May 24, 2021
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Human cellular/tissue-based products, 2. Human somatic stem cell-processed products
Non-proprietary Name	Human (autologous) oral mucosa-derived epithelial cell sheet
Brand Name	Ocural
Applicant	Japan Tissue Engineering Co., Ltd.
Date of Application	September 14, 2020 (Application for marketing approval)

Results of Deliberation

In its meeting held on May 24, 2021, the Committee on Regenerative Medical Products and Biotechnology made the following decision and concluded that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product may be approved. The approval is not classified as a conditional or time-limited approval. The re-examination period is 10 years.

The following approval conditions must be satisfied.

Approval Conditions

1. The applicant is required to take necessary measures such as dissemination of the guideline for proper use prepared in cooperation with relevant academic societies and conducting seminars to ensure that physicians with adequate knowledge and experience in limbal stem cell deficiency acquire full skills of the product usage and knowledge in complications associated with the procedures and that the physicians use the product in compliance with the “Indication or Performance” as well as “Dosage and Administration or Method of Use” at medical institutions with an established system for treatment of limbal stem cell deficiency.
2. Since only a limited number of patients participated in clinical studies of the product, the applicant is required to conduct a use-results survey covering all patients treated with the product in principle until the end of the re-examination period in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

3. The applicant is required to take necessary measures such as storage of reserve samples of the final product and retention of use records for 30 years to ensure appropriate handling in view of a risk of xenogeneic transplantation related to mouse embryonic 3T3-J2 cells used as feeder cells in the manufacturing process of the product.

Review Report

April 27, 2021
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Ocural
Classification	Human cellular/tissue-based products, 2. Human somatic stem cell-processed products
Non-proprietary Name	Human (autologous) oral mucosa-derived epithelial cell sheet
Applicant	Japan Tissue Engineering Co., Ltd.
Date of Application	September 14, 2020

Shape, Structure, Active Ingredients, Quantities, or Definition

The product is a regenerative medical product consisting of a cultured oral mucosal epithelium package including an oral mucosal epithelial cell sheet, the primary component, and a tissue transport set, the secondary component. The primary component is a cultured oral mucosal epithelium package produced from oral mucosal epithelial cells, which are derived from the patient's own oral mucosal tissue and cultured in sheet form. The secondary component is the tissue transport set consisting of tissue transport tubes for transport of the oral mucosal tissue collected at a medical institution and blood storage tubes for transport of blood for storage.

Application Classification	(1-1) New regenerative medical products
Items Warranting Special Mention	Orphan regenerative medical product (Orphan Regenerative Medical Product Designation No. 15 of 2020 [*R2 sai*]; PSEHB/MDED Notification No. 0319-2 dated March 19, 2020, issued by the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of Cellular and Tissue-based Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has a certain level of efficacy in the treatment of limbal stem cell deficiency, 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 or performance and dosage and administration or method of use shown below, with the following conditions.

Indications or Performance

Limbal stem cell deficiency

Dosage and Administration or Method of Use

Operations in manufacture of oral mucosal epithelial cell sheet

1. An area in the patient's intraoral buccal mucosal part is confirmed to be free from inflammation, infection, and scar, and approximately a 10 × 5 mm piece of the oral mucosal tissue is collected. The collected oral mucosal tissue is placed in a tissue transport tube and sent to the manufacturer.
2. Blood is collected in accordance with a conventional procedure. The collected blood is placed in a blood storage tube and sent to the manufacturer. This blood specimen is used as the reserve sample.

Operations in transplantation of oral mucosal epithelial cell sheet

The oral mucosal epithelial cell sheet is detached with a ring-shaped culture disk from the oral mucosal epithelium culture dish. Conjunctival scar tissue is removed from the eye surface of the patient wherever possible, and the oral mucosal epithelial cell sheet is transplanted onto the eye surface including the corneal limbus. The rim of the oral mucosal epithelial cell sheet is sutured where necessary. After the transplantation, the therapeutic contact lens is applied and tarsorrhaphy is performed where necessary.

Approval Conditions

1. The applicant is required to take necessary measures such as dissemination of the guideline for proper use prepared in cooperation with relevant academic societies and conducting seminars to ensure that physicians with adequate knowledge and experience in limbal stem cell deficiency acquire full skills of the product usage and knowledge in complications associated with the procedures and that the physicians use the product in compliance with the "Indication or Performance" as well as "Dosage and Administration or Method of Use" at medical institutions with an established system for treatment of limbal stem cell deficiency.
2. Since only a limited number of patients participated in clinical studies of the product, the applicant is required to conduct a use-results survey covering all patients treated with the product in principle until the end of the re-examination period in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.
3. The applicant is required to take necessary measures such as storage of reserve samples of the final product and retention of use records for 30 years to ensure appropriate handling in view of a risk of xenogeneic transplantation related to mouse embryonic 3T3-J2 cells used as feeder cells in the manufacturing process of the product.

Attachment

Review Report (1)

March 17, 2021

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

Product Submitted for Approval

Brand Name	Ocural
Classification	Human cellular/tissue-based products, 2. Human somatic stem cell-processed products
Non-proprietary Name	Human (autologous) oral mucosa-derived epithelial cell sheet
Applicant	Japan Tissue Engineering Co., Ltd.
Date of Application	September 14, 2020

Shape, Structure, Active Ingredients, Quantities, or Definition

The product is a regenerative medical product consisting of a cultured oral mucosal epithelium package including an oral mucosal epithelial cell sheet, the primary component, and a tissue transport set, the secondary component. The primary component is a cultured oral mucosal epithelium package produced from oral mucosal epithelial cells, which are derived from the patient's own oral mucosal tissue and cultured in sheet form. The secondary component is the tissue transport set consisting of tissue transport tubes for transport of the oral mucosal tissue collected at a medical institution and blood storage tubes for transport of blood for storage.

Proposed Indication or Performance

Limbal stem cell deficiency

Proposed Dosage and Administration or Method of Use

Operations in manufacture of oral mucosal epithelial cell sheet

1. An area in the patient's oral cavity is confirmed to be free from inflammation, infection, and scar, and approximately a 10 × 5 mm piece of the oral mucosal tissue is collected. The collected oral mucosal tissue is placed in a tissue transport tube and sent to the manufacturer.
2. Blood is collected in accordance with a conventional procedure. The collected blood is placed in a blood storage tube and sent to the manufacturer. This blood specimen is used as the reserve sample.

Operations in transplantation of oral mucosal epithelial cell sheet

The oral mucosal epithelial cell sheet is detached with a ring-shaped culture disk from the oral mucosal epithelium culture dish. Conjunctival scar tissue is removed from the eye surface of the patient wherever possible, and the oral mucosal epithelial cell sheet is transplanted onto the eye surface including the

corneal limbus. The rim of the oral mucosal epithelial cell sheet is sutured where necessary. After the transplantation, the therapeutic contact lens is applied and tarsorrhaphy is performed where necessary.

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List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed product

Ocural is a human somatic stem cell-processed product manufactured from oral mucosal epithelial cells, which are derived from the patient's own oral mucosal tissue and cultured in sheet form. Ocural is intended for use in repair of corneal epithelium defects and, more specifically, to be transplanted onto the eye surface of the patient with limbal stem cell deficiency (LSCD) with the expectation that the oral mucosal epithelial cells will be engrafted and epithelized. It is to be handled as a combination product consisting of the following primary component and secondary components:

Primary component: Cultured oral mucosal epithelium package containing oral mucosal epithelial cell sheet produced from oral mucosal epithelial cells, which are derived from the patient's own oral mucosal tissue and cultured in sheet form

Secondary component: Tissue transport set consisting of tissue transport tubes for transport of the oral mucosal tissue collected at a medical institution and blood storage tubes for transport of blood for storage

Ocural is designated as the orphan regenerative medical product with the intended indication or performance of "limbal stem cell deficiency" dated March 19, 2020 (Orphan Regenerative Medical Product Designation No. 15 of 2020 [*R2 sai*]).

1.2 Development history etc.

LSCD is a disease group characterized by a congenital or acquired deficiency or loss of corneal epithelial stem cells in the corneal limbus at the border between the cornea and conjunctiva, which would allow conjunctival epithelium to migrate onto the cornea and cover the surface, resulting in corneal opacity and reduced vision. LSCD can be caused by extrinsic factors such as thermal and chemical injuries as well as intrinsic factors such as Stevens-Johnson syndrome (SJS), ocular cicatricial pemphigoid (OCP), and aniridia, a developmental defect.

The fundamental treatment of LSCD is corneal epithelium reconstruction by supplying corneal epithelial stem cells. Although autologous and allogeneic corneal limbal transplantation procedures as well as a human (autologous) corneal limbus-derived corneal epithelial cell sheet transplantation procedure approved for marketing in March 2020 are already available for the treatment, these procedures have the following issues, and thus a new option for treatment of LSCD is needed. Amniotic membrane transplantation is occasionally performed on an area with the conjunctival scar tissue removed from the eye surface, but it is positioned as an adjunctive procedure performed with the corneal limbal transplantation because the recipient eye must have corneal epithelial stem cells left for corneal epithelium reconstruction.

- Autologous corneal limbal transplantation involves a highly invasive procedure because the corneal limbal tissue has to be extensively collected from the patient's eye as a graft and is not indicated for bilateral LSCD.
- Allogeneic corneal limbal transplantation requires post-transplant continuous treatment with immunosuppressants and involves a risk of rejection leading to graft failure, and the lack of donors has limited the operation.

- Human (autologous) corneal limbus-derived corneal epithelial cell sheet transplantation requires collection of a corneal limbal tissue for use as a material from the patient's own eye, of which the amount is smaller than that for autologous corneal limbal transplantation, and thus it is not indicated for patients with no corneal limbus tissue left for the collection.

Ocural is not a product that supplies corneal epithelial stem cells but a cell sheet consisting of oral mucosal epithelial cells containing oral mucosal epithelial stem cells and is expected to be a new option for treatment of LSCD with the following characteristics and advantages:

- Oral mucosal epithelial cells form non-keratinized stratified squamous epithelium as corneal epithelial cells do.
- Ocural does not require collection of corneal limbal tissue from the patient's own eye and can be indicated for bilateral LSCD irrespective of corneal limbal tissue left for the collection.
- Ocural is manufactured from the patient's own tissue and thus unlikely to cause rejection.

Nishida of the Department of Neural and Sensory Organ Surgery (Ophthalmology), Osaka University Graduate School of Medicine, et al. conducted a Japanese clinical study of Ocural in patients with LSCD (COMET01 study), and the marketing application for Ocural has been submitted, using data from the COMET01 study as the pivotal study results. The COMET01 study was initiated in August 2015 as an investigator-initiated trial under the Practical Research Project for Rare/Intractable Diseases of Ministry of Health, Labour and Welfare (MHLW) and Japan Agency for Medical Research and Development.

As of February 2021, Ocural has not been approved or marketed in any country or region.

2. Data Relating to Manufacturing Process and Specifications and Outline of the Review Conducted by PMDA

The primary component of Ocural is the cultured oral mucosal epithelium package containing oral mucosal epithelial cell sheet produced from oral mucosal epithelial cells, for which oral mucosal epithelial cells derived from the patient's own oral mucosal tissue were co-cultured with mouse embryonic cells (3T3-J2 cells) as feeder cells and proliferated, and the obtained cells were cultured in sheet form. The secondary component of Ocural is the tissue transport set consisting of tissue transport tubes and blood storage tubes used for transport of the collected oral mucosal tissue and blood for storage to the manufacturing site.

2.1 Manufacturing process

2.1.1 Manufacturing process

The manufacturing process of Ocural consists of manufacture of the cultured oral mucosal epithelium package, the primary component, and manufacture of the secondary component.

2.1.1.1 Manufacturing process of primary component

The manufacturing process of the cultured oral mucosal epithelium package, the primary component, consists of manufacture of feeder cells and that of the oral mucosal epithelial cell sheet.

2.1.1.1.1 Preparation and control of 3T3-J2 cells

As feeder cells, mouse embryonic 3T3-J2 cells are used. Using 3T3-J2 cells provided by H. Green in 20[redacted] (clone isolate from mouse total fetus established in 1963 by H. Green) as the source, the master cell bank (MCB), master working cell bank (MWCB), and working cell bank (WCB) were prepared.

Characterization and a purity test were performed on the MCB, WCB, and cells cultured beyond the upper limit of the passage generations or cells at the limit of *in vitro* cell age (CAL) from the step of MCB thawing and seeding in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q5A (R1) guideline ("Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" [PMSB/ELD Notification No. 329 dated February 22, 2000]) and ICH Q5D guideline ("Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products" [PMSB/ELD Notification No. 873 dated July 14, 2000]). Table 1 shows tests performed for adventitious agents. Results from these tests demonstrated the genetic stability during the manufacturing period and neither viral nor non-viral adventitious agents were detected within the extent of the test items performed.

MCB, MWCB, and WCB are stored at −[redacted]°C or lower. Although new MCB will be not prepared, new MWCB and WCB will be prepared where necessary.

Table 1. Tests for adventitious agents

Sterility test
Mycoplasma test
Extended S^+L^- assay
Extended XC plaque assay
Electron microscopy
Reverse transcriptase activity test
In vitro tests (MRC-5 cells, Vero cells, and NIH-3T3 cells)
In vivo tests (suckling mice, post-weaning mice, guinea pigs, and embryonated eggs)
Mouse antibody production test
Bovine aberrant virus test (bovine testis cells, bovine turbinate cells, and Vero cells)

2.1.1.1.2 Manufacturing process of feeder cells

The manufacturing process of feeder cells consists of processes for [redacted], [redacted], and [redacted].

A critical step includes [redacted].

2.1.1.1.3 Manufacturing process of oral mucosal epithelial cell sheet

The manufacturing process of oral mucosal epithelial cell sheet consists of processes for receipt of oral mucosal tissue, [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], packaging and labeling, inspection, and packing and shipment.

Critical steps identified include processes for [redacted].

2.1.1.2 Manufacturing process of tissue transport set

The manufacturing process of a tissue transport set consists of processes for [redacted] ([redacted]), packaging and labeling of the tissue transport set, and packing and shipping of the tissue transport set.

2.1.2 In-process control tests

Table 2 shows in-process control tests in the manufacturing process of feeder cells.

Table 2. In-process control tests in manufacturing process of feeder cells

Process	Test item
[redacted]	[redacted]
[redacted]	[redacted]
	[redacted]
[redacted]	[redacted]

Table 3 shows in-process control tests in the manufacturing process of the cultured oral mucosal epithelium package, the primary component.

Table 3. In-process control tests in manufacturing process of cultured oral mucosal epithelium package

Process	Test item
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table 4 shows in-process control tests in the manufacturing process of the tissue transport set, the secondary component.

Table 4. In-process control tests in manufacturing process of tissue transport set

Process	Test item
[redacted]	[redacted]
	Sterility test

2.2 Safety evaluation of adventitious agents

2.2.1 Oral mucosal tissue

The oral mucosal tissue used as a raw material of Ocural conforms to the Standards for Biological Ingredients (MHLW Ministerial Announcement No. 210, 2003).

2.2.2 Biological ingredients other than oral mucosal tissue

All of the 3T3-J2 cells, porcine trypsin, fetal bovine serum, calf serum, and bovine serum used in the manufacturing process of Ocural conform to the Standards for Biological Ingredients (MHLW Ministerial Announcement No. 210, 2003).

2.3 Manufacturing process development (comparability)

Main changes from the manufacturing process of the cultured oral mucosal epithelium package and tissue transport tube at the COMET01 study (process for clinical study) to the proposed commercial process are as shown below:

- Addition of [redacted] and [redacted], used as [redacted] and [redacted] in [redacted]
- Change of [redacted] in the final product
- Addition of [redacted] to [redacted]

For either change, comparability evaluation on quality attributes was performed and demonstrated comparability between the pre- and post-change products.

2.4 Characterization

Characterization was performed on the cultured oral mucosal epithelium package as shown in Table 5.

Table 5. Characterization items

Cell type	[redacted] immunostaining*1 ([redacted])
Immunohistological analysis	Immunostaining*2 ([redacted])
Viable cell density, cell viability	[redacted] ([redacted])

*1 [redacted]

*2 [redacted]

2.5 Evaluation of manufacturing process

2.5.1 Removal of process-related impurities

Process-related impurities include bovine serum, feeder cells, antibiotics (benzylpenicillin potassium, streptomycin sulfate, amphotericin B, and kanamycin sulfate), Impurity A, and Impurity B.

Benzylpenicillin potassium, streptomycin sulfate, amphotericin B, kanamycin sulfate, Impurity A, and Impurity B were considered unlikely to raise a safety concern in humans based on their measured residual values in the final product or [redacted] calculated from their estimated residual values, and thus no control items are specified for these substances. Residues of bovine serum and feeder cells, foreign impurities, on the other hand, are controlled by the product specifications (residual bovine serum albumin and residual rate of feeder cells).

2.5.2 Verification

Quality attributes required for Ocural include viable cell count, cell viability, [redacted], [redacted], [redacted], [redacted], and sterility.

At present, any source of variation has not been identified in the manufacturing process of the primary component, but to ensure the target quality attributes for each manufacturing step, a verification-based quality control strategy shown below has been constructed in light of quality risks that may be raised by variations in the quality attributes of oral mucosal tissue.

- Manufacturing process parameters and test items presented in Table 6

- In-process control tests (Table 3)
- Specifications for the primary component (Table 7)
- Confirmatory test (Sterility Test [membrane filtration method] in the Japanese Pharmacopoeia)

Table 6. Verification items performed in manufacturing process

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

* [redacted] uses measured results from the in-process control test performed on [redacted].

2.6 Control of Ocural

Tables 7 and 8 show specifications for the cultured oral mucosal epithelium package and tissue transport set. Because the shelf life of the primary component is limited to 60 hours [see Section 3], the sterility test is specified to be performed using [redacted] days before the release as a specimen. In addition to the specifications, the sterility confirmatory test (Sterility Test [membrane filtration method] in the Japanese Pharmacopoeia) is to be performed on [redacted] collected at the release. The result of the sterility confirmatory test is to be obtained after transplantation in the patient.

Table 7. Specifications for cultured oral mucosal epithelium package

Test item	Test method
Packaging	Visual inspection
Viable cell density	[redacted]
Cell viability	[redacted]
Percentage of [redacted] cells	Immunostaining [redacted]
Percentage of [redacted] cells	Immunostaining [redacted]
Residual rate of feeder cells	Immunostaining [redacted]
Residual bovine serum albumin	ELISA
Sterility test*	Membrane Filtration Method (Japanese Pharmacopoeia) (incubation time, [redacted] days)
Mycoplasma test	Nucleic amplification test (General Information in the Japanese Pharmacopoeia)
Bacterial endotoxins test	Gel-clot techniques or turbidimetric techniques (Japanese Pharmacopoeia)
Physical property test	[redacted]
Barrier function	[redacted]

* Use [redacted] days before the release.

Table 8. Specifications for tissue transport set

Test item	Test method
Packaging and labeling	Visual inspection
Description	Visual inspection
[redacted]	[redacted]

2.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA has concluded that the quality of Ocural is appropriately controlled.

3. Data Relating to Stability and Outline of the Review Conducted by PMDA

Table 9 shows an outline of the stability study of the cultured oral mucosal epithelium package.

Table 9. Stability study of cultured oral mucosal epithelium package

Number of batches	Process	Storage condition	Study period	Storage form
3	Process for clinical study	20°C	60, [redacted] hours	Primary container (polystyrene container, polyethylene lid, polyethylene dish holder, polystyrene pick-up handle, polyethylene terephthalate/[redacted] ring-shaped culture disk, polystyrene/[redacted] culture dish)
		28°C		

No clear changes were observed in quality attributes under either storage condition in the stability study. Taking account of the above, a shelf life of 60 hours has been proposed for the primary component when stored at 20°C to 28°C.

3.R Outline of the review conducted by PMDA

PMDA accepted the proposed storage condition and shelf life of the primary component on the basis of the submitted data.

4. Data Relating to Indication or Performance and Outline of the Review Conducted by PMDA

The applicant submitted the following data relating to the indication or performance of Ocural: Results from an immunohistological analysis on the oral mucosal epithelial cell sheet performed as an *in vitro* study (Attached document 3-2); and 2 reports of published literature (Reference documents 2 and 33) on *in vivo* studies of its transplantation in LSCD model rabbits.

4.1 *In vitro* study

4.1.1 Immunohistological analysis on oral mucosal epithelial cell sheet (Attached document 3-2)

Oral mucosal epithelial cell sheets prepared from oral mucosal tissues of subjects in the COMET01 study were subjected to immunofluorescence staining to evaluate protein expression of a cell marker representative of both oral mucosal epithelial cells and corneal epithelial cells (Marker 1), markers related to corneal barrier function (Markers 2 and 3), and an undifferentiated cell marker (Marker 4). Marker 1-positive cells were observed throughout the oral mucosal epithelial cell sheet, and Markers 2 and 3 were expressed in the cortical layer and Marker 4 in the basal layer.

4.2 *In vivo* studies

4.2.1 Performance evaluation 1 in study of autologous oral mucosal epithelial cell sheet transplantation in LSCD model rabbits (Reference document 2)

4.2.1.1 Test method

The ocular surface with the corneal limbus surgically removed in a New Zealand White (NZW) rabbit was treated with cytopathic [redacted] followed by surgical removal of the entire corneal epithelium to create the LSCD model. Using oral mucosal tissue collected from the animal subjected to creation of the LSCD model, a rabbit autologous oral mucosal epithelial cell sheet ("Ocural analogue") was prepared by basically the same manufacturing process as that for Ocural. The Ocural analogue was transplanted to the LSCD model rabbits after the scar tissue infiltrating the cornea had been surgically removed ("transplantation group"). LSCD model rabbits with the scar tissue infiltrating the cornea removed only were included in the control group ("non-transplantation group") (*Invest Ophthalmol Vis Sci.* 2005;46:1632-9). The quality of the Ocural analogue was confirmed to be similar to that of Ocural.

4.2.1.2 Presence and localization of undifferentiated cells in Ocural analogue

Presence and localization of undifferentiated cells in the Ocural analogue were evaluated by colony forming assay and immunofluorescence staining for an undifferentiated cell marker (p63). Cultures of cells in the primary culture obtained during preparation of the Ocural analogue and cells from the Ocural analogue were demonstrated to contain proliferative cells and have a colony-forming activity. In addition, the immunofluorescence staining on the Ocural analogue showed that p63-expressing cells were localized in the basal layer.

4.2.1.3 Assessment of corneal epithelium lesion

At Weeks 1, 2, and 4 of Ocural analogue transplantation, the extent of corneal epithelium lesion was assessed under slit lamp examination of the anterior segment and fluorescein staining (a method to stain areas lacking the barrier function owing to loss of epithelial cells). Compared with the non-transplantation group, the transplantation group was found to have transparent tissue on the corneal surface immediately after transplantation and until Week 4 without any area that lacked the barrier function and thus was stained with fluorescein.

4.2.1.4 Histopathological examination

Eyeballs were removed at Week 4 of Ocural analogue transplantation, stained with hematoxylin-eosin (HE) solution, and subjected to histopathologic examination. The transplanted site in the transplantation group was found to have morphological features similar to those in the normal corneal epithelium layer. In the non-transplantation group, on the other hand, goblet cells, originally present in the conjunctiva, were observed on the cornea with vascular invasion into the corneal stroma.

4.2.2 Performance evaluation 2 in study of autologous oral mucosal epithelial cell sheet transplantation in LSCD model rabbits (Reference document 33)

4.2.2.1 Test method

The ocular surface with the corneal limbus and entire corneal epithelium surgically removed in a NZW rabbit was treated with cytopathic n-heptanol to create the LSCD model. Using oral mucosal tissue collected from the animal subjected to creation of the LSCD model, an Ocural analogue was prepared

by basically the same manufacturing process as that for Ocural. The Ocural analogue was transplanted to the LSCD model rabbits after the scar tissue infiltrating the cornea had been surgically removed. From Week 4 of Ocural analogue transplantation to Week 22, epithelial cells were repeatedly removed from the central cornea (5 mm in diameter) of the same animal in a physical manner every 2 weeks (10 removals in total), and the extent of epithelium reconstruction was assessed until Week 24 of transplantation or 2 weeks after the 10th removal to investigate presence or absence of undifferentiated oral mucosal epithelial cells in the corneal limbus (Repeat wound-healing assay) (*Mol Ther.* 2014;22:1544-55). The quality of the Ocural analogue was confirmed to be similar to that of Ocural.

4.2.2.2 Localization of undifferentiated cells in Ocural analogue

To investigate localization of undifferentiated cells in the Ocural analogue, immunohistological examination was performed by staining a differentiated mucosal epithelium marker cytokeratin (CK4), basal cell marker (CK14), and undifferentiated cell marker (p63). CK4-positive cells were observed throughout the cell sheet except for the basal layer, and CK14 and p63 were expressed in the basal layer.

4.2.2.3 Assessment of corneal epithelium lesion and immunohistological examination

The extent of corneal epithelium lesion was assessed by observation of the anterior segment and fluorescein staining before Ocural analogue transplantation, immediately after transplantation, at Weeks 1, 2, and 3 of transplantation, before and after a physical removal of epithelial cells from the central cornea at Weeks 4 (before and after the first removal), Days 30, 32, 34, and Week 5 as well as before and after each of the physical removal at Weeks 6, 8, 10, 12, 14, 16, 18, 20, and 22 (before and after each of the second to 10th removals), and Week 24 (Figure 1).

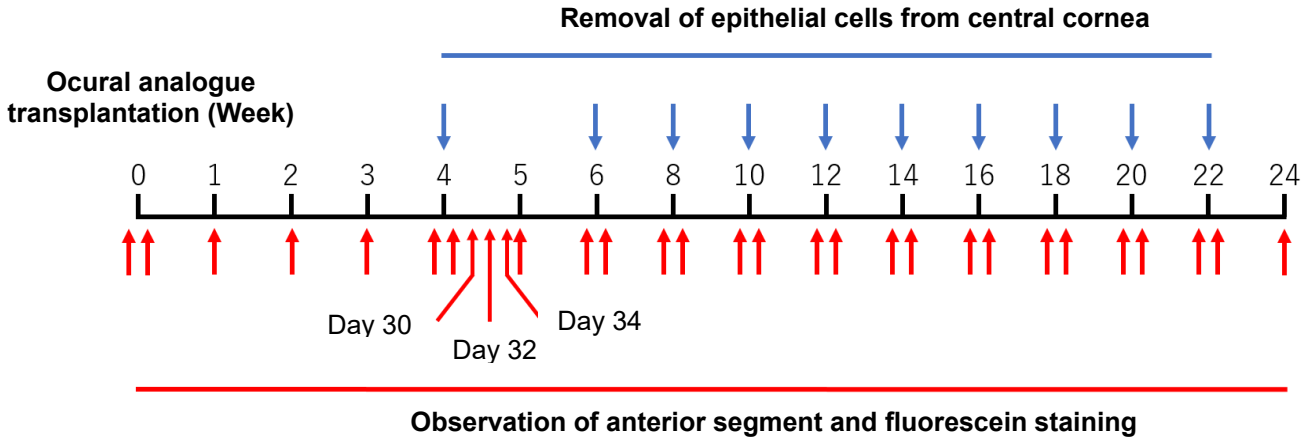

Figure 1. Schedule of removal of epithelial cells from central cornea and assessment

Transparent tissue was observed in the corneal surface at Week 4 of Ocural analogue transplantation without any area that lacked the barrier function and thus was stained with fluorescein. Furthermore, even on the region that underwent removal of epithelial cells every 2 weeks starting at Week 4 of Ocural analogue transplantation, the area that lacked epithelium and thus was stained with fluorescein was reduced with time, and transparent tissue was observed again. At Week 24, the ocular surface was kept transparent as well without any area stained with fluorescein.

Immunohistological examination on eyeballs removed at Week 24 of Ocural analogue transplantation showed expression of CK4, the differentiated mucosal epithelium marker, in the cortical layer in the reconstructed corneal epithelium but did not indicate expression of mucin (MUC)5, a marker of goblet cells, which are normally present in the conjunctiva.

4.R Outline of the review conducted by PMDA

The applicant's explanation about performance of Ocural:

On the basis of results from the immunohistological analysis on an oral mucosal epithelial cell sheet (Attached document 3-2), Ocural was considered to be comprised of stratified oral mucosal epithelial cells with stem cells in the basal layer and have barrier function.

Furthermore, in the performance evaluation study in LSCD model rabbits (Reference documents 2 and 33), transparent tissue was observed in the corneal surface throughout the observation period after transplantation of Ocural analogue containing undifferentiated cells and not stained with fluorescein. The above findings indicated that oral mucosal epithelial stem cells contained in the Ocural analogue transplanted to the LSCD model rabbits survived and proliferated, thereby leading to supply of oral mucosal epithelial cells, which enabled reconstruction and maintenance of the corneal epithelium.

On the basis of the above findings, when transplanted on the ocular surface lacking corneal epithelial stem cells in a patient with LSCD, Ocural is expected to protect the stroma from an external environment with its barrier function and allow stem cells contained in Ocural to survive and proliferate, thereby leading to supply of oral mucosal epithelial cells, which enable reconstruction of the corneal epithelium and its subsequent consistent maintenance.

PMDA's view:

Because no results from transplantation of Ocural itself in the LSCD model have been presented, it has limitations to evaluate performance of Ocural, but the applicant's explanation about performance of Ocural is understandable to some extent.

5. Data Relating to Biodistribution and Outline of the Review Conducted by PMDA

The applicant's explanation about biodistribution of Ocural, based on results from the studies of Ocural analogue transplantation in the LSCD model rabbits (Reference documents 2 and 33), the COMET01 study, a trial of Ocural in patients with LSCD, and the COMET01-FU study, an extension follow-up study (Attached documents 7-1 and 7-2):

For the survival period of Ocural, the Ocural analogue transplanted in the LSCD model rabbits maintained transparency of the corneal surface and protected it from fluorescein staining until Week 24 of transplantation, demonstrating reconstruction of the corneal epithelium [see Section 4.2]. The LSCD model is created by surgically removing corneal epithelium including corneal limbus and further treating the damaged ocular surface with cytopathic [redacted] or n-heptanol. In this model, therefore, corneal epithelium is unlikely to be reconstructed unless epithelial stem cells are externally supplied. The above views indicated that survival of cells derived from the test substance at the transplantation site for a certain period resulted in reconstruction and maintenance of the corneal epithelium.

In addition, in the COMET01 study in patients with LSCD at Stage III, which is a severity level defined as a condition of the corneal surface totally covered with conjunctival tissue, all of the 6 patients with Ocural transplanted achieved reconstruction of corneal epithelium at Week 52 of transplantation. In the COMET01-FU study, furthermore, 4 of the 6 patients were found to have the reconstructed corneal epithelium at Week 104 [see Sections 7.1 and 7.2]. In consideration that patients with LSCD at Stage III in the COMET01 study had no intact corneal limbus, the above finding indicates that cells in the transplanted Ocural surviving at the transplantation site for a certain period achieved reconstruction and maintenance of the corneal epithelium. Turnover intervals of corneal epithelium and oral mucosal epithelium in humans are approximately 14 days (*Invest Ophthalmol Vis Sci.* 1990;31:1957-62) and 14 to 24 days (*Exp Cell Res.* 2014;325:111-29), respectively. The area kept free from conjunctival epithelium invasion for a period beyond the concerned turnover interval is considered to be protected by oral mucosal epithelial cells consistently supplied by oral mucosal epithelium stem cells surviving in the cornea.

With respect to biodistribution of Ocural, cells in the Ocural transplanted on the ocular surface and their subsequent generations are considered to fall off by eyeblink, etc. finally and be eliminated mainly through the lacrimal duct and then nose into the throat. Cells transplanted in the cornea are, therefore, considered very unlikely to be widely distributed in tissues other than the transplantation site.

5.R Outline of the review conducted by PMDA

PMDA's view:

On the basis of anatomical characteristics of the site where Ocural is to be transplanted, the applicant explained that cells in Ocural transplanted on the ocular surface are unlikely to be widely distributed into tissues other than the cornea. The applicant's explanation is understandable to some extent.

Because there are no results from direct evaluation on the survival and maintenance period of transplanted cells, it has limitations to evaluate the survival and maintenance period of Ocural based on the submitted data. However, based on the following findings, cells in the transplanted Ocural are suggested to survive at the transplantation site for a certain period.

- In the performance evaluation study in LSCD model rabbits which would not be able to reconstruct the corneal epithelium without external supply of epithelial stem cells, the Ocural analogue transplantation led to reconstruction and maintenance of the corneal epithelium with oral mucosal epithelial cells.
- In the COMET01 and COMET01-FU studies in patients with LSCD at Stage III who had no intact corneal limbus, the transplantation of Ocural led to reconstruction and maintenance of the corneal epithelium with oral mucosal epithelial cells.

6. Data Relating to Non-clinical Safety and Outline of the Review Conducted by PMDA

The applicant submitted the following data relating to the non-clinical safety of Ocural: General toxicity study in nude rats, tumorigenicity tests (karyology test and soft agar colony formation assay), and safety of the impurities.

6.1 General toxicity study in nude rats (Attached document 6-1)

In this study, [redacted] of Ocural was subcutaneously administered at a single dose to nude rats, and necropsy was performed on Day 28. Compared with the untreated group, the treated group showed no toxicological changes attributable to Ocural throughout the body or at the transplantation site (subcutaneous region) (Table 10).

Table 10. General toxicity study in nude rats

Test system	Route of administration	Observation period	Test product	Dose	Major findings
Nude rats	Subcutaneous	28 days	Ocural was [redacted]	Male, 248.5 × 10^4 cells/body Female, 217 × 10^4 cells/body	No toxicological changes

6.2 Other safety

6.2.1 Tumorigenicity test

Karyology test and soft agar colony formation assay were performed. In these *in vitro* tests and the general toxicity study in nude rats, no findings such as proliferative lesions and atypical cells suggestive of tumorigenicity were found, and the applicant explained that the tumorigenicity risk of Ocural is low.

6.2.1.1 Karyology test (Attached document 6-2)

Chromosomal aberrations were observed in a part of the initial culture specimens in the karyology test (Table 11). Of the above findings, karyotype abnormality observed only in 1 cell from a patient CMT[redacted]1 was not classified as a chromosomal aberration according to the following definition in the International System for Human Cytogenetic Nomenclature (ISCN) 2016: "Loss of a single chromosome must be detected in ≥3 cells for listing in the karyotype because such cells are deemed to be clonal. Loss of ≤2 cells is deemed not to be clonal." In addition, trisomy in chromosome 7 was observed in 2 cells in the initial culture from a patient CMT[redacted]1 but no longer observed in the late culture, indicating that this finding was not a result from persistent amplification of karyotype abnormality during the manufacturing process. The applicant, therefore, explained that Ocural has no concerns in terms of the genetic stability.

Table 11. Karyology test

Patient*1	Result
CMT[redacted]1	No chromosomal aberration in cells in the initial*2 or overage culture*3
CMT[redacted]1	No chromosomal aberration in cells in the initial*2 or overage culture*3
CMT[redacted]1	No chromosomal aberration in cells in the initial*2 or overage culture*3
CMT[redacted]1	No chromosomal aberration in cells in the initial*2 or overage culture*3
CMT[redacted]1	No chromosomal aberration in cells in the initial*2 or overage culture*3
CMT[redacted]1	• Trisomy 7 in 2 cells and Karyotype 45,X,-Y in 1 cell was observed when 20 oral mucosal epithelial cells in the initial culture*2 were examined. • No chromosomal aberration in cells in the overage culture*3

*1 Human oral mucosal epithelial cells from 6 patients [redacted] were used as specimens
*2 Oral mucosal epithelial cells at [redacted] ([redacted]th generation)
*3 Overage oral mucosal epithelial cells from [redacted] of Ocural ([redacted]th generation)

6.2.1.2 Soft agar colony formation assay (Attached document 6-3)

[redacted] cells from 6 specimens of human oral mucosal epithelial cells (CMT[redacted]1, CMT[redacted]1, CMT[redacted]1, CMT[redacted]1, CMT[redacted]1, and CMT[redacted]1) ([redacted]th generation) and overage cells obtained by [redacted] of Ocural ([redacted]th generation) were seeded on the soft agar layer followed by incubation for [redacted] days. No anchorage-independent colony formation was observed.

6.2.2 Safety evaluation of impurities (Attached documents 2-7, 6-4, 6-5, and 6-6)

Impurities potentially remaining in the final product are bovine serum, feeder cells, antibiotics (benzylpenicillin potassium, streptomycin sulfate, amphotericin B, and kanamycin sulfate), Impurity A, and Impurity B. The safety of these impurities was evaluated based on their residual amounts in Ocural. The applicant explained that the results indicated that these impurities did not pose any safety risk in humans.

6.R Outline of the review conducted by PMDA

6.R.1 Local general toxicity evaluation of Ocural on the eye

PMDA asked the applicant to explain the following matters: Reason why the general toxicity study was not conducted with Ocural transplanted on the eye surface of the clinical application site; and local general toxicity evaluation of Ocural on the eye.

The applicant's explanation:

It is technically difficult to transplant Ocural on the eye surface of immunodeficiency animals (mice and rats). In addition, conducting an *in vivo* general toxicity study in which Ocural was transplanted on the eye surface of rabbits was determined to be difficult because for use of rabbits treated with immunosuppressants, many of treated rabbits would die, and even the surviving rabbits would scratch their eyes to cause the graft to fall off. Furthermore, to transplant a rabbit-derived analogue product on the ocular surface, a disease model must be established by removing the corneal limbus and detaching the cornea from the stroma, but the animal experiment facility had technical difficulties in establishing the concerned disease model, proceeding with the Ocural analogue transplantation procedure, and conducting the study in a sample size necessary for the safety evaluation. For the above reasons, local general toxicity studies with Ocural or Ocural analogue transplanted on the ocular surface were not conducted to evaluate general toxicity in eyes, but Ocural is considered unlikely to raise a local general toxicity concern in eyes for the following reasons:

- Histopathological examination in the subcutaneous dose general toxicity study in nude rats did not present any toxicological findings.
- In a study in which a rabbit autologous oral mucosal epithelial cell sheet or Ocural analogue prepared by basically the same manufacturing process as that for Ocural and confirmed to have quality similar to that of Ocural was transplanted in rabbit eyes, histopathological examination on the recipient eyes did not present any local toxicological findings in the eyes (*Invest Ophthalmol Vis Sci.* 2005;46:1632-9, *Mol Ther.* 2014;22:1544-55).

PMDA accepted the applicant's explanation.

6.R.2 Tumorigenicity evaluation of Ocural

PMDA asked the applicant to explain the following matters: Reason for not conducting the tumorigenicity test with Ocural transplanted on the eye surface of the clinical application site; and a risk of local tumorigenicity of Ocural on the eye.

The applicant's explanation:

For the reasons described in Section 6.R.1, conducting an *in vivo* tumorigenicity test in which Ocural was transplanted on the eye surface of rabbits was determined to be difficult. The local tumorigenicity risk in eyes with Ocural transplanted on the ocular surface has not been evaluated in animals, but the concerned risk is considered low for the following reasons:

- Starting material of Ocural is cells that are derived from oral mucosal epithelium and do not have pluripotency.
- No genetic modification is involved in the manufacturing process of Ocural.
- The *in vitro* tumorigenicity tests did not present any results suggestive of tumorigenicity.
- Histopathological examination in the subcutaneous dose general toxicity study in nude rats did not present any findings such as proliferative lesions and atypical cells suggestive of tumorigenicity.
- In a study in which a rabbit autologous oral mucosal epithelial cell sheet, Ocural analogue, was transplanted in rabbit eyes, no findings such as proliferative lesions and atypical cells suggestive of tumorigenicity were noted at the transplantation site until Week 24 of transplantation (*Invest Ophthalmol Vis Sci.* 2005;46:1632-9, *Mol Ther.* 2014;22:1544-55).
- In clinical studies of Ocural, no adverse events related to corneal tumorigenesis have been reported.

PMDA accepted the applicant's explanation about the feasibility of the tumorigenicity test with Ocural transplanted on the eye surface and the risk of local tumorigenicity of Ocural on the eye, but considers that post-marketing information about the tumorigenesis on the human eye needs to be collected.

7. Data Relating to Clinical Study Results and Outline of the Review Conducted by PMDA

The applicant submitted evaluation data on the efficacy and safety from 2 clinical studies shown in Table 12.

Table 12. List of clinical studies for efficacy and safety

Data category	Geographical location	Study identifier	Phase	Study population	No. of patients enrolled	Dosage regimen	Main endpoints
Evaluation	Japan	COMET01	III	Patients with LSCD	6	Single transplantation with 1 sheet of Ocural on the recipient eye after removal of conjunctival scar tissue from the cornea to the extent possible	Efficacy Safety
	Japan	COMET01-FU	III	Patients with LSCD	6	— (follow-up study in patients who completed the COMET01 study)	Efficacy Safety

7.1 Japanese phase III study (Attached document 7-1, COMET01 study [August 2015 to September 2017])

An open-label, uncontrolled, Japanese phase III study was conducted at 3 study centers to evaluate the efficacy and safety of Ocural transplanted in patients with LSCD (target sample size, 6 patients[1)]) who were assessed as Stage III according to the severity classification in Figure 2 by the investigator and eligibility assessment committee.[2)] Table 13 shows major inclusion and exclusion criteria.

In this study, the period from obtaining informed consent to transplantation of Ocural was referred to as the "run-in period," and that from the transplantation to Week 52 of transplantation was referred to as the "treatment period."

In light of effects on the efficacy and safety evaluation of Ocural, corneal transplantation, conjunctival epitheliectomy, amniotic membrane transplantation, and concomitant autologous serum eye-drops were prohibited. At Week 52 of transplantation of Ocural, information about the appropriateness or necessity for indicating each of corneal transplantation, conjunctival epitheliectomy, and cataract surgery was collected.

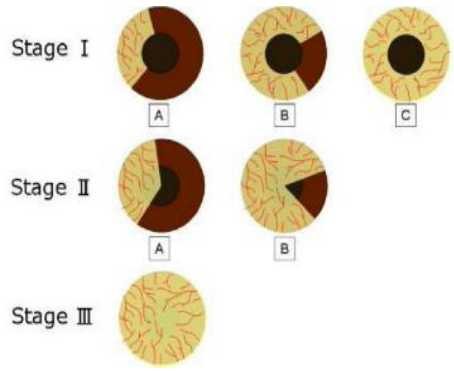	Stage I: No conjunctivalization involving the central cornea (5 mm in diameter) with the limbus in a condition of A to C A: Conjunctivalization <50% B: Conjunctivalization ≥50% and <100% C: 100% conjunctivalization
	Stage II: Conjunctivalization involving the central cornea (5 mm in diameter) with the limbus in a condition of A or B A: Conjunctivalization <50% B: Conjunctivalization ≥50% and <100%
	Stage III: Corneal surface totally covered with conjunctival tissue

Figure 2. Severity classification of LSCD

Table 13. Major inclusion and exclusion criteria

Inclusion criteria	Patients meeting all the following criteria: • The condition of limbal stem cell deficiency is classified as Stage III according to the severity classification. • The oral mucosa is free from scars and inflammation and has a region available for collection.
Exclusion criteria	Patients meeting any of the following criteria: • Patients with history of malignant tumor in <5 years or suspected malignant tumor • Patients with glaucoma with poor intraocular pressure control • Patients with diabetes mellitus with poor glycemic control • Patients with loss of central vision of the recipient eye • Patients with refractory and extreme lacrimation decreased • Patients who will receive intraocular surgery scheduled during the trial period • Patients with severe eyelid abnormality on the recipient eye

The following method of use was applied.

1) The primary efficacy endpoint was the success rate (%) of corneal epithelium reconstruction at Week 52 of transplantation of Ocural. On the condition that the expectation value for the primary endpoint was 80% with the threshold of 10%, the number of subjects required to perform a one-sample binomial test for threshold with two-sided significance level of 5% and power of ≥90% was calculated to be 5 patients. Taking potential drop-out into account, the target sample size was specified as 6 patients.

2) The eligibility assessment committee, which consisted of third-party members to confirm that subjects selected by the investigators or sub-investigators were eligible, examined the eligibility using the anterior segment image, and only those determined to be eligible by the committee were enrolled.

From the oral mucosal tissue free from scars and inflammation of the subject, approximately 10 × 5 mm piece is collected and subjected to separation of oral mucosal epithelial cells, which are then cultured in sheet form to obtain the product. The conjunctival scar tissue on the cornea of the recipient eye is removed wherever possible before transplantation of Ocural. After the transplantation with 1 sheet, a therapeutic soft contact lens is applied followed by tarsorrhaphy where necessary to close the eyelids.

Evaluation was scheduled at Week 52 of transplantation of Ocural.

Of 9 patients who started the enrollment procedure, 3 patients were determined to be ineligible owing to the severity of Stage III or less by the eligibility assessment committee and 6 patients were enrolled in this study. All of the 6 subjects who had undergone tissue collection and transplantation of Ocural were included in the safety analysis set and full analysis set (FAS). The FAS was the primary efficacy analysis set. None of the subjects discontinued after transplantation of Ocural, and all subjects completed the evaluation at Week 52.

Causative etiologies of LSCD in the 6 subjects were SJS in 2 subjects, OCP in 2 subjects, congenital aniridia in 1 subject, and idiopathic LSCD in 1 subject. Table 14 shows patient characteristics.

Table 14. Patient characteristics

Subject number	Age Sex	Causative etiology of LSCD	Ophthalmologic findings at enrollment		Ophthalmologic history	Previous ophthalmic surgery
A-3	57 Female	Congenital aniridia	Recipient eye	Eyelid ptosis	—	—
			Contralateral eye	—	—	—
			Both eyes	Corneal stromal opacity, corneal neovascularisation, cataract, superficial punctate keratopathy, conjunctival hyperaemia, congenital microphthalmos, conjunctivitis allergic	—	—
B-1	75 Female	SJS	Recipient eye	—	—	—
			Contralateral eye	Corneal keratosis	—	—
			Both eyes	Corneal opacity, corneal neovascularisation, symblepharon, conjunctival hyperaemia, superficial punctate keratopathy, trichiasis	—	—
C-1	28 Male	SJS	Recipient eye	—	—	—
			Contralateral eye	Ocular hypertension	—	—
			Both eyes	Suspected dry eye, trichiasis, blepharitis, superficial punctate keratopathy, conjunctival hyperaemia, conjunctivitis	—	—
C-2	80 Female	OCP	Recipient eye	Cataract, symblepharon	—	—
			Contralateral eye	—	Cataract	Amniotic membrane grafting, LKP, cataract surgery, allogeneic corneal limbal transplantation
			Both eyes	Dry eye, corneal stromal opacity, superficial punctate keratopathy, conjunctival hyperaemia	—	—
C-3	26 Male	Idiopathic LSCD	Recipient eye	—	—	—
			Contralateral eye	—	—	—
			Both eyes	Blepharitis, vernal keratoconjunctivitis, glaucoma, superficial punctate keratopathy, conjunctival hyperaemia	—	—
C-5	87 Male	OCP	Recipient eye	—	Cataract	Cataract surgery*
			Contralateral eye	Cataract	BRVO	Retinal photocoagulation
			Both eyes	Dry eye, ocular pemphigoid, symblepharon, superficial punctate keratopathy, conjunctival hyperaemia, conjunctivitis	Trachoma	—

* It was performed 2 years and 8 months before screening.

The primary efficacy endpoint was the success rate (%) of corneal epithelium reconstruction[3] at Week 52 of transplantation of Ocural. Successful corneal epithelium reconstruction[4] was assessed as change to Stage I (Stage IA-IC) in the LSCD severity, which was separately rated by the investigator and data monitoring committee[5] (and also by the eligibility assessment committee only at the screening). At Week 52 of transplantation, the LSCD severity centrally rated by the data monitoring committee was at Stage I in all of the 6 subjects, and the success rate (%) of corneal epithelium reconstruction was 100.0% (95% confidence interval [CI] [54.1, 100.0]), showing a statistically significant difference in comparison with the threshold of 10%[6] ($P \leq 0.0001$, two-sided significance level of 5%, one-sample binomial test). The investigator's rating presented comparable results to the above. Table 15 shows changes in the LSCD severity and outcome on corneal epithelium reconstruction in each subject.

Table 15. Change in the LSCD severity (Stage) in each subject

Subject number	Severity rating on recipient eye	Severity		Successful corneal epithelium reconstruction at Week 52
		At screening	Week 52 of transplantation	
A-3	Rated by investigator	III	IA	○
	Centrally rated	III/III	IB	
B-1	Rated by investigator	III	IA	○
	Centrally rated	IA/III	IA	
C-1	Rated by investigator	III	IA	○
	Centrally rated	III/III	IA	
C-2	Rated by investigator	III	IA	○
	Centrally rated	III/III	IA	
C-3	Rated by investigator	III	IA	○
	Centrally rated	III/III	IA	
C-5	Rated by investigator	III	IA	○
	Centrally rated	III/III	IA	

Central rating: Result rated by the data monitoring committee only at screening (left) and that rated by the eligibility assessment committee at screening (right) and all the points after transplantation, result rated by the data monitoring committee

Tables 16 and 17 show changes in subjective symptoms, the secondary efficacy endpoints.

Table 16. Change in subjective symptom from screening to Week 52 of transplantation

Subject number	Eye pain	Sensation of foreign body	Lacrimation	Photophobia	Dry feeling	Discomfort
A-3	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged
B-1	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged
C-1	Unchanged	Alleviated	Unchanged	Alleviated	Unchanged	Alleviated
C-2	Alleviated	Alleviated	Unchanged	Alleviated	Worsened	Worsened
C-3	Alleviated	Alleviated	Alleviated	Alleviated	Alleviated	Alleviated
C-5	Unchanged	Worsened	Unchanged	Worsened	Worsened	Alleviated

[3] Because conjunctivalization involving the central cornea would affect the visual acuity, successful corneal epithelium reconstruction was defined as Stage IA to IC, which indicates a condition free from conjunctivalization in the central cornea.

[4] The statistical analysis plan had specified that the analysis should be performed using the rating results made by the eligibility assessment committee at screening and those made by the data monitoring committee after the transplantation.

[5] The data monitoring committee rated the severity under a condition being blinded to subject information and sampling timepoint and using data randomized for treatment status on the eye to be rated in terms of the recipient or contralateral eye.

[6] It was specified on the basis of clinical outcome from allogeneic corneal limbal transplantation, the conventional treatment [For details, see Section 7.R.2.2].

Table 17. Summary of changes in subjective symptom from screening to Week 52 of transplantation

	Eye pain	Sensation of foreign body	Lacrimation	Photophobia	Dry feeling	Discomfort
Number of subjects rated	6	6	6	6	6	6
Alleviated	2 (33.3)	3 (50.0)	1 (16.7)	3 (50.0)	1 (16.7)	3 (50.0)
Unchanged	4 (66.7)	2 (33.3)	5 (83.3)	2 (33.3)	3 (50.0)	2 (33.3)
Worsened	0	1 (16.7)	0	1 (16.7)	2 (33.3)	1 (16.7)

Number of subjects (proportion, %)

Table 18 shows changes in corrected visual acuity, the secondary efficacy endpoint.[7)]

Table 18. Change in visual acuity

Subject number	At screening			Week 52 of transplantation		
	Landolt rings		ETDRS	Landolt rings		ETDRS
	Decimal visual acuity	Converted LogMAR value		Decimal visual acuity	Converted LogMAR value	
A-3	0.001	+3.00	+3.00	0.001	+3.00	+3.00
B-1	0.001	+3.00	+3.00	0.001	+3.00	+3.00
C-1	0.03	+1.52	+1.50	0.1	+1.00	+1.16
C-2	0.02	+1.70	+1.60	0.01	+2.00	+2.00
C-3	0.01	+2.00	+2.00	0.3	+0.52	+1.24
C-5	0.01	+2.00	+2.00	0.04	+1.40	+1.50
Mean ± SD	—	+2.20 ± 0.64	+2.18 ± 0.66	—	+1.82 ± 1.04	+1.98 ± 0.84

Counting fingers and hand motion were handled as decimal visual acuity 0.01 (LogMAR +2.00) and decimal visual acuity 0.001 (LogMAR +3.00), respectively.

Table 19 shows results from evaluation on quality of life (QOL) using the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) Japanese version (v1.4), the secondary efficacy endpoint.

Table 19. Changes in NEI VFQ-25 score from screening to Week 52 of transplantation

Subject number	At screening	Week 52 of transplantation
A-3	38.1	50.0
B-1	34.5	45.4
C-1	42.0	65.4
C-2	37.4	39.6
C-3	53.8	69.6
C-5	81.4	28.5
Mean ± SD	47.9 ± 17.8	49.8 ± 15.6
Median	40.1	47.7

Table 20 shows results on the secondary efficacy endpoints, severities of corneal opacity, corneal neovascularisation, and symblepharon.

7) An Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity value is determined by the following procedure.
The ETDRS visual acuity test chart is viewed with corrected vision at a 4-m distance ("4-m test"). The number of letters read correctly is specified as A. If A is ≥20, A + 30 is used as the total score, S. If A is ≤19, the first to sixth lines of the ETDRS visual acuity test chart are additionally viewed at a 1-m distance with vision further corrected by adding a sphere power of +0.75 diopters to the initial correction power used for the 4-m test. The number of letters read correctly is specified as B, and A + B is used as the total score, S. The S value determined above is substituted into the equation (X = −0.02S + 1.70), and the obtained X value is defined as "ETDRS" in the COMET01 and COMET01-FU studies. When visual acuity has to be measured by the other procedure, the following X value is applied: X = 2.00 for counting fingers; X = 3.00 for hand motion; X = 4.00 for light perception; and X = 5.00 in cases not eligible for light perception.

Table 20. Changes in Grade of corneal opacity, corneal neovascularisation, and symblepharon from screening to Week 52 of transplantation in the COMET01 study

Subject number	Corneal opacity*		Corneal neovascularisation**		Symblepharon***	
	At screening	Week 52 of transplantation	At screening	Week 52 of transplantation	At screening	Week 52 of transplantation
A-3	3	3	3	3	0	0
B-1	3	2	3	3	1	1
C-1	2	2	3	3	0	0
C-2	2	2	3	1	1	1
C-3	2	0	3	1	0	0
C-5	2	1	3	1	1	1

* Grade 0: Iris details observable because of clear cornea
Grade 1: Iris details observable but partially opaque
Grade 2: Iris details not observable but pupil margin slightly perceivable
Grade 3: Neither iris nor pupil margin details observable

** Grade 0: No neovascularisation
Grade 1: Neovascularisation only around cornea
Grade 2: Neovascularisation to pupil margin
Grade 3: Neovascularisation beyond pupil margin into central cornea

*** Grade 0: No symblepharon
Grade 1: Symblepharon only involving the conjunctival surface
Grade 2: Symblepharon involving <50% of the corneal surface
Grade 3: Symblepharon involving ≥50% of the corneal surface

Table 21 shows the appropriateness or necessity for indicating additional treatment to improve visual acuity at Week 52 of transplantation of Ocural, the secondary efficacy endpoint.

Table 21. Appropriateness or necessity for indicating additional treatment to improve visual acuity at Week 52 of transplantation of Ocural

Subject number	Additional treatment to improve visual acuity*	Appropriateness or necessity for indicating additional treatment
A-3	Corneal transplant to resolve corneal stromal opacity	Appropriate
	Conjunctival epitheliectomy	Not necessary
	Cataract surgery	Appropriate
B-1	Corneal transplant to resolve corneal stromal opacity	Appropriate
	Conjunctival epitheliectomy	Not appropriate
C-1	Corneal transplant to resolve corneal stromal opacity	Not necessary
	Conjunctival epitheliectomy	Not necessary
C-2	Corneal transplant to resolve corneal stromal opacity	Appropriate
	Conjunctival epitheliectomy	Not necessary
	Cataract surgery	Appropriate
C-3	Corneal transplant to resolve corneal stromal opacity	Not necessary
	Conjunctival epitheliectomy	Not necessary
C-5	Corneal transplant to resolve corneal stromal opacity	Not necessary
	Conjunctival epitheliectomy	Not necessary

* Corneal transplant to improve visual acuity and conjunctival epitheliectomy were commonly considered for all the subjects. For a subject requiring consideration of the other additional treatment, appropriateness of the concerned treatment was also considered.

Adverse events[8)] occurred in 1 subject during the run-in period and in all of the 6 subjects during the treatment period. During the run-in period, none of the deaths, other serious adverse events, and adverse events for which a causal relationship to tissue collection could not be ruled out occurred. During the treatment period, no deaths occurred, and serious adverse events other than deaths occurred in 2 subjects (cellulitis and dacryocystitis in 1 subject each), but a causal relationship to Ocural was denied for both events. In addition, adverse events for which a causal relationship to Ocural could not be ruled out occurred in all of the 6 subjects during the treatment period, and these were corneal epithelium defect in 5 subjects, corneal neovascularisation in 3 subjects, and corneal opacity in 1 subject.

8) Medical Dictionary for Regulatory Activities Japanese version (MedDRA/J) Ver 20.1

7.2 Japanese phase III study (Attached document 7-2, COMET01-FU study [November 2016 to August 2018])

An open-label, uncontrolled study was conducted at 3 study centers to evaluate the long-term efficacy and safety of Ocural in patients who had completed the COMET01 study. The follow-up period was 52 weeks from the last day of examination and observation at Week 52 to Week 104 of transplantation of Ocural. This study enrolled 6 patients, all of whom were included in the efficacy and safety analysis populations. None of the subjects discontinued after the start of this study, and all subjects completed it. None of them deviated from the protocol either.

Neither prohibited concomitant drugs nor therapies were specified in this study.

The success rate (%) of corneal epithelium reconstruction at Week 104 of transplantation of Ocural, the efficacy endpoint, was 66.7% (4 of 6) of subjects (95% CI [22.3, 95.7]), and the severity in 2 subjects who had not been assessed as successful reconstruction (Subjects A-3 and C-1) was rated as Stage III and Stage IIB, respectively. Table 22 shows change in the LSCD severity in each subject from screening for the COMET01 study.

Table 22. Change in the LSCD severity (Stage) in each subject

Subject number	Severity rating on recipient eye	Severity		
		At screening for the COMET01 study	Week 52 of transplantation	Week 104 of transplantation
A-3	Rated by investigator	III	IA	IA
	Centrally rated	III/III	IB	III
B-1	Rated by investigator	III	IA	IA
	Centrally rated	IA/III	IA	IA
C-1	Rated by investigator	III	IA	IA
	Centrally rated	III/III	IA	IIB
C-2	Rated by investigator	III	IA	IA
	Centrally rated	III/III	IA	IB
C-3	Rated by investigator	III	IA	IA
	Centrally rated	III/III	IA	IA
C-5	Rated by investigator	III	IA	IA
	Centrally rated	III/III	IA	IA

Central rating: Result rated by the data monitoring committee only at screening (left) and that rated by the eligibility assessment committee at screening (right) and all the points after transplantation, result rated by the data monitoring committee

Tables 23 and 24 show changes in subjective symptoms in each subject from screening.

Table 23. Changes in subjective symptoms from screening for the COMET01 study to Week 104 of transplantation of Ocural

Subject number	Eye pain	Sensation of foreign body	Lacrimation	Photophobia	Dry feeling	Discomfort
A-3	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged
B-1	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged
C-1	Worsened	Alleviated	Unchanged	Alleviated	Unchanged	Alleviated
C-2	Unchanged	Alleviated	Unchanged	Alleviated	Unchanged	Worsened
C-3	Unchanged	Alleviated	Alleviated	Alleviated	Alleviated	Alleviated
C-5	Worsened	Worsened	Unchanged	Worsened	Worsened	Worsened

Table 24. Summary of changes in subjective symptoms from screening for the COMET01 study to Week 104 of transplantation of Ocural

	Eye pain	Sensation of foreign body	Lacrimation	Photophobia	Dry feeling	Discomfort
Number of subjects rated	6	6	6	6	6	6
Alleviated	0	3 (50.0)	1 (16.7)	3 (50.0)	1 (16.7)	2 (33.3)
Unchanged	4 (66.7)	2 (33.3)	5 (83.3)	2 (33.3)	4 (66.7)	2 (33.3)
Worsened	2 (33.3)	1 (16.7)	0	1 (16.7)	1 (16.7)	2 (33.3)

Number of subjects (proportion, %)

Table 25 shows change in corrected visual acuity in each subject.[7)]

Table 25. Change in corrected visual acuity

Subject number	At screening for the COMET01 study			Week 104 of transplantation		
	Landolt rings		ETDRS	Landolt rings		ETDRS
	Decimal visual acuity	Converted LogMAR value		Decimal visual acuity	Converted LogMAR value	
A-3	0.001	+3.00	+3.00	0.001	+3.00	+3.00
B-1	0.001	+3.00	+3.00	0.001	+3.00	+3.00
C-1	0.03	+1.52	+1.50	0.06	+1.22	+1.44
C-2	0.02	+1.70	+1.60	0.001	+3.00	+3.00
C-3	0.01	+2.00	+2.00	0.1	+1.00	+1.04
C-5	0.01	+2.00	+2.00	0.03	+1.52	+1.50
Mean ± SD	—	+2.20 ± 0.64	+2.18 ± 0.66	—	+2.12 ± 0.97	+2.16 ± 0.93

Counting fingers and hand motion were handled as decimal visual acuity 0.01 (LogMAR +2.00) and decimal visual acuity 0.001 (LogMAR +3.00), respectively.

Table 26 shows results from evaluation on QOL in each subject using NEI VFQ-25 Japanese version (v1.4).

Table 26. Changes in NEI VFQ-25 score from screening for the COMET01 study to Week 104 of transplantation

Subject number	At screening	Week 104 of transplantation
A-3	38.1	37.7
B-1	34.5	31.7
C-1	42.0	78.0
C-2	37.4	44.3
C-3	53.8	59.1
C-5	81.4	61.3
Mean ± SD	47.9 ± 17.8	52.0 ± 17.3
Median	40.1	51.7

Table 27 shows severities of corneal opacity, corneal neovascularisation, and symblepharon in each subject.

Table 27. Changes in Grade of corneal opacity, corneal neovascularisation, and symblepharon from screening for the COMET01 study to Week 104 of transplantation

Subject number	Corneal opacity*		Corneal neovascularisation**		Symblepharon***	
	At screening	Week 104 of transplantation	At screening	Week 104 of transplantation	At screening	Week 104 of transplantation
A-3	3	2	3	3	0	0
B-1	3	2	3	3	1	1
C-1	2	2	3	3	0	0
C-2	2	2	3	1	1	1
C-3	2	0	3	0	0	0
C-5	2	2	3	2	1	1

* Grade 0: Iris details observable because of clear cornea
Grade 1: Iris details observable but partially opaque
Grade 2: Iris details not observable but pupil margin slightly perceivable
Grade 3: Neither iris nor pupil margin details observable

** Grade 0: No neovascularisation
Grade 1: Neovascularisation only around cornea
Grade 2: Neovascularisation to pupil margin
Grade 3: Neovascularisation beyond pupil margin into central cornea

*** Grade 0: No symblepharon
Grade 1: Symblepharon only involving the conjunctival surface
Grade 2: Symblepharon involving <50% of the corneal surface
Grade 3: Symblepharon involving ≥50% of the corneal surface

Table 28 shows practice of additional treatment to improve visual acuity, and none of the subjects received additional treatment.

Table 28. Practice of additional treatment to improve visual acuity

Subject number	Additional treatment to improve visual acuity (reason for omission of the additional treatment)	Time of additional treatment
A-3	—*(hospitalization schedule could not be arranged owing to subject's convenience)	—
B-1	— (penetrating keratoplasty was highly likely to result in rejection owing to remarkable vascular invasion in the stroma)	—
C-1	— (unnecessary)	—
C-2	— (hospitalization schedule could not be arranged owing to subject's convenience)	—
C-3	— (unnecessary)	—
C-5	— (unnecessary)	—

* No additional treatment

Adverse events[9)] occurred in all of the 6 subjects after Week 52 of transplantation of Ocural. No deaths occurred, and a serious adverse event other than deaths occurred in 1 subject (cataract in 1 subject), but a causal relationship to Ocural was denied for this event. Adverse events for which a causal relationship to Ocural could not be ruled out occurred in 2 subjects (corneal epithelium defect and punctate keratitis in 1 subject and corneal epithelium defect in 1 subject).

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

The COMET01 and COMET01-FU studies, from which results were submitted as evaluation data in this application, were conducted in an open-label uncontrolled manner, and the evaluation method of the efficacy in clinical studies in patients with LSCD has not been established. PMDA reviewed the efficacy of Ocural in Section 7.R.2 in view of the following investigations:

Investigations

- Whether it is possible to evaluate the efficacy of Ocural based on results from the COMET01 and COMET01-FU studies, which are open-label uncontrolled studies

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- Appropriateness of the evaluation method of the efficacy (endpoints, evaluation points, and threshold)
- Some of the severity rating results differed between the investigator and data monitoring committee

7.R.2 Efficacy

7.R.2.1 Reason why the COMET01 study was conducted in an open-label uncontrolled manner

The applicant's explanation on conducting the COMET01 study as an open-label uncontrolled study:
When the COMET01 study was planned, conventional treatment for LSCD established in Japan was limited to allogeneic corneal limbal transplantation and autologous corneal limbal transplantation, and the COMET01 study was conducted in an open-label uncontrolled manner for the following reasons:
Reason why it was designed as an uncontrolled study

- For allogeneic corneal limbal transplantation, there is a chronic shortage of donors, requiring patients to wait for an eye donated for transplantation, and thus the enrollment is difficult. Allogeneic corneal limbal transplantation performed to treat LSCD frequently results in rejection with poor long-term prognosis. Especially, in patients with SJS or OCP, which can cause bilateral LSCD, its clinical outcome is unsatisfactory owing to underlying chronic inflammation and decreased lacrimation (*N Engl J Med.* 1999;340:1697-1703).
- Because the corneal limbal tissue collected for autologous corneal limbal transplantation is large in size, requiring a procedure highly invasive in the donor eye, such a transplantation has not been positively chosen and has been rarely performed.

Patients at Stage III have no normal corneal limbus left, and removal of the conjunctival scar tissue alone does not enable corneal epithelium reconstruction, and thus, the applicant considers it possible to evaluate the efficacy of Ocural by confirming corneal epithelium reconstruction even in an uncontrolled study.

Reason why it was designed as an open-label study

- It is difficult to blind the physician and subject to information about whether the transplantation of Ocural has been performed during the procedure with Ocural for medical care of LSCD and monitoring.

PMDA concluded that the above applicant's explanation is understandable and that it is acceptable for the applicant to have conducted the COMET01 study as an open-label uncontrolled study.

7.R.2.2 Efficacy endpoints, evaluation points, and threshold in the COMET01 study

The applicant's explanation about reasons for establishing the primary endpoint as the success rate (%) of corneal epithelium reconstruction at Week 52 of transplantation of Ocural, the secondary endpoints as corrected visual acuity, etc., and the efficacy threshold for the primary endpoint as 10%:
The fundamental treatment of LSCD is corneal epithelium reconstruction. The efficacy of Ocural is, therefore, evaluable on the success rate (%) of corneal epithelium reconstruction.

The evaluation points were specified through the following considerations. On the basis of a report (*Eye* 2004;18:241-8) showing that it took 35.6 ± 60.2 days for the autologous corneal limbus graft to achieve corneal epithelialization, a post-transplantation period of approximately 3 months might be enough for the cultured oral mucosal epithelium to complete epithelialization. On the other hand, some reports (*Invest Ophthalmol Vis Sci.* 1981;21:434-41, *Surv Ophthalmol.* 1997;41:275-313) indicated that it would take up to 1 year for the corneal epithelium graft to epithelialize and stabilize the recipient site. On the basis of these reports, to confirm normal restoration of the defective corneal epithelium with cultured oral mucosal epithelium with transplantation of Ocural, the follow-up period of approximately 1 year was considered necessary. The applicant planned to evaluate the success rate (%) of corneal epithelium reconstruction at Week 52 of transplantation.

In addition to the above, corrected visual acuity was included in the secondary endpoints to evaluate improvement of the clinical conditions.

For the efficacy threshold of the primary endpoint, a literature search meeting the following 4 requirements extracted 2 reports of published literature (*Ophthalmology.* 2002;109:1278-84, *Graefes Arch Clin Exp Ophthalmol.* 2011;249:1697-704). On the basis of these reports, the success rate (%) of corneal epithelium reconstruction in patients who underwent allogeneic corneal limbal transplantation was estimated to be 8.3% (1 of 12 eyes),[10)] and the efficacy threshold or clinically meaningful response rate was established at 10%. The published literature used in estimating the above value, however, presented long-term results with the follow-up period longer than 1 year.

- A report should present data that allow determination of the success rate (%) of corneal epithelium reconstruction in patients who have undergone allogeneic corneal limbal transplantation for treatment of SJS or OCP, which is a representative cause of LSCD and frequently results in severe LSCD at Stage III.
- A report should present data allow efficacy evaluation of single transplantation.
- A report should not cover corneal transplantation performed simultaneously to resolve stromal opacity.
- A report should present data with the follow-up period of ≥1 year.

PMDA's view:

The efficacy endpoints and evaluation points are acceptable. On the other hand, setting the efficacy threshold at 10%, the primary endpoint, is inappropriate for the following reasons:

- The 2 existing reports on allogeneic corneal limbal transplantation used in establishing the threshold by the applicant present long-term results with the follow-up period of >1 year, and the threshold was not established on the basis of results at 1 year of transplantation.
- There is an additional report (*Ophthalmology.* 2002;109:1159-66) that presents the clinical outcome of approximately 75% at 1 year of allogeneic corneal limbal transplantation.

10) In the report by Ilari et al. (*Ophthalmology.* 2002;109:1278-84), of treated eyes meeting the extraction requirements, 1 of 6 treated eyes was determined to have achieved successful corneal epithelium reconstruction, and in the remaining report by Han et al. (*Graefes Arch Clin Exp Ophthalmol.* 2011;249:1697-704), of 6 treated eyes meeting the extraction requirements, none was determined to have achieved successful reconstruction. In total, the success rate (%) of corneal epithelium reconstruction in patients who underwent allogeneic corneal limbal transplantation was estimated to be 8.3% (1 of 12 eyes).

PMDA decided to evaluate the efficacy on the basis of not only results from comparison between the success rate (%) of corneal epithelium reconstruction in the COMET01 study and threshold but also the estimated success rate (%) of corneal epithelium reconstruction, results on the secondary endpoints, and results at 2 years of transplantation in the COMET01-FU study.

7.R.2.3 Reason for the difference in LSCD severity rating results between the investigator and data monitoring committee

The applicant's explanation about the difference in LSCD severity rating results on Subject B-1 at screening between the investigator (Stage III) and data monitoring committee (Stage IA):
The following 2 reasons are considered to have caused the different rating results.

- Of 96 rating points in 6 subjects in total, 16 rating points[11)] in 5 subjects were given rating results that differed between the investigator and data monitoring committee (including rating points on the contralateral eye). Patients eligible for the study including Subject B-1 commonly have remarkable corneal stromal opacity and inflammation, which would make it difficult to identify the roughness of the anterior surface, which is important in rating the severity. In light of the above, the anterior condition in this subject might have been difficult to assess.
- The investigator rated the test eye condition by observing the test eye in detail under slit lamp examination and evaluating time-course information including findings at the previous observation, while the data monitoring committee rated it only with images at one point, which contained limited information. The difference in information volume between the raters was considered to affect the rating.

PMDA's view:
Although clear reasons for different severity rating results being given to the same subject have to be considered unknown, the above applicant's explanation is understandable to some extent. In addition, the efficacy analysis excluding data in Subject B-1, who was given different results at screening, indicated successful corneal epithelium reconstruction in all the remaining 5 subjects or the success rate of 100.0% (95% CI [47.8, 100.0]). The different rating results at screening in Subject B-1 were considered unlikely to affect conclusion on the efficacy of Ocural.

For the COMET01 study, the statistical analysis plan prepared after the start of the study (version 1.0 prepared on [redacted], 20[redacted]) included a statement to the effect that rating results of the eligibility assessment committee would be used in eligibility evaluation at screening, but the protocol did not include this. The concerned statement would affect the primary endpoint of Ocural. In view of open-label uncontrolled design of this study, it should have been originally included in the protocol before the start of the study.

11) The 16 rating points in 5 subjects include 4 rating points on the recipient eye and 1 rating point on the contralateral eye in Subject A-3, 1 and 5 rating points in Subject B-1, 2 and 0 rating points in Subject C-1, 1 and 0 rating points in Subject C-2, and 0 and 2 rating points in Subject C-3. Points with different rating results on the recipient eye were at screening in Subject B-1 (Stage III rated by the investigator and Stage IA rated by data monitoring committee); Weeks 2, 52, 78, and 104 of transplantation in Subject A-3 (Stage IA at all the points by the investigator and Stage IB, IB, IIB, and III at the respective points by data monitoring committee); Weeks 78 and 104 in Subject C-1 (Stage IA at both points by the investigator and Stage IIB at both points by the data monitoring committee); and Week 104 in Subject C-2 (Stage IA by the investigator and Stage IB by the data monitoring committee).

7.R.2.4 Efficacy

7.R.2.4.1 Corneal epithelium reconstruction

The applicant's explanation:

Because the COMET01 and COMET01-FU studies presented the following results, the efficacy of Ocural has been demonstrated.

The success rate (%) of corneal epithelium reconstruction at Week 52 of transplantation of Ocural, the primary endpoint, was 100.0% (6 of 6) of subjects (95% CI [54.1, 100.0]), showing a statistically significant difference in comparison with the predetermined threshold of 10% ($P \leq 0.0001$, two-sided significant level of 5%, one-sample binomial test). Furthermore, at Week 104 of transplantation of Ocural, the rate remained 66.7% (4 of 6) of subjects (95% CI [22.3, 95.7]), demonstrating maintenance of corneal epithelium reconstruction.

PMDA's view:

The efficacy of Ocural can be evaluated based on data from the COMET01 study, conducted as an open-label, uncontrolled study [see Section 7.R.2.1]. However, the efficacy threshold for the primary endpoint is not appropriately established in the COMET01 study [see Section 7.R.2.2], and PMDA cannot determine that the efficacy of Ocural is demonstrated just because the success rate (%) of corneal epithelium reconstruction at Week 52 of transplantation, the primary endpoint in the COMET01 study, showed a statistically significant difference in comparison with the threshold. Allogeneic corneal limbal transplantation, a conventional treatment of LSCD, on the other hand, leads to poor long-term prognosis due to immunological rejections, etc., requiring multiple transplantations owing to graft failure. Taking account of the above points, PMDA finds clinical significance in the study results showing that all of the 6 subjects who had undergone single transplantation of Ocural achieved successful corneal epithelium reconstruction in the COMET01 study and 4 of the 6 subjects maintained the reconstructed epithelium for an extended period in the COMET01-FU study. PMDA therefore concluded that the efficacy of Ocural is demonstrated to a certain extent.

7.R.2.4.2 Visual acuity

The applicant's explanation about results on visual acuity:

Table 29 shows changes in visual acuity in each subject in the COMET01 and COMET01-FU studies.

Table 29. Change in corrected visual acuity (visual acuity test with Landolt rings)

Subject number	At screening		Week 52 of transplantation		Week 104 of transplantation	
	Decimal visual acuity	Converted LogMAR value	Decimal visual acuity	Converted LogMAR value	Decimal visual acuity	Converted LogMAR value
A-3	0.001	+3.00	0.001	+3.00	0.001	+3.00
B-1	0.001	+3.00	0.001	+3.00	0.001	+3.00
C-1	0.03	+1.52	0.1	+1.00	0.06	+1.22
C-2	0.02	+1.70	0.01	+2.00	0.001	+3.00
C-3	0.01	+2.00	0.3	+0.52	0.1	+1.00
C-5	0.01	+2.00	0.04	+1.40	0.03	+1.52
Mean ± SD	—	+2.20 ± 0.64	—	+1.82 ± 1.04	—	+2.12 ± 0.97

Counting fingers and hand motion were handled as decimal visual acuity 0.01 (LogMAR +2.00) and decimal visual acuity 0.001 (LogMAR +3.00), respectively.

From screening to Week 52 of transplantation, visual acuity improved in 3 subjects, remained unchanged in 2 subjects, and worsened in 1 subject. In addition, a change in the converted logarithmic minimum angle of resolution (LogMAR) value (mean ± standard deviation [SD]), a scale of visual acuity, was −0.383 ± 0.637, indicating an improving trend.

From screening to Week 104 of transplantation, visual acuity improved in 3 subjects, remained unchanged in 2 subjects, and worsened in 1 subject. From Week 52 to Week 104 of transplantation, visual acuity improved in none of the subjects, remained unchanged in 2 subjects, and worsened in 4 subjects. A change in the converted LogMAR value (mean ± SD) from screening to Week 104 of transplantation was −0.080 ± 0.771, indicating a slightly improving trend, but that from Week 52 to Week 104 of transplantation was +0.303 ± 0.385, indicating a worsening trend.

PMDA asked the applicant to explain reasons for the worsening trend of visual acuity from Week 52 to Week 104 of transplantation in each subject.

The applicant's explanation:
From Week 52 to Week 104 of transplantation, visual acuity worsened in Subjects C-1, C-2, C-3, and C-5. In Subject C-1, corneal opacity worsened from Grade 1 at Week 24 to Grade 2 at Week 52 and subsequent points. The worsened corneal opacity is considered to have negatively affected visual acuity. In Subject C-2, cataract was found in the recipient eye at the enrollment in the COMET01 study, and lens opacity, when rated according to Emery-Little Classification, worsened from Grade 2 at screening to Grade 4 at Week 104. The progression of cataract is considered to have decreased visual acuity. In Subjects C-3 and C-5, data on decimal visual acuity showed a worsening trend, but data on Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity, as presented in Table 30, did not show such a trend. The worsening changes in these subjects are considered to fall within a diurnal variation.

Table 30. Results on corrected visual acuity in subjects showing a worsening trend of visual acuity from Week 52 to Week 104 of transplantation

Subject number		At screening	Week 24	Week 52	Week 78	Week 104
C-1	Decimal visual acuity	0.03	0.3	0.1	0.2	0.06
	Converted LogMAR value	+1.52	+0.52	+1.00	+0.70	+1.22
	ETDRS	+1.50	+0.46	+1.16	+1.04	+1.44
C-2	Decimal visual acuity	0.02	0.02	0.01	0.01	0.001
	Converted LogMAR value	+1.70	+1.70	+2.00	+2.00	+3.00
	ETDRS	+1.60	+2.00	+2.00	+2.00	+3.00
C-3	Decimal visual acuity	0.01	0.15	0.3	0.1	0.1
	Converted LogMAR value	+2.00	+0.82	+0.52	+1.00	+1.00
	ETDRS	+2.00	+1.18	+1.24	+2.00	+1.04
C-5	Decimal visual acuity	0.01	0.03	0.04	0.04	0.03
	Converted LogMAR value	+2.00	+1.52	+1.40	+1.40	+1.52
	ETDRS	+2.00	+1.52	+1.50	+1.54	+1.50

Counting fingers and hand motion were handled as decimal visual acuity 0.01 (LogMAR +2.00) and decimal visual acuity 0.001 (LogMAR +3.00), respectively.

PMDA's view:
From screening to Week 52 of transplantation, visual acuity improved in 3 of 6 subjects (Subjects C-1, C-3, and C-5) and was maintained in 2 of 6 subjects (Subjects A-3 and B-1). These results are considered meaningful.

From Week 52 to Week 104 of transplantation, on the other hand, visual acuity worsened in 4 of 6 subjects (Subjects C-1, C-2, C-3, and C-5). Especially, in Subject C-2, visual acuity worsened from screening to both Weeks 52 and 104. PMDA views these results as follows:

- In Subject C-1, the decreased visual acuity can be explained by the worsened corneal opacity. Transplantation of Ocural may have had a limited positive effect on the ocular surface.
- In Subject C-2, the decreased visual acuity can be explained by progression of cataract.
- In Subjects C-3 and C-5, the worsening changes in visual acuity can be explained to fall within a diurnal variation.

Because visual acuity improved or was maintained in all the subjects in the COMET01 and COMET01-FU studies except for Subject C-2 with progressed cataract, Ocural was confirmed to have a positive effect on visual acuity to a certain extent.

7.R.2.4.3 Additional treatment of keratoplasty

PMDA asked the applicant to explain the meaning of prior transplantation of Ocural in patients with stromal opacity, etc. requiring keratoplasty to improve visual acuity.

The applicant's explanation:
A two-step operation consisting of cultured autologous oral mucosal epithelium transplantation for corneal epithelium reconstruction with adequate antiinflammatory therapy and subsequent penetrating or lamellar keratoplasty (LKP) in patients with LSCD complicated by corneal stroma vascular invasion and corneal stromal opacity reduced a risk of epithelial rejection and achieved favorable visual acuity improvement (*Ophthalmology.* 2013;120:193-200, *Am J Ophthalmol.* 2006;142:757-764, etc.). On the basis of the above findings, additional treatment of keratoplasty after transplantation of Ocural in patients with remarkable vascular invasion into the corneal stroma is expected to improve visual acuity.

PMDA can understand to a certain extent that keratoplasty for improved visual acuity in patients with LSCD who have received Ocural is expected to improve visual function. In the trial, however, none of the subjects have undergone keratoplasty after transplantation of Ocural, and results of keratoplasty after use of Ocural remain unknown. At present, it has limitations to discuss meaning of prior transplantation of Ocural in patients requiring keratoplasty for improved visual acuity. When a case of keratoplasty performed after transplantation of Ocural is reported in a post-marketing surveillance, it is desirable to discuss the meaning of transplantation of Ocural prior to keratoplasty based on collected information about visual acuity, etc., and such a discussion is considered to be beneficial in evaluating the usefulness of Ocural.

7.R.3 Safety

7.R.3.1 Adverse events in the COMET01 and COMET01-FU studies

The applicant's explanation about the safety of Ocural:
Adverse events during the run-in and treatment periods in the COMET01 study and the COMET01-FU study are as shown below.

During the run-in period in the COMET01 study, arthralgia occurred in 1 subject. The event was not serious, and its causal relationship to tissue collection was denied.

Table 31 shows local adverse events in the eyes during the treatment period in the COMET01 study and the COMET01-FU study.

Table 31. Local adverse events in the eyes during the treatment period in the COMET01 study and the COMET01-FU study

	Recipient eye	Contralateral eye
All adverse events	6 (100.0)	5 (83.3)
Serious adverse events	0	2 (33.3)
Major adverse events		
Corneal epithelium defect	6 (100.0)	4 (66.7)
Eye pain	3 (50.0)	1 (16.7)
Corneal neovascularisation	3 (50.0)	0
Corneal opacity	1 (16.7)	0
Punctate keratitis	1 (16.7)	0
Chalazion	1 (16.7)	0
Ocular hypertension	1 (16.7)	0
Cataract	0	1 (16.7)
Dacryocystitis	0	1 (16.7)

Number of subjects with the event (incidence, %)
Medical Dictionary for Regulatory Activities Japanese version (MedDRA/J) Ver 20.1

Of the events presented in Table 31, events in the recipient eye were corneal epithelium defect, corneal neovascularisation, corneal opacity, and punctate keratitis, and a causal relationship to Ocural could not be ruled out for all of these events.

Adverse events during the treatment period in the COMET01 study and the COMET01-FU study except for local adverse events in the eyes were rash in 2 subjects, and tinea pedis, cellulitis, herpes zoster, diabetes mellitus, alanine aminotransferase (ALT) increased, bone density decreased, vomiting, headache, gastrointestinal disorder, constipation, pruritus, proctitis, toothache, and nasopharyngitis in 1 subject each. A causal relationship to Ocural was denied for all of these events [for serious events, see Section 7.1].

7.R.3.2 Major safety endpoints

Tables 32 and 33 show incidences of superficial punctate keratopathy, corneal epithelium defect, corneal keratosis, conjunctival hyperaemia, corneal infection, and endophthalmitis, the safety endpoints for the COMET01 study.

The applicant's explanation about the safety related to each of these events:

Table 32. Change in condition of safety endpoints from screening to Week 52 of transplantation (recipient eye)

Subject number	Superficial punctate keratopathy	Corneal epithelium defect	Corneal keratosis	Conjunctival hyperaemia	Corneal infection	Endophthalmitis
A-3	Alleviated	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged
B-1	Unchanged	Worsened	Unchanged	Alleviated	Unchanged	Unchanged
C-1	Alleviated	Worsened	Unchanged	Unchanged	Unchanged	Unchanged
C-2	Alleviated	Unchanged	Unchanged	Alleviated	Unchanged	Unchanged
C-3	Alleviated	Unchanged	Unchanged	Alleviated	Unchanged	Unchanged
C-5	Unchanged	Unchanged	Unchanged	Alleviated	Unchanged	Unchanged

Table 33. Summary of changes in condition of safety endpoints from screening to Week 52 of transplantation (recipient eye)

	Superficial punctate keratopathy	Corneal epithelium defect	Corneal keratosis	Conjunctival hyperaemia	Corneal infection	Endophthalmitis
Number of subjects rated	6	6	6	6	6	6
Alleviated	4 (66.7)	0	0	4 (66.7)	0	0
Unchanged	2 (33.3)	4 (66.7)	6 (100.0)	2 (33.3)	6 (100.0)	6 (100.0)
Worsened	0	2 (33.3)	0	0	0	0

Number of subjects (proportion, %)
MedDRA/J Ver 20.1

(a) Superficial punctate keratopathy

In the preoperative recipient eye, superficial punctate keratopathy was observed in all the subjects. In the postoperative recipient eye at Week 52 of transplantation of Ocural, superficial punctate keratopathy resolved (superficial punctate keratopathy invisible) or was resolving in 4 subjects, and the condition remained unchanged in 2 subjects. None of the subjects experienced worsening.

(b) Corneal epithelium defect

In the preoperative recipient eye, corneal epithelium defect was not observed in all of the subjects. A total of 5 subjects experienced at least one event of corneal epithelium defect during the study, and 2 subjects were found to have corneal epithelium defect at Week 52 of transplantation of Ocural. All the events were mild.[12)]

(c) Conjunctival hyperaemia

In the preoperative recipient eye, conjunctival haemorrhage was observed in all the subjects. In the postoperative recipient eye at Week 52 of transplantation of Ocural, conjunctival hyperaemia resolved (conjunctival hyperaemia invisible) or was resolving in 4 subjects, and the condition remained unchanged in 2 subjects. None of the subjects experienced worsening.

(d) Corneal keratosis, corneal infection, and endophthalmitis

In the recipient eye, none of corneal keratosis, corneal infection, and endophthalmitis occurred throughout the trial.

12) Local adverse events in the eyes were rated according to the following criteria:
Mild: Readily tolerable sign or symptom
Moderate: Sign or symptom interfering with activity of daily living
Severe: Sign or symptom precluding working or activity of daily living

PMDA's view:
The safety profile did not raise any particular concern because no adverse events requiring particular attention occurred in subjects who had received Ocural in the COMET01 and COMET01-FU studies; the events specified as the safety endpoints for the COMET01 study were resolving in most of the subjects after transplantation of Ocural; and the events found to be worsened after the transplantation were mild in severity. On the other hand, the number of subjects included in the clinical studies was very limited, and information should be continuously collected in a post-marketing surveillance.

7.R.3.3 Potential underestimation of adverse events

PMDA asked the applicant to explain potential underestimation of abnormal findings associated with subjective symptoms such as punctate keratitis and corneal infection owing to absence of corneal sensory neurons in Ocural.

The applicant's explanation:

- In the COMET01 and COMET01-FU studies, subjects were observed for abnormal findings such as punctate keratitis and corneal infection by the investigator daily during the hospitalization period and once every 2 to 4 weeks after discharge. It is considered unlikely to have overlooked these abnormal findings if any.
- For punctate keratitis, "superficial punctate keratopathy" was specified as the safety endpoint in the COMET01 study, and its occurrence was examined at every scheduled visit. In the COMET01-FU study, an adverse event of punctate keratitis occurred in 1 subject. As described above, the investigator observed each subject for abnormal findings such as punctate keratitis at every visit and appropriately reported adverse events if found.
- Corneal infection was also specified as the safety endpoint in the COMET01 study, and subjects were observed for its occurrence at every scheduled visit. Throughout a period from screening to Week 52 of transplantation of Ocural, no relevant symptoms were observed. In the COMET01-FU study, none of the subjects experienced corneal infection.

PMDA considers that the applicant's explanation about clinical studies is acceptable; however, abnormal findings of a corneal disease which is originally associated with subjective symptoms may not manifest after transplantation of Ocural, delaying discovery of the disease. For the risk minimization, the following caution should be provided to healthcare professionals using labeling and other information leaflet to inform: Patients who have received Ocural should be continuously followed up.

7.R.3.4 Risk of infections

PMDA asked the applicant to explain a risk of infections after transplantation of Ocural, more specifically, whether corneal infection or endophthalmitis may be raised as problems in clinical settings.

The applicant's explanation:

- The invasive procedure in the ocular surface associated with transplantation of Ocural may cause a corneal infection, but post-operative use of antimicrobial agents can prevent the onset. In addition,

the operation for transplantation of Ocural, which should be invasive only in the ocular surface, is considered unlikely to cause endophthalmitis.

- Conventional ophthalmologic practices can manage infections, not requiring Ocural-specific practices. A caution calling attention to corneal infections and endophthalmitis is considered unnecessary.

PMDA's view:
The applicant's explanation that conventional post-operative ophthalmologic measures can prevent the infections is understandable, although patients who have received Ocural should be carefully monitored for any onset of a corneal infection. In addition, PMDA accepted the applicant's explanation that transplantation of Ocural, which should be invasive only in the ocular surface, is unlikely to cause endophthalmitis.

7.R.3.5 Defective graft

PMDA asked the applicant to explain a risk of defective Ocural graft, more specifically, whether poor survival of the graft, breakage and deviation of the graft, and neoplastic transformation of the graft may be raised as problems in clinical settings.

The applicant's explanation:
(a) Poor survival of the graft
Poor survival of the graft may be caused by a corneal infection or inflammation after transplantation of Ocural. These potential causes can be prevented by post-operative use of antimicrobial agents and anti-inflammatory agents such as steroids as with that for the other ophthalmic surgery.

(b) Breakage and deviation of the graft
Deviation and breakage of the graft may be caused by strong physical irritation on the ocular surface after transplantation of Ocural. These potential causes can be prevented by suture of the Ocural rim, use of a therapeutic contact lens, and tarsorrhaphy where necessary.

(c) Neoplastic transformation of the graft
Non-clinical studies suggested that a tumorigenicity risk of Ocural would be low. In addition, no tumor lesion was found at the transplantation site of Ocural in the COMET01 and COMET01-FU studies, and neoplastic transformation of the graft after transplantation of Ocural is considered unlikely to be raised as a problem in clinical settings.

PMDA's view:
The applicant's explanation that appropriate post-operative treatment can reduce a risk of poor graft survival, and breakage and deviation of the graft is acceptable. Although none of the findings and events related to neoplastic transformation of the graft have been observed in non-clinical or clinical studies, information on the neoplastic transformation should be collected through a post-marketing surveillance as it is deemed as a potential risk.

7.R.4 Clinical positioning

The applicant's explanation about clinical positioning of Ocural in treatment of LSCD:
The following problems exist in the conventional procedures for corneal epithelium reconstruction in treatment of LSCD, allogeneic and autologous corneal limbal transplantations, and the human (autologous) corneal limbus-derived corneal epithelial cell sheet approved in March 2020 for the indication of LSCD.

- Allogeneic corneal limbal transplantation leads to poor prognosis owing to infective keratitis and immunological rejections, and furthermore the shortage of donors is serious.
- Autologous corneal limbal transplantation requires extensive piece of corneal limbal tissue collected from the contralateral eye of the patient, requiring a procedure highly invasive in the donor eye, and thus it has not been positively chosen in Japan. In addition, this transplantation is not applicable to bilateral LSCD.
- Human (autologous) corneal limbus-derived corneal epithelial cell sheet may achieve corneal epithelium reconstruction, using patient's own corneal epithelial cells, but it is not applicable to patients in whom collecting a raw material of corneal limbal tissue is difficult or an invasive procedure in the corneal limbus should be avoided. Furthermore, some of causative etiologies are excluded from the indication.

Compared with the above options, Ocural has the following advantages and thus is positioned as a new option in treatment of LSCD:

- Because the patient's own cells are used in the treatment, it has no risk of immunological rejections, which is a problem associated with the allogeneic corneal limbal transplantation.
- Ocural does not require collection of corneal limbal tissue, and thus it can offer a therapeutic option to patients with LSCD to whom autologous corneal limbal transplantation or human (autologous) corneal limbus-derived corneal epithelial cell sheet cannot be applied owing to no corneal limbus left for collection or in whom an invasive procedure in the normal corneal limbus should be avoided.

PMDA accepted the above applicant's explanation.

7.R.5 Indication or performance

The proposed "Indication or Performance" of Ocural was "limbal stem cell deficiency" and "Precautions Concerning Indication or Performance" were not specified.

The applicant's explanation:
Transplantation of Ocural in the COMET01 study in patients with LSCD improved the LSCD severity and resulted in corneal epithelium reconstruction, and Ocural was considered to be positioned as a new option in treatment of LSCD [see Section 7.R.4]. The "Indication or Performance" of Ocural was proposed to be "limbal stem cell deficiency."

On the basis of Sections "7.R.2 Efficacy," "7.R.3 Safety," and "7.R.4 Clinical positioning" as well as the following review, PMDA concluded the "Indication or Performance" and "Precautions Concerning Indication or Performance" sections of Ocural should be established as show below.

Indication or Performance
Limbal stem cell deficiency

Precautions Concerning Indication or Performance
- Ocural should be used in the following patients:
  "In the affected eye, conjunctivalization involves ≥50% of the entire corneal limbus and extends to an area within 5 mm in diameter including the central cornea in the affected eye" or "removal of conjunctival scar tissue in the affected eye (amniotic membrane transplantation where necessary) is not effective, and conjunctivalization extends to an area within 5 mm in diameter including the central cornea in the affected eye."
- Because Ocural is not intended to treat any cause of limbal stem cell deficiency, Ocural should be used after the causative disease of limbal stem cell deficiency is controlled or the cause is removed.

7.R.5.1 LSCD severity

PMDA asked the applicant to explain severity of LSCD eligible for Ocural.

The applicant's explanation:
The efficacy and safety of Ocural were demonstrated in the COMET01 study in patients with LSCD at Stage III rated according to the severity classification, and Ocural should be indicated for patients at Stage III.

The COMET01 study only included patients at Stage III defined as a condition of the corneal surface totally covered with conjunctival tissue. On the other hand, conventional treatment available for patients at Stage IIB defined as a condition of conjunctivalization involving the central cornea and ≥50% of the entire corneal limbus is limited to allogeneic and autologous corneal limbal transplantations and human (autologous) corneal limbus-derived corneal epithelial cell sheet transplantation, which have the problems presented in Section 7.R.4. Ocural consists of oral mucosal epithelial cells that include stem cells derived from oral mucosal epithelium, and its transplantation is presumed to lead to restoration of the corneal epithelium. In view of the above presumed mechanism of action, Ocural is expected to be effective even in treatment of LSCD at Stage IIB and serves as an option of the treatment.

In addition, Ocural can serve as a treatment option for patients with conjunctivalization involving the central cornea and covering <50% of the corneal limbus (Stage IIA according to the severity classification) who have undergone removal of conjunctival scar tissue (amniotic membrane transplantation where necessary) due to conventional eligibility for removal of conjunctival scar tissue (and amniotic membrane transplantation where necessary) but have failed to achieve corneal epithelium reconstruction.

Furthermore, affected eyes at Stages IA to IC with the central cornea free from conjunctivalization do not need Ocural because these are kept under clinical observation.

PMDA's view:
The above applicant's explanation about the eligible LSCD severity is acceptable, so that Ocural would be recommended for patients with LSCD at Stage III, corresponding to the patient population of the COMET01 study. In addition, even for patients with LSCD at Stage IIB or Stage IIA, Ocural can be meaningful as a new option for treatment if they have undergone removal of conjunctival scar tissue (amniotic membrane transplantation where necessary) but failed to achieve corneal epithelium reconstruction, taking into account that the conventional treatment has problems [see Section 7.R.4] and LSCD is a serious disease adversely affecting activities of daily living (ADL), etc. Caution statements on the LSCD severity eligible for Ocural should be included in the "Precautions Concerning Indication or Performance" section.

7.R.5.2 Causative etiology of LSCD

PMDA asked the applicant to explain the appropriateness of specifying the indication of Ocural as "limbal stem cell deficiency" of any causative etiology.

The applicant's explanation:
Ocural is an oral mucosal epithelial cell sheet manufactured using the patient's own oral mucosal tissue as a raw material and can be indicated for a particular class of LSCD caused by refractory corneal and conjunctival epithelium diseases such as SJS and OCP, which frequently result in severe conditions. In addition, Ocural may be indicated for the patients in whom an invasive procedure in the intact eye should be avoided or intact corneal limbus is not adequately left for treatment of the affected eye.

The COMET01 study enrolled patients with LSCD caused by SJS, OCP, congenital aniridia, and idiopathic LSCD and demonstrated the efficacy and safety of Ocural in these patients. The efficacy and safety of Ocural in patients with LSCD caused by injuries and diseases other than the above were discussed on the basis of LSCD etiology classification presented in published literature (*Cornea.* 2019;38:364-75) as shown below. For LSCD of any etiology, Ocural can be indicated as long as care and treatment have been provided to the ocular surface condition, comorbidities, and general conditions before transplantation of Ocural wherever possible, and the disease is controlled.

(a) Acquired nonimmune-mediated LSCD
Causes of acquired nonimmune-mediated LSCD include chemical injury (alkali, acid), thermal injury, severe pterygium, etc. Such extrinsic factors damage corneal epithelial stem cells in the corneal limbus in most of the cases, leading to development of LSCD. In addition to conjunctivalization of the corneal epithelium, decreased lacrimation and symblepharon depending on an etiology and chronic inflammation in some patients may occur. For transplantation of Ocural, stabilization of the ocular surface condition as well as control of comorbidities potentially affecting the ocular surface such as glaucoma and diabetes mellitus are required; however, as long as appropriate control is ensured, transplantation of Ocural is deemed possible.

Furthermore, in patients with acquired nonimmune-mediated LSCD, the oral mucosa used as a raw material of Ocural is free from abnormalities specific to the etiology. An oral mucosal tissue piece, if

collected from the normal tissue visually free from infection, inflammation, and scars, will allow manufacture of the proper quality product.

Ocural, when transplanted in place of the extrinsically damaged corneal epithelium, is presumed to achieve its reconstruction and maintenance with the cultured oral mucosal epithelium and thus is expected to be effective. A safety risk of Ocural can be avoided by appropriate care and treatment given to control and stabilize symptoms of the etiology.

(b) Acquired primary immune-mediated LSCD

Causes of acquired primary immune-mediated LSCD include not only SJS and OCP, with which patients were enrolled in the COMET01 study, but also allergy (vernal keratoconjunctivitis and atopic keratoconjunctivitis) and graft versus host disease. Inflammation associated with immunological reactions of any etiology damages corneal epithelial stem cells in the corneal limbus, leading to development of LSCD.

In patients with acquired primary immune-mediated LSCD, the first priority must be given to care and treatment appropriate for the etiology to stabilize the general condition (especially inflammatory reactions). In addition to conjunctivalization of the corneal epithelium, decreased lacrimation, symblepharon, and trichiasis depending on an etiology and chronic inflammation in some patients may occur. Once the general condition is stabilized in these patients, the ocular surface condition has to be stabilized. For transplantation of Ocural, stabilization of the general and ocular surface conditions as well as control of comorbidities potentially affecting the ocular surface such as glaucoma and diabetes mellitus are required; however, as long as appropriate control is ensured, transplantation of Ocural is deemed possible.

Although patients with graft versus host disease may have a disease-specific abnormality in the oral mucosa, an oral mucosal tissue, if collected from the normal tissue after visual inspection for any abnormality, will allow manufacture of the proper quality product.

Ocural, when transplanted in place of the corneal epithelium damaged by inflammation associated with immunological reactions, is presumed to achieve its reconstruction and maintenance with the cultured oral mucosal epithelium and thus is expected to show its efficacy. A safety risk of Ocural in the local sites (eye and oral cavity) and whole body can be avoided by appropriate care and treatment given to stabilize symptoms of the etiology adequately.

(c) Hereditary LSCD

A cause of hereditary LSCD includes congenital aniridia, with which patients were enrolled in the COMET01 study. Other possible causes were autoimmune polyglandular syndrome, xeroderma pigmentosum, and epidermolysis bullosa (*Cornea.* 2006;25:112-4, *Eye [Lond]* 2004;18:741-3, *Cornea.* 2010;29:462-4, etc.), but all of these were found in case reports. Details of their history leading to LSCD remain unclear. In patients with hereditary LSCD, the first priority must be given to care and treatment appropriate for the etiology to stabilize the general condition. Once the general condition is stabilized, transplantation of Ocural should be considered.

Although patients with autoimmune polyglandular syndrome or epidermolysis bullosa may have an etiology-specific abnormality (erythema, blister, scar, etc.) in the oral mucosa, an oral mucosal tissue will allow manufacture of the proper quality product, if collected from the normal tissue after visual inspection for any abnormality.

Evidence on the mechanism of development of hereditary LSCD is limited, but Ocural, when transplanted in place of the corneal epithelium damaged by the hereditary disease, is presumed to achieve its reconstruction and maintenance with the cultured oral mucosal epithelium and thus is expected to show its efficacy. A safety risk of Ocural in the local sites (eye and oral cavity) and whole body can be avoided by care and treatment given to stabilize symptoms of the etiology adequately.

PMDA's view:
The applicant's explanation is acceptable. Ocural, which does not use corneal cells, may be indicated for LSCD of any causative etiology as long as the oral mucosal tissue piece is collected from the normal tissue. The "Precautions Concerning Indication or Performance" section, however, should include the caution statement that the causative disease of LSCD should be controlled or removed before use of Ocural. Because use experience with Ocural is very limited, characteristics of the patients enrolled in the clinical studies such as etiology should be provided in the "Clinical Studies" section of the package insert, and information about etiology of LSCD treated with Ocural and result of manufacture of Ocural should be collected after the market launch.

7.R.5.3 Use of Ocural in patients with remarkable corneal stroma vascular invasion or corneal stromal opacity

In Subject B-1 in the COMET01 and COMET01-FU studies, keratoplasty was not performed owing to remarkable corneal stroma vascular invasion, which led to a decision that penetrating keratoplasty would be highly likely to result in rejection [see Table 28 in Section 7.2]. Concerning this case, PMDA asked the applicant to explain the meaning of use of Ocural in patients with remarkable corneal stroma vascular invasion or corneal stromal opacity.

The applicant's explanation:

- In patients with remarkable corneal stroma vascular invasion, keratoplasty is one of the options for treatment and can be performed under anti-inflammatory management with steroids or immunosuppressive management with cyclosporine where necessary.
- In Subject B-1, the cornea of the recipient eye was covered by conjunctival scar tissue, precluding assessment of an extent of stroma vascular invasion before transplantation of Ocural, but keratoplasty under immunosuppressive management was considered possible. At both Weeks 52 and 104 of transplantation of Ocural, keratoplasty was positively considered.
- In this subject, however, the contralateral eye was found to have keratinization at start of the trial and experienced worsening of LSCD during the trial period, resulting in a severer condition than that in the recipient eye. The following decision was made on the recipient eye in a relatively favorable condition: Its conservation was more beneficial than keratoplasty, which had a risk of rejection, etc. potentially decreasing visual acuity.

Then, Ocural has the following clinical advantages, and transplantation of Ocural is considerably meaningful even in patients who do not receive additional treatment of keratoplasty to improve visual acuity with cleared corneal stroma.

- Without treatment, any eye with LSCD would be continuously worsening as observed in the contralateral eye in Subject B-1. Transplantation of Ocural can stop worsening of LSCD.
- In patients with low visual acuity, transplantation of Ocural is presumed to improve visual function by clearing opacity of the corneal epithelium even if the decimal visual acuity remains unchanged.
- Transplantation of Ocural can be expected to alleviate subjective symptoms such as eye pain, sensation of foreign body, lacrimation, photophobia, dry feeling, and discomfort.

PMDA concluded that the following applicant's explanation is understandable and acceptable: Ocural is considered less useful in patients with remarkable corneal stroma vascular invasion or corneal stromal opacity than in patients without corneal opacity when used alone but its use is meaningful to a certain extent.

7.R.6 Dosage and administration or method of use

The proposed "Dosage and Administration or Method of Use" and "Precautions Concerning Dosage and Administration or Method of Use" of Ocural were established based on the COMET01 study as shown below.

Dosage and Administration or Method of Use

Operations in manufacture of oral mucosal epithelial cell sheet

1. An area in the patient's oral cavity is confirmed to be free from inflammation, infection, and scar, and approximately a 10 × 5 mm piece of the oral mucosal tissue is collected. The collected oral mucosal tissue is placed in a tissue transport tube and sent to the manufacturer.
2. Blood is collected in accordance with a conventional procedure. The collected blood is placed in a blood storage tube and sent to the manufacturer. This blood specimen is used as the reserve sample.

Operations in transplantation of oral mucosal epithelial cell sheet

The oral mucosal epithelial cell sheet is detached with a ring-shaped culture disk from the oral mucosal epithelium culture dish. Conjunctival scar tissue is removed from the eye surface of the patient wherever possible, and the oral mucosal epithelial cell sheet is transplanted onto the eye surface including the corneal limbus. The rim of the oral mucosal epithelial cell sheet is sutured where necessary. After the transplantation, the therapeutic contact lens is applied and tarsorrhaphy is performed where necessary.

Precautions Concerning Dosage and Administration or Method of Use

Precautions during manufacture of oral mucosal epithelial cell sheet

1. The transplantation plan including scheduled dates of tissue collection and transplantation should be developed using the specified format designated by the marketing authorization holder.
2. It should be confirmed that the tissue transport tube and blood storage tube are containers dedicated to the patient by checking the labels before tissue collection.

3. Collection of the oral mucosal tissue and its immersion into the tissue transportation fluid should be performed in a clean environment.
4. The oral mucosal tissue piece that is intact and includes the basal lamina should be collected.
5. Alternative treatment should be considered in advance because the cultured oral mucosal epithelium package may not be released or the transplanted oral mucosal epithelial cell sheet may not survive.

Precautions during oral mucosal epithelial cell sheet transplantation

1. It should be confirmed that the transportation container is sealed at the delivery of the cultured oral mucosal epithelium package. If the seal is broken, the package should not be opened, and the marketing authorization holder should be contacted.
2. To prevent mix-up, it should be confirmed that the oral mucosal epithelial cell sheet to be transplanted is dedicated to the patient by checking the label on the cultured oral mucosal epithelium package.
3. The cultured oral mucosal epithelium package should be stored in a transportation container or at 20°C to 28°C until just before use.
4. To protect from drying, the oral mucosal epithelial cell sheet should be kept immersed in HBSS or an intraocular perfusate in the culture dish for cultured oral mucosal epithelium until just before transplantation.
5. If symblepharon may occur, an appropriate procedure should be performed before transplantation.
6. Any fluid should be removed from the eye surface before placing the oral mucosal epithelial cell sheet.
7. The oral mucosal epithelial cell sheet should be placed on the eye surface in the right-side-up position, preventing the sheet from being placed upside-down.
8. Onto the oral mucosal epithelial cell sheet placed on the eye surface, an intraocular perfusate should be slowly dropped to protect it from drying.
9. The oral mucosal epithelial cell sheet should be removed from a ring-shaped culture disk by applying a scalpel to the internal circumference of the ring.

PMDA's view:

It is acceptable to establish the "Dosage and Administration or Method of Use" based on the conditions in the COMET01 study, which demonstrated the clinical usefulness of Ocural. As a result of review for collection of the oral mucosal tissue, measures after transplantation of Ocural, and the possibility of re-transplantation of Ocural as shown below, the "Dosage and Administration or Method of Use" and "Precautions Concerning Dosage and Administration or Method of Use" sections should be specified as shown below.

Dosage and Administration or Method of Use (Underline denotes additions, and strikethrough denotes deletions.)

Operations in manufacture of oral mucosal epithelial cell sheet

1. An area in the patient's intraoral <u>buccal mucosal part</u> is confirmed to be free from inflammation, infection, and scar, and approximately a 10 × 5 mm piece of the oral mucosal tissue is collected. The collected oral mucosal tissue is placed in a tissue transport tube and sent to the manufacturer.

2. Blood is collected in accordance with a conventional procedure. The collected blood is placed in a blood storage tube and sent to the manufacturer. This blood specimen is used as the reserve sample.

Operations in transplantation of oral mucosal epithelial cell sheet

The oral mucosal epithelial cell sheet is detached with a ring-shaped culture disk from the oral mucosal epithelium culture dish. Conjunctival scar tissue is removed from the eye surface of the patient wherever possible, and the oral mucosal epithelial cell sheet is transplanted onto the eye surface including the corneal limbus. The rim of the oral mucosal epithelial cell sheet is sutured where necessary. After the transplantation, the therapeutic contact lens is applied and tarsorrhaphy is performed where necessary.

Precautions Concerning Dosage and Administration or Method of Use

Precautions during manufacture of oral mucosal epithelial cell sheet

1. The transplantation plan including scheduled dates of tissue collection and transplantation should be developed using the specified format designated by the marketing authorization holder.
2. It should be confirmed that the tissue transport tube and blood storage tube are containers dedicated to the patient by checking the labels before tissue collection.
3. Collection of the oral mucosal tissue and its immersion into the tissue transportation fluid should be performed in a clean environment.
4. The oral mucosal tissue piece should be collected from ~~that is~~ the intact tissue by deeply cutting the tissue to the lamina propria so that the tissue piece ~~and~~ includes reliably the basal lamina ~~should be collected~~.
5. Alternative treatment should be considered in advance because the cultured oral mucosal epithelium package may not be released or the transplanted oral mucosal epithelial cell sheet may not survive.

Precautions during oral mucosal epithelial cell sheet transplantation

1. It should be confirmed that the transportation container is sealed at the delivery of the cultured oral mucosal epithelium package. If the seal is broken, the package should not be opened, and the marketing authorization holder should be contacted.
2. To prevent mix-up, it should be confirmed that the oral mucosal epithelial cell sheet to be transplanted is dedicated to the patient by checking the label on the cultured oral mucosal epithelium package.
3. The cultured oral mucosal epithelium package should be stored in a transportation container or at 20°C to 28°C until just before use.
4. To protect from drying, the oral mucosal epithelial cell sheet should be kept immersed in HBSS or an intraocular perfusate in the culture dish for cultured oral mucosal epithelium until just before transplantation.
5. If symblepharon may occur, an appropriate procedure should be performed before transplantation.
6. Any fluid should be removed from the eye surface before placing the oral mucosal epithelial cell sheet.
7. The oral mucosal epithelial cell sheet should be placed on the eye surface in the right-side-up position, preventing the sheet from being placed upside-down.
8. Onto the oral mucosal epithelial cell sheet placed on the eye surface, an intraocular perfusate should be slowly dropped to protect it from drying.

9. The oral mucosal epithelial cell sheet should be removed from a ring-shaped culture disk by applying a scalpel to the internal circumference of the ring.

7.R.6.1 Collection of oral mucosal tissue

The proposed "Dosage and Administration or Method of Use" did not specify the collection site of the oral mucosal tissue piece, and PMDA asked the applicant to explain the presumed collection site of the oral mucosal tissue piece after marketing and the appropriateness of the proposed settings for collection site of the oral mucosal tissue piece.

The applicant's explanation about the collection site of the oral mucosal tissue piece in the COMET01 study and relevant measures:

- In the COMET01 study, the collection site of the oral mucosal tissue piece had been specified as an area visually free from scars and inflammation, but details were not specified. In all the subjects, the oral mucosal tissue piece was collected from the readily accessible buccal mucosal part.
- The labial mucosa and sublingual mucosa, classified into the covering mucosa group as with the buccal mucosa, and gingival mucosa, classified into the masticatory mucosa group, are more difficult to collect and manage after procedure than the buccal mucosa. The collection site of the oral mucosal tissue piece should be specified as the buccal mucosal part after marketing.
- In view of the above, the "Dosage and Administration or Method of Use" section of Ocural will be specified that "An area in the patient's intraoral buccal mucosal part is confirmed to be free from inflammation, infection, and scar, and approximately a 10 × 5 mm piece of the oral mucosal tissue is collected. The collected oral mucosal tissue is placed in a tissue transport tube and sent to the manufacturer."

Most of ophthalmologists do not have experience with the technique in the oral cavity. In light of this situation, PMDA asked the applicant to explain the following points:

- Procedure and technique for collection of the oral mucosal tissue
- Precautions concerning collection of oral mucosal tissue
- Method to explain to collectors the procedure and technique for collection of the oral mucosal tissue as well as precautions concerning tissue collection
- Necessity of cooperation with dental surgery department

The applicant's explanation:

Procedure and technique for collection of the oral mucosal tissue

- After oral cleaning and disinfection on perioral area and collection site, an oral mucosal tissue piece is collected from the buccal mucosal part of the patient with a scalpel or scissors, and the collection site is sutured.
- The oral mucosal tissue piece is placed in a tissue transport tube filled with the tissue transportation fluid and then confirmed to be immersed in the fluid.
- The incised wound at the oral mucosa collection site is visually inspected for its healing.

Precautions concerning collection of oral mucosal tissue
Because stem cells are present in the basal lamina of mucosal epithelium, the oral mucosal tissue piece should be collected by deeply cutting the tissue to the lamina propria so that the piece includes the entire mucosal epithelium stratum.

Method to explain to collectors the procedure and technique for collection of the oral mucosal tissue as well as precautions concerning tissue collection
The procedure for collection of the oral mucosal tissue shown above can be performed by an ophthalmologist, and cooperation with a dental surgery department is not considered essential. In view of the situation that general ophthalmologists have limited experience with the technique in the oral cavity, the applicant plans to hold training sessions to adequately explain the procedure and technique for collection of the oral mucosal tissue as well as precautions concerning the tissue collection after the market launch.

PMDA's view:
It is appropriate for the applicant to specify in the "Dosage and Administration or Method of Use" section that the oral mucosal tissue piece should be collected from the intraoral buccal mucosal part. From a viewpoint of ensuring collection of the oral mucosal tissue piece with proper material attributes, the following precaution is important information: Because stem cells are present in the basal lamina of mucosal epithelium, the oral mucosal tissue piece should be collected by deeply cutting the tissue to the lamina propria so that the piece includes the entire mucosal epithelium stratum. Therefore, the "Precautions Concerning Dosage and Administration or Method of Use" section should include the precaution statement that the tissue piece should be collected by deeply cutting the tissue to the lamina propria to ensure that it includes the basal lamina.

To ensure appropriate collection of the oral mucosal tissue piece necessary for manufacture of Ocural, the procedure and technique for collection of the oral mucosal tissue and relevant precautions should be understood through precaution statements in the labeling and other information leaflet and training sessions for physicians. In addition, a system that allows cooperation with a dental surgery department, etc. is recommended to be established.

7.R.6.2 Measures after transplantation of Ocural

PMDA asked the applicant to explain precautions for necessary measures after transplantation of Ocural.

The applicant's explanation:
- After the transplantation of Ocural, the therapeutic contact lens is applied and tarsorrhaphy is performed where necessary.
- During the clinical studies, the therapeutic contact lens was continuously used to the extent possible to protect the corneal epithelium and ensure appropriate evaluation of the efficacy and safety. After the market launch, removal of the contact lens will be considered according to the patient's condition around 3 months after transplantation of Ocural at which corneal epithelialization is presumed to be completed.

- In a patient who has undergone tarsorrhaphy, the suture should be loosened around 1 week of the operation to inspect progress of the corneal epithelium reconstruction. If the epithelium reconstruction is confirmed and no epithelium defect is observed, tarsal suture is removed.
- The applicant considers that it is unnecessary to include caution statements about timing of removals of the therapeutic contact lens and of the tarsal suture after transplantation of Ocural in the package insert, etc., but plans to explain these matters adequately at training sessions held by the marketing authorization holder.

PMDA's view:
Findings on the efficacy and safety after removal of the therapeutic contact lens in the clinical studies are not available, but the applicant's explanation that the removal will be considered around 3 months is understandable to a certain extent and acceptable. In addition, the applicant's explanation about timing of removal of the tarsal suture is acceptable, and the applicant's measure to adequately explain precautions after transplantation of Ocural at training sessions held by the marketing authorization holder is also acceptable.

7.R.6.3 Possibility of re-transplantation

PMDA asked the applicant to explain the possibility of recurrence or relapse of LSCD after transplantation of Ocural and the appropriateness for re-transplantation in the recurrent or relapsed case.

The applicant's explanation:
- Although no recurrence or relapse occurred in the COMET01 or COMET01-FU study, the possibility of relapse or recurrence after transplantation of Ocural cannot be ruled out in patients with acquired primary immune-mediated LSCD or hereditary LSCD.
- If relapse or recurrence of LSCD associated with the etiology or graft failure of Ocural due to physical stimulation occurs, re-transplantation of Ocural may be considered.

Then, patients with relapse or recurrence of LSCD associated with the etiology, if applicable, should meet the following criteria for re-transplantation of Ocural to undergo the procedure:
- The cause of LSCD is identified, and the anterior segment of the affected eye is stabilized with appropriate treatment of decreased lacrimation, symblepharon, and chronic inflammation.
- The severity of LSCD is applicable to "Stage III," "Stage IIB," or "Stage IIA and removal of conjunctival scar tissue (amniotic membrane transplantation where necessary) is not effective."
- The affected eye is confirmed to be free from inflammation and infection, and alleviation of conjunctivalization has not been observed for 3 months (at Stage IIA, removal of conjunctival scar tissue [amniotic membrane transplantation where necessary] is also confirmed to be ineffective).

PMDA's view:
Re-transplantation of Ocural was not performed in the clinical studies, and it is therefore difficult to determine the appropriateness of the above criteria for the re-transplantation, but the potential presence of patients who experience relapse or recurrence of LSCD after transplantation of Ocural and need re-transplantation is understandable. The applicant is required to collect post-marketing information about the safety and efficacy of re-transplantation of Ocural.

8. Data Relating to Risk Analysis and Outline of the Review Conducted by PMDA

The applicant's explanation about a post-marketing surveillance plan of Ocural:

Clinical experience with Ocural is very limited, and the safety information about Ocural has not been adequately collected. The applicant therefore plans a post-marketing surveillance to evaluate the safety and efficacy of Ocural in all patients treated with Ocural in post-marketing clinical practice.

The safety specification of this surveillance is to collect all the adverse events associated with use of Ocural.

The sample size for the surveillance is planned to be 200 patients per year in light of the expected number of patients receiving Ocural after marketing.

The follow-up period was specified as a period from the tissue collection for manufacture of Ocural to Week 52 of transplantation in light of a report on transplantation of cultured autologous oral mucosal epithelium (*Br J Ophthalmol.* 2011;95:942-6) showing that conditions of conjunctivalization, corneal opacity, and corneal neovascularisation were stabilized with limited changes after 1 year of the transplantation. To collect information about the safety and efficacy of re-transplantation of Ocural, patients who have undergone re-transplantation within 52 weeks of the prior transplantation will be followed up until Week 52 of the last transplantation.

PMDA's view:

Because clinical experience with Ocural is very limited, a post-marketing surveillance needs to be conducted in all patients treated with Ocural to collect information about the safety and efficacy of Ocural after marketing in a prompt and unbiased manner. PMDA accepted the above applicant's explanation about the surveillance plan (safety specification, planned sample size for the surveillance, and follow-up period).

The post-marketing surveillance should collect information about the causative etiology and result of manufacture of Ocural. Information about appropriate tissue collection for manufacture of Ocural, if additionally available, should be provided to healthcare professionals in an appropriate and prompt manner.

9. Results of Compliance Assessment Concerning the New Regenerative Medical Product Application Data and Conclusion Reached by PMDA

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

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

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

The new regenerative medical product application data (Attached documents 7-1 and 7-2) 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.

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

On the basis of the data submitted, PMDA has concluded that Ocural has a certain level of efficacy in the treatment of "limbal stem cell deficiency," and that Ocural has acceptable safety in view of its benefits. Ocural is clinically meaningful because it provides a new treatment option for patients with LSCD.

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

Review Report (2)

April 27, 2021

Product Submitted for Approval

Brand Name	Ocural
Non-proprietary Name	Human (autologous) oral mucosa-derived epithelial cell sheet
Applicant	Japan Tissue Engineering Co., Ltd.
Date of Application	September 14, 2020

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

As a result of the review in Section "7.R.2 Efficacy" of the Review Report (1), PMDA has concluded that Ocural is shown to demonstrate a certain level of efficacy in the treatment of LSCD.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.2 Safety

As a result of the review in Section "7.R.3 Safety" of the Review Report (1), PMDA has concluded that the safety profile of Ocural does not raise any particular concern.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.3 Clinical positioning and indication or performance

As a result of the review in Sections "7.R.4 Clinical positioning" and "7.R.5 Indication or performance" of the Review Report (1), PMDA concluded that the "Indication or Performance" and "Precautions Concerning Indication or Performance" sections of Ocural should be specified as show below.

Indication or Performance

Limbal stem cell deficiency

Precautions Concerning Indication or Performance

- Ocural should be used in the following patients:
  "In the affected eye, conjunctivalization involves ≥50% of the entire corneal limbus and extends to an area within 5 mm in diameter including the central cornea in the affected eye" or "removal of conjunctival scar tissue in the affected eye (amniotic membrane transplantation where necessary) is not effective, and conjunctivalization extends to an area within 5 mm in diameter including the central cornea in the affected eye."
- Because Ocural is not intended to treat any cause of limbal stem cell deficiency, Ocural should be used after the causative disease of limbal stem cell deficiency is controlled or the cause is removed.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

PMDA instructed the applicant to specify the "Indication or Performance" and "Precautions Concerning Indication or Performance" sections as described above. The applicant responded appropriately, and PMDA accepted.

1.4 Dosage and administration or method of use

As a result of the review in Section "7.R.6 Dosage and administration or method of use" of the Review Report (1), PMDA has concluded that the "Dosage and Administration or Method of Use" and "Precautions Concerning Dosage and Administration or Method of Use" sections should be specified as shown below.

Dosage and Administration or Method of Use (Underline denotes additions, and strikethrough denotes deletions.)

Operations in manufacture of oral mucosal epithelial cell sheet

1. An area in the patient's intraoral <u>buccal mucosal part</u> is confirmed to be free from inflammation, infection, and scar, and approximately a 10 × 5 mm piece of the oral mucosal tissue is collected. The collected oral mucosal tissue is placed in a tissue transport tube and sent to the manufacturer.
2. Blood is collected in accordance with a conventional procedure. The collected blood is placed in a blood storage tube and sent to the manufacturer. This blood specimen is used as the reserve sample.

Operations in transplantation of oral mucosal epithelial cell sheet

The oral mucosal epithelial cell sheet is detached with a ring-shaped culture disk from the oral mucosal epithelium culture dish. Conjunctival scar tissue is removed from the eye surface of the patient wherever possible, and the oral mucosal epithelial cell sheet is transplanted onto the eye surface including the corneal limbus. The rim of the oral mucosal epithelial cell sheet is sutured where necessary. After the transplantation, the therapeutic contact lens is applied and tarsorrhaphy is performed where necessary.

Precautions Concerning Dosage and Administration or Method of Use

Precautions during manufacture of oral mucosal epithelial cell sheet

1. The transplantation plan including scheduled dates of tissue collection and transplantation should be developed using the specified format designated by the marketing authorization holder.

2. It should be confirmed that the tissue transport tube and blood storage tube are containers dedicated to the patient by checking the labels before tissue collection.
3. Collection of the oral mucosal tissue and its immersion into the tissue transportation fluid should be performed in a clean environment.
4. The oral mucosal tissue piece should be collected from ~~that is~~ the intact tissue by deeply cutting the tissue to the lamina propria so that the tissue piece ~~and~~ includes reliably the basal lamina ~~should be collected~~.
5. Alternative treatment should be considered in advance because the cultured oral mucosal epithelium package may not be released or the transplanted oral mucosal epithelial cell sheet may not survive.

Precautions during oral mucosal epithelial cell sheet transplantation

1. It should be confirmed that the transportation container is sealed at the delivery of the cultured oral mucosal epithelium package. If the seal is broken, the package should not be opened, and the marketing authorization holder should be contacted.
2. To prevent mix-up, it should be confirmed that the oral mucosal epithelial cell sheet to be transplanted is dedicated to the patient by checking the label on the cultured oral mucosal epithelium package.
3. The cultured oral mucosal epithelium package should be stored in a transportation container or at 20°C to 28°C until just before use.
4. To protect from drying, the oral mucosal epithelial cell sheet should be kept immersed in HBSS or an intraocular perfusate in the culture dish for cultured oral mucosal epithelium until just before transplantation.
5. If symblepharon may occur, an appropriate procedure should be performed before transplantation.
6. Any fluid should be removed from the eye surface before placing the oral mucosal epithelial cell sheet.
7. The oral mucosal epithelial cell sheet should be placed on the eye surface in the right-side-up position, preventing the sheet from being placed upside-down.
8. Onto the oral mucosal epithelial cell sheet placed on the eye surface, an intraocular perfusate should be slowly dropped to protect it from drying.
9. The oral mucosal epithelial cell sheet should be removed from a ring-shaped culture disk by applying a scalpel to the internal circumference of the ring.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

PMDA instructed the applicant to specify the “Dosage and Administration or Method of Use” and “Precautions Concerning Dosage and Administration or Method of Use” sections as described above. The applicant responded appropriately, and PMDA accepted.

1.5 Post-marketing surveillance plan (draft)

In the present application, the applicant proposed a plan of post-marketing surveillance covering all patients treated with Ocural to evaluate the safety of Ocural in post-marketing clinical practice. The planned sample size was 200 patients per year, and the observation period was from the tissue collection

for manufacture of Ocural to Week 52 of transplantation (for patients who have undergone re-transplantation within 52 weeks of the prior transplantation, to Week 52 of the last transplantation).

As a result of the review in Section "8. Data Relating to Risk Analysis and Outline of the Review Conducted by PMDA" of the Review Report (1), PMDA has concluded that the post-marketing surveillance plan is acceptable as developed by the applicant.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

In view of the above discussion and the following correction presented by the applicant, PMDA has concluded that the post-marketing surveillance should be conducted as provided in Table 34.

Correction

- In light of the number of patients awaiting corneal transplant, the number of patients who might use Ocural was surveyed again. On the basis of the survey result, the planned sample size of the surveillance was revised to approximately 300 patients per year.

Table 34. Outline of post-marketing surveillance plan (draft)

Objective	Evaluation of the safety and efficacy of Ocural
Survey method	All-case surveillance
Registration period for survey	From day of approval to 108 weeks before the end of re-examination period
Observation period	From the tissue collection for manufacture of Ocural to Week 52 of transplantation (for patients who have undergone re-transplantation within 52 weeks of the prior transplantation, to Week 52 of the last transplantation).
Population	Patients with LSCD
Planned sample size	Approximately 300 patients per year
Main survey items	Safety specification: All adverse events associated with use of Ocural Efficacy: LSCD severity, corrected visual acuity, etc.

1.6 Others

1.6.1 Designation as designated regenerative medical product

In accordance with the "Concept for designation of biological products and specified biological products as well as designated regenerative medical products" (PFSB/ELD Notifications No. 1105-1 and 2 dated November 5, 2014), PMDA has concluded that Ocural should be designated as a designated regenerative medical product because mouse cells (3T3-J2 cells) are used as feeder cells in the manufacturing process of Ocural, which is a product using the autologous oral mucosal tissue as a raw material; and the manufacturing process does not include inactivation or removal of pathogens.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the indication or performance and the dosage and administrations or method of use as shown below, with the following approval conditions. Because the product is designated as an orphan regenerative medical product, the re-examination period is 10 years. The product is designated as a specified regenerative medical product.

Indication or Performance

Limbal stem cell deficiency

Dosage and Administration or Method of Use

Operations in manufacture of oral mucosal epithelial cell sheet

1. An area in the patient's intraoral buccal mucosal part is confirmed to be free from inflammation, infection, and scar, and approximately a 10 × 5 mm piece of the oral mucosal tissue is collected. The collected oral mucosal tissue is placed in a tissue transport tube and sent to the manufacturer.
2. Blood is collected in accordance with a conventional procedure. The collected blood is placed in a blood storage tube and sent to the manufacturer. This blood specimen is used as the reserve sample.

Operations in transplantation of oral mucosal epithelial cell sheet

The oral mucosal epithelial cell sheet is detached with a ring-shaped culture disk from the oral mucosal epithelium culture dish. Conjunctival scar tissue is removed from the eye surface of the patient wherever possible, and the oral mucosal epithelial cell sheet is transplanted onto the eye surface including the corneal limbus. The rim of the oral mucosal epithelial cell sheet is sutured where necessary. After the transplantation, the therapeutic contact lens is applied and tarsorrhaphy is performed where necessary.

Approval Conditions

1. The applicant is required to take necessary measures such as dissemination of the guideline for proper use prepared in cooperation with relevant academic societies and conducting seminars to ensure that physicians with adequate knowledge and experience in limbal stem cell deficiency acquire full skills of the product usage and knowledge in complications associated with the procedures and that the physicians use the product in compliance with the "Indication or Performance" as well as "Dosage and Administration or Method of Use" at medical institutions with an established system for treatment of limbal stem cell deficiency.
2. Since only a limited number of patients participated in clinical studies of the product, the applicant is required to conduct a use-results survey covering all patients treated with the product in principle until the end of the re-examination period in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.
3. The applicant is required to take necessary measures such as storage of reserve samples of the final product and retention of use records for 30 years to ensure appropriate handling in view of a risk of xenogeneic transplantation related to mouse embryonic 3T3-J2 cells used as feeder cells in the manufacturing process of the product.

Appendix

List of Abbreviations

3T3-J2 cell	Mouse embryonic cell
ADL	Activities of daily living
ALT	Alanine aminotransferase
Application	Marketing application
BRVO	Branch retinal vein occlusion
CD	Cluster of differentiation
CI	Confidence interval
CK	Cytokeratin
ELISA	Enzyme linked immunosorbent assay
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full analysis set
HE	Hematoxylin-eosin
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH Q5A (R1) guideline	"Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" (PMSB/ELD Notification No. 329 dated February 22, 2000)
ICH Q5D guideline	"Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products" (PMSB/ELD Notification No. 873 dated July 14, 2000)
ISCN	An International System for Human Cytogenetic Nomenclature
LKP	Lamellar keratoplasty
logMAR	Logarithmic minimum angle of resolution
LSCD	Limbal stem cell deficiency
MCB	Master cell bank
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MRC-5 cell	Human fetal lung fibroblast
MUC	Mucin
MWCB	Master working cell bank
NEI VFQ-25	The 25-item National Eye Institute Visual Function Questionnaire
NIH-3T3 cell	Mouse embryonic cell
NZW	New Zealand White
OCP	Ocular cicatricial pemphigoid
Ocural	Ocural
PMDA	Pharmaceuticals and Medical Devices Agency
QOL	Quality of life
SJS	Stevens-Johnson syndrome
WCB	Working cell bank
Vero cell	African green monkey kidney epithelial cell
[redacted]	[redacted]