Increased body temperature at 1-8 hours post-dose (38.3°C at pre-dose and at 0.5 hours post-dose, 38.7°C-38.8°C at 1-8 hours post-dose, 38.4°C at 24 hours post-dose)	4.2.1.3-9 (Reference data)
Motor coordination	Rat (SD)	10M/group	Motor coordination	0, 1, 3, 10 mg/kg (Oral)	No effects	4.2.1.3-10 (Reference data)
Cardiovascular system	hERG-transfected HEK293 cells	—	hERG current	1 µmol/L (0.40 µg/mL)	Percent inhibition of hERG current (Mean ± SD) • 8.5 ± 2.7% inhibition	4.2.1.3-2 (Reference data)
				0.248 µmol/L (0.1 µg/mL), 0.744 µmol/L (0.3 µg/mL), 2.48 µmol/L (1 µg/mL)	Percent inhibition of hERG current (Mean ± SD) • 0.248 µmol/L: 5.0 ± 7.2% inhibition • 0.744 µmol/L: 3.2 ± 4.3% inhibition • 2.48 µmol/L: 12.8 ± 4.1% inhibition	4.2.1.3-3 4.2.1.3-4 (Reference data)
	Dog (Beagle)	4M	ECG, blood pressure, heart rate, body temperature	0, 4, 40, 400 mg/kg (Oral)	• Non-dose-dependent shortening of QTcF and QTcQ at all dose levels • Increased body temperature at 1-20 hours post-dose at all dose levels (a 1.75°C rise at 4 mg/kg, a 1.88°C rise at 40 mg/kg, a 1.85°C rise at 400 mg/kg) • There were no consistent changes in mean heart rate or arterial blood pressure.	4.2.1.3-5
Respiratory system	Rat (Han Wistar)	8M/group	Respiratory rate, tidal volume	0, 4, 40, 400 mg/kg (Oral)	No effects	4.2.1.3-6

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacologic effects of motugivatrep

The applicant's explanation about the mechanism of action of motugivatrep in the treatment of dry eye disease: TRPV1 is a cation channel that is activated by capsaicin, heat, inflammatory mediators, osmotic stress, etc. Patients with dry eye disease are known to have tear hyperosmolarity and elevated levels of

inflammatory mediators in tears, and these stimuli activate or sensitize TRPV1 (*Invest Ophthalmol Vis Sci*. 2011; 52: 485-93, *Pain*. 2016; 157: 1346-62, etc.), lowering the activation threshold of corneal sensory nerves (Clinical practice guidelines). Motugivatrep inhibits TRPV1 and is mainly expected to normalize corneal sensation and improve subjective symptoms of dry eye by inhibiting TRPV1 expressed on the free nerve endings distributed in the corneal epithelia of the trigeminal nerve that is responsible for corneal sensation.

In addition, patients with dry eye disease have increased tear levels of CCL5, substance P, IFNγ, etc., which have been reported to play a role in the development of dry eye disease such as corneal epithelial disorder (*Curr Eye Res*. 2012; 37: 12-7, *Cornea*. 2023; 42: 557-64, etc.). Motugivatrep may also improve one of objective findings of dry eye, i.e. corneal epithelial disorder, by suppressing CCL5 expression in corneal epithelial cells, the release of substance P from the trigeminal nerve's free endings, and IFNγ production from T cells via TRPV1 inhibition.

Based on the submitted data, PMDA concluded that motugivatrep was shown to inhibit TRPV1, and that the effects of motugivatrep in the treatment of dry eye disease can be explained.

3.R.2 Safety pharmacology studies

The applicant's explanation about increased body temperature and shortened QT interval observed in safety pharmacology studies:

Although multiple TRPV1 antagonists were previously developed as oral analgesics, their main side effects of increased body temperature, sometimes to 40°C, were reported, etc., leading to development termination (*Pharmacol Rev*. 2009; 61: 225-7). TRPV1 antagonists are considered to alter core body temperature via thermoregulatory centers in the hypothalamus (*Elife*. 2022; 11: e80139) by inhibiting TRPV1 expressed in viscera (*Pharmacol Rev*. 2009; 61: 225-7, *J Neurosci*. 2007; 27: 7459-68). Since tonic activation of TRPV1 inhibits skin vasoconstriction and thermogenesis, TRPV1 antagonists disinhibit these thermoeffectors, causing increased body temperature (*J Neurosci*. 2007; 27: 7459-68). Also in safety pharmacology studies of orally administered motugivatrep, increased body temperature was observed. However, as no systemic effects that would cause safety issues, associated with increased body temperature, were observed, there should be little concern about the clinical use of motugivatrep because systemic exposure from eye drops is limited.

Given that a correlation between the shortening of QT interval and an increase in core body temperature in dogs has been reported (*Br J Pharmacol*. 2008; 154: 1474-81), shortened QT interval observed in a safety pharmacology study of motugivatrep in dogs is considered secondary to increased body temperature, and motugivatrep should have little pro-arrhythmic potential.

PMDA’s view:

The applicant's explanation (shortened QT interval observed in a safety pharmacology study is considered secondary to increased body temperature, and motugivatrep should have little pro-arrhythmic potential) is understandable. However, given that after oral administration of motugivatrep, increased body temperature and shortened QT interval were observed from the low dose onwards, and that an adequate margin of safety was not achieved, the possibility of increased body temperature and shortened QT interval following ocular

instillation of motugivatrep needs to be determined, taking also account of clinical study results [see Section 7.R.3].

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 motugivatrep, in the form of the results from oral and intravenous studies in rats and dogs and ocular instillation studies in dogs and rabbits, etc. Plasma concentrations of motugivatrep were determined by liquid chromatography-tandem mass spectrometry (LC/MS/MS) (lower limit of quantification [LLOQ], rats [50.0 ng/mL], dogs [0.100 ng/mL (repeated-dose studies) or 10.0 ng/mL (a single-dose study)], rabbits [2.00 ng/mL]). Radioactivity concentrations in samples were determined by liquid scintillation counter, high performance liquid chromatography-radioactivity detection (HPLC-RAD), or quantitative whole-body autoradiography.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2-1, 4.2.2.2-2)

Table 5 shows the pharmacokinetic parameters of motugivatrep following a single intravenous or oral dose of ^{14}C-motugivatrep in rats and dogs.

Table 5. Single-dose pharmacokinetic parameters of motugivatrep

Species	Route of administration	Dose (mg/kg)	Number of animals	C_{max} (μg/mL)	t_{max} (h)	AUC_{last} (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_d (mL/kg)	F (%)
Rat	IV	1	3M[a)]	–	–	32.0	6.9	32.8	326	–
			3F[a)]	–	–	39.3	10.2	27.1	398	–
	Oral	3	3M[a)]	4.48	8	71.2	6.0	–	–	80.5
			3F[a)]	4.82	8	88.5	9.1	–	–	85.5
Dog	IV	1	3M	–	–	5.24	7.6	203	2,230	–
			3F	–	–	6.32	6.5	169	1,590	–
	Oral	5	3M	1.26	2	18.2	8.8	–	–	69.1
			3F	1.10	4	15.4	7.2	–	–	48.0

Mean; –, Not applicable or not calculated
a) No. of animals per time point, n = 5 at the last time point (at 48 hours post-dose) only.

4.1.2 Repeated-dose studies (Toxicokinetics) (CTD 4.2.2.2-3, 4.2.2.2-4, 4.2.2.2-5)

Toxicokinetics were evaluated in 4-week repeated-dose toxicity studies in rabbits and dogs and a 39-week repeated-dose toxicity study in dogs, in which 50 μL/eye of 0.3%, 1%, or 3% motugivatrep suspension was instilled into both eyes 8 times or 6 times daily. The pharmacokinetic parameters of motugivatrep are shown in Table 6. Following ocular instillation of motugivatrep in rabbits and dogs, motugivatrep exposure increased with increasing dose over the dose range tested. When motugivatrep exposure on Day 1 was compared with that on Day 28 in rabbits, a trend towards increased exposure after repeated dosing was observed at all dose levels. When motugivatrep exposure on Day 1 was compared with that on Day 273 in dogs, a trend towards increased exposure after repeated dosing was observed in the 3% motugivatrep group; however, there were no clear increases in exposure in the 0.3% and 1% motugivatrep groups. Although there were no clear gender

differences in motugivatrep exposure following 4-week ocular instillation in rabbits and dogs, motugivatrep exposure tended to be higher in female dogs than in male dogs following 39-week ocular instillation.

Table 6. Pharmacokinetic parameters of motugivatrep following repeated ocular instillation

Species	Duration of dosing (Dosing frequency)	Concentration	Day of blood sampling	No. of animals	C_{max} (ng/mL)	t_{max} (h)	AUC_{last} (ng·h/mL)
Rabbit	4 weeks (8 times/day)	0.3%	Day 1	3M	32.9 ± 3.4	0.67 ± 0.29	272 ± 59
				3F	37.9 ± 5.4	0.67 ± 0.29	299 ± 69
			Day 28	3M	51.4 ± 10.1	1.2 ± 0.8	629 ± 63
				3F	46.1 ± 10.2	0.50 ± 0.00	572 ± 141
		1%	Day 1	3M	107 ± 19	1.5 ± 0.9	1,110 ± 300
				3F	108 ± 43	1.0 ± 0.9	1,010 ± 230
			Day 28	3M	151 ± 13	3.2 ± 4.2	1,830 ± 220
				3F	146 ± 30	8.2 ± 7.8	2,110 ± 480
		3%	Day 1	6M	300 ± 43	2.4 ± 2.8	2,840 ± 710
				6F	367 ± 66	1.7 ± 0.5	3,700 ± 950
			Day 28	6M	398 ± 80	6.0 ± 5.9	4,570 ± 1,330
				6F	485 ± 139	2.1 ± 3.0	6,060 ± 1,640
Dog	4 weeks (8 times/day)	0.3%	Day 1	3M	23.2 ± 9.5	0.67 ± 0.29	191 ± 92
				3F	16.7 ± 7.3	0.83 ± 0.29	145 ± 71
			Day 28	3M	24.8 ± 10.3	0.50 ± 0.00	223 ± 122
				3F	24.8 ± 12.7	0.50 ± 0.00	235 ± 143
		1%	Day 1	3M	52.7 ± 38.9	1.2 ± 0.8	505 ± 391
				3F	69.1 ± 56.4	1.7 ± 0.6	646 ± 615
			Day 28	3M	57.6 ± 39.2	1.7 ± 2.0	558 ± 504
				3F	84.1 ± 45.9	0.83 ± 0.29	817 ± 618
		3%	Day 1	6M	216 ± 72	1.1 ± 0.7	2,410 ± 840
				6F	270 ± 146	1.0 ± 0.5	2,310 ± 1,490
			Day 28	6M	272 ± 77	0.75 ± 0.27	2,830 ± 860
				6F	293 ± 131	1.2 ± 0.7	2,880 ± 1,610
	39 weeks (6 times/day)	0.3%	Day 1	3M	14.4 ± 5.1	5.8 ± 0.3	122 ± 54
				3F	19.1 ± 3.6	6.3 ± 0.6	215 ± 40
			Day 273	3M	11.8 ± 2.9	5.5 ± 0.0	136 ± 52
				3F	20.8±4.8	5.8±0.3	297 ± 82
		1%	Day 1	3M	23.5 ± 14.4	6.0 ± 0.0	186 ± 96
				3F	66.4 ± 35.2	6.3 ± 0.6	764 ± 335
			Day 273	3M	20.5 ± 8.2	6.3 ± 0.6	206 ± 70
				3F	53.9 ± 21.6	13 ± 10	774 ± 183
		3%	Day 1	6M	59.7 ± 31.6	6.0 ± 0.5	719 ± 457
				6F	98.1 ± 35.0	7.0 ± 1.1	1,210 ± 490
			Day 273	6M	96.8 ± 50.8	6.3 ± 0.6	1,320 ± 900
				6F	180 ± 58	6.2 ± 0.7	2,710 ± 1,080

Mean ± SD

4.1.3 *In vitro* cell permeability (CTD 4.2.2.2-6 [Reference data])

The cell permeability of motugivatrep (1 μmol/L) was evaluated in human colorectal adenocarcinoma cells (Caco-2 cells). The apparent apical-to-basal permeability coefficient (P_{app}) was 26.1×10^{-6} cm/sec.[4)]

4.2 Distribution

4.2.1 Plasma protein binding and distribution in blood cells (CTD 4.2.2.3-1)

Using the plasma from rat, dog, and human, the plasma protein binding of motugivatrep (1, 10, or 100 μmol/L) was determined using an equilibrium dialysis method. The plasma protein binding of motugivatrep (mean ± SD) was 99.8 ± 0.12%,[5)] 99.5 ± 0.04%, and 99.3 ± 0.08%, respectively.

[4)] When mannitol 0.033 μmol/L was added, the P_{app} was 3.70×10^{-6} cm/sec.
[5)] When motugivatrep 1 μmol/L was added to rat plasma, unbound motugivatrep was below the detection limit, which was not used for calculating the mean.

Using the whole blood from rat, dog, and human, the blood to plasma partition ratio of motugivatrep (1, 10, or 100 µmol/L) was determined. The blood to plasma partition ratios of motugivatrep were 0.560 to 0.592, 0.427 to 0.487, and 0.537 to 0.711, respectively.

4.2.2 Tissue distribution (CTD 4.2.2.3-2)

Following a single oral dose of ^{14}C-motugivatrep 3 mg/kg in male albino and pigmented rats, tissue distribution[6)] was determined[7)] by quantitative whole-body autoradiography.

In albino rats, high radioactivity concentrations were observed in the gastrointestinal contents, gastrointestinal mucosa, adrenal gland, and liver. The highest levels of radioactivity occurred at 6 hours post-dose in most tissues, and radioactivity declined to near the LLOQ at 7 days post-dose.

In pigmented rats, radioactivity levels in most tissues at 3 and 7 days post-dose were similar to those in albino rats, and radioactivity declined below or near the LLOQ at 28 days post-dose. The highest level of radioactivity was found in melanin-pigmented fur among the tissues examined, but radioactivity declined to below the LLOQ at 28 days post-dose.

4.2.3 Ocular tissue distribution (CTD 4.2.2.3-3 [Reference data])

Table 7 shows motugivatrep concentrations in ocular tissues following a single instillation of 40 µL/eye of 0.3% motugivatrep suspension into both eyes of male rabbits.

Table 7. Motugivatrep concentrations in ocular tissues following a single ocular instillation of motugivatrep in rabbits (lacrimal fluid, aqueous humor, and vitreous body [ng/mL]; cornea, conjunctiva, iris-ciliary body, and chorioretina [ng/g])

Tissue	5 minutes post-dose	10 minutes post-dose	15 minutes post-dose	30 minutes post-dose	1 hour post-dose	2 hours post-dose	4 hours post-dose	6 hours post-dose	24 hours post-dose
Lacrimal fluid	182,000 ± 140,000	2,830 ± 1,850	1,020 ± 672	490 ± 507	1,230 ± 2,260	70.4 ± 38.6	3,310 ± 8,030	86.8 ± 91.0	20.7 ± 25.8
Cornea	—	—	445 ± 66.1	522 ± 364	142 ± 69.6	72.0 ± 66.2	27.7 ± 27.4	—	—
Conjunctiva	—	—	1,090 ± 314[a)]	591 ± 533	168 ± 150	85.4 ± 10.9	125 ± 109	—	—
Aqueous humor	—	—	0.379 ± 0.261	2.12 ± 1.71	1.15 ± 0.313	0.496 ± 0.0834	0.201 ± 0.0874	—	—
Iris-ciliary body	—	—	28.1 ± 8.85	85.0 ± 54.0	89.5 ± 26.0	85.8 ± 106	22.9 ± 4.99	—	—
Vitreous body	—	—	1.32 ± 1.14	1.14 ± 1.13	0.792 ± 0.475	0.534 ± 0.244	0.525 ± 0.431	—	—
Chorioretina	—	—	6.57 ± 1.58	12.0 ± 4.35	14.6 ± 7.83	10.8 ± 1.36	17.7 ± 4.51	—	—

Mean ± SD; —, Not measured
Cornea, conjunctiva, aqueous humor, iris-ciliary body, vitreous body, and chorioretina, 4 animals/4 eyes per time point; lacrimal fluid, 3 animals/5-6 eyes
a) Calculated from 3 eyes after excluding 1 eye with a clearly high value (10,300 ng/g).

6) Organs tested: adrenal gland, aorta, blood, bone, bone marrow, brain, bulbourethral gland, cecum contents, cecum mucosa, epididymis, exorbital lacrimal gland, eye, fat (brown), fat (white), fur (white fur and pigmented fur in pigmented rats), Harderian gland, intraorbital lacrimal gland, kidney (cortex), kidney (medulla), large intestine contents, large intestine mucosa, liver, lung, lymph node, muscle, myocardium, nasal mucosa, pancreas, periodontal ligament, pineal body, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, skin (white skin and pigmented skin in pigmented rats), small intestine contents, small intestine mucosa, spinal cord, spleen, gastric contents, gastric mucosa, testes, thymus, thyroid gland, tongue, tooth pulp, urinary bladder, uveal tract (pigmented rats only)

7) Tissue radioactivity concentrations were determined at 2 hours, 6 hours, 1 day, 2 days, 3 days, and 7 days post-dose in albino rats and at 3 days, 7 days, and 28 days post-dose in pigmented rats.

4.3 Metabolism

4.3.1 *In vitro* studies (CTD 4.2.2.4-1, 4.2.2.4-4 [Reference data])

When ^{14}C-motugivatrep 10 μmol/L was incubated with rat, dog, or human hepatocytes, ^{14}C-motugivatrep was mainly detected unchanged in all animal species tested. As the metabolites of ^{14}C-motugivatrep, a total of 12 metabolites (7 different mono-hydroxylated forms, a mono-hydroxylated ketone, a ketone, a glucuronide conjugate, a sulfate conjugate, a mono-hydroxylated sulfate conjugate) were detected. No human-specific metabolites were identified.

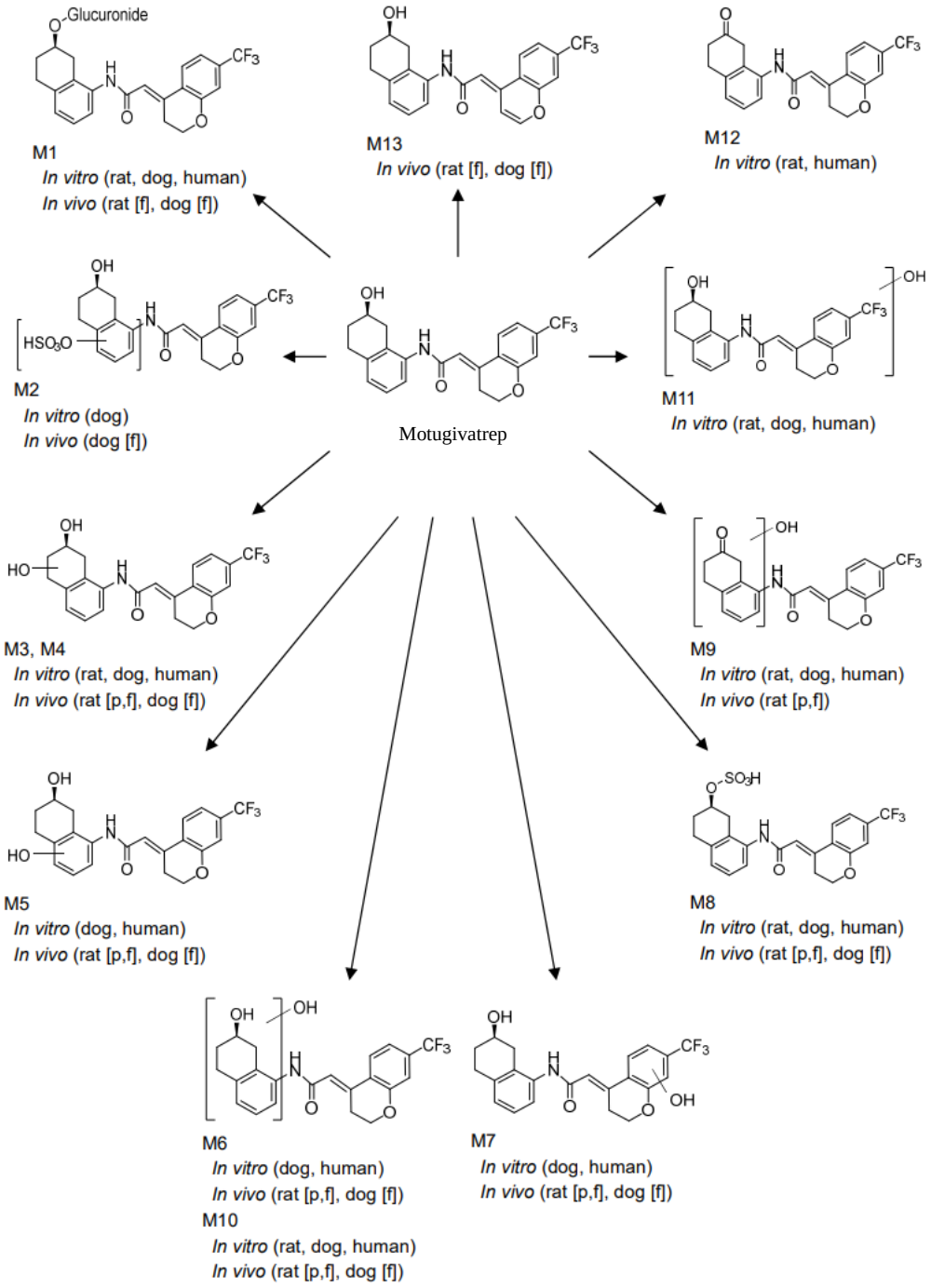
When motugivatrep 10 μmol/L was incubated with human CYP expression system (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4), motugivatrep was metabolized by CYP3A4, CYP2C19, and CYP2D6.

4.3.2 *In vivo* studies (CTD 4.2.2.4-2, 4.2.2.4-3)

Following a single oral dose of ^{14}C-motugivatrep 3 mg/kg in rats, a total of 9 radioactive components and a total of 8 radioactive components were present in the plasma and feces, respectively, and the predominant component was unchanged motugivatrep. A total of 10 radioactive components were present in the urine, each of which accounted for<1% of the administered radioactivity, and unchanged motugivatrep was not detected. Based on the results of structural analysis by LC/MS/MS, as motugivatrep metabolites in the feces, a glucuronide conjugate, a sulfate conjugate, 6 different mono-hydroxylated forms, a mono-hydroxylated ketone, and an unsaturated form were proposed. Due to low levels of radioactivity in the plasma and urine, structural analysis of metabolites was not performed.

Following a single intravenous dose of ^{14}C-motugivatrep 1 mg/kg or a single oral dose of ^{14}C-motugivatrep 5 mg/kg in dogs, only unchanged motugivatrep was detected in the plasma. Due to low levels of radioactivity in the urine, the urinary metabolic profile was not obtained. In the feces, a total of 13 radioactive components were present, and the predominant component was unchanged motugivatrep. Based on the results of structural analysis by LC/MS/MS, as motugivatrep metabolites in the feces, a glucuronide conjugate, a mono-hydroxylated sulfate conjugate, a sulfate conjugate, 6 different mono-hydroxylated forms, and an unsaturated form were proposed.

Based on the above metabolism studies, the proposed metabolic pathways of motugivatrep are shown in Figure 1.



p in parenthesis denotes plasma
f in parenthesis denotes feces

Figure 1. Proposed metabolic pathways of motugivatrep in rats, dogs, and humans

4.4 Excretion

4.4.1 Urinary and fecal excretion (CTD 4.2.2.5-1, 4.2.2.5-2)

Table 8 shows the recoveries of radioactivity following a single oral or intravenous dose of ^{14}C-motugivatrep in rats and dogs.

Table 8. Recoveries of radioactivity following administration of ^{14}C-motugivatrep

Species	Route of administration	Dose (mg/kg)	Number of animals	Sample	Sample collection period (h)	Recovery of administered radioactivity (%)
Rat	Oral	3	4M	Urine	0-48	3.04 ± 1.35
					0-168	3.77 ± 1.54
				Feces	0-48	79.0 ± 1.97
					0-168	86.0 ± 1.79
Dog	IV	1	3M	Urine	0-48 a)	4.09 ± 0.23
				Feces	0-48 a)	75.3 ± 6.70
	Oral	5	3M	Urine	0-48	3.80 ± 1.30
					0-168	4.86 ± 1.00
				Feces	0-48	68.9 ± 6.75
					0-168	83.1 ± 2.51

Mean ± SD

a) [redacted]. The results of analysis of samples collected from 48 hours post-dose through euthanasia were also used to calculate the recoveries of radioactivity.

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition and enzyme induction (CTD 4.2.2.6-1, 4.2.2.6-2, 4.2.2.6-4 ([Reference data])

Using human liver microsomes, the potential of motugivatrep (0.01, 0.1, 0.5, 1, or 5 µmol/L) to inhibit CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4)[8)] was assessed. Although motugivatrep showed weak time-dependent inhibition of CYP2B6,[9)] the IC_{50} values of motugivatrep for all CYP isoforms including CYP2B6 were higher than 5 µmol/L.

Using human liver microsomes, the inhibitory effects of motugivatrep (0.25 µmol/L) on uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1) and UGT2B7[10)] were assessed. Motugivatrep did not inhibit UGT1A1 or UGT2B7.

Using cryopreserved human hepatocytes, the potential of motugivatrep (1, 10, or 30 µmol/L) to induce CYP isoforms (CYP1A2, CYP2B6, and CYP3A4) was assessed. While motugivatrep at ≥10 µmol/L increased CYP2B6 and CYP3A4 mRNA expression, motugivatrep 1 µmol/L did not increase the mRNA level of any CYP isoform.

Referring to a population pharmacokinetic analysis based on the data from a foreign phase I study, the steady-state C_{max} following instillation of one drop of 0.3% motugivatrep suspension into both eyes 4 times daily in patients with dry eye disease was predicted.[11)] Given this predicted steady-state C_{max} (1.92 ng/mL [0.00476 µmol/L]) and the human plasma protein binding of motugivatrep (99.3%), ocular instillation of motugivatrep is unlikely to cause drug interactions via inhibition or induction of the above isoforms.

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8) The following compounds were used as substrates of CYP isoforms: phenacetin for CYP1A2, coumarin for CYP2A6, bupropion for CYP2B6, paclitaxel for CYP2C8, diclofenac for CYP2C9, S-mephenytoin for CYP2C19, bufuralol for CYP2D6, chlorzoxazone for CYP2E1, testosterone and midazolam for CYP3A4

9) After incubation with motugivatrep 5 µmol/L for 5 minutes or 30 minutes, the substrate was added. Motugivatrep caused 1.1% and 36.7% inhibition, respectively.

10) The following compounds were used as substrates of UGT isoforms: β-estradiol for UGT1A1, 3'-azido-3'-deoxythymidine for UGT2B7

11) Using plasma motugivatrep concentration data obtained from Study 3260A1-1000-EU in which motugivatrep was administered orally in healthy adult subjects [see Section 6.2.1], a population pharmacokinetic analysis was performed. The pharmacokinetics of motugivatrep were described by [redacted] model. In this model, following ocular instillation of motugivatrep, [redacted], plasma concentrations of motugivatrep following ocular instillation of motugivatrep were predicted. When one drop of 0.3% motugivatrep suspension was instilled into both eyes 4 times daily, the predicted steady-state C_{max}, C_{trough}, and $AUC_{0\text{-}24,ss}$ were 1.92 ng/mL, 1.61 ng/mL, and 42.4 ng·h/mL, respectively.

4.5.2 Transporter inhibition potential (CTD 4.2.2.6-3)

Using Caco-2 cells endogenously expressing p-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), HEK293 cells expressing various human transporters (organic anion transporting polypeptide 1B1 [OATP1B1], OATP1B3, organic anion transporter 1 [OAT1], OAT3, organic cation transporter 2 [OCT2], multidrug and toxin extrusion 1 [MATE1], and MATE2-K), and bile salt export pump (BSEP)-expressing vesicles, the inhibitory effects of motugivatrep (0.025, 0.25, or 2.5 µmol/L [P-gp and BCRP] or 0.25 µmol/L [OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2-K, and BSEP]) on these transporters[12)] were assessed. Although the IC_{50} values for these transporters other than P-gp and BCRP were higher than the concentrations tested, the IC_{50} values for P-gp and BCRP were calculated to be 2.5 and 0.25 µmol/L, respectively, indicating the potential of motugivatrep to inhibit P-gp and BCRP.

Referring to a population pharmacokinetic analysis based on the data from a foreign phase I study, the steady-state C_{max} following instillation of one drop of 0.3% motugivatrep suspension into both eyes 4 times daily was predicted.[11)] Given this predicted steady-state C_{max} (1.92 ng/mL [0.00476 µmol/L]), the human plasma protein binding of motugivatrep (99.3%), and the cutoff value based on the ICH M12 guideline taking account of the possibility that motugivatrep is absorbed in the gastrointestinal tract via the nasolacrimal duct, ocular instillation of motugivatrep is unlikely to cause drug interactions via transporter inhibition.

4.R Outline of the review conducted by PMDA

PMDA concluded that the submitted study results gave a grasp of the *in vivo* behavior of motugivatrep to a certain extent.

5. Toxicology and Outline of the Review Conducted by PMDA

The applicant submitted the results from the following toxicity studies: single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and local tolerance studies and other toxicity studies (a phototoxicity study, a skin sensitization study, and a skin photosensitization study). Corn oil was used as the vehicle for oral administration.

5.1 Single-dose toxicity

The acute toxicity of motugivatrep was assessed in single oral dose and single intravenous dose toxicity studies in mice and rats, and the results are shown in Table 9. Following oral administration, no mortalities or acute symptoms occurred in mice or rats. Following intravenous administration of motugivatrep, acute symptoms (hunched position, piloerection, ataxia, etc.) occurred at 100 mg/kg in mice, and mortalities and acute symptoms (coma, ataxia, etc.) occurred at 50 and 100 mg/kg in rats. Based on the above, the approximate lethal dose by oral route was determined to be >2,000 mg/kg in mice and rats, and the approximate lethal doses by intravenous route were determined to be >100 mg/kg in mice and <50 mg/kg in rats.

[12)] The following compounds were used as substrates of transporters: ^{3}H-digoxin for P-gp, ^{3}H-estrone sulfate for BCRP/OAT3,^{3}H-estradiol 17β-D-glucuronide for OATP1B1/OATP1B3, ^{3}H-4-aminohippuric acid for OAT1, ^{14}C-metformin for OCT2/MATE1/MATE2-K, ^{3}H-taurocholic acid for BSEP

Although no single-dose toxicity studies in dogs were conducted, no mortalities or abnormal clinical signs were observed in a study in which dogs received ascending doses up to 500 mg/kg of motugivatrep, and the approximate lethal dose by oral route was determined to be >500 mg/kg in dogs (Table 9).

Table 9. 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	2,000	None	>2,000	4.2.3.1-1 (Reference data)
Male and female rats (Han Wistar)	Oral	2,000	None	>2,000	4.2.3.1-2 (Reference data)
Male and female mice (CD-1)	IV	50, 100	100 (male and female): hunched position, piloerection 100 (male): ataxia, ptosis, decreased respiratory rate, labored breathing	>100	4.2.3.1-3 (Reference data)
Male and female rats (Han Wistar)	IV	50, 100	[Mortalities] 100 (1 of 2 females, 3 of 4 males), 50 (1 of 2 females, 1 of 5 males) 50: coma, ataxia, decreased respiratory rate, labored breathing, gasping respiration	<50	4.2.3.1-4 (Reference data)
Male and female dogs (Beagle)	Oral	100→ 200→ 350→ 500 [a)]	≥100: increased plasma total bilirubin (male and female), increased plasma cholesterol (male only)	>500	4.2.3.2-5 (Reference data)

a) A study in which ascending doses of motugivatrep (one dose per day) were given for 4 days

5.2 Repeated-dose toxicity

Repeated ocular instillation toxicity studies were conducted in rabbits and dogs (Table 10). No toxicology findings were observed in any of the studies. The no-observed-adverse-effect level (NOAEL) in a 39-week repeated ocular instillation toxicity study in dogs was determined to be 3% in both males and females. The AUC_{last} values of 3% motugivatrep suspension at Week 39 were 1,320 ng·h/mL in males and 2,710 ng·h/mL in females, which were 31-fold and 64-fold the predicted human exposure[11] ($AUC_{0\text{-}24h}$ = 42.4 ng·h/mL), respectively.

Table 10. Overview of repeated ocular instillation toxicity studies

Test system	Route of administration	Duration of dosing (Dosing frequency)	Concentration (%)	Noteworthy findings	NOAEL (Concentration: %)	Attached document CTD
Male and female rabbits (JW)	Ocular instillation	4 weeks (8 times[a)]/day) + 4-week recovery period	0 (formulation vehicle[b)]), 0.3, 1, 3	None	3	4.2.3.2-1
Male and female dogs (Beagle)	Ocular instillation	4 weeks (8 times[a)]/day) + 4-week recovery period	0 (formulation vehicle[b)]), 0.3, 1, 3	None	3	4.2.3.2-2
Male and female dogs (Beagle)	Ocular instillation	39 weeks (6 times[a)]/day) + 4-week recovery period	0 (formulation vehicle[c)]), 0.3, 1, 3	None	3	4.2.3.2-3

a) 50 µL/eye was instilled into both eyes (approximately 1 hour apart).
b) Vehicle for non-clinical formulations (containing [redacted]mg, [redacted]mg, and [redacted]mg per mL)
c) Vehicle for the proposed product (containing boric acid [redacted]mg, borax [redacted]mg, tyloxapol [redacted]mg, methylcellulose [redacted]mg, and zinc chloride [redacted]mg per mL)

Repeated oral dose toxicity studies were conducted in rats and dogs (Table 11). In a 26-week repeated oral dose toxicity study in rats, increases in adrenal and thyroid weights were observed, but were considered of little toxicological significance because histopathological examination revealed no abnormalities etc. The NOAEL was determined to be 50 mg/kg in both males and females. The AUC_{last} values of motugivatrep at 50 mg/kg at

Week 26 were 312,000 ng·h/mL in males and 913,000 ng·h/mL in females, which were ≥7,300-fold and ≥21,000-fold the predicted human exposure ($AUC_{0\text{-}24h}$ = 42.4 ng·h/mL), respectively. Increased plasma bilirubin observed in the motugivatrep group was considered attributable to interference of motugivatrep metabolites with the assay.

Table 11. Overview of repeated oral dose toxicity studies

Test system	Route of administration	Duration of dosing (Dosing frequency)	Doses (mg/kg)	Noteworthy findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (Han Wistar)	Oral	4 weeks (QD) + 2-week recovery period	0, 2.7, 9.0, 277.5	≥2.7: increased plasma total bilirubin (male and female)[a)] 277.5: increases in adrenal (male and female)/thyroid (female) weights[b)] These findings were reversible.	277.5	4.2.3.2-7
Male and female dogs (Beagle)	Oral	4 weeks (QD) + 2-week recovery period	0, 4.5, 22.9, 371.3	≥4.5: increased plasma total bilirubin (male and female),[a)] centrilobular hepatocellular inflammation (male and female),[c)] a trend towards decreased fibrinogen (male and female)[d)] 371.3: soft/watery feces, increased plasma cholesterol[b)] (male and female) These findings were reversible.[e)]	371.3	4.2.3.2-8
Male and female rats (SD)	Oral	26 weeks (QD) + 4-week recovery period	0, 0.5, 5, 50	≥5: increased adrenal weights (female)[b)] 50: increases in adrenal and thyroid weights (male)[b)] These findings were reversible.	50	4.2.3.2-10

a) The finding was attributable to interference of motugivatrep metabolites with the Jendrassik-Grof method and was not considered due to changes in plasma bilirubin.
b) The findings were considered of little toxicological significance because the findings were not associated with histopathological changes and were reversible.
c) The finding was considered of little toxicological significance because the finding was of minimal or mild severity and reversible without clinical chemistry abnormalities suggestive of hepatocellular injury.
d) The finding was considered of little toxicological significance because the finding was reversible without other clinical chemistry abnormalities suggestive of hepatocellular injury or decreased hepatic function.
e) Increased plasma total bilirubin was observed also after a recovery period.

5.3 Genotoxicity

As *in vitro* studies, a bacterial reverse mutation assay (Ames assay) and a gene mutation assay using mouse lymphoma L5178Y cells were performed, which produced negative results (Table 12). As an *in vivo* study, a bone marrow micronucleus assay in rats was performed (Table 12). In this study, the frequency of micronucleated immature erythrocytes was slightly higher in the motugivatrep 2,000 mg/kg group than in the negative control group, and the difference was statistically significant, but the criteria for a positive response were not met. Thus, motugivatrep was considered not to have clastogenic potential.

Table 12. 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, TA1537, TA98, TA100 *Escherichia coli*: WP2 *uvrA*	S9−/+	0,[a)] 5, 17, 50, 167,[b)] 500,[c)] 1,667 [c)] µg/plate	Negative	4.2.3.3.1-1
	Gene mutation assay using cultured mammalian cells	Mouse lymphoma L5178Y cells	S9− (24 hours)	0, [a)] 20, 30, 50, [c)] 70, [d) c)] 100 [d) c)] µg/mL	Negative	4.2.3.3.1-2
			S9− (4 hours)	0, [a)] 5, 15, 50, 150, [d) c)] 500 [d) c)] µg/mL		
			S9+ (4 hours)	0, [a)] 10, 20, 40, 80, [d) c)] 160 [d) c)] µg/mL		
In vivo	Rat micronucleus assay	Male rat (SD) bone marrow		0, 200, 600, 2,000 mg/kg/day (oral, 2 days)	Negative	4.2.3.3.2-3

a) DMSO
b) Test article precipitation was observed in the pre-incubation method.
c) Test article precipitation was observed in the plate incorporation and pre-incubation methods.
d) Test article precipitation was observed.
e) ≥50% inhibition of cell growth

5.4 Carcinogenicity

A 26-week oral carcinogenicity study was conducted in rasH2-Tg mice (Table 13). As neoplastic lesions, the incidences of hemangiosarcoma in the whole body or spleen and bronchiole-alveolar adenoma or carcinoma in the lung tended to be higher in the motugivatrep ≥10 mg/kg groups than in the control group, but were not dose-related or were within the historical control range of the laboratory. Thus, these findings were considered unrelated to motugivatrep. No non-neoplastic lesions were observed.

The no-observed-effect level (NOEL) for carcinogenicity was determined to be 100 mg/kg/day. The AUC_{last} values of motugivatrep at the NOEL for carcinogenicity at Week 4 were 71,600 ng·h/mL in males and 91,300 ng·h/mL in females, which were ≥1,600-fold and ≥2,100-fold the predicted human exposure ($AUC_{0\text{-}24h}$ = 42.4 ng·h/mL), respectively.

Table 13. Overview of carcinogenicity study in rasH2-Tg 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
					Vehicle	Motugivatrep				
					0	1	10	100		
				N	25M 25F	25M 25F	25M 25F	25M 25F		
Male and female mice (rasH2-Tg)	Oral	26 weeks	Neoplastic lesions						100	4.2.3.4.1-2
			Whole body/ Hemangiosarcoma[a)]	M	3	2	2	1		
				F	3	3	7	2		
			Spleen/Hemangiosarcoma	M	1	0	2	1		
				F	0	0	2	2		
			Lung/Bronchiole-alveolar adenoma	M	0	0	3	3		
				F	2	1	2	2		
			Lung/Bronchiole-alveolar carcinoma	M	0	0	0	0		
				F	1	0	0	2		
			Lung/Bronchiole-alveolar adenoma and carcinoma[b)]	M	0	0	3	3		
				F	3	1	2	4		
			Other findings							
			Survival rate (%)	M	100	92	100	100		
				F	96	96	96	92		
			Non-neoplastic lesions: None							

a) The sum of mice with hemangiosarcoma in any organ/tissue
b) The sum of mice with alveolar adenoma/carcinoma

A 24-month oral carcinogenicity study was conducted in rats (Table 14). As neoplastic lesions, the incidences

of fibroadenoma and adenocarcinoma in the mammary gland tended to be higher in females in the motugivatrep 50 mg/kg group than in the control group, but were within the historical control range of the laboratory. Thus, these findings were considered unrelated to motugivatrep. As non-neoplastic lesions, increased incidence and severity of atrophy of quadriceps femoris muscle were observed in males in the motugivatrep ≥5 mg/kg groups.

Based on the above, the NOEL for carcinogenicity was determined to be 50 mg/kg/day. The AUC_{last} values of motugivatrep at the NOEL for carcinogenicity at Week 26 were 368,000 ng·h/mL in males and 829,000 ng·h/mL in females, which were ≥8,600-fold and ≥19,000-fold the predicted human exposure ($AUC_{0\text{-}24h}$ = 42.4 ng·h/mL), respectively.

Table 14. 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
					Vehicle	Motugivatrep				
					0	0.5	5	50		
				N	60M 60F	60M 60F	60M 60F	60M 60F		
Male and female rats (SD)	Oral	24 months[a)]	Neoplastic lesions						50	4.2.3.4.1-3
			Mammary gland/ Fibroadenoma	M	2	0	0	2		
				F	26	29	26	31		
			Mammary gland/ Adenocarcinoma	M	1	1	0	0		
				F	9	8	9	17		
			Other findings							
			Survival rate	M	48	48	63	45		
				F	25	28	47	47		
			≥5: increased incidence and severity of atrophy of quadriceps femoris muscle (male) 50: decreases in body weight/food consumption							

a) Since the cumulative mortality in females in the vehicle control group reached 75%, all surviving females were necropsied at Week 99.

5.5 Reproductive and developmental toxicity

A study of fertility and early embryonic development to implantation was conducted in rats (Table 15). No toxicological findings were observed, and the NOAEL for male and female fertility, general toxicity, and early embryonic development was determined to be 50 mg/kg/day. The AUC_{last} values of motugivatrep at the NOAEL on Day 1 in a 26-week repeated oral dose toxicity study in rats [see Section 5.2] were 396,000 ng·h/mL in males and 500,000 ng·h/mL in females, which were ≥9,300-fold and ≥11,000-fold the predicted human exposure ($AUC_{0\text{-}24h}$ = 42.4 ng·h/mL), respectively.

Embryo-fetal development studies were conducted in rats and rabbits (Table 15). No abnormalities were observed in rats. In rabbits, abortion occurred at 200 mg/kg. The middle and post-middle periods are known to be vulnerable to abortion associated with reduced food consumption in pregnant rabbits (*J Toxicol Sci*. 2006; 31: 169-75). As reduced food consumption or no food consumption was observed in the rabbit that aborted in the 200 mg/kg group (1 of 22 rabbits), the finding was considered unrelated to motugivatrep. Increased incidences of visceral abnormalities (cerebral ventricle dilatation, aortic stenosis, etc.) and visceral variations (absent accessory lobe of the lung, retrocaval ureter) were observed in embryos/fetuses, and a relationship to motugivatrep could not be ruled out for absent accessory lobe of the lung observed in the motugivatrep 200 mg/kg group. Other findings were considered unrelated to motugivatrep because the incidences were

within the historical control range of the laboratory or those findings may spontaneously occur (*Congenit Anom*. 2012; 52: 155-61) etc.

Based on the above, the NOAELs for embryo-fetal development in rats and rabbits were determined to be 50 mg/kg/day and 40 mg/kg/day, respectively. The C_{max} and $AUC_{0\text{-}24h}$ were 40,300 ng/mL and 787,000 ng·h/mL (on gestation day 17), respectively, in rats, which were ≥20,000-fold and ≥18,000-fold the predicted human exposure ($AUC_{0\text{-}24h}$ = 42.4 ng·h/mL), respectively. The C_{max} and $AUC_{0\text{-}24h}$ were 1,560 ng/mL and 30,300 ng·h/mL (on gestation day 18), respectively, in rabbits, which were ≥810-fold and ≥710-fold the predicted human exposure ($AUC_{0\text{-}24h}$ = 42.4 ng·h/mL), respectively.

A study on pre- and postnatal development, including maternal function, was conducted in rats (Table 15). No effects on maternal reproductive function were observed. Based on the above, the NOAEL for offspring was determined to be 50 mg/kg/day. The AUC_{last} of motugivatrep in dams at the NOAEL for offspring on lactation day 20 was 603,000 ng·h/mL, which was ≥14,000-fold the predicted human exposure ($AUC_{0\text{-}24h}$ = 42.4 ng·h/mL).

Table 15. Overview of reproductive and developmental toxicity studies

Type of study	Test system	Route of administration	Duration of dosing (Dosing frequency)	Doses (mg/kg)	Noteworthy findings	NOAEL (mg/kg/day)	Attached document CTD
Fertility and early embryonic development to implantation	Male and female rats (SD)	Oral	Males: from 2 weeks prior to mating until the day before necropsy (42 days) (QD)	0, 2, 10, 50	<u>Parental animals (male)</u> None <u>Fertility (male)</u> None	Parental animals General toxicity: 50 Fertility: 50	4.2.3.5.1-1
			Females: from 2 weeks prior to mating through gestation day 6 (QD)	0, 2, 10, 50	<u>Parental animals (female)</u> None <u>Fertility (female)</u> None <u>Early embryonic development</u> None	Parental animals General toxicity: 50 Fertility: 50 Early embryonic development: 50	
Embryo-fetal development	Female rat (SD)	Oral	From gestation day 6 through gestation day 17 (QD) Caesarean section: Gestation day 20	0, 2, 10, 50	<u>Dams</u> None <u>Embryo-fetal development</u> None	Dams: 50 Embryo-fetal development: 50	4.2.3.5.2-2
	Female rabbit (NZW)	Oral	From gestation day 6 through gestation day 19 (QD) Caesarean section: Gestation day 28	0, 10, 40, 200	<u>Dams</u> 200: abortion[a)] <u>Embryo-fetal development</u> ≥10: a trend towards increased mean post-implantation loss[b)] 200: increased incidences of visceral abnormalities (cerebral ventricle dilatation, aortic stenosis, etc.)[c)]/visceral variations (absent accessory lobe of the lung, retrocaval ureter)[d)]	Dams: 200 Embryo-fetal development: 40	4.2.3.5.2-4
Pre- and postnatal development, including maternal function	Female rat (SD)	Oral	From gestation day 6 through lactation day 20 (QD)	0, 2, 10, 50	<u>Dams</u> None <u>F_1 pups</u> 50: increased mean post-implantation loss of F_2 fetuses[e)]	Dams: 50 Offspring: 50	4.2.3.5.3-1

a) The finding was associated with reduced or no food consumption and was considered unrelated to motugivatrep.
b) Although the mean percentages of post-implantation loss in the motugivatrep ≥40 mg/kg groups were slightly above the historical control range of the laboratory, the number of dams with post-implantation loss was similar to that in the control group, and the finding was considered unrelated to motugivatrep.
c) The findings were considered unrelated to motugivatrep because the incidences were within the historical control range of the laboratory or those findings may spontaneously occur.
d) The incidence of fetuses with retrocaval ureter was slightly above the historical control range of the laboratory, and the finding was considered unrelated to motugivatrep.
e) The finding was considered unrelated to motugivatrep because there were no effects on body weights or observations during mid pregnancy of F_1 dams, and except for 1 animal with no viable embryos among 16 animals, post-implantation loss per litter was within the range of the control group.

5.6 Local tolerance

An ocular irritation study of motugivatrep was conducted (Table 16), and no ocular irritation was observed. No findings indicative of ocular irritation were observed in this study or in a 39-week repeated ocular instillation toxicity study in dogs [see Section 5.2]. The formulations used in these studies had the same composition as the proposed product, and their quality attributes affecting local tolerance (pH, osmolarity) were also similar. Thus, motugivatrep was considered unlikely to induce local irritation.

Table 16. Overview of local tolerance study

Type of study	Test system	Test method	Noteworthy findings	Attached document CTD
Ocular irritation	Male rabbit (JW)	100 µL/eye of saline, the proposed product, or the proposed product spiked with chlorhexidine gluconate (a preservative) was instilled into both eyes 6 times daily (approximately 1 hour apart) for 7 days, and ophthalmic examinations (macroscopic examination, ophthalmoscopy, fundus examination) were performed.	None	4.2.3.6-1

5.7 Other toxicity studies

5.7.1 Phototoxicity

A phototoxicity study of motugivatrep was conducted (Table 17), and motugivatrep was considered negative for phototoxicity. In addition, motugivatrep concentrations in melanin-containing tissues (fur, the uveal tract) at 28 days post-dose were below or slightly above the LLOQ in a tissue distribution study of a single oral dose of motugivatrep in pigmented rats [see Section 4.2.2], and no motugivatrep-related phototoxicity findings (erythema, papule, etc.) were observed in clinical studies of motugivatrep.[13)] Thus, motugivatrep was considered to have little phototoxic potential.

Table 17. Overview of phototoxicity study

Type of study	Test system	Test method	Noteworthy findings	Attached document CTD
Phototoxicity	Mouse fibroblasts Balb/c 3T3	Motugivatrep 0, 1.9, 2.66, 3.72, 5.21, 7.29, 10.2, 14.3, or 20[a)] µg/mL UVA (5 J/cm^2) irradiation	Not phototoxic	4.2.3.7.7-5 (Reference data)

a) Since test article precipitation was observed, the results at this dose level were not used for assessment.

5.7.2 Skin sensitization study

A skin sensitization study of motugivatrep was conducted (Table 18), and motugivatrep was not considered a dermal sensitizer.

Table 18. Overview of skin sensitization study

Type of study	Test system	Test method	Noteworthy findings	Attached document CTD
Local lymph node assay (LLNA)	Female mouse (CBA/J)	Mice were treated with 0.3%, 1%, or 3% motugivatrep suspension for non-clinical studies, positive control (25% v/v hexyl cinnamaldehyde), vehicle control (a 4:1 v/v mixture of acetone and olive oil), or formulation vehicle control once daily by topical application at the dorsum of each ear for 3 days.	None	4.2.3.7.7-1

5.7.3 Skin photosensitization study

A skin photosensitization study of motugivatrep was conducted (Table 19), and motugivatrep was considered to have no skin photosensitizing potential.

13) Part B (conducted on an outpatient basis) of Study 1-01, Study 2-01, Study 3-01, and Study 3-02

Table 19. Overview of skin photosensitization study

Type of study	Test system	Test method	Noteworthy findings	Attached document CTD
Harber method	Female guinea pig (Hartley)	After 0.1 mL of 0.3%, 1%, or 3% motugivatrep suspension for non-clinical studies, positive control (2% TCSA solution), or negative control (saline) was applied openly on the back skin of each guinea pig, ultraviolet irradiation (UVB 1 J/cm^2 followed by UVA 30 J/cm^2) was performed, which was repeated a total of 3 times (photosensitization). At 21 days after photosensitization, 0.05 mL of 0.3%, 1%, or 3% motugivatrep suspension for non-clinical studies was applied openly on a different back skin area, [a)] and UVA 9 J/cm^2 was irradiated (challenge). At 24 and 48 hours after challenge, skin reactions were assessed.	None	4.2.3.7.7-2

a) Animals sensitized with positive control were challenged with positive control (0.2% TCSA solution) or acetone.

5.7.4 Toxicologic evaluation of impurities

Impurity A is an impurity in the drug substance with an acceptance criterion (≤[redacted]%) of greater than the qualification threshold specified in the ICH Q3A guideline (0.15%). Thus, its general toxicity and genotoxicity were assessed based on the results from 4-week repeated oral dose toxicity studies with the test material containing [redacted]% Impurity A in rats and dogs [see Section 5.2] and the results from Ames assay and gene mutation assay using mammalian cells [see Section 5.3]. Although the intake of this impurity in general toxicity studies was ≥1000-fold the expected human intake of Impurity A[14)] from the proposed product ([redacted] mg/kg/day), no findings of toxicological significance were observed, and the genotoxicity studies produced negative results. Given these findings, there should be little safety concern about this impurity.

5.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations, PMDA concluded that there are no particular problems with the toxicity of motugivatrep.

5.R.1 Sufficiency of testing of genotoxicity

The applicant's explanation about the sufficiency of testing of genotoxicity, taking account of the motugivatrep concentration of the proposed product (an ophthalmic suspension) (0.3% [3,000 μg/mL]):

The motugivatrep concentrations tested in *in vitro* genotoxicity studies of motugivatrep [see Section 5.3] were up to 833 μg/mL in the Ames assay and up to 500 μg/mL in a study using mouse lymphoma L5178Y cells. Based on the plasma concentrations of motugivatrep (C_{max}) at the highest dose of 2,000 mg/kg/day that produced a negative result in a rat bone marrow micronucleus assay, and at the NOELs for carcinogenicity (100 mg/kg/day in rasH2 mice and 50 mg/kg/day in rats) in carcinogenicity studies of motugivatrep [see Section 5.4], the motugivatrep concentrations tested in *in vivo* studies were 73.8 μg/mL in the rat bone marrow micronucleus assay, 6.64 μg/mL (male) and 8.20 μg/mL (female) in the carcinogenicity study in rasH2 mice, and 19.9 μg/mL (male) and 40.4 μg/mL (female) in the carcinogenicity study in rats. All of the motugivatrep concentrations tested *in vitro* and *in vivo* were below the motugivatrep concentration of the proposed product (0.3% [3,000 μg/mL]). In *in vitro* genotoxicity studies of motugivatrep, as test article precipitation was observed, testing at the motugivatrep concentration of the proposed product was not sufficient. However, negative results were obtained even at the highest concentration tested. The mutagenicity of motugivatrep was assessed *in silico* by structure-activity relationship evaluation with Case Ultra (Ver.

[14)] Intake of Impurity A when one drop (40 μL/eye) of the proposed product is instilled into both eyes 4 times daily in humans weighing 60 kg

[redacted]). Motugivatrep was negative for mutagenicity based on both knowledge-based and statistical-based methods.

Generally, eye drops are considered to be diluted in the tear film to approximately one-tenth the original strength immediately after instillation (*Journal of the Japanese Society for Cataract Research.* 2021; 33: 32-6). Also when motugivatrep is instilled into the eye, the local concentration should be diluted to a concentration of approximately 0.03% (300 μg/mL), which is below the concentrations tested in the *in vitro* genotoxicity studies. The solubility of motugivatrep in water is low, i.e., 0.2 μg/mL, and following ocular instillation of the proposed product, motugivatrep should be present mostly as insoluble particulate matter on the ocular surface. Thus, it is not expected that motugivatrep would interact directly with DNA or other chromosomal material. The tumorigenesis of poorly soluble particles is considered to involve the oxidative DNA attack by reactive oxygen species, generated during chronic inflammation (*Inhal Toxicol.* 2007; 19 Suppl 1: 189-98). In repeated ocular instillation studies of motugivatrep at concentrations up to 3% (4 weeks in rabbits, 4 weeks and 39 weeks in dogs), no inflammatory changes on the ocular surface were observed [see Section 5.2].

Based on the above, motugivatrep at the clinical concentration is unlikely to cause genotoxicity, either directly or indirectly.

PMDA concluded that the applicant's explanation is acceptable.

5.R.2 Need for assessment using juvenile animals

Given the possibility that motugivatrep will be used also in pediatric patients with dry eye disease, PMDA asked the applicant to explain the need for assessment of motugivatrep using juvenile animals.

The applicant's explanation:

Based on the ICH S11 guideline, the need for assessment of motugivatrep using juvenile animals was determined from the following standpoints: evaluation of (1) the effects of motugivatrep on developing tissues/organs via systemic exposure and (2) the local effects of motugivatrep on ocular tissues.

(1) Effects of motugivatrep on developing tissues/organs via systemic exposure

Given the following points, although risk assessment in children aged <10 years is difficult, as the existing non-clinical information indicates that motugivatrep is unlikely to affect the development of systemic tissues/organs, and abnormal temperature sensations such as increased body temperature, as a concern to be noted, have been identified in clinical studies of motugivatrep [see Section 7.R.3], assessment of motugivatrep using juvenile animals is considered to have little significance.

- Given the idea that there are no major differences in the expression levels of general drug metabolizing enzymes and transporters between children aged ≥10 years and adults ["Considerations for the Clinical Evaluation of Drugs in Pediatric Patients (10 or 12 Years of Age and Older) Who Can be Evaluated Together with Adults" (MHLW/PSEHB/PED Administrative Notice dated June 30, 2020)], the steady-state plasma exposure following 4 daily instillations of one drop of motugivatrep into both eyes in children aged 10 years

(C_{max} = 5.16 ng/mL, $AUC_{0\text{-}24h}$ = 114 ng·h/mL)[15] was predicted. When the plasma exposure (C_{max} = 96.8 ng/mL, AUC_{last} = 1,320 ng·h/mL) at the NOAEL (3%) in a 39-week repeated ocular instillation toxicity study in dogs [see Section 5.2] is compared with the predicted plasma exposure in children, the safety margin is ≥10-fold.

- Given maternal plasma exposure on lactation day 20 (C_{max} = 36,000 ng/mL, $AUC_{0\text{-}24h}$ = 603,000 ng·h/mL) at the NOAEL (50 mg/kg/day) in a study for effects on pre- and postnatal development, including maternal function, in rats [see Section 5.5] and the properties of motugivatrep relating to milk excretion (molecular weight, lipid solubility, half-life, etc.), F_1 pups were considered to be exposed to motugivatrep via milk, but there were no effects on the development of tissues/organs of F_1 pups.
- In TRPV1 knockout mice, no effects on survival have been observed, and no clear effects on the development of systemic tissues/organs have been reported (*Nat Neurosci*. 2006; 9: 93-8, *Mol Pharmacol*. 2004; 66: 204-8, etc.).

(2) Local effects of motugivatrep on ocular tissues

After ocular instillation, motugivatrep is distributed primarily into the cornea and conjunctiva, i.e., the application site, and its distribution in other ocular tissues is limited [see Section 4.2.3]. The development of human ocular tissues, including the posterior segment of the eye, is complete histologically by around 5 years of age (*Invest Ophthalmol Vis Sci*. 2007; 48: 4989-99, *Birth Defects Res.* 2017; 109: 1540-67, *Jpn J Ophthalmol*. 2009; 53: 7-11, etc.). Given that the corneal (the application site) curvature develops at the age of 4 to 9 years (Manual for clinical practice in pediatric ophthalmology [in Japanese]. Nippon Ijishinpou Co., Ltd. 2023; 1-12), and that the difference in the expression level of TRPV1 in the cornea and conjunctiva between children and adults is unknown, etc., the possibility that motugivatrep affects the development of ocular tissues in children aged <10 years cannot be ruled out. However, knowledge of TRPV1 expression levels in ocular tissues associated with developmental growth of animals is limited (*Histol Histopathol*. 2013; 28: 1507-16); there are differences in ocular anatomy between humans and animals (*Humana Press, New York*. 2013: 1-21); and eye-opening has not yet occurred in animals during a period corresponding to the stage of early development of human ocular tissues (*Anat Histol Embryol.* 2017; 46: 423-30), etc. Given these findings, evaluation of the effects of motugivatrep on ocular tissues after ocular instillation of motugivatrep in juvenile animals has little significance.

PMDA's view:

The applicant's view (For risk assessment of motugivatrep in pediatric patients with dry eye disease, assessment of motugivatrep using juvenile animals has little significance) is acceptable. Although no toxicological findings of concern were observed in toxicity studies of motugivatrep in adult animals, there is no clinical experience with motugivatrep in children; motugivatrep has a novel mechanism of action; and the currently available information regarding the effects of TRPV1 inhibition on the development of tissues/organs is limited. Given these points and the anticipated risk associated with motugivatrep (abnormal temperature sensations such as increased body temperature associated with TRPV1 inhibition), whether to use motugivatrep in pediatric

[15] Given that the mean body weight in the motugivatrep group was 63.16 kg in Study 1-01 (this mean body weight was used for predicting the steady-state plasma exposure), the predicted plasma exposure in children weighing 23 kg, which is the lower limit of normal body weight in children aged 10 years (the 3rd percentile of girls), was calculated based on body weight.

patients with dry eye disease and safety measures such as precautionary statements in the package insert should be discussed, taking also account of clinical study results etc. [see Sections 7.R.3 and 7.R.4].

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

No data from biopharmaceutic studies have been submitted.

Plasma concentrations of motugivatrep were determined by LC/MS/MS (LLOQ, 1 ng/mL [Study 3260A1-1000-EU], 0.01 ng/mL [Study 1-01]).

In the clinical development of motugivatrep, 2 different formulations of the drug product were used. Early formulations were used in a phase I/II study (Study 1-01), and the proposed product or formulations that differ only in the motugivatrep concentration from the proposed product were used in a phase II study (Study 2-01) and phase III studies (Studies 3-02 and 3-01). As an oral formulation, [redacted] of motugivatrep was used in a foreign phase I study (Study 3260A1-1000-EU).

6.2 Clinical pharmacology

The applicant submitted the results from clinical studies in patients with dry eye disease as evaluation data and the results from a clinical study in healthy adult subjects as reference data.

6.2.1 Studies in healthy adult subjects

6.2.1.1 Foreign phase I study (CTD 5.3.3.1-1, Study 3260A1-1000-EU [[redacted] 20[redacted] to [redacted] 20[redacted], Reference data])

Table 20 shows the pharmacokinetic parameters of motugivatrep following a single oral dose of motugivatrep 2.5, 7.5, 15, 30, or 60 mg in non-Japanese healthy adult subjects. The C_{max} and AUC_{last} increased in a dose-proportional manner over the dose range tested. Table 21 and Table 22 show the changes from baseline in body temperature and heat pain perception threshold (HPPT)[16)] following oral administration of motugivatrep, respectively. Following oral administration of motugivatrep, increased body temperature and increased HPPT were observed. Table 23 shows the change from baseline in corrected QT interval by Fridericia's formula (QTcF) following oral administration of motugivatrep. Following oral administration of motugivatrep, shortened QT interval was observed.

[16)] The probe was positioned on the volar aspect of the forearm. From a baseline of 32°C, probe temperature was increased at a rate of 1°C/sec (the maximum temperature was 52°C). Temperature at the first perception of heat or pain was measured in triplicate and averaged.

Table 20. Pharmacokinetic parameters of motugivatrep following a single oral dose

Treatment group (mg)	N	C_{max} (ng/mL)	AUC_{last} (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	V_z/F (L)	CL/F (L/h)
2.5	6 [a)]	17.1 ± 5.88	92.5 ± 58.3	1.27 [1, 1.5]	2.4, 8.1	178, 237	255, 1,140
7.5	6 [b)]	52.2 ± 11.6	526 ± 321	1.5 [1.5, 3]	16.6 ± 5.3	398 ± 182	268 ± 47.1
15	6 [b)]	90.4 ± 28.7	778 ± 523	1.5 [1, 2]	15.9 ± 4.5	499 ± 186	359 ± 46.2
30	6	221 ± 61.2	1,630 ± 618	1.5 [0.75, 2]	11.5 ± 2.4	323 ± 105	332 ± 106
60	6 [a)]	391 ± 93.8	4,270 ± 1,470	2 [1.5, 3]	14.4, 18.9	333, 461	268, 282

Mean ± SD or Median [Range]; Individual values are listed for N = 2 or 1.
a) N = 2 for $t_{1/2}$, V_z/F, and CL/F
b) N = 3 for $t_{1/2}$, V_z/F, and CL/F

Table 21. Change from baseline in body temperature following a single oral dose (°C)

Treatment group (mg)	N	Baseline	2 hours post-dose	4 hours post-dose	8 hours post-dose	24 hours post-dose	72 hours post-dose
Placebo	10	35.9 ± 0.43 [34.9, 36.4]	0.38 ± 0.45 [−0.1, 1.2]	0.26 ± 0.52 [−0.5, 1.4]	0.49 ± 0.48 [−0.1, 1.5]	0.12 ± 0.37 [−0.6, 0.8]	0.17 ± 0.39 [−0.5, 0.8]
2.5	6	36.1 ± 0.19 [35.8, 36.3]	0.63 ± 0.41 [0.2, 1.1]	1.18 ± 0.28 [0.8, 1.5]	0.97 ± 0.41 [0.5, 1.7]	0.25 ± 0.16 [0.1, 0.5]	-0.05 ± 0.16 [−0.2, 0.2]
7.5	6	35.9 ± 0.38 [35.4, 36.2]	1.03 ± 0.41 [0.7, 1.8]	1.18 ± 0.53 [0.3, 1.9]	1.50 ± 0.46 [1.0, 2.3]	0.53 ± 0.59 [−0.5, 1.2]	0.22 ± 0.43 [−0.3, 0.8]
15	6	36.1 ± 0.36 [35.5, 36.5]	1.20 ± 0.42 [0.8, 1.9]	1.38 ± 0.41 [0.9, 2.1]	1.58 ± 0.39 [1.2, 2.2]	0.68 ± 0.51 [0.2, 1.6]	0.22 ± 0.46 [−0.3, 1.0]
30	6	36.1 ± 0.21 [35.8, 36.4]	0.85 ± 0.22 [0.5, 1.1]	1.38 ± 0.32 [1.0, 1.9]	1.48 ± 0.71 [0.1, 2.0]	0.62 ± 0.34 [0.2, 1.2]	0.22 ± 0.17 [0.0, 0.5]
60	6	36.1 ± 0.40 [35.5, 36.6]	1.10 ± 0.57 [0.3, 2.0]	1.5 ± 0.46 [0.8, 2.2]	1.53 ± 0.40 [1.1, 2.3]	0.97 ± 0.52 [0.5, 1.8]	0.55 ± 0.56 [−0.2, 1.2]

Mean ± SD [Range]

Table 22. Change from baseline in HPPT following a single oral dose (°C)

Treatment group (mg)	N	Baseline	2 hours post-dose	4 hours post-dose	8 hours post-dose	24 hours post-dose	72 hours post-dose
Placebo	10	37.3 ± 1.90	0.65 ± 2.44	1.29 ± 2.73	0.28 ± 2.57	−0.15 ± 2.07	0.82 ± 3.30
2.5	6	39.5 ± 4.20	5.75 ± 3.08	3.74 ± 4.62	1.66 ± 4.14	0.51 ± 2.61	−0.99 ± 5.22
7.5	6	37.3 ± 1.59	8.74 ± 4.24	10.76 ± 2.76	8.74 ± 3.89	5.44 ± 5.70	0.43 ± 3.21
15	6	38.7 ± 2.73	7.72 ± 5.66	7.87 ± 4.26	7.09 ± 3.43	5.08 ± 3.83	1.53 ± 1.84
30	6	39.4 ± 2.68	9.08 ± 3.53	9.74 ± 2.53	9.55 ± 2.02	6.54 ± 2.68	1.03 ± 4.07
60	6	36.9 ± 1.13	12.77 ± 1.25	13.04 ± 1.76	12.62 ± 1.45	11.47 ± 1.05	8.29 ± 4.14

Mean ± SD

Table 23. Change from baseline in QTcF following a single oral dose (ms)

Treatment group (mg)	N	Baseline	2 hours post-dose	4 hours post-dose	8 hours post-dose	24 hours post-dose	72 hours post-dose
Placebo	10	388 ± 11.9	−0.167 ± 10.2	0.833 ± 9.95	−3.47 ± 8.43	−1.77 ± 12.1	0.0333 ± 9.91
2.5	6	394 ± 20.9	−14.7 ± 4.66	−8.33 ± 4.32	−13.7 ± 8.40	−9.33 ± 7.02	−6.33 ± 10.9
7.5	6	391 ± 12.8	−11.9 ± 12.7	−3.61 ± 10.4	−8.11 ± 6.13	−8.11 ± 10.5	0.0556 ± 11.1
15	6	381 ± 21.9	−11.6 ± 6.23	−12.0 ± 8.63	−11.5 ± 8.9	−4.64 ± 9.28	3.36 ± 13.2
30	6	389 ± 15.3	−16.9 ± 10.8	−10.6 ± 2.16	−16.1 ± 8.68	−13.1 ± 25.1	4.78 ± 13.1
60	6	385 ± 17.5	−12.8 ± 7.06	−10.2 ± 9.42	14.7 ± 10.6	−10.3 ± 7.64	−9.17 ± 9.73

Mean ± SD

6.2.2 Studies in patients with dry eye disease

6.2.2.1 Foreign phase I/II study (CTD 5.3.3.2-1, Study 1-01 [October 2019 to March 2020])

The study consisted of Part A and Part B. The pharmacokinetics of single ascending doses of motugivatrep were assessed in non-Japanese patients with dry eye disease in Part A. The pharmacokinetics of multiple ascending doses of motugivatrep were assessed in Japanese and non-Japanese patients with dry eye disease in Part B. A single drop of 0.03%, 0.1%, 0.3%, or 1% motugivatrep ophthalmic suspension was instilled into both eyes (Part A), or one drop of 0.3% or 1% motugivatrep ophthalmic suspension was instilled into both eyes 4 times daily for 4 weeks (Part B).

Table 24 and Table 25 show the pharmacokinetic parameters of motugivatrep and the change from baseline in body temperature following a single ocular instillation of motugivatrep in Part A, respectively.

In Part B, the C_{max} and AUC_{last} (mean ± SD) after the first ocular instillation of motugivatrep were 0.10 ± 0.05 ng/mL and 0.27 ± 0.14 ng·h/mL (0.3% motugivatrep suspension), respectively, and 0.77 ± 1.07 ng/mL and 1.19 ± 1.20 ng·h/mL (1% motugivatrep suspension), respectively, in Japanese subjects, and 0.18 ± 0.13 ng/mL and 0.38 ± 0.21 ng·h/mL (0.3% motugivatrep suspension), respectively, and 0.49 ± 0.48 ng/mL and 1.10 ± 0.92 ng·h/mL (1% motugivatrep suspension), respectively, in non-Japanese subjects. Table 26 shows the C_{trough} of motugivatrep in plasma on Days 2, 4, and 8 following repeated ocular instillation and the accumulation ratios. There were no clear differences in the pharmacokinetic parameters or accumulation ratio between Japanese and non-Japanese subjects. Although plasma concentrations of motugivatrep were determined until Day 8, the plasma concentrations predicted from a population pharmacokinetic analysis based on the data from a foreign phase I study [11] indicated that a steady-state was reached by Day 8. Table 27 shows the change from baseline in body temperature following repeated ocular instillation of motugivatrep. Following ocular instillation of motugivatrep, no increases in body temperature were observed.

Table 24. Pharmacokinetic parameters of motugivatrep following single ocular instillation (Part A)

Population	Treatment group	N	C_{max} (ng/mL)	AUC_{last} (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	V_d/F (L)	CL/F (L/h)
Non-Japanese	0.03%	6[a)]	0.04 ± 0.02	0.29 ± 0.16	3.00 [2.00, 8.00]	5.97, 5.99	3,910, 8,220	452, 954
	0.1%	6	0.13 ± 0.10	1.02 ± 0.83	6.00 [4.00, 12.0]	—	—	—
	0.3%	5	0.10 ± 0.06	0.85 ± 0.46	12.0 [4.00, 12.0]	—	—	—
	1%	4[b)]	0.69 ± 0.29	5.16 ± 2.54	10.0 [2.00, 12.0]	14.0	15,700	781

Mean ± SD or Median [Range]; Individual values are listed for N = 2 or 1.; —, Not calculated
a) N = 2 for $t_{1/2}$, V_d/F, and CL/F
b) N = 1 for $t_{1/2}$, V_d/F, and CL/F

Table 25. Change from baseline in body temperature following single ocular instillation (°C, Part A)

Treatment group	N	Baseline	2 hours post-dose	4 hours post-dose	8 hours post-dose	12 hours post-dose	24 hours post-dose
Placebo	8	36.8 ± 0.23 [36.5, 37.2]	0.00 ± 0.25 [−0.5, 0.3]	−0.08 ± 0.35 [−0.7, 0.2]	0.04 ± 0.26 [−0.3, 0.6]	−0.01 ± 0.26 [−0.4, 0.4]	0.00 ± 0.19 [−0.4, 0.2]
0.03%	6	36.8 ± 0.19 [36.5, 37.0]	−0.15 ± 0.18 [−0.4, 0.1]	−0.18 ± 0.24 [−0.6, 0.0]	0.06 ± 0.11 [−0.1, 0.2]	0.12 ± 0.11 [0.0, 0.3]	−0.10 ± 0.19 [−0.4, 0.1]
0.1%	6	36.7 ± 0.15 [36.5, 36.9]	0.07 ± 0.18 [−0.2, 0.3]	−0.03 ± 0.18 [−0.3, 0.2]	0.18 ± 0.18 [0.0, 0.5]	0.22 ± 0.21 [0.0, 0.5]	−0.18 ± 0.38 [−0.9, 0.2]
0.3%	5	36.8 ± 0.14 [36.6, 37.0]	−0.14 ± 0.05 [−0.2, −0.1]	−0.10 ± 0.12 [−0.3, 0.0]	−0.12 ± 0.28 [−0.4, 0.3]	0.10 ± 0.10 [0.0, 0.2]	0.10 ± 0.14 [0.0, 0.3]
1%	4	36.6 ± 0.18 [36.4, 36.8]	0.30 ± 0.18 [0.1, 0.5]	0.28 ± 0.25 [0.0, 0.6]	0.40 ± 0.29 [0.1, 0.7]	0.13 ± 0.13 [0.0, 0.3]	−0.03 ± 0.19 [−0.3, 0.1]

Mean ± SD [Range]

Table 26. C_{trough} of motugivatrep in plasma over time and accumulation ratios following repeated ocular instillation (Part B)

Race	Treatment group	N	Day 2 (ng/mL)	Day 4 (ng/mL)	Day 8 (ng/mL)	Accumulation ratio (Day 4/Day2)	Accumulation ratio (Day 8/Day 2)
Japanese	0.3%	6	0.52 ± 0.40	0.92 ± 0.83	1.48 ± 0.98	1.85 ± 0.92	3.59 ± 2.33
Non-Japanese		6	0.69 ± 0.43	1.04 ± 0.45	1.16 ± 0.39	1.66 ± 0.48	2.11 ± 0.92
Japanese	1%	6	1.12 ± 0.75	1.98 ± 1.84	3.31 ± 2.95	1.85 ± 1.03	3.11 ± 1.90
Non-Japanese		6	1.84 ± 0.87	2.61 ± 1.36	4.13 ± 2.33	1.49 ± 0.55	2.47 ± 1.52

Mean ± SD

Table 27. Change from baseline in body temperature following repeated ocular instillation (°C, Part B)

Race	Treatment group	N	Baseline	Day 2 (at 0 hours)	Day 4 (at 0 hours)	Day 8 (at 0 hours)
Japanese	Placebo	6	36.6 ± 0.16 [36.4, 36.8]	0.05 ± 0.18 [−0.2, 0.2]	0.03 ± 0.15 [−0.1, 0.2]	0 ± 0.21 [−0.2, 0.4]
Non-Japanese		14	36.7 ± 0.22 [36.4, 37.0]	−0.01 ± 0.16 [−0.4, 0.2]	−0.05 ± 0.27 [−0.6, 0.4]	−0.06 ± 0.22 [−0.5, 0.2]
Japanese	0.3%	6	36.6 ± 0.12 [36.4, 36.7]	0.25 ± 0.14 [0.1, 0.5]	0.17 ± 0.19 [−0.1, 0.4]	0.37 ± 0.21 [0.0, 0.6]
Non-Japanese		14	36.6 ± 0.17 [36.4, 36.9]	0.14 ± 0.15 [−0.1, 0.3]	0.19 ± 0.25 [−0.2, 0.6]	0.19 ± 0.19 [−0.1, 0.5]
Japanese	1%	6	36.9 ± 0.20 [36.6, 37.1]	0.03 ± 0.14 [−0.2, 0.2]	−0.22 ± 0.21 [−0.6, 0.0]	0.03 ± 0.20 [−0.3, 0.3]
Non-Japanese		14	36.8 ± 0.28 [36.4, 37.3]	−0.01 ± 0.29 [−0.6, 0.4]	−0.14 ± 0.29 [−0.6, 0.3]	−0.10 ± 0.37 [−0.8, 0.4]

Mean ± SD [Range]

6.2.2.2 Japanese phase II study (CTD 5.3.5.1-1, Study 2-01 [December 2020 to September 2021])

Following instillation of one drop of 1%, 0.3%, or 0.1% motugivatrep ophthalmic suspension or placebo into both eyes 4 times daily for 4 weeks in Japanese patients with dry eye disease, the changes from baseline in body temperature (mean ± SD [Number of subjects]) were −0.05 ± 0.36°C (72), −0.02 ± 0.30°C (79), or −0.07 ± 0.37°C (79), or 0.02 ± 0.33°C (81), respectively, and there were no increases in body temperature following ocular instillation of motugivatrep. The changes from baseline in QTcF (mean ± SD [Number of subjects]) were 5.0 ± 9.5 ms (8), 0.8 ± 7.8 ms (10), or 2.4 ± 6.6 ms (10), or −1.9 ± 5.8 ms (10), respectively, and there were no effects of ocular instillation of motugivatrep on QT interval. Motugivatrep and its metabolites in plasma were measured in 9 patients in the 1% motugivatrep group. Although motugivatrep was detected in plasma from 6 patients, no metabolites were detected in plasma from any patient.

6.R Outline of the review conducted by PMDA

PMDA's view:

Based on the submitted study results, there is no particular problem with the pharmacokinetics of motugivatrep.

With respect to the risk of increases in body temperature and HPPT and shortened QT interval associated with motugivatrep, increases in body temperature and HPPT and shortened QT interval were observed following a single oral dose of motugivatrep. Meanwhile, in clinical pharmacology studies of ocular instillation of motugivatrep, HPPT was not assessed, but increased body temperature or shortened QT interval was not observed. The risk of these events associated with motugivatrep needs to be determined, taking also account of the safety results from ocular instillation clinical studies of motugivatrep [see Section 7.R.3].

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 3 studies presented in Table 28.

Table 28. Listing of main efficacy and safety clinical studies

Phase	Study ID	Geographical location	Study population	Allocation or number of subjects enrolled	Dosing regimen (One drop of the following formulation was instilled into both eyes 4 times daily)	Main endpoints [Primary endpoint]
II	2-01	Japan	Dry eye disease patients with corneal epithelial disorder	(1) 85 (2) 87 (3) 87 (4) 85	(1) 1% motugivatrep ophthalmic suspension (2) 0.3% motugivatrep ophthalmic suspension (the proposed product) (3) 0.1% motugivatrep ophthalmic suspension (4) Placebo	Efficacy/safety, clinical optimal dose [Change from baseline in total corneal fluorescein staining score of all zones of the study eye at Week 4]
III	3-02	Japan	Patients with dry eye disease	(1) 269 (2) 267	(1) 0.3% motugivatrep ophthalmic suspension (the proposed product) (2) Placebo	Efficacy/safety [Change from baseline in DEQS summary score at Week 4]
III	3-01	Japan	Patients with dry eye disease	162	0.3% motugivatrep ophthalmic suspension (the proposed product)	Safety/efficacy

7.1 Phase II study

7.1.1 Japanese phase II study (CTD 5.3.5.1-1, Study 2-01 [December 2020 to September 2021])

A placebo-controlled, randomized, double-masked, parallel-group study was conducted at 40 sites in Japan to evaluate the efficacy, safety, and clinical optimal dose of motugivatrep in dry eye disease patients with corneal epithelial disorder (Table 29) (target sample size, 332 subjects [83 per group][17)]).

[17)] For the primary endpoint of the change from baseline in total corneal fluorescein staining score of all zones of the study eye at Week 4, assuming a change from baseline of −3.2 in the 0.3% motugivatrep group and a change from baseline of −1.2 in the placebo group and a common standard deviation of 4.44, 79 patients per group were required to provide 80% power at a two-sided significance level of 5% for a pairwise comparison between the 2 groups. Taking into account dropouts etc., the sample size was determined.

Table 29. Key inclusion and exclusion criteria etc.

[Key inclusion criteria]
1. ≥20 years of age at the time of signing the informed consent form
2. Subjective symptoms of dry eye that had persisted for ≥180 days before informed consent in both eyes
3. All of the following criteria were met at screening and baseline.
    a. A mean tear break-up time (BUT) of ≤5 seconds in both eyes
    b. A corneal fluorescein staining (CFS) score (using Baylor criteria) of 2 to 4 for the central zone of at least one eye (the same eye at screening and baseline), a total score of 4 to 20 for all zones, and a score of ≥1 for at least one of the four peripheral corneal regions (superior, inferior, nasal, and temporal)
    c. A visual analog scale (VAS) score for eye dryness of ≥40 with a 5-item Dry Eye Questionnaire (DEQ-5) total score of ≥6

[Key exclusion criteria]
At screening
1. Unable to discontinue the use of contact lenses (for any intended use) from the screening test day to the end of the treatment period
At screening and baseline
2. Active ocular disease other than dry eye (including infection of the eyeball or ocular adnexa, allergic disease, or proliferative disease) in either eye. Patients with a chronic disease that did not require treatment and was unlikely to progress during study treatment were permitted.
3. A history of corneal transplantation or punctal occlusion in either eye, or a plan to undergo corneal transplantation or punctal occlusion before the end of the treatment period
4. Using punctal plugs in either eye or had punctal plugs removed within 30 days of screening, or anticipated punctal plug insertion before the end of the treatment period
5. Unable to discontinue therapeutic agents for dry eye (e.g., diquafosol sodium, rebamipide) from 28 days before the start of treatment to the end of the treatment period.
6. Unable to discontinue all topical ophthalmic agents (e.g., eye drops, eye ointments, intraocular injections, topical administration to skin around the eyelid) (except for test agents used for ophthalmological examination), nasal drops, and Chinese herbal medicine from the first day of the run-in period until the end of the treatment period.
7. Unable to discontinue use of ethical or over-the-counter drugs/supplements that contained the following from the first day of the run-in period to the end of the treatment period.
    a. Components that affect tear production or secretion or sensory nerves (e.g., antihistamines, anticholinergic drugs, cholinergic drugs, opioids, anti-inflammatory analgesics, corticosteroids, β-blockers, immunosuppressants, omega-3 fatty acids)
    b. Substrates of drug efflux transporters (BCRP or P-gp)
8. Had undergone eye surgery that can damage sensory nerves on the ocular surface or surgery that induces morphological changes in the eye (e.g., cataract surgery, corneal refractive surgery, ptosis surgery) in either eye within 365 days of screening, or a plan to undergo such surgery during the study period.

[Others]
The number of patients with Schirmer's test I result of ≤5 mm in the study eye at the start date of the treatment period was controlled at no more than 20% of all randomized patients.

The study consisted of a 2-week run-in period and a 4-week treatment period.

During the run-in period, one drop of placebo was to be instilled into both eyes 4 times daily (at least 3 hours apart). During the treatment period, one drop of 1%, 0.3% (the proposed product), or 0.1% motugivatrep ophthalmic suspension or placebo was to be instilled into both eyes 4 times daily (at least 3 hours apart). The use of therapeutic agents for dry eye was prohibited.[18)]

All of 344 subjects randomized[19)] in the treatment period (85 in the 1% motugivatrep group, 87 in the 0.3% motugivatrep group, 87 in the 0.1% motugivatrep group, 85 in the placebo group) received at least 1 dose of study drug during the treatment period and were included in the safety population and in the full analysis set (FAS). The FAS was used as the primary efficacy population for the study.

18) Concomitant use of the following drugs etc. was prohibited.
- From 28 days before the start of treatment to the end of the treatment period: therapeutic agents for dry eye (e.g., diquafosol sodium, rebamipide)
- From the first day of the run-in period to the end of the treatment period: all topical ophthalmic agents including over the counter drugs /pharmacist intervention required medicines and supplements (e.g., eye drops, eye ointments, intraocular injections, topical administration to skin around the eyelid) except for test agents used for ophthalmological examination, all nasal drops, antihistamines, anticholinergic drugs, cholinergic drugs, opioids, anti-inflammatory analgesics, corticosteroids, β-blockers, immunosuppressants, omega-3 fatty acids, Chinese herbal medicine, drugs that contained substrates of drug efflux transporters (BCRP or P-gp), treatments that may damage the eye surface or improve eye symptoms (e.g., eye massage, warm compresses, eye washing) (Eye washing to remove staining dye after the completion of all tests at each visit was permitted), and nasal irrigation before daily patient's assessment.
- From the screening test day to the end of the treatment period: surgery of eyes and ocular adnexa (e.g., cataract surgery, corneal refractive surgery, lacrimal duct surgery), punctal plug insertion, and wearing contact lenses after the start of screening test

19) Randomization was stratified by total CFS score of all zones (<[redacted]/≥[redacted]), Schirmer's test value (≤[redacted] mm/>[redacted] mm), and VAS score for eye dryness (<[redacted]/≥[redacted]) in the study eye at the start date of the treatment period and site.

The rates of study discontinuation were 15.3% (13 of 85 subjects) in the 1% motugivatrep group, 9.2% (8 of 87 subjects) in the 0.3% motugivatrep group, 6.9% (6 of 87 subjects) in the 0.1% motugivatrep group, and 4.7% (4 of 85 subjects) in the placebo group. The main reasons for study discontinuation were study participant's decision (2 in the 1% motugivatrep group, 2 in the 0.3% motugivatrep group, 2 in the 0.1% motugivatrep group, 2 in the placebo group), adverse events or worsening of complications (5 in the 1% motugivatrep group, 2 in the 0.3% motugivatrep group), protocol deviation (1 in the 1% motugivatrep group, 1 in the 0.3% motugivatrep group, 2 in the 0.1% motugivatrep group, 1 in the placebo group), inclusion criteria not satisfied or exclusion criteria met (1 in the 0.1% motugivatrep group), and the investigator's decision (5 in the 1% motugivatrep group, 3 in the 0.3% motugivatrep group, 1 in the 0.1% motugivatrep group, 1 in the placebo group).

Table 30 shows the primary efficacy endpoint of the change from baseline in the total CFS score of all zones of the study eye [for definition, see Section 10] at Week 4. There were no statistically significant differences between the 0.3% motugivatrep and placebo groups.

Table 30. Change from baseline in total CFS score of all zones of the study eye at Week 4 (FAS, LOCF)

	1% motugivatrep (N = 85)	0.3% motugivatrep (N = 87)	0.1% motugivatrep (N = 87)	Placebo (N = 85)
Baseline	9.0 ± 3.9 (n = 85)	8.9 ± 3.8 (n = 87)	8.9 ± 3.8 (n = 87)	9.2 ± 3.8 (n = 84)
Change from baseline	−3.3 ± 4.0 (n = 79[a)])	−4.0 ± 3.0 (n = 85[a)])	−3.9 ± 4.0 (n = 85[a)])	−3.2 ± 3.3 (n = 83[a)])
Difference from placebo [95% CI]	−0.1 [−1.3, 1.0]	−0.8 [−1.7, 0.2]	−0.7 [−1.8, 0.4]	
P-value[b)]	—	0.1181	—	

Mean ± SD

a) Excluding patients if the change from baseline could not be calculated due to the lack of total CFS score of all zones at baseline or post-baseline.

b) T-test with a two-sided significance level of 5%. *P*-values for comparisons between the 1% motugivatrep and placebo groups and between the 0.1% motugivatrep and placebo groups are not listed because the overall type I error rate was not controlled.

The incidences of adverse events were 29.4% (25 of 85 subjects) in the 1% motugivatrep group, 18.4% (16 of 87 subjects) in the 0.3% motugivatrep group, 13.8% (12 of 87 subjects) in the 0.1% motugivatrep group, and 17.6% (15 of 85 subjects) in the placebo group. The main adverse events are shown in Table 31.

There were no deaths or serious adverse events.

The incidences of adverse events leading to study drug discontinuation were 5.9% (5 of 85 subjects) in the 1% motugivatrep group, 2.3% (2 of 87 subjects) in the 0.3% motugivatrep group, 0% (0 of 87 subjects) in the 0.1% motugivatrep group, and 0% (0 of 85 subjects) in the placebo group.

The incidences of adverse drug reactions were 23.5% (20 of 85 subjects) in the 1% motugivatrep group, 11.5% (10 of 87 subjects) in the 0.3% motugivatrep group, 5.7% (5 of 87 subjects) in the 0.1% motugivatrep group, and 8.2% (7 of 85 subjects) in the placebo group.

Table 31. Adverse events reported by ≥2% of subjects in any group (Safety population)

	1% motugivatrep (N = 85)	0.3% motugivatrep (N = 87)	0.1% motugivatrep (N = 87)	Placebo (N = 85)
Feeling cold	8 (9.4)	4 (4.6)	0	0
Vision blurred	2 (2.4)	1 (1.1)	0	0
Sensitive skin	2 (2.4)	1 (1.1)	0	0
Foreign body sensation in eyes	2 (2.4)	0	1 (1.1)	2 (2.4)
Abnormal sensation in eye	2 (2.4)	0	1 (1.1)	0
Eye discharge	2 (2.4)	0	0	0
Blepharitis	0	0	1 (1.1)	3 (3.5)
Corneal erosion	0	0	0	2 (2.4)
Eyelids pruritus	0	0	0	2 (2.4)

n (%) MedDRA/J version 23.1

7.2 Phase III studies

7.2.1 Japanese phase III study (CTD 5.3.5.1-2, Study 3-02 (January 2023 to October 2023])

A placebo-controlled, randomized, double-masked, parallel-group study was conducted at 62 sites in Japan to evaluate the efficacy and safety of motugivatrep in patients with dry eye disease (Table 32) (target sample size, 498 subjects [249 per group][20]).

Table 32. Key inclusion and exclusion criteria etc.

[Key inclusion criteria]
1. ≥18 years of age at the time of signing the informed consent form
2. Subjective symptoms of dry eye that had persisted for ≥180 days before informed consent in both eyes
3. All of the following criteria were met at screening and baseline.
   a. A score of ≥1 for at least 1 item among the items included in the definition of DEQS (Dry eye-related quality of life score questionnaire) summary score and a VAS score for eye dryness of ≥40 with a DEQ-5 total score of ≥6
   b. A mean BUT of ≤5 seconds in both eyes

[Key exclusion criteria]
At screening
1. Unable to discontinue the use of contact lenses (for any intended use) from the screening test day to the end of the treatment period
2. A history of corneal transplantation or punctal occlusion in either eye, or a plan to undergo corneal transplantation or punctal occlusion before the end of the treatment period
3. Using punctal plugs in either eye or had punctal plugs removed within 30 days of screening, or anticipated punctal plug insertion before the end of the treatment period
4. Had undergone eye surgery that can damage sensory nerves on the ocular surface or surgery that induces morphological changes in the eye (e.g., cataract surgery, corneal refractive surgery, ptosis surgery), IPL therapy, or thermal pulsation therapy in either eye within 365 days of screening, or a plan to undergo such surgery/therapy during the study period.
At screening and baseline
5. Active ocular disease other than dry eye (including infection of the eyeball or ocular adnexa, allergic disease, or proliferative disease) in either eye. Patients with a chronic disease that did not require treatment and was unlikely to progress during study treatment were permitted.
6. A disease that possibly impacts the subjective symptoms of dry eye (e.g., cataract) other than diseases causing dry eye (e.g., Sjogren's syndrome, chronic graft versus host disease, conjunctivochalasis, or meibomian gland dysfunction)
7. Unable to discontinue therapeutic agents for dry eye (e.g., diquafosol sodium, rebamipide) and therapeutic agents for keratoconjunctival epithelial disorders (e.g., sodium hyaluronate) from 28 days before the start of treatment to the end of the treatment period.
8. Unable to discontinue all topical ophthalmic agents (e.g., eye drops, eye ointments, intraocular injections, topical administration to skin around the eyelid) including over-the-counter drugs and pharmacist intervention required medicines (except for test agents used for ophthalmological examination) from the first day of the run-in period.
9. Unable to discontinue treatments that may damage the eye surface or improve eye symptoms (e.g., eye massage, warm compresses) from the first day of the run-in period to the end of the treatment period

[Others]
The number of patients with Schirmer's test I result of ≤5 mm in the study eye at the start date of the treatment period was controlled at no more than 20% of all randomized patients.

The study consisted of a 2-week run-in period and an 8-week treatment period.

During the run-in period, one drop of placebo was to be instilled into both eyes 4 times daily (at least 3 hours apart). During the treatment period, one drop of 0.3% motugivatrep ophthalmic suspension (the proposed

[20] For the primary endpoint of the change from baseline in the DEQS summary score at Week 4, assuming a difference of −3.5 between the 0.3% motugivatrep and placebo groups and a standard deviation of 11.4, 224 patients per group were required to provide 90% power at a two-sided significance level of 5% for a pairwise comparison between the 2 groups. Taking into account dropouts etc., the sample size was determined.

product) or placebo was to be instilled into both eyes 4 times daily (at least 3 hours apart). The use of therapeutic agents for dry eye etc. was prohibited.[21)]

All of 535 subjects randomized[22)] in the treatment period (268 in the 0.3% motugivatrep group, 267 in the placebo group) received at least 1 dose of study drug and were included in the FAS. The FAS was used as the primary efficacy population for the study. After including 1 subject who was not randomized but received motugivatrep, 536 subjects (269 in the 0.3% motugivatrep group, 267 in the placebo group) were included in the safety population.

The rates of study discontinuation were 3.0% (8 of 268 subjects) in the 0.3% motugivatrep group and 3.0% (8 of 267 subjects) in the placebo group. The main reasons for study discontinuation were adverse events or complications (3 in the 0.3% motugivatrep group, 3 in the placebo group) and study participant's decision (3 in the 0.3% motugivatrep group, 2 in the placebo group).

Table 33 shows the primary efficacy endpoint of the change from baseline in the DEQS summary score at Week 4. There was a statistically significant difference between the 0.3% motugivatrep and placebo groups.

Table 33. Change from baseline in DEQS summary score at Week 4 (FAS)

	0.3% motugivatrep (N = 268)	Placebo (N = 267)
Baseline	37.74 ± 20.77	38.85 ± 20.20
Change from baseline[a)]	−16.76 [−18.40, −15.12]	−14.36 [−16.01, −12.72]
Difference from placebo[a)]	−2.40 [−4.72, −0.07]	
P-value[a), b)]	0.0433	

Mean ± SD or Least-squares mean [95% CI]

a) A MMRM model with treatment, visit, and treatment-by-visit interaction as fixed effects and DEQS summary score at baseline as a covariate. An unstructured covariance matrix was used to model the correlation among repeated measurements.

b) A two-sided significance level of 5%

The incidences of adverse events were 19.7% (53 of 269 subjects) in the 0.3% motugivatrep group and 14.6% (39 of 267 subjects) in the placebo group. The main adverse events are shown in Table 34.

There were no deaths or serious adverse events.

[21)] Concomitant use of the following drugs etc. was prohibited.

- From 28 days before the start of treatment to the end of the treatment period: therapeutic agents for dry eye (e.g., diquafosol sodium, rebamipide) and therapeutic agents for keratoconjunctival epithelial disorders (e.g., sodium hyaluronate)
- From the first day of the run-in period to the end of the treatment period: corticosteroids (topical administration to skin was permitted except for skin around the eyelid), drugs that affect tear production or secretion (e.g., antihistamines, anticholinergic drugs, cholinergic drugs), supplements that may impact the symptoms of dry eye (e.g., omega-3 fatty acids), and all topical ophthalmic agents (e.g., eye drops, eye ointments, intraocular injections, topical administration to skin around the eyelid) including over-the-counter drugs and pharmacist intervention required medicines (except for test agents used for ophthalmological examination)
- From the first day of the run-in period to the end of the treatment period: treatments that may impact the symptoms of dry eye (e.g., eye massage, warm compresses)
- From the screening test day to the end of the treatment period: surgery of eyes and ocular adnexa (e.g., cataract surgery, corneal refractive surgery, lacrimal duct surgery), punctal plug insertion, wearing contact lenses after the start of screening test, and IPL therapy and thermal pulsation therapy for diseases that impact the symptoms of dry eye such as meibomian gland dysfunction

[22)] Randomization was stratified by VAS score for eye dryness (<[redacted]/≥[redacted]) and total CFS score of all zones of the study eye (<[redacted]/≥[redacted]) at the start date of the treatment period.

The incidences of adverse events leading to study drug discontinuation were 1.1% (3 of 269 subjects) in the 0.3% motugivatrep group and 1.1% (3 of 267 subjects) in the placebo group.

The incidences of adverse drug reactions were 5.6% (15 of 269 subjects) in the 0.3% motugivatrep group and 3.7% (10 of 267 subjects) in the placebo group.

Table 34. Adverse events reported by ≥2% of subjects in either group (Safety population)

	0.3% motugivatrep (N = 269)	Placebo (N = 267)
COVID-19	7 (2.6)	2 (0.7)
Feeling cold	6 (2.2)	0
Nasopharyngitis	4 (1.5)	7 (2.6)

n (%) MedDRA/J version 25.1

7.2.2 Japanese long-term treatment study (CTD 5.3.5.2-1, Study 3-01 [January 2023 to May 2024])

An uncontrolled, open-label study was conducted at 22 sites in Japan to evaluate the long-term safety and efficacy of motugivatrep in patients with dry eye disease (Table 35) (target sample size, 150 subjects (≥70 subjects on motugivatrep monotherapy, a total of ≥50 subjects treated with motugivatrep in combination with other therapeutic agents for dry eye etc.[23)] [≥10 subjects for each therapeutic agent]).

Table 35. Key inclusion and exclusion criteria etc.

[Key inclusion criteria]
1. ≥18 years of age at the time of signing the informed consent form
2. Subjective symptoms of dry eye that had persisted for ≥180 days before informed consent in both eyes
3. All of the following criteria were met at screening and baseline.
   a. A score of ≥1 for at least 1 item among the items included in the definition of DEQS summary score and a VAS score for eye dryness of ≥40 with a DEQ-5 total score of ≥6
   b. A mean BUT of ≤5 seconds in both eyes

[Key exclusion criteria]
At screening
1. Unable to discontinue the use of contact lenses (for any intended use) from the screening test day to the end of the treatment period
2. A history of corneal transplantation or punctal occlusion in either eye, or a plan to undergo corneal transplantation or punctal occlusion before the end of the treatment period
3. Using punctal plugs in either eye or had punctal plugs removed within 30 days of screening, or anticipated punctal plug insertion before the end of the treatment period
4. Had undergone eye surgery that can damage sensory nerves on the ocular surface or surgery that induces morphological changes in the eye (e.g., cataract surgery, corneal refractive surgery, ptosis surgery), IPL therapy, or thermal pulsation therapy in either eye within 365 days of screening, or a plan to undergo such surgery/therapy during the study period.
At screening and baseline
5. Active ocular disease other than dry eye (including infection of the eyeball or ocular adnexa, allergic disease, or proliferative disease) in either eye. Patients with a chronic disease that did not require treatment and was unlikely to progress during study treatment were permitted.
6. A disease that possibly impacts the subjective symptoms of dry eye (e.g., cataract) other than diseases causing dry eye (e.g., Sjogren's syndrome, chronic graft versus host disease, conjunctivochalasis, or meibomian gland dysfunction)
7. Unable to discontinue therapeutic agents for dry eye (e.g., diquafosol sodium, rebamipide) and therapeutic agents for keratoconjunctival epithelial disorders (e.g., sodium hyaluronate) from 28 days before the start of the treatment period to the end of the treatment period. Patients who were enrolled as those on combination therapy with other therapeutic agents for dry eye etc. were not to be excluded even if they continued to use any one of diquafosol sodium, rebamipide, or sodium hyaluronate.
8. Unable to discontinue all topical ophthalmic agents (e.g., eye drops, eye ointments, intraocular injections, topical administration to skin around the eyelid) including over-the-counter drugs and pharmacist intervention required medicines (except for test agents used for ophthalmological examination) from the end of screening test. The use of artificial tears (preservative-free) up to the day before the start date of the treatment period was permitted.
9. Unable to discontinue treatments that may damage the eye surface or improve eye symptoms (e.g., eye massage, warm compresses) from the start of screening test to the end of the treatment period.

[Others]
The number of patients with Schirmer's test I result of ≤5 mm in the study eye at the start date of the treatment period was controlled at no more than 20% of all patients.

[23)] Diquafosol sodium ophthalmic solution and rebamipide ophthalmic suspension indicated for dry eye, and sodium hyaluronate ophthalmic solution indicated for keratoconjunctival epithelial disorders associated with dry eye syndrome (dry eye)

The study consisted of a 52-week treatment period only. Patients were enrolled as those on motugivatrep monotherapy or those on combination therapy with other therapeutic agents for dry eye etc.

One drop of 0.3% motugivatrep ophthalmic suspension (the proposed product) was to be instilled into both eyes 4 times daily (at least 3 hours apart). The use of therapeutic agents for dry eye etc. was prohibited.[24)] However, patients enrolled as those on combination therapy with other therapeutic agents for dry eye etc. were to receive any one of diquafosol sodium, rebamipide, or sodium hyaluronate at a stable dosage regimen from 28 days before the start of the treatment period to the end of the treatment period. Patients were to remain on the same drug, but switching to another product containing the same active substance at the same concentration was permitted.

All of 162 enrolled subjects (105 on monotherapy, 57 on combination therapy) received at least 1 dose of motugivatrep and were included in the safety population and in the FAS. The FAS was used as the primary efficacy population for the study.

The rate of study discontinuation was 8% (13 of 162 subjects) (monotherapy, 9.5% [10 of 105 subjects]; combination therapy, 5.3% [3 of 57 subjects]). The main reasons for study discontinuation were study participant's decision (8 subjects) (6 subjects on monotherapy, 2 subjects on combination therapy) and adverse event (3 subjects) (2 subjects on monotherapy, 1 subject on combination therapy).

The incidence of adverse events was 45.1% (73 of 162 subjects) (monotherapy, 39.0% [41 of 105 subjects]; combination therapy, 56.1% [32 of 57 subjects]). The main adverse events are shown in Table 36.

No deaths were reported.

The incidence of serious adverse events was 1.9% (3 of 162 subjects) (monotherapy, 1.9% [2 of 105 subjects (pneumonia; and joint injury, 1 subject each)]; combination therapy, 1.8% [1 of 57 subjects (pyelonephritis [1 subject])]), and a causal relationship to motugivatrep was denied for all those events.

The incidence of adverse events leading to motugivatrep discontinuation was 1.9% (3 of 162 subjects) (monotherapy, 1.9% [2 of 105 subjects]; combination therapy, 1.8% [1 of 57 subjects]).

[24)] Concomitant use of the following drugs etc. was prohibited.

- From 28 days before the start of the treatment period to the end of the treatment period: therapeutic agents for dry eye (e.g., diquafosol sodium, rebamipide), therapeutic agents for keratoconjunctival epithelial disorders (e.g., sodium hyaluronate), and over-the-counter drugs/pharmacist intervention required medications for dry eye
- From the screening test day to the end of the treatment period: corticosteroids (topical administration to skin was permitted except for skin around the eyelid), drugs that affect tear production or secretion (e.g., antihistamines, anticholinergic drugs, cholinergic drugs), supplements that may impact the symptoms of dry eye (e.g., omega-3 fatty acids), all topical ophthalmic agents (e.g., eye drops, eye ointments, intraocular injections, topical administration to skin around the eyelid) including over-the-counter drugs and pharmacist intervention required medicines (except for test agents used for ophthalmological examination), surgery of eyes and ocular adnexa (e.g., cataract surgery, corneal refractive surgery, lacrimal duct surgery), punctal plug insertion, wearing contact lenses after the start of screening test, IPL therapy and thermal pulsation therapy for diseases that impact the symptoms of dry eye such as meibomian gland dysfunction, and treatments that may damage the eye surface or improve eye symptoms (e.g., eye massage, warm compresses)

The incidence of adverse drug reactions was 14.8% (24 of 162 subjects) (monotherapy, 12.4% [13 of 105 subjects]; combination therapy, 19.3% [11 of 57 subjects]).

Table 36. Adverse events reported by ≥2% of subjects in the overall population (Safety population)

	Overall population (N = 162)	Subjects on monotherapy (N = 105)	Subjects on combination therapy (N = 57)
Feeling cold	12 (7.4)	5 (4.8)	7 (12.3)
Nasopharyngitis	10 (6.2)	6 (5.7)	4 (7.0)
COVID-19	6 (3.7)	2 (1.9)	4 (7.0)
Eye discharge	6 (3.7)	1 (1.0)	5 (8.8)
Influenza	5 (3.1)	4 (3.8)	1 (1.8)
Cough	5 (3.1)	3 (2.9)	2 (3.5)
Back pain	4 (2.5)	2 (1.9)	2 (3.5)
Conjunctivitis allergic	4 (2.5)	2 (1.9)	2 (3.5)

n (%) MedDRA/J version 25.1

7.R Outline of the review conducted by PMDA

7.R.1 Development plan

The applicant's explanation about the development plan for motugivatrep:

In Japan, dry eye is mainly defined by tear film instability and ocular discomfort or visual disturbance. The diagnostic criteria are a BUT of ≤5 seconds (a measure of tear film stability) and the presence of subjective symptoms of ocular discomfort, visual disturbance, etc. (Clinical practice guidelines). Subjective symptoms of dry eye occur regardless of the cause or type of dry eye and are essential for a diagnosis of dry eye. Thus, motugivatrep, which is mainly expected to improve subjective symptoms of dry eye [see Section 3], was developed, considering that motugivatrep can become a therapeutic agent that can be administered to all patients diagnosed with dry eye according to its definition and diagnostic criteria.

Based on the above development strategy and the results from clinical studies such as a Japanese phase II study conducted to evaluate the dose-response relationship of motugivatrep (Study 2-01), the applicant decided to plan and conduct a placebo-controlled, randomized, double-masked, parallel-group study, i.e., a Japanese phase III study (Study 3-02), construct a clinical data package, positioning the results from this study as pivotal clinical data, and evaluate the efficacy and safety of motugivatrep in Japanese patients with dry eye disease. Study 3-02 had a treatment duration of 8 weeks as described later, in which concomitant use with the existing therapeutic agents for dry eye was prohibited as shown in footnote 21. Since motugivatrep is intended to be administered for long periods for the treatment of dry eye disease, and its concomitant use with the existing therapeutic agents for dry eye is also envisaged, the applicant decided to conduct a separate, uncontrolled, open-label, long-term treatment study with a treatment duration of 52 weeks in which its concomitant use with the existing therapeutic agents for dry eye was permitted (Japanese Study 3-01) and evaluate the long-term efficacy and safety of motugivatrep and the efficacy and safety of motugivatrep in combination with the existing therapeutic agents for dry eye.

In addition, the applicant explained about the plan of Study 3-02 as follows.

○ Study population

As the target population for motugivatrep was considered all patients with dry eye disease, patients with a BUT of ≤5 seconds and certain subjective symptoms of dry eye, according to the diagnostic criteria, were eligible for inclusion in Study 3-02, regardless of factors contributing to unstable tear film that causes dry eye or the presence or absence of corneal epithelial disorder that may accompany dry eye.

The following inclusion criteria as to subjective symptoms were set for the following reasons, and patients who met all of these criteria were included in the study.

- A score of ≥1 for at least 1 item among the items included in the definition of DEQS summary score: Although the DEQS summary score was used for the primary endpoint as described later, a cutoff value for the diagnosis of dry eye disease had not been reported at the time of developing the plan. Thus, a cutoff value of ≥1[25)] was chosen so that as a minimum, improvement of dry eye disease by study drug can be observed.
- A VAS score for eye dryness of ≥40: As eye dryness is a typical subjective symptom of dry eye, this criterion was set, referring to phase III studies of other therapeutic agents for dry eye conducted in the US.
- A DEQ-5 total score of ≥6: This criterion was set because Dry Eye Workshop (DEWS) II recommended "a DEQ-5 total score of ≥6" as a screening criterion for the diagnosis of dry eye (*Ocul Surf*. 2017; 15: 802-12).

Multiple subjective symptom criteria were set as inclusion criteria for the following reasons:

As described above, a cutoff value of the DEQS summary score had not been reported at the time of developing the plan, and it was considered difficult to appropriately set inclusion criteria as to subjective symptoms using the DEQS summary score only. Thus, complementary items were considered necessary.

The symptoms of dry eye can change with external factors such as season and living environment. Thus, patients with transient dry eye disease were excluded by enrolling patients with subjective symptoms of dry eye that had persisted for ≥180 days in both eyes.

○ Efficacy endpoint

For the following reasons, "the change from baseline in the DEQS summary score at Week 4" was chosen as the primary endpoint.

- Since motugivatrep was mainly expected to improve subjective symptoms of dry eye, the applicant decided to evaluate the change from baseline, using DEQS. DEQS assesses subjective symptoms of dry eye. DEQS was developed in Japan and was considered suitable for evaluation in Japanese patients with dry eye disease.
- Week 4 was selected as the timing of the primary endpoint because a difference in the change from baseline in the DEQS summary score between the placebo and each of the motugivatrep groups was detected at Week 1 and maintained up to Week 4 in Study 2-01.

[25)] At the time of filing the present application, an optimal cutoff value of ≥15 for diagnosing dry eye disease has been reported (*Sci Rep*. 2024; 14: 4623). At the start of the treatment period in Study 3-02, the proportions of patients with a DEQS summary score of ≥15 were 86.9% (233 of 268 patients) in the 0.3% motugivatrep group and 88.8% (237 of 267 patients) in the placebo group.

A secondary endpoint of BUT was also selected to evaluate the effect of motugivatrep on tear film stability, which is the essence of dry eye.

○ Dosing regimen

In pharmacology studies in a rat model of dry eye [see Section 3.1], an increase in the SPK score[3)] was inhibited by 4 daily instillations of 0.3% motugivatrep suspension, and inhibition of an increase in the blink rate was sustained through 4 hours after a single instillation of motugivatrep. Thus, assuming that the optimal dosing frequency is 4 times daily, its clinical development proceeded. Since there was no particular problem in Study 2-01 etc., a dosing regimen of one drop 4 times daily was chosen.

With respect to the concentration of motugivatrep, the following results of Study 2-01 indicated that motugivatrep has its maximum effect in improving subjective symptoms of dry eye and no safety issues at a concentration of 0.3%. Thus, a concentration of 0.3% was chosen.

- A secondary endpoint of the change from baseline in the DEQS summary score at each time point showed a trend towards consistent improvements from Week 1 to Week 4 in the 0.3% motugivatrep group compared with the placebo group. This improvement trend was greater in the 0.3% motugivatrep group than in the 1% or 0.1% motugivatrep group.
- The incidences of adverse events in the 1% motugivatrep, 0.3% motugivatrep, 0.1% motugivatrep, and placebo groups were 29.4% (25 of 85 subjects), 18.4% (16 of 87 subjects), 13.8% (12 of 87 subjects), and 17.6% (15 of 85 subjects), respectively, showing a trend towards a dose-dependent increase. On the other hand, the incidences of adverse events assessed by the investigator (sub-investigator) as moderate or severe for which a causal relationship to study drug could not be ruled out were 2.4% (2 of 85 subjects) in the 1% motugivatrep group and 1.2% (1 of 85 subjects) in the placebo group, and no such events were observed in the 0.3% or 0.1% motugivatrep group.

○ Treatment duration

While the pivotal phase III studies of the existing therapeutic agents for dry eye had a treatment duration of up to 4 weeks, motugivatrep is intended to be administered for long periods for the treatment of dry eye disease. Taking account of the medical expert's advice on visit intervals for patients with dry eye disease, a treatment duration of 8 weeks was selected so as to assess the efficacy and safety of longer treatment with motugivatrep in a placebo-controlled, double-masked study.

PMDA’s view:

With regard to the inclusion criteria as to subjective symptoms of dry eye for Study 3-02, the patient population to be enrolled using combinations of multiple subjective symptom criteria should have been defined at the time of developing the plan. However, it is understandable that the study population was dry eye patients with certain subjective symptoms, and there is no major problem with the evaluation of the efficacy of motugivatrep. Based on the above, the efficacy and safety of motugivatrep can be evaluated based on a clinical data package containing Study 3-02 as the pivotal clinical study.

7.R.2 Efficacy

The applicant's explanation about the efficacy of motugivatrep in the treatment of dry eye disease:
In Study 3-02, a pairwise comparison between 0.3% motugivatrep ophthalmic suspension and placebo showed a statistically significant difference in the primary endpoint of the change from baseline in the DEQS summary score at Week 4, demonstrating the superiority of motugivatrep over placebo (Table 33).

Table 37 shows the DEQS summary score and BUT over time. The trend favored 0.3% motugivatrep ophthalmic suspension compared to placebo in these endpoints up to Week 8.

Table 37. DEQS summary score etc. over time (Study 3-02, FAS)

		0.3% motugivatrep	Placebo
DEQS summary score			
Baseline		37.74 ± 20.77 (268)	38.85 ± 20.20 (267)
Change from baseline	Week 4	−16.60 ± 15.76 (259)	−14.53 ± 15.36 (258)
	Week 8	−18.02 ± 15.87 (252)	−16.88 ± 16.15 (255)
BUT of study eye			
Baseline		2.943 ± 1.057 (268)	2.886 ± 1.023 (267)
Change from baseline	Week 4	0.737 ± 1.408 (259)	0.677 ± 1.837 (257)
	Week 8	0.844 ± 1.523 (252)	0.687 ± 1.445 (255)

Mean ± SD (Number of subjects)

A core mechanism of dry eye is considered a vicious circle of tear film instability, corneal epithelial disorder, and decreased wettability of the corneal epithelium (Clinical practice guidelines). The presence of corneal epithelial disorder is not essential for a diagnosis of dry eye, but is one of important findings. Thus, the effect of corneal epithelial disorder at baseline on the efficacy of motugivatrep was assessed. The presence of corneal epithelial disorder was defined as a CFS score of ≥1 in either eye at baseline. Table 38 shows the results of subgroup analyses by the presence or absence of corneal epithelial disorder.

The trend favored 0.3% motugivatrep ophthalmic suspension compared to placebo in the DEQS summary score across all subgroups. On the other hand, BUT improvement tended to differ according to the presence or absence of corneal epithelial disorder, and a smaller increase in BUT was observed in the 0.3% motugivatrep group than in the placebo group in the subgroup without corneal epithelial disorder. The number of patients in the subgroup without corneal epithelial disorder was limited, and this result may have been incidental, but may also indicate the following: While motugivatrep improved corneal epithelial disorder and corneal wettability by reducing the production of inflammatory mediators through TRPV1 inhibition in the subgroup of patients with corneal epithelial disorder, motugivatrep did not improve BUT through this mechanism in the subgroup of patients without corneal epithelial disorder.

Table 38. DEQS summary score etc. over time in subgroups with or without corneal epithelial disorder at baseline (Study 3-02, FAS)

		Subgroup with corneal epithelial disorder at baseline (Total CFS score of ≥1 for all zones of either eye)		Subgroup without corneal epithelial disorder at baseline (Total CFS score of 0 for all zones of both eyes)	
		0.3% motugivatrep	Placebo	0.3% motugivatrep	Placebo
DEQS summary score					
Baseline		36.40 ± 19.90 (221)	38.49 ± 19.56 (219)	44.01 ± 23.66 (47)	40.45 ± 23.06 (48)
Change from baseline	Week 4	−16.03 ± 15.32 (213)	−14.48 ± 15.21 (210)	−19.24 ± 17.61 (46)	−14.79 ± 16.18 (48)
	Week 8	−17.21 ± 15.40 (210)	−16.79 ± 15.75 (207)	−22.07 ± 17.69 (42)	−17.26 ± 17.97 (48)
BUT of study eye					
Baseline		2.916 ± 1.050 (221)	2.804 ± 1.032 (219)	3.069 ± 1.094 (47)	3.259 ± 0.901 (48)
Change from baseline	Week 4	0.790 ± 1.420 (213)	0.641 ± 1.805 (209)	0.493 ± 1.339 (46)	0.837 ± 1.985 (48)
	Week 8	0.880 ± 1.380 (210)	0.643 ± 1.366 (207)	0.667 ± 2.110 (42)	0.876 ± 1.751 (48)
Total CFS score of all zones of study eye					
Baseline		5.4 ± 4.4 (221)	5.3 ± 4.1 (219)		
Change from baseline	Week 4	−1.7 ± 3.4 (213)	−1.5 ± 3.6 (209)		
	Week 8	−2.2 ± 3.4 (210)	−2.0 ± 3.6 (207)		

Mean ± SD (Number of subjects)

Among the presumed factors contributing to unstable tear film in the pathogenesis of dry eye disease, reduced lacrimal secretion can be confirmed by a specific method. Reduced lacrimal secretion was defined as Schirmer's test I result of ≤5 mm[26] in either eye at baseline. Table 39 shows the results of subgroup analyses according to the presence or absence of reduced lacrimal secretion. The trend favored placebo compared to 0.3% motugivatrep ophthalmic suspension in the DEQS summary score in the subgroup with reduced lacrimal secretion. However, the trend favored 0.3% motugivatrep ophthalmic suspension compared to placebo in BUT even in this subgroup. In a similar subgroup (the definition of this subgroup partially differs from the above subgroup), i.e., the subgroup with Schirmer's test I result of ≤5 mm in the study eye at baseline (regardless of test result in the other eye), the trend favored 0.3% motugivatrep ophthalmic suspension compared to placebo in the change from baseline in the DEQS summary score (−13.84 ± 9.94 [23 subjects] in the 0.3% motugivatrep group and −13.80 ± 15.35 (20 subjects) in the placebo group at Week 4; −17.17 ± 13.65 [23 subjects] in the 0.3% motugivatrep group and −15.62 ± 14.25 [19 subjects] in the placebo group at Week 8). Taking also into account that consistent results were not obtained, the results of the DEQS summary score in the subgroup with reduced lacrimal secretion may have been incidental due to the limited number of patients in this subgroup, and do not deny the efficacy of motugivatrep in dry eye disease patients with reduced lacrimal secretion.

Table 39. DEQS summary score etc. over time in subgroups with or without reduced lacrimal secretion at baseline (Study 3-02, FAS)

		Subgroup with reduced lacrimal secretion at baseline (Schirmer's test I result of ≤5 mm in either eye)		Subgroup without reduced lacrimal secretion at baseline (Schirmer's test I result of >5 mm in both eyes)	
		0.3% motugivatrep	Placebo	0.3% motugivatrep	Placebo
DEQS summary score					
Baseline		35.51 ± 18.94 (36)	37.92 ± 22.40 (37)	38.08 ± 21.05 (232)	38.99 ± 19.88 (230)
Change from baseline	Week 4	−11.71 ± 11.78 (36)	−13.50 ± 15.47 (36)	−17.38 ± 16.20 (223)	−14.70 ± 15.37 (222)
	Week 8	−14.86 ± 14.00 (36)	−15.89 ± 15.09 (34)	−18.55 ± 16.13(216)	−17.03 ± 16.34 (221)
BUT of study eye					
Baseline		2.892 ± 1.178 (36)	2.356 ± 0.951 (37)	2.951 ± 1.040 (232)	2.971 ± 1.010 (230)
Change from baseline	Week 4	0.675 ± 1.260 (36)	0.559 ± 1.395 (36)	0.747 ± 1.433 (223)	0.697 ± 1.901 (221)
	Week 8	0.903 ± 1.379 (36)	0.616 ± 1.339 (34)	0.835 ± 1.548 (216)	0.698 ± 1.464 (221)

Mean ± SD (Number of subjects)

At the time of developing the plan of Study 3-02, the clinically meaningful minimum difference in the change

[26] Though not mentioned in the latest diagnostic criteria of dry eye in Japan, this cutoff value was used in the diagnostic criteria of dry eye up to 2016. This cutoff value is also used in the diagnostic criteria of Sjogren's syndrome, which is the leading cause of aqueous-deficient dry eye.

in the DEQS summary score had not been established, and no cutoff values of the DEQS summary score for the diagnosis of dry eye disease or severity classification had been reported. Also at the time of filing the present application, the clinically meaningful minimum difference in the change in the DEQS summary score has not been established, whereas a cutoff value of ≥15.0 for the diagnosis of dry eye disease, and cutoff values of ≥15.0 and <20.0, ≥20.0 and <26.8, and ≥26.8 for mild, moderate, and severe eye dry disease, respectively, have been reported (*Sci Rep*. 2024; 14: 4623). The diagnostic criteria of dry eye include a BUT of ≤5 seconds. Considering that the efficacy of motugivatrep should be clinically meaningful if patients no longer fulfill the diagnostic criteria of dry eye or have mild disease, the proportions of patients in the categories based on these cutoff values over time were analyzed retrospectively (Table 40). The trend consistently favored 0.3% motugivatrep ophthalmic suspension compared to placebo based on both criteria and at both time points.

Table 40. Proportion of patients with DEQS summary score below a cutoff value or BUT above a cutoff value over time (Study 3-02, FAS)

	0.3% motugivatrep	Placebo
Proportion of patients with DEQS summary score <15.0		
Baseline	13.1 (35/268)	11.2 (30/267)
Week 4	44.8 (116/259)	40.3 (104/258)
Week 8	48.8 (123/252)	43.5 (111/255)
Proportion of patients with DEQS summary score <20.0		
Baseline	20.9 (56/268)	20.2 (54/267)
Week 4	59.1 (153/259)	48.4 (125/258)
Week 8	61.9 (156/252)	55.3 (141/255)
Proportion of patients with DEQS summary score <26.8		
Baseline	34.7 (93/268)	32.2 (86/267)
Week 4	72.2 (187/259)	62.0 (160/258)
Week 8	75.0 (189/252)	69.0 (176/255)
Proportion of patients with BUT >5.0 seconds in study eye		
Baseline	0 (0/268)	0 (0/267)
Week 4	19.7 (51/259)	12.8 (33/257)
Week 8	24.2 (61/252)	16.5 (42/255)

% (n/N)

Figure 2 shows the change from baseline in the DEQS summary score over time following long-term treatment and following combination therapy with the currently approved drugs in Study 3-01. Although these results were obtained from an uncontrolled, open-label study, there was no trend towards reduced effects with prolonged treatment with motugivatrep alone or in combination with other drugs.

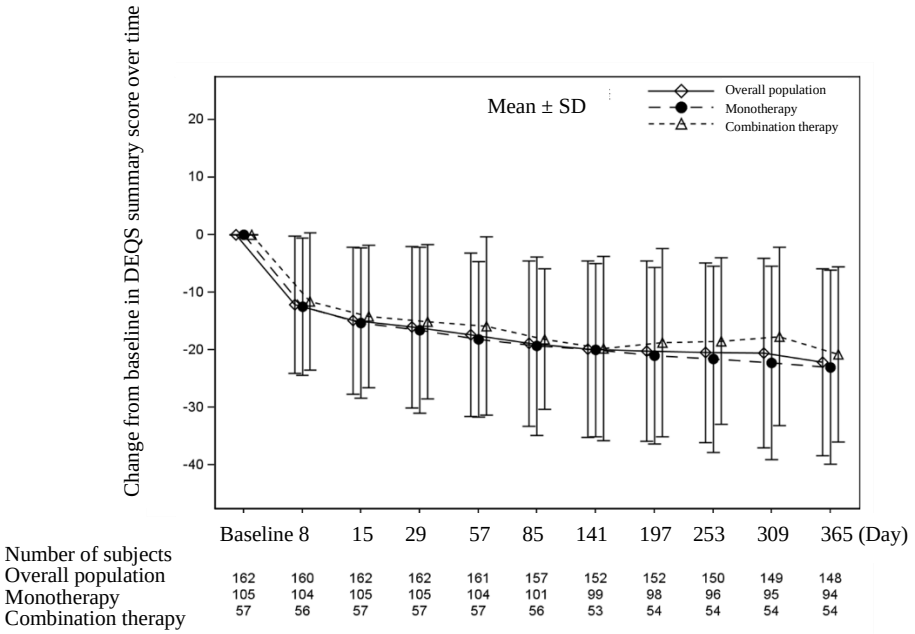


Figure 2. Change from baseline in DEQS summary score over time (Study 3-01, FAS)

As described above, Study 3-02 demonstrated the superiority of motugivatrep over placebo in the primary endpoint of the change from baseline in the DEQS summary score at Week 4. The 0.3% motugivatrep group showed a trend towards consistent improvements also in BUT, a measure of objective findings, and no patient population in which the efficacy of motugivatrep clearly cannot be expected was identified. Although the clinically meaningful minimum difference in the DEQS summary score in patients with dry eye disease is unknown, retrospective analyses using the cutoff values of the DEQS summary score for the diagnosis and severity classification of dry eye disease showed a trend towards consistent improvements in the 0.3% motugivatrep group. As to the long-term efficacy of motugivatrep, though the results were obtained from an uncontrolled, open-label study, there was no trend towards reduced efficacy of motugivatrep, regardless of whether motugivatrep was used alone or in combination with the currently approved drugs. Given the above findings, the efficacy of motugivatrep in Japanese patients with dry eye disease was demonstrated.

PMDA's conclusion:

Since Study 3-02 demonstrated the superiority of motugivatrep over placebo in the primary endpoint of the change from baseline in the DEQS summary score at Week 4, etc., the efficacy of motugivatrep in the treatment of dry eye disease was demonstrated.

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

7.R.3 Safety

The applicant's explanation about the safety of motugivatrep based on the results from Studies 2-01, 3-02, and 3-01:

Table 41 shows a summary of safety data and the incidence of the main adverse events in Studies 2-01, 3-02, and 3-01. The incidences of overall adverse events and adverse drug reactions tended to increase dose-dependently in Study 2-01. Those incidences tended to be higher in the 0.3% motugivatrep group than in the

placebo group in Study 3-02. Those incidences tended to be higher in subjects on combination therapy than in subjects on monotherapy in Study 3-01. While the incidence of adverse events leading to treatment discontinuation tended to increase dose-dependently in Study 2-01, there were no clear differences between the 0.3% motugivatrep and placebo groups in Study 3-02. No deaths were reported in any of the studies. In Study 3-01, serious adverse events occurred, but a causal relationship to motugivatrep was denied for all those events [see Sections 7.1 and 7.2]. Based on the above, the applicant considered that the observed dose-dependent increase in the risk of adverse events associated with motugivatrep was unlikely to lead to a serious outcome.

Table 41. Summary of safety data and the incidence of the main adverse events in clinical studies (Safety population)

Study ID	2-01				3-02		3-01			Patients treated with 0.3% motugivatrep ophthalmic suspension (Proposed product)[a] (N = 518)
Treatment group (N)	1% motugivatrep (N = 85)	0.3% motugivatrep (N = 87)	0.1% motugivatrep (N = 87)	Placebo (N = 85)	0.3% motugivatrep (N = 269)	Placebo (N = 267)	Total (N = 162)	Monotherapy (N = 105)	Combination therapy (N = 57)	
Total drug exposure (patient-years)	5.85	6.34	6.36	6.35	40.55	40.35	153.53	98.69	54.84	200.41
All adverse events	25 (29.4) 533.37	16 (18.4) 283.14	12 (13.8) 199.86	15 (17.6) 258.80	53 (19.7) 149.98	39 (14.6) 105.92	73 (45.1) 65.52	41 (39.0) 52.73	32 (56.1) 95.03	142 (27.4) 93.17
Death	0	0	0	0	0	0	0	0	0	0
Serious adverse events	0	0	0	0	0	0	3 (1.9) 1.97	2 (1.9) 2.05	1 (1.8) 1.84	3 (0.6) 1.51
Adverse events leading to treatment discontinuation	5 (5.9) 86.10	2 (2.3) 31.75	0	0	3 (1.1) 7.41	3 (1.1) 7.44	3 (1.9) 1.96	2 (1.9) 2.03	1 (1.8) 1.83	8 (1.5) 4.00
Adverse drug reactions	20 (23.5) 409.70	10 (11.5) 170.20	5 (5.7) 81.35	7 (8.2) 115.43	15 (5.6) 38.70	10 (3.7) 25.31	24 (14.8) 17.63	13 (12.4) 14.65	11 (19.3) 23.23	49 (9.5) 27.11
Abnormal temperature sensations[b]	14 (16.5) 265.77	5 (5.7) 82.30	1 (1.1) 15.74	0	13 (4.8) 33.07	0	17 (10.5) 11.90	9 (8.6) 9.74	8 (14.0) 15.84	35 (6.8) 18.59
Feeling cold	8 (9.4) 145.23	4 (4.6) 65.25	0	0	6 (2.2) 15.07	0	12 (7.4) 8.24	5 (4.8) 5.27	7 (12.3) 13.80	22 (4.2) 11.48
Cold feeling in eye[c]	0	0	0	0	3 (1.1) 7.48	0	1 (0.6) 0.66	1 (1.0) 1.02	0	4 (0.8) 2.01
Feeling hot	1 (1.2) 17.29	0	0	0	0	0	1 (0.6) 0.66	1 (1.0) 1.02	0	1 (0.2) 0.50
Warmness in eyes[c]	2 (2.4) 35.09	0	0	0	0	0	0	0	0	0
Thermohypoaesthesia	0	0	0	0	0	0	2 (1.2) 1.31	1 (1.0) 1.02	1 (1.8) 1.83	2 (0.4) 1.00
Increased body temperature	1 (1.2) 17.14	1 (1.1) 15.92	0	0	0	0	0	0	0	1 (0.2) 0.50
Pyrexia	0	0	1 (1.1) 15.74	0	5 (1.9) 12.39	0	3 (1.9) 1.96	2 (1.9) 2.04	1 (1.8) 1.83	8 (1.5) 4.01
Hot flush	1 (1.2) 17.10	0	0	0	0	0	0	0	0	0
Dysaesthesia	1 (1.2) 17.10	0	0	0	0	0	0	0	0	0
Local ocular adverse events[d]	11 (12.9) 208.82	6 (6.9) 99.34	7 (8.0) 114.40	12 (14.1) 202.07	25 (9.3) 66.22	18 (6.7) 46.58	30 (18.5) 22.51	16 (15.2) 18.06	14 (24.6) 31.32	61 (11.8) 34.45
Blurred vision	2 (2.4) 35.04	1 (1.1) 15.92	0	0	3 (1.1) 7.48	0	1 (0.6) 0.66	1 (1.0) 1.02	0	5 (1.0) 2.51
Systemic adverse events[e]	18 (21.2) 345.66	13 (14.9) 224.40	5 (5.7) 80.06	4 (4.7) 64.47	35 (13.0) 93.05	24 (9.0) 62.40	63 (38.9) 52.68	33 (31.4) 40.03	30 (52.6) 80.75	111 (21.4) 68.10

Upper row, n (%); Lower row, Exposure-adjusted incidence rate (Number of patients with event per 100 patient-years) (Exposure time was calculated as the time to the first event or duration of total drug exposure.)

MedDRA/J version 23.1 was used for Study 2-01, and MedDRA/J version 25.1 was used for Studies 3-02 and 3-01. As to LLTs to be counted, PTs and SOCs at higher levels of the hierarchy remained unchanged between the versions.

Unless otherwise specified, events are coded to the MedDRA PTs.

a) Data from the 0.3% motugivatrep group in Studies 2-01 and 3-02 and data from subjects treated with 0.3% motugivatrep ophthalmic suspension (the proposed product) in Study 3-01 were pooled.

b) PTs: feeling cold, feeling hot, thermohypoaesthesia, increased body temperature, pyrexia, hot flush, and dysaesthesia
LLTs: cold feeling in eye and warmness in eyes

c) LLT under the PT "abnormal sensation in eye"

d) SOC: Eye disorders

e) SOCs: Other than eye disorders

Taking account of the incidence of adverse events in clinical studies, the pharmacologic effects of motugivatrep, etc., PMDA focused its safety review on the following events.

7.R.3.1 Abnormal temperature sensations

The applicant's explanation:

Events related to temperature sensations were considered adverse drug reactions characteristic of antagonists of TRPV1, which plays a key role in temperature sensation (*J Neurobiol*. 2004; 61: 3-12, *Nature*. 1997; 389: 816-24, etc.). "Abnormal temperature sensations" were defined as MedDRA/J PTs "feeling cold," "feeling hot," "thermohypoaesthesia," "increased body temperature," "pyrexia," "hot flush," and "dysaesthesia" and LLTs "cold feeling in eye" and "warmness in eyes." Those events were counted in Studies 2-01, 3-02, and 3-01. Abnormal temperature sensations occurred only in subjects treated with motugivatrep, i.e., 50 of 690 subjects. The incidence of abnormal temperature sensations increased dose-dependently in Study 2-01. In Study 3-01, the incidence tended to be slightly higher in subjects on combination therapy than in subjects on monotherapy (Table 41).

○ Increased body temperature or pyrexia

Although multiple TRPV1 antagonists were previously developed as oral analgesics, their main side effects of increased body temperature, sometimes to 40°C, were reported, leading to development termination (*Pharmacol Rev*. 2009; 61: 225-7, *Journal of Biochemistry.* 2013; 85: 561-5, etc.). Increased body temperature was reported also with motugivatrep in Study 3260A1-1000-EU in which motugivatrep was orally administered [see Section 6.2.1.1]. However, increased body temperature associated with TRPV1 antagonists is plasma drug concentration-dependent, and TRPV1 antagonists are thought to alter core body temperature by inhibiting TRPV1 located in viscera (*Pharmacol Rev*. 2009; 61: 225-7, *J Neurosci*. 2007; 27: 7459-68). Thus, this event is unlikely to become a problem because eye drops are primarily designed for local action on the eye, and systemic exposure from eye drops is limited. Indeed, in ocular instillation studies, e.g., Study 2-01, there were no clinically relevant changes in body temperature, and the reported adverse events of increased body temperature or pyrexia were all mild in severity and non-serious with an outcome of "resolved." Pyrexia leading to treatment discontinuation occurred in 1 subject, but was considered an incidental event in daily life, and its causal relationship to motugivatrep was denied. Increased body temperature for which a causal relationship to motugivatrep could not be ruled out occurred in 1 subject, but resolved with continued treatment.

Based on the above, the applicant considers that there is no serious concern about increased body temperature or pyrexia associated with ocular instillation of motugivatrep.

○ Effect on heat pain perception threshold (HPPT)

In Study 3260A1-1000-EU in which motugivatrep was orally administered, a dose-dependent increase in HPPT, which was likely associated with TRPV1 inhibition, was observed [see Section 6.2.1.1]. Although the effect of ocular instillation of motugivatrep on HPPT was not investigated, as a relevant adverse event, thermohypoaesthesia was reported by 2 subjects in Study 3-01. The event reported by 1 subject was moderate in severity and non-serious, leading to treatment discontinuation. The event reported by the other subject

was mild in severity and non-serious, and treatment was continued. In both cases, the outcome was "resolved." A thermal burn, which is considered a risk associated with reduced thermal nociception, was not reported in these 2 subjects or in ocular instillation studies of motugivatrep.

○ Feeling cold and feeling hot

Feeling cold was the most common adverse event. Feeling cold including cold feeling in eye (counted as PT "abnormal sensation in eye") occurred in 33 of 690 subjects treated with motugivatrep, and a causal relationship to motugivatrep could not be ruled out for all those events. Only the event reported by 1 subject in Study 3-01 was moderate in severity, and other events were mild in severity. In 3 subjects in Study 2-01 (2 in the 1% motugivatrep group, 1 in the 0.3% motugivatrep group) and 1 subject in Study 3-01, feeling cold led to motugivatrep discontinuation, with an outcome of "resolved." Other study participants continued treatment with motugivatrep even after the occurrence of feeling cold, and the outcome was "resolved" for all those events.

Feeling hot including warmness in eyes (counted as PT "abnormal sensation in eye") occurred in 4 of 690 subjects treated with motugivatrep, and a causal relationship to motugivatrep could not be ruled out for all those events. All those events were mild in severity and did not lead to motugivatrep discontinuation, with an outcome of "resolved."

Based on the above, there should be no serious concerns about severe increased body temperature or pyrexia, or increased HPPT potentially leading to a serious outcome following ocular instillation of motugivatrep. On the other hand, the events of mild increased body temperature, feeling cold, etc., were observed following administration of motugivatrep. "Abnormal temperature sensations" will be listed as an important potential risk in the risk management plan, and its incidence, etc., in clinical practice, will be further investigated via post-marketing surveillance etc.

PMDA’s view:

In Study 2-01 etc. in which motugivatrep was instilled into the eyes at the concentrations up to 1%, clinically relevant increased body temperature did not occur [see Section 6.2], and no severe or serious adverse events of abnormal temperature sensations were reported. However, the minimum plasma concentration at which motugivatrep causes potentially clinically relevant increased body temperature or increased HPPT has not been determined, and adverse events of abnormal temperature sensations occurred only in subjects treated with motugivatrep in ocular instillation clinical studies of motugivatrep. Given these points, the risk of abnormal temperature sensations associated with motugivatrep eye drops cannot be ruled out. Especially in low-body-weight patients such as children, plasma concentrations of motugivatrep are likely to be increased as compared with adults. Thus, prior to the use of motugivatrep, its risks and benefits should be weighed carefully. With respect to the risk of thermal burns including low temperature heat burns associated with increased HPPT, prior to the use of motugivatrep, it is necessary to ensure that the patient understands that a thermal burn including low temperature heat burn is caused by contact with a heat source and is able to avoid a heat source even if abnormal temperature sensations occur. The IMPORTANT PRECAUTIONS section of

the package insert should advise these points. It is also necessary to investigate the incidence of abnormal temperature sensations etc. via post-marketing investigation etc.

7.R.3.2 Shortened QT interval

The applicant's explanation:

In Study 3260A1-1000-EU in which motugivatrep was administered orally, increased body temperature, and shortened QT interval, which was considered associated with increased body temperature, were observed [see Section 6.2.1.1]. On the other hand, collected vital signs data showed no clinically relevant changes in body temperature, and ECGs revealed no effects on QT interval in Study 2-01 [see Section 6.2.2.2]. In ocular instillation studies, as an adverse event possibly related to shortened QT interval or arrhythmia, dizziness for which a causal relationship to motugivatrep could not be ruled out occurred in 1 subject in the 0.3% motugivatrep group of Study 2-01, but no information suggesting its relationship with arrhythmia was reported.

Drug-induced short QT syndrome is a rarely reported condition, and few fatal arrhythmias and sudden cardiac death cases associated with drug-induced short QT have been reported. No clinical issues have been identified at present (*Rev Port Cardiol*. 2018; 37: 435-46).

Based on the above, there is little concern about proarrhythmia in the clinical use of motugivatrep.

PMDA's view:

Given the discussion on increased body temperature in Section 7.R.3.1, the possibility that ocular instillation of motugivatrep also causes shortened QT interval cannot be ruled out. Although it is not clear whether shortened QT interval caused by motugivatrep can lead to arrhythmia etc., based on the currently available information, the applicant's explanation that there is little concern about proarrhythmia associated with motugivatrep is understandable to some extent. Although a relevant precautionary statement in the package insert is unnecessary at present, it is necessary to collect post-marketing information through routine pharmacovigilance practices and continuously review the need for additional pharmacovigilance activities etc., based on the obtained information.

7.R.3.3 Blurred vision

The applicant's explanation:

In Studies 2-01, 3-02, and 3-01, mild blurred vision occurred only in subjects treated with motugivatrep (7 of 690 subjects), and a causal relationship to motugivatrep could not be ruled out for all those events. Moderate or severe blurred vision, serious blurred vision, or blurred vision leading to an accident or the patient's injury was not reported. Taking also into account that motugivatrep is a white ophthalmic suspension, the IMPORTANT PRECAUTIONS section of the package insert will advise that caution should be exercised when operating machinery, driving a car, etc.

PMDA's view:
Given that blurred vision occurred only in subjects treated with motugivatrep, and that motugivatrep is an ophthalmic suspension, as explained by the applicant, the package insert should advise that caution should be exercised when operating machinery, driving a car, etc. following administration of motugivatrep. It is necessary to collect post-marketing information through routine pharmacovigilance practices and continuously review the need for additional pharmacovigilance activities etc., based on the obtained information.

Based on the considerations in Section 7.R.3, no serious safety concerns about ocular instillation of motugivatrep in patients with dry eye disease have been suggested, and the risk of motugivatrep can be managed by appropriately conducting routine risk minimization activities.

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

7.R.4 Pediatric use of motugivatrep

The applicant's explanation about the pediatric use of motugivatrep:
All of ocular instillation clinical studies of motugivatrep enrolled adult patients with dry eye disease. A certain number of pediatric patients with dry eye disease also exist in clinical practice.

There should be no differences in the etiology, pathology, diagnosis, and treatment of dry eye disease between adults and children (*Ocul Surf*. 2024; 31: 11-20). The target of motugivatrep, TRPV1, is expressed in the human trigeminal ganglion at prenatal and adult stages of life, and its distribution does not change substantially with growth and aging (*J Anat*. 2016; 229: 755-67). Thus, the efficacy of motugivatrep is expected also in children.

For the following reasons, motugivatrep should have acceptable safety also in pediatric patients with dry eye disease, though such patients were not enrolled in clinical studies.
• As explained in Section 5.R.2, in TRPV1 knockout mice, no effects on survival have been observed, and no clear effects on the development of systemic tissues/organs have been reported. There is also no report suggesting that inhibition of TRPV1-mediated signaling affects growth or organ development in humans.
• Although the pharmacokinetics of motugivatrep were not assessed in children, higher motugivatrep exposure is anticipated in children compared with adults. Especially in young and low-body-weight children, the possibility of reaching motugivatrep exposure levels that result in abnormal temperature sensations, such as increased body temperature, which is a risk factor for sudden infant death syndrome, and increased HPPT, which can cause a thermal burn, cannot be ruled out. However, such events can be managed as long as the physician provides appropriate guidance, and parents etc. appropriately supervise the child. Other than these events, there is no serious safety concern in children.

However, as there is no clinical experience with motugivatrep in children at present, motugivatrep should be administered with caution in children. "Pediatric safety information" will be listed as important missing information in the risk management plan, and information on the safety etc. of motugivatrep in clinical practice

will be collected via post-marketing surveillance etc. to determine the safety profile etc. of motugivatrep in children.

PMDA’s view:
The applicant's explanation that the efficacy of motugivatrep is expected also in pediatric patients with dry eye disease is understandable to some extent, and the existence of pediatric patients with dry eye disease for whom motugivatrep is a treatment option, is not denied. Meanwhile, since children are generally lighter than adults, and plasma concentrations of motugivatrep are likely to be increased in children compared with adults, children are at an increased risk of abnormal temperature sensations etc., as discussed in Section 7.R.3.1. Thus, the package insert should include precautionary statements as shown in Section 7.R.3.1, and "Pediatric Use" in the PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS section of the package insert should advise that parents etc. should be instructed to fully understand the risk of abnormal temperature sensations, carefully check the child's body temperature, and take measures to keep the child away from a heat source that can cause a thermal burn. It is also necessary to determine the safety profile of motugivatrep in children via post-marketing surveillance etc., and the obtained information should be provided to healthcare professionals in clinical practice, as appropriate.

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

7.R.5 Clinical positioning and indication

PMDA’s view:
Based on the submitted data and the considerations in Sections 7.R.2 and 7.R.3, the efficacy and safety of motugivatrep in the treatment of dry eye disease were demonstrated. Since motugivatrep normalizes corneal sensation through a mechanism different from that of currently approved drugs and is administered with an expectation of mainly improving subjective symptoms of dry eye, it can be positioned as a treatment option for dry eye disease. The proposed indication of "dry eye disease" is acceptable.

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

7.R.6 Dosage and administration

PMDA's conclusion:
Based on the submitted data and the considerations in Sections 7.R.2, 7.R.3, and 7.R.4, using 0.3% motugivatrep ophthalmic suspension (the proposed product) and the dosing regimen selected for Study 3-02, the efficacy and acceptable safety of motugivatrep were demonstrated in patients with dry eye disease, and therefore the proposed dosage and administration statement of "The usual dose is one drop instilled into the eye 4 times daily." is acceptable.

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

7.R.7 Post-marketing investigations

The applicant's explanation:

Adverse drug reactions reported in clinical studies were all non-serious, and there were no serious concerns about the safety of motugivatrep. However, it is important to investigate the incidence of abnormal temperature sensations (as explained in Section 7.R.3.1) and determine the safety profile of motugivatrep in pediatric patients (as explained in Section 7.R.4). At present, no TRPV1 antagonists including motugivatrep have been approved in Japan or overseas, and its safety information is limited. The risk of adverse events may be increased when motugivatrep is used in combination with other therapeutic agents for dry eye. Treatment of dry eye disease is likely to be continued for long periods, i.e., >1 year. Given these points, a post-marketing use-results survey with an observation period of up to 2 years in adult and pediatric patients with dry eye disease will be conducted to collect information on the long-term safety of motugivatrep in clinical practice.

PMDA's conclusion:

As discussed in Sections 7.R.3 and 7.R.4, based on the information obtained to date, motugivatrep should have acceptable safety. However, it is necessary to collect information on the long-term safety of motugivatrep in pediatric patients, in clinical practice via post-marketing surveillance etc. and determine its safety profile. Then, the obtained information should be provided to healthcare professionals in clinical practice as appropriate.

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 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 5.3.5.1-2 and 5.3.5.2-1) 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 motugivatrep has efficacy in the treatment of dry eye disease, and that motugivatrep has acceptable safety in view of its benefits. The drug product is not classified as a poisonous drug or a powerful drug, and its drug substance is classified as a powerful drug. Motugivatrep is clinically meaningful because it offers a new treatment option for patients with dry eye disease.

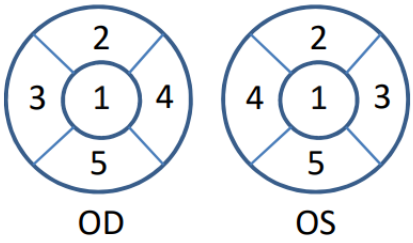
PMDA has concluded that motugivatrep may be approved if motugivatrep is not considered to have any particular problems based on comments from the Expert Discussion.

10. Others

The definition of the study eye in each clinical study is shown below.

Study ID	Definition
2-01	The study eye was defined as the eye meeting the key inclusion criteria 3.b. presented in Table 29. If both eyes met the criteria, the eye with the greater total CFS score of all zones at baseline was designated as the study eye. If the total CFS scores of all zones were equal for both eyes, the eye with the greater central CFS score at baseline was designated as the study eye. If the central CFS scores were equal for both eyes, the right eye was designated as the study eye.
3-02 3-01	The study eye was defined as the eye with the greater total CFS score of all zones at baseline. If the total CFS scores of all zones were equal for both eyes, the right eye was designated as the study eye.

The definitions of endpoints etc. in clinical studies are shown below.

Endpoint	Definition
DEQS summary score	The DEQS questionnaire consists of 6 items [eye symptoms] and 9 items [the impact on daily life]. Patients assess their frequency and degree over the past 7 days, and each question is scored on a scale of 0 (never), 1 (hardly bothered me/not very bothersome), 2 (bothered me a little/a little bothersome), 3 (bothered me/bothersome), and 4 (bothered me very much/very bothersome). The summary score for DEQS is calculated using the following formula (a maximum summary score of 100). DEQS summary score = (the sum of the scores)/the number of questions answered × 25 Calculate if ≥10 items are answered. [Eye symptoms] 1) Grittiness (sensation of something in your eye) 2) Dry eyes 3) Sore eyes 4) Tired eyes 5) Heavy eyelids 6) Red eyes [Impact on daily life] 7) Difficulty keeping my eyes open 8) Vision became blurry when engaging in activities that required sustained visual attention 9) Light was too bright 10) Eye symptoms worsened when reading newspapers, magazines or books 11) Eye symptoms worsened when watching TV or when using a computer/mobile phone 12) Eye symptoms reduced my ability to concentrate 13) Eye symptoms interfered with work, housework or studying 14) Tended to avoid leaving the house because of eye symptoms 15) Felt down due to eye symptoms
BUT	A fluorescein strip wet with one drop of saline etc. is applied to the conjunctival sac, and study participants are instructed to blink several times to determine the time it takes for tear breakup (seconds). The test is repeated until 3 values are obtained that differ by <3 seconds. The 3 measurements are averaged for BUT.
Corneal fluorescein staining score	Fluorescein staining dots on the cornea of each eye is counted and graded in 5 distinct zones (central, superior, temporal, nasal, and inferior) (See the figure below). The scores of all zones are summed to give a total score for all zones (a maximum total score of 25). [Grading based on the number of fluorescein staining dots on the cornea] Graded on a scale of 0 (no dots), 1 (1-5 dots), 2 (6-15 dots), 3 (16-30 dots), and 4 (≥31 dots) [Point is added to the score for the presence of area of confluence] +1 point (for the presence of 1 area of confluence), +2 points for scores between 1 to 3 (if there are ≥2 areas of confluence), +1 for a score of 4 (if there are ≥2 areas of confluence)  OD = Oculus Dexter (right eye), OS = Oculus Sinister (Left eye) 1: central, 2: superior, 3: temporal, 4:nasal, 5: inferior
Schirmer's test I	Tear secretion for 5 minutes under spontaneous blinking without topical anesthesia is measured in millimeters (mm), using a Schirmer's test strip with markings for measurement.
DEQ-5 total score	Patients answer the questions (the frequency and intensity of eye discomfort, the frequency and intensity of eye dryness, the frequency of watery eyes [your eyes look or feel excessively watery]). Patients rate the frequency during a typical day in the past month on a scale of 0 (never), 1 (rarely), 2 (sometimes), 3 (frequently), and 4 (constantly) and rate the intensity at the end of the day (within 2 hours of going to bed) on a scale of 0 (never have it) and 1 (not at all intense) to 5 (very intense). Total DEQ-5 score is the sum of scores for frequency and intensity of dryness and discomfort plus frequency of watery eyes (a maximum total score of 22).

Review Report (2)

November 18, 2025

Product Submitted for Approval

Brand Name	Avarept Ophthalmic Suspension 0.3%
Non-proprietary Name	Motugivatrep
Applicant	Senju Pharmaceutical Co., Ltd.
Date of Application	January 17, 2025

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, safety, pediatric use, clinical positioning, indication, dosage and administration, post-marketing investigations, and risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusions concerning the efficacy, safety, pediatric use, clinical positioning, indication, dosage and administration, and post-marketing investigations of motugivatrep presented in the Review Report (1) and made the following comments.

- Given that dry eye is a multifactorial disease, and that motugivatrep has a different mechanism of action from the currently approved drugs, continued investigation of the long-term efficacy of motugivatrep and whether the efficacy of motugivatrep differs according to the subtype of dry eye or the presence or absence of a corneal epithelial disorder is recommended.
- Although motugivatrep is an eye drop, as TRPV1 is expressed in sensory neurons throughout the body, it is necessary to continue to monitor whether long-term treatment with motugivatrep may cause systemic adverse drug reactions.
- It is necessary to continue to monitor whether abnormal temperature sensations associated with motugivatrep may pose a concern in children as well as in elderly patients and those with decreased cognitive function.

Based on the considerations in Section "7.R.7 Post-marketing investigations" in the Review Report (1) and the comments from the Expert Discussion, PMDA has concluded that the risk management plan (draft)

for motugivatrep should include the safety specification presented in Table 42, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 43. PMDA requested the applicant to present outlines of specified use-result surveys (draft).

Table 42. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
None	· Abnormal temperature sensations	· Pediatric safety information
Efficacy specification		
None		

Table 43. 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 · Specified use-results survey (Long-term treatment) · Specified use-results survey (Children)	None	· Disseminate data gathered during early post-marketing phase vigilance

The applicant explained that as shown in Table 44 and Table 45, specified use-results surveys will be conducted to investigate the long-term safety of motugivatrep in pediatric patients in clinical practice.

Table 44. Outline of specified use-results survey (Long-term treatment) (draft)

Objective	To collect and assess information on the long-term safety of motugivatrep in clinical practice.
Survey method	Central registry system
Population	Patients with dry eye disease (All ages)
Observation period	2 years
Planned sample size	866 patients
Main survey items	• Safety specification: abnormal temperature sensations • Patient characteristics (body weight, dry eye condition [corneal staining score, subtype], complication/underlying disease, medical history, etc.) • Use of motugivatrep • Prior treatments, concomitant medications, concomitant therapies • Adverse events • Clinical symptoms and signs of dry eye

Table 45. Outline of specified use-results survey (Children) (draft)

Objective	To collect and assess information on the safety of motugivatrep in pediatric patients with dry eye disease.
Survey method	Central registry system
Population	Patients with dry eye disease aged <15 years
Observation period	2 years
Planned sample size	1,080 patients
Main survey items	• Safety specification: abnormal temperature sensations, pediatric safety information • Patient characteristics (body weight, dry eye condition [corneal staining score, subtype], complication/underlying disease, medical history, etc.) • Use of motugivatrep • Prior treatments, concomitant medications, concomitant therapies • Adverse events • Clinical symptoms and signs of dry eye

PMDA accepted these outlines (draft) and considers that the collected information should be provided to healthcare providers etc. appropriately and promptly.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition. As the product is a drug with a new active ingredient, the re-examination period is 8 years.

Indication

Dry eye disease

Dosage and Administration

The usual dose is one drop instilled into the eye 4 times daily.

Approval Condition

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

Appendix

List of Abbreviations

AUC	Area under the concentration-time curve
AUC_{last}	Area under the concentration-time curve up to last observed concentration
BCRP	Breast cancer resistance protein
BSEP	Bile salt export pump
BUT	Tear break up time
C_{max}	Maximum concentration
C_{trough}	Trough concentration
Caco-2 cells	Human colorectal adenocarcinoma cell
CCL	CC-chemokine ligand
CD	Cluster of differentiation
CHO cells	Chinese hamster ovary cells
CI	Confidence interval
CL	Total body clearance
Clinical practice guidelines	Dry Eye Clinical Practice Guidelines: *Journal of Japanese Ophthalmological Society*. 2019; 123: 489-592
COSY	Correlation spectroscopy
CPP	Critical process parameter
CQA	Critical quality attribute
CYP	Cytochrome P450
DEQ-5	5-Item dry eye questionnaire
DEQS	Dry eye-related quality of life score questionnaire
ELISA	Enzyme-linked immunosorbent assay
F	Bioavailability
HEK293 cells	Human embryonic kidney cell line 293
hERG	Human *ether-a-go-go* related gene
HMBC	Heteronuclear multiple bond correlation
HPLC	High performance liquid chromatography
HPLC-RAD	High performance liquid chromatography-radioactivity detection
HPPT	Heat pain perception threshold
HSQC	Heteronuclear single quantum coherence spectroscopy
$5\text{-}HT_{2A}$	5-Hydroxytryptamine receptor 2A
$5\text{-}HT_{2B}$	5-Hydroxytryptamine receptor 2B
IC_{50}	Concentration that results in 50% inhibition
ICH	International council for harmonisation of technical requirements of pharmaceuticals for human use
ICH M12 guideline	"Guideline on drug interaction studies" (PSB/PED Notification No. 1127-2 dated November 27, 2024)
ICH Q1E guideline	"Guideline on Evaluation of Stability Data" (PMSB/ELD Notification No. 0603004 dated June 3, 2003)
ICH Q3A guideline	"Revision of the Guideline on Impurities in New Drug Substances" (PMSB/ELD Notification No.1216001 dated December 16, 2002)
ICH S11 guideline	"Guideline on Nonclinical Safety Testing in Support of Development of Paediatric Pharmaceuticals" (PSEHB/PED Notification No. 0330-1 dated March 30, 2021)
IFNγ	Interferon gamma
IPL	Intense pulsed light
IR	Infrared absorption spectroscopy
JW	Japanese white
LC/MS/MS	Liquid chromatography-tandem mass spectrometry

MATE	Multidrug and toxin extrusion
MedDRA/J	Medical dictionary for regulatory activities Japanese version
MMRM	Mixed-effects models for repeated measures
motugivatrep	Motugivatrep
NMR	Nuclear magnetic resonance spectroscopy
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
P_{app}	Apparent permeability coefficient
P-gp	P-glycoprotein
PMDA	Pharmaceuticals and Medical Devices Agency
QTcF	Corrected QT interval by Fridericia
QTcQ	Corrected QT interval by animal-specific formula
ROESY	Rotating frame nuclear Overhauser effect spectroscopy
SD	Sprague-dawley
SPK score	Superficial punctate keratopathy score
$t_{1/2}$	Elimination half-life
t_{max}	Time to reach maximum concentration
TCSA	3,3',4',5-Tetrachlorosalicylanilide
The product	Avarept Ophthalmic Suspension 0.3%
TRPA1	Transient receptor potential cation channel subfamily A member 1
TRPM8	Transient receptor potential cation channel subfamily M member 8
TRPV1	Transient receptor potential cation channel subfamily V member 1
TRPV3	Transient receptor potential cation channel subfamily V member 3
TRPV4	Transient receptor potential cation channel subfamily V member 4
UGT	Uridine diphosphate glucuronosyl transferase
UV/VIS	Ultraviolet-visible spectroscopy
V_d	Volume of distribution
VAS	Visual analog scale

※Clinical study ID numbers are abbreviated, e.g., Study SJP-0132/1-01 is Study 1-01.