February 13, 2023
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 1. Human Somatic Cell-processed Products
Non-proprietary Name	Neltependocel
Brand Name	Vyznova
Applicant	Aurion Biotech Japan, LLC
Date of Application	June 21, 2022 (Application for marketing approval)

Results of Deliberation

In the meeting held on February 13, 2023, the Committee on Regenerative Medicine Products and Biotechnology reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product may be approved. The conditional and time-limited approval is not applicable to the product. 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 the physicians with adequate knowledge and experience in bullous keratopathy acquire full skills of the product usage and knowledge in complications associated with the procedures and that physicians use the product in compliance with the “Indication or Performance” and “Dosage and Administration or Method of Use” at medical institutions with an established system for treatment of bullous keratopathy.
2. Since only a limited number of Japanese 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 after the market launch until data from a certain number of patients are collected in order to identify 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.

Review Report

February 2, 2023
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	Vyznova
Classification	Human Cellular/Tissue-based Products 1. Human Somatic Cell-processed Products
Non-proprietary Name	Neltependocel
Applicant	Aurion Biotech Japan, LLC
Date of Application	June 21, 2022

Shape, Structure, Active Ingredients, Quantities, or Definition

The product is a regenerative medical product comprised of the primary component of a corneal endothelial cell preparation containing fully differentiated cultured human corneal endothelial cells and the secondary component of perfusate. The primary component is a corneal endothelial cell preparation containing fully differentiated cultured human corneal endothelial cells, a culture of corneal endothelial cells isolated from the corneal tissue obtained from a human donor, as component cells. In addition, the secondary component is perfusate used for perfusing the anterior chamber before transplant of the corneal endothelial cell preparation.

Application Classification	(1-1) New regenerative medical product
Items Warranting Special Mention	Orphan regenerative medical product (Orphan Regenerative Medical Product Designation No. 22 of 2022 [*R4 sai*]; PSEHB/MDED Notification No. 0228-1 dated February 28, 2022, by the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare [MHLW])
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 efficacy in the treatment of bullous keratopathy, 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 approval conditions.

Indication or Performance

Bullous keratopathy

Dosage and Administration or Method of Use

After an incision is made at the corneal limbus, while the anterior chamber is perfused with intraocular perfusate for maintenance, degenerated corneal endothelial cells and extracellular matrix are stripped from the posterior surface of the cornea with a corneal endothelium stripper. Then, the perfusate is applied (100 μL/dose, approximately 2 doses). The incision is sutured. Next, an injection needle is inserted through the corneal limbus into the anterior chamber, and the perfusate is suctioned for removal. Then, 300 μL of the corneal endothelial cell preparation (1.0×10^6 cells) is transplanted into the anterior chamber. The patient is immediately placed in a prone position and held for 3 hours to enhance adhesion of the transplanted cells.

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 the physicians with adequate knowledge and experience in bullous keratopathy acquire full skills of the product usage and knowledge in complications associated with the procedures and that physicians use the product in compliance with the “Indication or Performance” and “Dosage and Administration or Method of Use” at medical institutions with an established system for treatment of bullous keratopathy.
2. Since only a limited number of Japanese 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 after the market launch until data from a certain number of patients are collected in order to identify 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.

Attachment

Review Report (1)

December 8, 2022

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	Vyznova
Classification	Human Cellular/Tissue-based Products 1. Human Somatic Cell-processed Products
Non-proprietary Name	Neltependocel
Applicant	Aurion Biotech Japan, LLC
Date of Application	June 21, 2022

Shape, Structure, Active Ingredients, Quantities, or Definition

The product is a regenerative medical product comprised of the primary component of a corneal endothelial cell preparation containing fully differentiated cultured human corneal endothelial cells and the secondary component of perfusate. The primary component is a corneal endothelial cell preparation containing fully differentiated cultured human corneal endothelial cells, a culture of corneal endothelial cells isolated from the corneal tissue obtained from a human donor, as component cells. In addition, the secondary component is perfusate used for perfusing the anterior chamber before transplant of the corneal endothelial cell preparation.

Proposed Indication or Performance

Bullous keratopathy

Proposed Dosage and Administration or Method of Use

After an incision is made at the corneal limbus, while the anterior chamber is perfused with intraocular perfusate for maintenance, degenerated corneal endothelial cells and extracellular matrix are stripped from the posterior surface of the cornea with a corneal endothelium stripper. Then, the perfusate is applied (100 μL/dose, approximately 2 doses). The incision is sutured. Next, the perfusate is suctioned for removal. Then, 300 μL of the corneal endothelial cell preparation (1.0×10^6 cells) is transplanted into the anterior chamber. The patient is immediately placed in a prone position and held for 3 hours to enhance adhesion of the transplanted cells.

Table of Contents

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

Vyznova is a regenerative medical product in which the component cell is fully differentiated cultured human corneal endothelial cells (CHCECs), a culture of corneal endothelial cells isolated from the corneal tissue obtained from a human donor. Vyznova has biological functions similar to those of human corneal endothelial cells. When transplanted into the anterior chamber in a patient with bullous keratopathy, Vyznova adheres to and spreads over an area where corneal endothelial cells have been lost. Vyznova is intended to restore corneal transparency by reaching a damaged area of the corneal endothelium and reconstructing a corneal endothelium monolayer there and is presented as a combination product comprised of the following primary component and secondary component.

Primary component: A corneal endothelial cell preparation containing fully differentiated CHCECs, a culture of corneal endothelial cells isolated from the corneal tissue obtained from a human donor as component cells.

Secondary component: Perfusate for perfusing the anterior chamber before cell transplant

Vyznova was designated as an orphan regenerative medical product with the intended indication or performance of "bullous keratopathy" on February 28, 2022 (Orphan Regenerative Medical Product Designation No. 22 of 2022 [*R4 sai*]).

1.2 Development history etc.

Bullous keratopathy is a progressed condition of corneal endothelial damage caused by various corneal endothelial diseases or surgical trauma (ocular surgery) in which the corneal endothelial cell density is decreased to an unmeasurable level and is known as a disease accompanied by reduced vision, eye pain, etc. owing to corneal oedema or haziness, which impairs corneal transparency.

Bullous keratopathy has been conventionally treated by corneal transplant, which replaces the damaged corneal tissue with normal corneal tissue from a donor, but donor corneas are always in short supply, and the corneal transplant is highly invasive and can cause a significant burden on elderly patients and patients with a high-risk eye. Because of these issues, development of a new therapeutic procedure for this disease has been desired.

For development of Vyznova, a clinical research in patients with bullous keratopathy (Study CHCEC R-01) was initiated in accordance with the Guidelines for clinical research using human stem cells (MHLW Ministerial Announcement No. 380 of 2010) in [redacted] by Kinoshita, et al., Department of Ophthalmology, University Hospital, Kyoto Prefectural University of Medicine, and then an investigator-initiated phase II study (Study CHCEC-201) was initiated in [redacted] and an investigator-initiated phase III study (Study CHCEC-301) was initiated in [redacted] (both supported by a Research Project for Practical Applications of Regenerative Medicine of the Japan Agency for Medical Research and Development). A regulatory application for Vyznova mainly based on results from Studies CHCEC-201 and CHCEC-301 has been submitted.

As of November 2022, Vyznova is not approved or marketed in any country or region.

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

The primary component of Vyznova is a corneal endothelial cell preparation containing fully differentiated CHCECs, a culture of corneal endothelial cells isolated from the corneal tissue obtained from a human donor as component cells. It is presented as a cell suspension that contains 1.33×10^6 CHCECs per tube (400 μL in volume) as well as adjunctive ingredients of Opti-MEM I and Rho-associated coiled-coil forming kinase (ROCK) inhibitor of Y-27632 ([redacted]M). The secondary component of Vyznova is perfusate used for perfusing the anterior chamber before transplant of the corneal endothelial cell preparation. It is presented in a tube each containing 1,200 μL of Opti-MEM I spiked with Y-27632 ([redacted]M).

2.1 Manufacturing process

2.1.1 Manufacturing process

The manufacturing process of Vyznova consists of manufacture of a corneal endothelial cell preparation, the primary component, and that of perfusate, the secondary component.

2.1.1.1 Manufacturing process of primary component

The manufacturing process of the corneal endothelial cell preparation, the primary component, consists of acceptance of human cornea, [redacted], packaging and labeling, and storage and testing.

The critical process step is [redacted]. In the [redacted] process, [redacted] cells from [redacted] process are used.

2.1.1.2 Manufacturing process of secondary component

The manufacturing process of perfusate, the secondary component, consists of preparation of perfusate, sterile filtration and filling, [redacted], packaging and labeling, and storage and testing.

The critical process steps are [redacted], and [redacted].

Process validation of the manufacturing process of the secondary component has been implemented at the commercial production scale.

2.1.2 In-process control tests

Tables 1 and 2 show acceptance tests of raw materials and in-process control tests in the manufacturing process of the corneal endothelial cell preparation, the primary component.

Table 1. Acceptance tests of raw materials

Test item	Test method
Check of certificate of analysis on the donor	Serological examination for infections (HIV-1, HIV-2, HBV, HCV, HTLV-1, HTLV-2, syphilis)
	Eligibility for corneal donor (history taking, etc.)
	[redacted]
	[redacted]
Appearance of container	Visual inspection (container free from cracks and without leakage, turbidity, and freezing of the medium)
Time from collection	≤[redacted] days after collection
Temperature during transport	[redacted]°C
Duration of transport	≤[redacted] hours
Virus free test	Nucleic-acid-amplification test for infections with [redacted] (HIV-1, HIV-2, HBV, HCV, HTLV-1, HTLV-2)

Table 2. In-process control tests in manufacturing process of corneal endothelial cell preparation

Process	Test item
In-process control test 1 ([redacted])	Cell morphology, [redacted], viability
In-process control test 2 ([redacted])	Cell morphology, [redacted], viability
In-process control test 3 ([redacted])	Cell morphology, [redacted], viability
In-process control test 4 ([redacted])	Cell morphology, [redacted], viability, identification ([redacted]),*1 purity ([redacted]),*1 purity ([redacted]),*1 sterility ([redacted]),*1 mycoplasma test, bacterial endotoxins test, virus free test ([redacted])*1
In-process control test 5 ([redacted])	Sterility ([redacted])*2

*1 [redacted]

*2 [redacted]

2.2 Safety evaluation of adventitious agents

2.2.1 Human cornea

Human cornea, a raw material of Vyznova, is collected from a donor postmortem at a facility certified by the Eye Bank Association of America (EBAA) in the US, and the donor has undergone a physical examination, history taking (past history, prior transplant and blood transfusions), and serological examination for infections (human immunodeficiency virus [HIV]-1, HIV-2, hepatitis B virus [HBV], hepatitis C virus [HCV], human T-cell leukaemia virus [HTLV]-1, HTLV-2, and syphilis) antemortem or postmortem. In addition, the acceptance tests of human cornea include virus free tests by nucleic acid amplification test targeting [redacted] (HIV-1, HIV-2, HBV, HCV, HTLV-1, and HTLV-2) (Table 1). Because the human cornea is tissue provided after the donor's death, it has not been subjected to examinations in view of window period required in (3) under 1 Standards for human cell- and tissue-based ingredients, 3 General rules for human-derived ingredients in the Standards for biological ingredients (MHLW Ministerial Announcement No. 210 of 2003).

2.2.2 Biological raw materials other than human cornea

Biological raw materials used in the manufacturing process of Vyznova other than human cornea are fetal bovine serum (FBS), human plasma transferrin, and bovine collagen, all of which conform to the Standards for Biological Ingredients (MHLW Ministerial Announcement No. 210 of 2003).

2.3 Manufacturing process development (comparability)

Major changes to the manufacturing process of Vyznova during development are as described below (corresponding processes are referred to as Process A, Process B, Process C, Process D, Process E1, Process E2', Process E2, and proposed process).

Process A to Process B: Change in [redacted], and change to [redacted], [redacted] ([redacted]) [redacted] process
Process B to Process C: Change to [redacted] process
Process C to Process D: Change in [redacted], change to [redacted], and change to [redacted] process
Process D to Process E1: Change in [redacted] and change to [redacted], and change in [redacted]
Process E1 to Process E2': Change to [redacted]
Process E2' to Process E2: Change to [redacted]
Process E2 to proposed process: Change in [redacted], change in [redacted]

Products manufactured through Process E1 was used in Study CHCEC-201, products manufactured through Process E2' was used in non-clinical safety study (soft agar colony formation assay), and products manufactured through Process E2 was used in non-clinical safety study (general toxicity study) and Study CHCEC-301. Products manufactured through Processes B to E2 were used in Study CHCEC R-01 (clinical research).

Whenever the process was changed to Process E1, Process E2, and the proposed process, comparability assessment was performed for quality attributes. The quality attributes of the pre- and post-change product were shown to be comparable.

2.4 Characterization

Characterization of CHCECs was performed as shown in Table 3.

Table 3. Characterization items

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

2.5 Evaluation of manufacturing process

2.5.1 Removal of process-related impurities

For Material A, Material B, Material C, Material D, Material E, [redacted] (Material F, Material G, Material H, and Material I and Material J), Material K, and Material L, which are used in the manufacturing process, the safety evaluation was performed based on their estimated amounts administered per transplant procedure, which were calculated from the measured or estimated residual amounts in the final product. These process-related impurities were considered unlikely to raise safety concerns in humans, and thus no control items are specified for them.

2.5.2 Verification

Quality attributes required for Vyznova include description, [redacted], viability, [redacted], [redacted], [redacted], cell surface antigen purity ([redacted], [redacted], [redacted], [redacted], [redacted], [redacted]), sterility, mycoplasma, bacterial endotoxins, and adventitious viruses.

A verification-based quality control strategy has been constructed for the manufacturing process of the primary component to ensure that the target quality attributes are achieved in each production. The verification items are as shown below.

- Acceptance tests of raw materials (Table 1)
- In-process control tests (Table 2)
- Specification tests (Table 5)
- [redacted]
- [redacted]
- Manufacturing process parameters listed in Table 4

Table 4. Manufacturing process parameters specified as verification control items

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

2.6 Control of product

Tables 5 and 6 show specifications for the corneal endothelial cell preparation, the primary component, and perfusate, the secondary component.

Because the shelf life of the corneal endothelial cell preparation is limited to 27 hours [see Section "3. Stability and Outline of the Review Conducted by PMDA"], determination of release uses results from [redacted] for [redacted], [redacted], [redacted], and [redacted]. In addition, [redacted] and [redacted] for the final product, conformity to the specifications is determined [redacted]. For sterility, [redacted], [redacted] is used for determination of release.

In addition to the above specification tests, [redacted] ([redacted]) is performed on the final product to ensure its sterility, and the results of [redacted] become available at [redacted].

For perfusate, [redacted] and [redacted] are subjected to sterility and bacterial endotoxins tests, and [redacted], description and pH are measured and checked before release. Perfusate is stored at [redacted].

Table 5. Specifications for corneal endothelial cell preparation

Test item	Test method	Acceptance criteria	Test specimen
Description	Visual inspection	Colorless to pale red suspension	[redacted]
[redacted]	Hemocytometer (trypan blue staining)	[redacted] × 10^6 cells/mL	[redacted]
Viability	Hemocytometer (trypan blue staining)	≥ [redacted]%	[redacted]
Identification	Immunostaining ([redacted])	Positive	[redacted]*1
Purity	ELISA ([redacted])	≥ [redacted] g/mL	[redacted]*1
Purity	Flow cytometry ([redacted])	[redacted]: ≥ [redacted]% [redacted]: ≥ [redacted]%; [redacted]: ≤ [redacted]% [redacted]: ≤ [redacted]% [redacted]: ≤ [redacted]% [redacted]: ≤ [redacted]%	[redacted]*1
Sterility	[redacted] ([redacted])	Negative	[redacted]*1*2
Mycoplasma test	Nucleic acid amplification test (General Information in the Japanese Pharmacopoeia)	Negative	[redacted]
Bacterial endotoxins test	Turbidimetric techniques (Japanese Pharmacopoeia)	< [redacted] EU/mL	[redacted]
Virus free test	Nucleic acid amplification test ([redacted])	Negative	[redacted]*1

*1 [redacted]
*2 [redacted]

Table 6. Specifications for perfusate

Test item	Test method	Acceptance criteria
Description	Visual inspection	Colorless to pale red clear liquid
pH	pH Determination (Japanese Pharmacopoeia)	[redacted] - [redacted]
Sterility*1	Membrane filtration method (Japanese Pharmacopoeia)	Conformance
Bacterial endotoxins*1	Turbidimetric techniques (Japanese Pharmacopoeia)	< [redacted] EU/mL

*1 [redacted]

2.R Outline of the review conducted by PMDA

On the basis of the data submitted and results of the review described below, PMDA has concluded that the quality of Vyznova is appropriately controlled.

2.R.1 Viral risk of human cornea

PMDA asked the applicant to explain viral safety of the final product for the following reasons: (a) Examinations were not performed on human cornea, a raw material of Vyznova, in view of window period for the donor; and (b) extensive tests for absence of viruses potentially present in humans such as retrovirus test, *in vitro* tests, and *in vivo* tests were not included throughout the manufacturing process.

The applicant's response:

In view of points described below, the concerned raw material is considered to have viral safety to a certain extent.

- Donors for Vyznova undergo the same examinations as with those for conventional corneal transplant.
- Viruses potentially causing serious diseases (HIV, hepatitis viruses, and HTLV) are tested in not only a serological examination on the donor but also an examination by nucleic acid amplification test, which is performed as an acceptance test.
- To prevent diseases such as corneal endotheliitis and herpetic keratitis, tests for [redacted], [redacted], [redacted], [redacted], and [redacted] are performed as in-process control tests.

- In clinical studies (Studies CHCEC-201 and CHCEC-301) and clinical research (Study CHCEC R-01), no adverse drug reactions attributable to donor-derived viruses have occurred.

Taking account of the applicant's explanation, PMDA confirmed that certain risk management has been implemented, although a risk of viruses attributable to the concerned raw material cannot be ruled out completely.

3. Stability and Outline of the Review Conducted by PMDA

Table 7 shows an outline of the stability study of corneal endothelial cell preparations.

Table 7. Stability study of corneal endothelial cell preparations

Batch	Process	Storage condition	Study period	Storage form
S01-21002	Proposed process*1	2°C-8°C	0 hours	Primary container
S01-21003*2	Proposed process*1	2°C-8°C	0 hours	(tube)
S01-21005	Proposed process*1	2°C-8°C	0 hours	Secondary package: Paper carton

*1

*2

In the stability study of corneal endothelial cell preparations, was demonstrated to be . On the basis of the above, a shelf life of 27 hours was proposed for a corneal endothelial cell preparation when stored at 2°C to 8°C and protected from light. In addition, .

Table 8 shows an outline of the stability study of perfusate.

Table 8. Stability study of perfusate

Batch	Storage condition	Storage form
220525-A 220525-B 220525-C	2°C-8°C, hours	Primary container (tube) Secondary package, paper carton

In the stability study of perfusate, no clear changes were observed in quality attributes throughout the study period. On the basis of the above, a shelf life of 30 hours was proposed for perfusate when stored at 2°C to 8°C and protected from light.

3.R Outline of the review conducted by PMDA

PMDA confirmed the following findings: Of specimen of the primary component used in the stability study, 1 batch ( ) was found to be for ( ) at the beginning of (at the time of), but it was in the test for at (at the time of); and at hours was found in batch but not in .

On the basis of the above, PMDA has concluded that storage conditions and shelf lives for the primary and secondary components are acceptable.

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

The applicant submitted data relating to indication or performance of Vyznova in the form of results from an *in vitro* study where immunohistochemistry was performed on CHCECs and an *in vivo* study where CHCECs or animal-derived corneal endothelial cells were transplanted into the anterior chamber of bullous keratopathy model animals.

4.1 *In vitro* study (analysis on proteins involved in corneal stromal tissue) (CTD 3.2.1.3 and CTD 3.2.7.4)

Immunohistochemistry was performed on CHCECs for expression of the proteins relevant to functions of corneal endothelial cells, presented below. Expression of all the proteins was confirmed.

- [redacted]
- [redacted]
- [redacted]

4.2 *In vivo* study

4.2.1 Anterior chamber transplant study of cultured allogeneic corneal endothelial cells in rabbit and monkey bullous keratopathy models (CTD 4.2.1.1-1)

Japanese White rabbits and cynomolgus monkeys underwent excision of the crystalline lens followed by incision at the corneal limbus and stripping of the corneal endothelial cells to prepare bullous keratopathy models. A total of 2.0×10^5 DiI-labeled rabbit corneal endothelial cells (RCECs) or monkey corneal endothelial cells (MCECs) were transplanted into the anterior chamber of the animal model with or without Y-27632 ([redacted] M). Survival of the transplanted cells was assessed by immunohistochemistry.

In the rabbit bullous keratopathy model, slit lamp microscopy was performed for corneal transparency and thickness. Observations over 14 days of RCEC transplant revealed that RCECs adhered to the corneal endothelium basement membrane and formed a hexagonal-lattice structure of monolayer in the presence of Y-27632. At 1 day of transplant, the cornea was found to be opaque with moderate edema <800 μm in thickness, but at 14 days, the corneal thickness was reduced to 409 μm with corneal transparency restored. In addition, immunohistochemistry on the eyeball at 14 days revealed expression of DiI, [redacted], and [redacted]. In the recipient eyeball without Y-27632, fewer cells survived than those in the recipient eyeball with Y-27632, and expression of α-smooth muscle actin (α-SMA), a fibroblast marker, was observed.

In the cynomolgus monkey bullous keratopathy model, slit lamp microscopy was performed for corneal transparency and specular microscopy for cell density. Observations over 3 months of MCEC transplant revealed that the cells formed a hexagonal-lattice structure of monolayer at the cell density ≥2,000 cells/mm^2 and expressed [redacted] and [redacted] in the presence of Y-27632. In the absence of Y-27632, MCECs were found in a fibroblast-like form and expressed [redacted] and [redacted] at lower levels than those in the presence of Y-27632. The cornea was found to be transparent during the observation period regardless of Y-27632.

4.2.2 Anterior chamber transplant study of cultured allogeneic corneal endothelial cells and CHCECs in monkey bullous keratopathy model (CTD 4.2.1.1-2)

In the cynomolgus monkeys bullous keratopathy model, a total of 5.0×10^5 MCECs or CHCECs were transplanted into the left anterior chamber with or without Y-27632 ([redacted]M). Cell density was calculated by specular microscopy and corneal transparency was evaluated by slit lamp microscopy, along with fluoroimmunohistochemistry on the eyeball.

Observations over 1 year after MCEC transplant revealed that the cornea was transparent, and the cells formed a hexagonal-lattice structure of monolayer at the cell density ≥2,000 cells/mm^2 in the presence of Y-27632 at up to 1 year. Immunohistochemistry on the eyeball revealed expression of [redacted] and [redacted]. In the absence of Y-27632, examinations for cell density and structure were not available owing to the opaque cornea.

In the presence of Y-27632, observations over 3 months after CHCEC transplant revealed that the cornea was transparent, and the cells formed a hexagonal-lattice structure of monolayer at the cell density of 2,890 cells/mm^2. Immunohistochemistry on the eyeball revealed expression of [redacted] and [redacted]. In the absence of Y-27632, the cornea was found to be opaque.

4.R Outline of the review conducted by PMDA

The applicant's explanation about performance of Vyznova:

In healthy humans, corneal endothelial cells spread over the posterior surface of the cornea like cobblestones in a hexagonal shape at the density of ≥2,000 cells/mm^2 (*Journal of Japanese Ophthalmological Society.* 2014;118;81-83) and enhance drainage of fluid into the anterior chamber through [redacted] and [redacted], involving mitigation of corneal oedema, making the cornea transparent, and maintenance of the normal corneal thickness (*Ophthalmological Clinical Practices Qualifying Experts* [in Japanese]; Nakayama Shoten Co., Ltd.).

An immunohistological analysis on the CHCECs showed expression of [redacted], [redacted], and [redacted].

In the rabbit and cynomolgus monkey bullous keratopathy models, CHCECs or cultured allogeneic corneal endothelial cells were transplanted into the anterior chamber. All the transplant procedures resulted in formation of a hexagonal-lattice structure of monolayer on the posterior surface of the cornea and, in the presence of Y-27632, restoration of corneal transparency. Immunohistochemistry on the eyeball revealed stained images of [redacted] and [redacted].

As described above, CHCECs transplanted into the anterior chamber of a patient with bullous keratopathy adhere to the posterior surface of the cornea where the corneal endothelial cell density is low and reconstruct corneal endothelium tissue in a hexagonal-lattice structure of monolayer, thereby exerting the effect. In the absence of Y-27632, the transplanted cells were turned into a fibroblast-like

form and expressed [redacted] and [redacted], cellular function markers, at low levels. Y-27632 is therefore considered to contribute to maintenance of transplanted CHCEC's morphology and functions.

PMDA accepted the applicant's explanation.

5. Biological Disposition and Outline of the Review Conducted by PMDA

The applicant submitted data relating to biological disposition of Vyznova in a form of results from a biological disposition study in mice and an anterior chamber transplant study of MCECs and CHCECs in a cynomolgus monkey bullous keratopathy model.

5.1 Anterior chamber transplant study of CHCECs in mice (CTD 4.2.2.3-1)

A total of 2×10^4 quantum dots 655 (QDs655)-labeled CHCECs were transplanted into the right anterior chamber each of 3 mouse bullous keratopathy models with corneal endothelial cells fallen off by cryoinjury and 3 normal mice. The recipient eyeballs at 3, 24, and 48 hours of transplant were subjected to a fluorescence imaging system to determine QDs655 fluorescence intensity *in vivo* and *ex vivo*. In addition, histopathological examination was performed on the eyeballs at 3, 24, and 48 hours of transplant as well as the heart, lung, kidney, spleen, and liver at 48 hours, using a high-speed multiphoton confocal laser scanning microscope.

The *in vivo* examination using the fluorescence imaging system showed a decrease in fluorescence intensity with time. The *ex vivo* examination showed that ratios of fluorescence intensity at 24 and 48 hours to that at 3 hours in the mouse bullous keratopathy models were kept higher than those in the intact mice. The histopathological examination using the high-speed multiphoton confocal laser scanning microscope confirmed that CHCECs survived on the posterior surface of the cornea. At 48 hours of transplant, CHCECs were detected in the lung of all the mouse bullous keratopathy models observed and in the lung and liver of the normal mice.

5.2 Anterior chamber transplant study of cultured allogeneic corneal endothelial cells and CHCECs in monkey bullous keratopathy model (CTD 4.2.1.1-2)

In the cynomolgus monkey bullous keratopathy model prepared by a sequence of manipulations for removal of the crystalline lens, incision at the corneal limbus, and stripping of the corneal endothelial cells, a total of 5.0×10^5 MCECs or CHCECs were transplanted into the left anterior chamber, and the cornea was observed at 3 months or 1 year of transplant using slit lamp and specular microscopes. In the CHCEC-recipient monkeys, various organs[1)] at 14 days of transplant were subjected to polymerase chain reaction (PCR) targeting human genome deoxyribonucleic acid (gDNA) (human Kelch-like protein17 [KLHL17] and nephrocystin4 [NPHP4]) to examine biological distribution of the CHCECs. The PCR analysis did not detect expression of human gDNA in any organ analyzed.

1) Cerebral cortex, cerebellum, pituitary gland, spinal cord, thyroid, adrenal gland, heart, cava, lung, kidney, ureter, bladder, uterus, uterine cervix, ovary, fallopian tube, esophagus, stomach, duodenum, small intestine, colon, liver, pancreas, striated muscle, skin, peripheral nerve, breast, thymus, and spleen

5.R Outline of the review conducted by PMDA

The applicant's explanation about biological disposition of Vyznova:

In the mouse bullous keratopathy model, CHCECs transplanted into the anterior chamber were found to survive on the posterior surface of the cornea, indicating adequate distribution of the transplanted CHCECs from the anterior chamber to the cornea. As described in Section "4.2.2 Anterior chamber transplant study of cultured allogeneic corneal endothelial cells and CHCECs in monkey bullous keratopathy model," in the cynomolgus monkey bullous keratopathy model, transplant of MCECs into the anterior chamber led to observation of a hexagonal-lattice structure of monolayer suggestive of survival of functional corneal endothelial cells and maintenance of corneal transparency at up to 1 year. The transplanted CHCECs are considered to survive on the cornea for at least 1 year.

Regarding distribution of Vyznova into organs and tissues other than the eyeball, in the normal mice in which CHCECs were transplanted into the anterior chamber, CHCECs were detected in the lung and liver. The concerned finding is considered to reflect distribution of free CHCECs that did not adhere to the cornea, passed the trabecular meshwork at the angle, entered the Schlemm's canal and then vein, circulated systemically, and finally reached the lung and liver. The mouse bullous keratopathy model was found to have more intense fluorescence in the eyeball than the normal mice, suggesting that CHCECs efficiently adhered to the cornea and scarcely were left unattached to the cornea in the mouse bullous keratopathy model. In the cynomolgus monkey bullous keratopathy model in which CHCECs were transplanted into the anterior chamber, on the other hand, no human gDNA derived from the CHCECs were detected in any organs other than the eye. On the basis of the above findings, CHCECs transplanted into the anterior chamber of a patient with bullous keratopathy are considered unlikely to be distributed into organs outside the eyeball.

PMDA accepted the applicant's explanation.

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

The applicant submitted data relating to non-clinical safety of Vyznova in a form of results from a general toxicity study in rabbits transplanted with CHCECs, tumorigenicity tests (a karyotype analysis and a soft agar colony formation assay), and an immunological tolerance study in mice.

6.1 General toxicity study of Vyznova transplanted into the anterior chamber of rabbits (CTD 4.2.3.1-2)

CHCECs were transplanted into the left anterior chamber of Kbl:JW rabbits, and necropsy was performed on Day 15 post-transplant. Inflammatory changes were locally observed in the cornea, conjunctiva, and iris of the eye (Table 9).

Table 9. General toxicity study of Vyznova transplanted into the anterior chamber

Test system	Transplantation route	Observation period	Process	Dose	Major findings
Rabbits (both sexes)	Into the anterior chamber	15 days	Process E2	1.5×10^6 cells/ eye/body	Transplantation site (eye): Redness and edema, transiently increased intraocular pressure and increased corneal thickness were observed. The slit lamp microscopy showed opaque cornea, redness and hypertrophy of the iris, redness and edema of the conjunctiva, and translucent and opaque anterior chamber. The histopathological examination showed inflammatory cell infiltration in the iris, ciliary body, conjunctiva, and cornea. Whole body: No toxicological changes

6.2 Other safety

6.2.1 Tumorigenicity test

A karyotype analysis and a soft agar colony formation assay were performed as *in vitro* tests.

6.2.1.1 Karyotype analysis (CTD 4.2.3.7.7-2)

A karyotype analysis study comprised of a detailed analysis on G-band and mode analysis was performed on 5 batches of Vyznova. Chromosome aberrations were observed in a part of the specimens (Table 10).

Table 10. Karyotype analysis of Vyznova

CHCEC batch number	Process	Result
CT12-2*[1]	Process E2	No chromosome aberrations were observed.
CR02	Process E2	No chromosome aberrations were observed.
CT19-1	Process E2	Of 50 cells subjected to mode analysis, 2 cells had trisomy 7.*[2] Of 20 cells subjected to detailed analysis on G-band, 1 cell had translocation in chromosome 12, 1 cell had translocations in chromosomes 13 and 14, and 1 cell had loss of chromosome 22 and partial replacement with unknown chromosome.*[3]
C45	Process E1	No chromosome aberrations were observed.
C44	Process E1	Of 50 cells subjected to mode analysis, 4 cells had trisomy 12.*[2]

*1 Batch used in Study CHCEC-301

*2 It was considered as clonal proliferation according to the definition (at least 2 cells involved in proliferation or structural rearrangement of the same chromosome should be deemed as clonal cells) in the International System for Human Cytogenomic Nomenclature (ISCN)2020 (*Cytogenet Genome Res.* 2020;160:341-503).

*3 Translocation, loss, and partial replacement occurring at different sites of the chromosome in 1 cell each were not deemed as chromosome aberrations in view of the definitions in the ISCN2020.

Of 12 CHCEC batches that were manufactured through Process B, Process C, and Process D, transplanted in the subjects in Study CHCEC R-01, and subjected to the karyotype analysis, 8 batches were found to have chromosome aberrations in a part of the specimens (Table 11).

Table 11. Karyotype analysis of CHCECs transplanted in subjects in Study CHCEC R-01

CHCEC batch number	Process,*1 number of passages*2	Result
C40	Process D, 2 passages	Of 50 cells subjected to mode analysis, 26 cells had trisomy 12.*3
C39	Process D, 2 passages	Of 50 cells subjected to mode analysis, 5 cells had trisomy 12.*3
C38	Process D, 5 passages	Of 20 cells subjected to detailed analysis on G-band, 20 cells had inversion in chromosome 9.*4
C33-5	Process D, 5 passages	Of 20 cells subjected to detailed analysis on G-band, 1 cell had translocations in chromosomes 1 and 10.*5
C33-2	Process D, 4 passages	Of 20 cells subjected to detailed analysis on G-band, 1 cell had translocations in chromosomes 4 and 6.*5
C32-2	Process C, 5 passages	Of 50 cells subjected to mode analysis, 18 cells had trisomy 12.*3
C24	Process B, 3 passages	No chromosome aberrations were observed.
C23	Process B, 2 passages	No chromosome aberrations were observed.
C22	Process B, 2 passages	Of 50 cells subjected to mode analysis, 2 cells had trisomy 12.*3
C21	Process B, 2 passages	Of 20 cells subjected to detailed analysis on G-band, 1 cell had translocations in chromosomes 2 and 7.*5
C16	Process B, 3 passages	No chromosome aberrations were observed.
C15	Process B, 3 passages	No chromosome aberrations were observed.

*1 Comparability of Process B, Process C, and Process D to the proposed process has not been confirmed [see Section "2.3 Manufacturing process development (comparability)"].
*2 The number of passages in the proposed process is 3 [see Section "2.3 Manufacturing process development (comparability)"].
*3 In view of the definitions in the ISCN2020, it was considered as clonal proliferation.
*4 All of 20 cells had inversion, which was deemed as a chromosome attribute derived from the donor cell.
*5 Translocation, which was observed only in 1 cell, was not deemed as a chromosome aberration in view of the definitions in the ISCN2020.

6.2.1.2 Soft agar colony formation assay (CTD 4.2.3.7.7-1)

Cells (3 passages) derived from CHCECs (Batch number, R01), which were manufactured through Process E2',[2)] were seeded in a soft agar layer and cultured for 21 days. No colony formation indicative of anchorage-independent cell growth was detected.

6.2.2 Immunological tolerance study in mice (CTD 4.2.3.7.7-3)

The following study was conducted: Mouse primary corneal endothelial cells (mpCECs) prepared from the cornea of C57BL/6 mice or C57BL/6 mouse splenocytes were transplanted into the anterior chamber of intact Balb/c mice or Balb/c mouse bullous keratopathy models with corneal endothelial cells fallen off by cryoinjury, and at 1 week of transplant, C57BL/6 mouse splenocytes were transplanted in the auricle to induce alloantigen-specific delayed type hypersensitivity (DTH). In the intact Balb/c mice, the auricle thickness was not increased by transplant of either mpCECs or C57BL/6 mouse splenocytes into the anterior chamber, suggesting that the anterior chamber has immune privilege (*J Immunol Res.* 2018;1679197:1-12). In the Balb/c mouse bullous keratopathy model with the immune privilege potentially compromised by corneal injury, on the other hand, transplant of C57BL/6 mouse splenocytes into the anterior chamber increased the auricle thickness but transplant of mpCECs into the anterior chamber did not. Therefore, mpCECs when transplanted into the anterior chamber were considered unlikely to induce alloantigen-specific DTH.

6.2.3 Safety evaluation of impurities

Impurities potentially remaining in the final product are Material A, Material B, Material C, Material D, Material E, [redacted] (Material F, Material G, Material H, Material I, Material J Material K, and Material L. The applicant has discussed that the safety evaluation based on their residual amounts in Vyznova raises few safety concerns for humans.

2) Comparability to the proposed process has not been confirmed.

6.2.4 Safety evaluation of adjunctive ingredient of the primary component and secondary component (perfusate)

The adjunctive ingredient of the primary component and an ingredient of the secondary component (perfusate) are Y-27632 and Opti-MEM I. The applicant has discussed that the safety evaluation of each adjunctive ingredient based on the toxicity study results, etc. in view of contents of these adjunctive ingredients in Vyznova in clinical use raises few safety concerns for humans.

6.R Outline of the review conducted by PMDA

Concerning trisomies 7 and 12 detected in the karyotype analysis [see Section "6.2.1.1 Karyotype analysis"], PMDA asked the applicant to explain a tumorigenicity risk of Vyznova and post-marketing risk management.

The applicant's explanation:

For the following reasons, Vyznova is considered unlikely to have a tumorigenicity risk. However, because the number of patients transplanted with Vyznova is limited, tumorigenicity is planned to be included in the post-marketing surveillance as a survey item to collect information about intraocular and ocular surface proliferative lesions through slit lamp microscopy.

- Because normal human corneal endothelial cells do not divide or proliferate in the body (*Standard Ophthalmology Edition 13* [in Japanese], Igaku-Shoin Ltd.), Vyznova is not considered to proliferate in the anterior chamber, where it is injected, or any other sites throughout the body. Of note, the cells transplanted into the anterior chamber adhere to the posterior surface of the cornea and form a functional hexagonal-lattice structure of monolayer [see Section "4.R Outline of the review conducted by PMDA"]. If they are proliferative, the structure would be disordered, losing the function.
- In the soft agar colony formation assay, no colony formation indicative of anchorage-independent cell growth was detected.
- In Study CHCEC R-01, a part of batches that were manufactured through Process B, C, D, or E1 and found to have chromosome aberrations [see Section "6.2.1.1 Karyotype analysis"] were transplanted in 26 patients (Table 12), but ocular tumor lesions were not detected in any of the patients by slit lamp microscopy throughout the observation period of 36 to 60 months, and non-ocular tumor lesions related to Vyznova transplant were not detected either. Although comparability of these batches and ones used in the soft agar colony formation assay to batches manufactured through the proposed process has not been confirmed, the batches at both development stages were found to have chromosome aberrations, and thus the applicant considers it possible to discuss the tumorigenicity risk of Vyznova based on results in Study CHCEC R-01, which used the concerned batches.

Table 12. Transplant of batches with chromosome aberrations in Study CHCEC R-01

CHCEC batch number	Process	Result	Number of recipients
C44	Process E1	Trisomy 12	2
C40	Process D	Trisomy 12	5
C39	Process D	Trisomy 12	4
C38	Process D	Inversion in chromosome 9	1
C33-5	Process D	Translocations in chromosomes 1 and 10	3
C33-2	Process D	Translocations in chromosomes 4 and 6	4
C32-2	Process C	Trisomy 12	3
C22	Process B	Trisomy 12	2
C21	Process B	Translocations in chromosomes 2 and 7	2

PMDA's view:

On the basis of the data submitted and the review described below, clinical use of Vyznova is acceptable from a viewpoint of the non-clinical safety on the condition that the recipient of Vyznova will be continuously monitored.

- Although the karyotype analysis presented findings suggestive of clonal proliferation, Vyznova is considered to have few tumorigenicity risks based on currently available information in view of the following points: (a) Vyznova is derived from somatic cells and thus unlikely to undergo malignant transformation; and (b) no tumor lesions have been detected in either the eye or the other sites in human recipients of the batches with karyotype aberrations.
- Because Vyznova is considered unlikely to be distributed from the eye to other tissues and survive there [see Section "5.R Outline of the review conducted by PMDA"], the risk of Vyznova causing tumor lesions in other tissues than the eye is low.
- Proliferative lesions in the eye can be detected by slit lamp microscopy.

The local safety in the human eye is additionally discussed in Section "7.R.3 Safety."

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

The applicant submitted the efficacy and safety evaluation data from 2 clinical studies and data from 1 clinical research as reference data, as shown in the table.

Table 13. List of clinical studies for efficacy and safety

Data category	Region	Study identifier	Phase	Study population	Number of subjects	Dosage regimen	Main endpoints
Evaluation	Japan	Study CHCEC-201	II	Bullous keratopathy (Grade 4)	15	Transplant of 2×10^5, 5×10^5 or 1×10^6 CHCECs/eye into the anterior chamber (n = 5/group)	Efficacy Safety
		Study CHCEC-301	III		12	Transplant of 1×10^6 CHCECs/eye into the anterior chamber	
Reference		Study CHCEC R-01*	—		38	Transplant of 0.5-1 $\times 10^6$ CHCECs/eye into the anterior chamber	

* Products manufactured through Processes B to E were used (quality comparability of Processes B to D to the proposed process has not been confirmed) [see Section "2.3 Manufacturing process development (comparability)"].

7.1 Japanese Phase II study (CTD 5.3.5.2.1, Study CHCEC-201, [Study period, [redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, randomized, parallel-group study was conducted at 3 study centers in Japan to evaluate the safety and efficacy of Vyznova transplanted in a single procedure into the anterior chamber of patients (target sample size, 15 patients; 5 in each of the low [2×10^5 cells/eye], middle [5×10^5 cells/eye], and high [1×10^6 cells/eye] dose groups) who were diagnosed with bullous keratopathy (Grade 4 according to the Grading for Corneal Endothelial Damage [*Journal of Japanese Ophthalmological Society.* 2014;118:81-3]). In this study, the "Run-in period" was defined as a period from the day of informed consent to the day before transplant, and the "Treatment period" was as a period from the day of transplant to Week 52 of transplant.

Table 14. Major inclusion and exclusion criteria

Inclusion criteria	• Patients with best-corrected visual acuity <0.5 • Patients with no corneal endothelial cells or the corneal endothelial cells at the density <500 cells/mm^2 observed under the corneal endothelium specular microscope • Patients with the corneal thickness ≥630 μm and corneal epithelial oedema • Patients aged ≥20 and <90 years at the time of informed consent regardless of sex
Exclusion criteria	• Patients with active corneal infection (bacteria, fungi, virus, etc.) • Patients with glaucoma accompanied by poor intraocular pressure control according to the ophthalmologist • Patients with coexisting systemic autoimmune disease (systemic lupus erythematosis [SLE], Behcet's disease, etc.)

The following method of use was employed.

In principle, the surgery is performed under local anesthesia. Before the surgery, 2% pilocarpine hydrochloride is applied to the eye, and immediately before the surgery, oxybuprocaine hydrochloride ophthalmic solution and 0.1% adrenaline solution are applied. An incision approximately 1.6 mm in length is created at the corneal limbus of the patient, and corneal endothelial cells in an area approximately 8 mm in diameter are removed. If manipulation in the anterior chamber is difficult owing to corneal epithelium disorder or corneal oedema, corneal epithelial abrasion shall be performed in advance. The area where the corneal endothelium has been removed is confirmed. In addition, the anterior chamber is perfused with intraocular perfusate. Then, the anterior chamber is perfused with Opti-MEM I containing [redacted]M Y-27632 (secondary component). After suture of the wound, dexamethasone 1 mg is applied subconjunctivally. A total of 3 to 15×10^5 CHCECs are suspended in 450 μL of Opti-MEM I containing [redacted]M Y-27632, and 300 μL of the suspension is injected into the anterior chamber using a 26G needle. The patient is placed in a prone position for 3 hours after the surgery.

Of note, cataract operation and coreoplasty were allowed up to 4 weeks before the transplant.

Of 16 patients enrolled, 15 patients (5 in each of the low, middle, and high dose groups) received transplant of Vyznova, excluding 1 patient who withdrew the consent, and were included in the safety analysis population and full analysis set (FAS). The FAS served as the efficacy analysis population.

Bullous keratopathy in the patients were classified into the following etiological subtypes: Fuchs endothelial corneal dystrophy in 5 patients (2 in the low dose group, 2 in the middle dose group, 1 in the high dose group), pseudophakic bullous keratopathy and similar pathological conditions in 5 patients (2,

2, 1), pseudophakic bullous keratopathy and laser iridotomy-induced bullous keratopathy in 4 patients (0, 1, 3), and pseudophakic bullous keratopathy in 1 patient (1, 0, 0). In the high dose group, 1 patient had a prior corneal transplant, and in the middle dose group, 1 had a prior CHCEC transplant in Study CHCEC R-01, but the past recipient eyes in both patients were non-target ones in this study. In addition, all of 15 patients previously had ocular surgery other than corneal transplant.

The efficacy primary endpoint was "proportion of patients who achieved the corneal endothelial cell density ≥1,000 cells/mm^2 at Week 12 of transplant," and the results in this study were 80.0% (4 of 5) of patients in the low dose group, 100.0% (4 of 4) of patients[3)] in the middle dose group, and 100.0% (5 of 5) of patients in the high dose group. Table 15 shows changes in corneal endothelial cell density, corneal thickness, and best-corrected visual acuity over time. In addition, corneal epithelial oedema was "not observed" in all the patients at Week 12 of transplant and was observed in "none" of them at Week 52 except 1 patient in the middle dose group.

3) One patient in the middle dose group failed to provide the measured corneal endothelial cell density at Week 12 of transplant (residual corneal stroma oedema precluded counting of corneal endothelial cells) and thus was excluded from the efficacy analysis population.

Table 15. Changes in corneal endothelial cell density, corneal thickness, and best-corrected visual acuity over time (Study CHCEC-201, target eye, FAS)

	Baseline	Week 1	Week 2	Week 4	Week 8	Week 12	Week 24	Week 52
Corneal endothelial cell density (cells/mm^2)								
Low dose	0	0	0	3 2088.7 ± 1441.8 1041, 3733	4 1889.3 ± 835.2 983, 2818	5 1504.2 ± 762.4 916, 2831	5 1494.6 ± 693.8 808, 2643	5 1434.0 ± 643.0 755, 2434
Middle dose	1 465.0	0	0	3 3000.7 ± 373.7 2585, 3309	3 3247.3 ± 150.7 3082, 3377	4 3237.5 ± 278.3 2982, 3495	4 2996.3 ± 513.1 2368, 3606	4 2810.5 ± 410.8 2404, 3296
High dose	1 368.0	1 2755.0	1 2770.0	4 2903.3 ± 1210.5 1285, 3978	5 2397.6 ± 993.3 1307, 3536	5 2792.6 ± 1400.1 1110, 4338	5 2513.2 ± 1470.6 822, 3915	5 2448.4 ± 1496.1 417, 3600
Corneal thickness (μm)								
Low dose	5 721.6 ± 34.7 693, 781	5 749.0 ± 69.4 667, 855	5 682.4 ± 72.9 603, 801	5 578.6 ± 121.9 429, 759	5 572.2 ± 88.0 490, 712	5 559.4 ± 89.9 449, 692	5 556.8 ± 72.5 477, 671	5 560.6 ± 65.9 502, 673
Middle dose	5 728.4 ± 85.9 655, 840	5 747.8 ± 82.3 683, 874	5 691.8 ± 76.5 634, 781	5 643.2 ± 104.6 560, 795	5 619.6 ± 117.4 504, 805	5 600.4 ± 77.4 516, 701	5 598.8 ± 70.1 512, 665	5 587.6 ± 67.8 514, 676
High dose	5 736.8 ± 60.9 686, 826	5 677.0 ± 74.3 567, 755	5 720.4 ± 156.1 570, 928	5 615.0 ± 118.1 489, 757	5 586.0 ± 93.8 471, 729	5 540.4 ± 57.8 461, 610	5 554.0 ± 29.2 517, 587	5 552.6 ± 37.3 491, 585
Best-corrected visual acuity (logMAR)								
Low dose	5 1.080 ± 0.522 0.40, 1.70	5 1.177 ± 0.478 0.40, 1.52	5 1.128 ± 0.530 0.22, 1.52	5 0.604 ± 0.301 0.22, 1.00	5 0.413 ± 0.246 0.10, 0.70	5 0.318 ± 0.131 0.10, 0.40	5 0.438 ± 0.280 0.05, 0.82	5 0.388 ± 0.174 0.10, 0.52
Middle dose	5 0.958 ± 0.538 0.40, 1.52	5 1.019 ± 0.563 0.70, 2.00	5 0.768 ± 0.340 0.40, 1.22	5 0.561 ± 0.449 0.15, 1.22	5 0.495 ± 0.587 0.10, 1.52	5 0.485 ± 0.596 0.05, 1.52	5 0.415 ± 0.640 0.00, 1.52	5 0.398 ± 0.579 0.00, 1.40
High dose	5 1.229 ± 0.366 0.70, 1.52	5 1.103 ± 0.357 0.52, 1.40	5 1.023 ± 0.581 0.22, 1.70	5 0.695 ± 0.702 0.00, 1.70	5 0.520 ± 0.551 0.00, 1.22	5 0.317 ± 0.283 0.05, 0.70	5 0.283 ± 0.297 -0.08, 0.70	5 0.229 ± 0.229 -0.08, 0.52

Top, Number of patients; Middle, Mean ± standard deviation (SD) ; Bottom, Minimum, maximum

Adverse events occurred in 4 of 5 patients (80.0%) in the low dose group, 5 of 5 patients (100.0%) in the middle dose group, and 5 of 5 patients (100.0%) in the high dose group.

Table 16. Adverse events reported by ≥2 patients overall

Preferred term (PT)	Low dose (n = 5)	Middle dose (n = 5)	High dose (n = 5)
Eye pain	20.0% (1/5)	40.0% (2/5)	40.0% (2/5)
Nasopharyngitis	20.0% (1/5)	40.0% (2/5)	0.0% (0/5)
Eyelid oedema	0.0% (0/5)	20.0% (1/5)	20.0% (1/5)
Lacrimation increased	0.0% (0/5)	40.0% (2/5)	0.0% (0/5)
Constipation	0.0% (0/5)	20.0% (1/5)	20.0% (1/5)
Intraocular pressure increased	20.0% (1/5)	0.0% (0/5)	20.0% (1/5)
Musculoskeletal pain	20.0% (1/5)	20.0% (1/5)	0.0% (0/5)
Insomnia	20.0% (1/5)	0.0% (0/5)	20.0% (1/5)

Serious adverse events were gastric cancer, papillary thyroid cancer, and gastrointestinal submucosal tumour in 1 patient in the low dose group and femoral neck fracture in 1 patient in the middle dose group, but all of them were assessed as causally “unrelated” to Vyznova. No deaths were reported.

7.2 Japanese phase III study (CTD 5.3.5.2.2, Study CHCEC-301, [Study period, [redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted at 3 study centers in Japan to evaluate the efficacy and safety of CHCECs transplanted at 1×10^6 cells/eye in a single procedure into the anterior chamber of the target eye in patients (target sample size, 12 patients[4)]) who were diagnosed with bullous keratopathy (Grade 4 according to the Grading for Corneal Endothelial Damage). In this study, the "Run-in period" was defined as a period from the day of informed consent to the day before transplant, and the "Treatment period" was as a period from the day of transplant to Week 24 of transplant.

Table 17. Major inclusion and exclusion criteria

Inclusion criteria	• Patients with best-corrected visual acuity <0.5 • Patients with no corneal endothelial cells or the corneal endothelial cells at the density <500 cells/mm^2 observed under the corneal endothelium specular microscope • Patients with the corneal thickness ≥630 μm and corneal epithelial oedema • Patients aged ≥20 and <90 years at the time of informed consent regardless of sex
Exclusion criteria	• Patients with active corneal infection (bacteria, fungi, virus, etc.) • Patients with glaucoma accompanied by poor intraocular pressure control according to the ophthalmologist • Patients with coexisting systemic autoimmune disease (SLE, Behcet's disease, etc.) • Patients who have had CHCECs injected into the other eye in a clinical study in the past 52 weeks

The following method of use was employed.

In principle, surgery is performed under local anesthesia. Before the surgery, 2% pilocarpine hydrochloride is applied to the eye, and immediately before the surgery, oxybuprocaine hydrochloride ophthalmic solution and 0.1% adrenaline solution are applied. An incision approximately 1.6 mm in length is created at the corneal limbus of the patient, and corneal endothelial cells in an area approximately 8 mm in diameter are removed. If manipulation in the anterior chamber is difficult owing to corneal epithelium disorder or corneal oedema, corneal epithelial abrasion shall be performed in advance. The area in the anterior chamber where the corneal endothelium has been removed is confirmed. In addition, the anterior chamber is perfused with intraocular perfusate. Then, the anterior chamber is perfused with Opti-MEM I containing [redacted]M Y-27632 (secondary component). After suture of the wound, dexamethasone 1 mg is applied subconjunctivally. A total of 1.33×10^6 CHCECs are suspended in 400 μL of Opti-MEM I containing [redacted]M Y-27632, and 300 μL of the suspension is injected into the anterior chamber using a 26G needle. The patient is placed in a prone position for 3 hours after the surgery.

Of note, cataract operation and coreoplasty were allowed up to 4 weeks before the transplant.

Of 13 patients enrolled, 12 patients received transplant of Vyznova, excluding 1 patient who withdrew the consent, and were included in the safety analysis population and FAS. The FAS served as the efficacy analysis population.

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4) The sample size was specified based on the primary endpoint, which was "proportion of patients who achieved the corneal endothelial cell density ≥1,000 cells/mm^2 at Week 24 of transplant," as follows: On the hypothesis that the expected proportion in the Vyznova group is 70%, the number of patients required to perform the hypothesis test for the threshold of 10% at a one-sided significant level of 2.5% with the power of 95% was calculated to be 9, and with patients to be potentially excluded from the analysis taken into account, the sample size of 12 patients was specified.

Bullous keratopathy in the patients were classified into the following etiological subtypes: Fuchs endothelial corneal dystrophy in 5 patients, Fuchs endothelial corneal dystrophy and laser iridotomy-induced bullous keratopathy in 1 patient, pseudophakic bullous keratopathy and laser iridotomy-induced bullous keratopathy in 1 patient, exfoliation syndrome–related bullous keratopathy in 1 patient, exfoliation syndrome–related bullous keratopathy and pseudophakic bullous keratopathy in 1 patient, and other pathological conditions in 3 patients. A total of 11 patients had no prior corneal transplant, and 1 patient had prior corneal transplant (on the non-target eye). All of 12 patients previously had ocular surgery other than corneal transplant, and all had received crystalline lens replacement.

The "proportion of patients who achieved the corneal endothelial cell density ≥1,000 cells/mm^2 at Week 24 of transplant," efficacy primary endpoint, was 100.0% (12 of 12 patients), which was significantly different from the predetermined threshold of 10%[5] (one-sided *P* value <0.001, one-sided significance level of 2.5%, exact test for binomial proportion).

Table 18 shows changes in corneal endothelial cell density, corneal thickness, and best-corrected visual acuity over time. In addition, corneal epithelial oedema was observed in "none" of 12 patients at Week 24.

Table 18. Changes in corneal endothelial cell density, corneal thickness, and best-corrected visual acuity over time (Study CHCEC-301, target eye, FAS)

	Baseline	Week 1	Week 2	Week 4	Week 8	Week 12	Week 24
Corneal endothelial cell density (cells/mm^2)	0	1 348.0	0	10 4347.8 ± 646.7 2700, 4998	9 4280.9 ± 872.6 2516, 5571	11 4343.8 ± 1039.1 1676, 5379	12 4081.8 ± 1080.0 1726, 5373
Corneal thickness (μm)	12 788.5 ± 156.7 657, 1212	12 746.6 ± 132.4 601, 1094	12 694.6 ± 137.8 545, 1081	12 645.6 ± 119.0 521, 979	12 632.5 ± 99.4 520, 894	12 611.8 ± 72.0 498, 743	12 599.3 ± 68.6 493, 728
Best-corrected visual acuity (logMAR)	12 0.817 ± 0.492 0.40, 2.00	12 0.882 ± 0.442 0.30, 1.52	12 0.625 ± 0.396 0.15, 1.52	12 0.449 ± 0.410 0.00, 1.40	12 0.275 ± 0.242 0.00, 0.70	12 0.151 ± 0.196 0.00, 0.70	12 0.086 ± 0.222 -0.18, 0.70

Top, Number of patients; Middle, Mean ± SD; Bottom, Minimum, maximum

[5] Without treatment, the cultured corneal endothelial cell density >1,000 cells/mm^2 is medically impossible, and thus the proportion expected to be achieved without treatment is 0%. The threshold of 10% was therefore specified in this study.

Table 19 shows results on the efficacy by patient.

Table 19. Results on efficacy in the target eye by patient

Patient number	Corneal endothelial cell density (cells/mm^2)		Corneal thickness (μm)		Best-corrected visual acuity (logMAR)	
	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24
[redacted]	Unobservable	3476	931	624	0.52	-0.18
[redacted]	Unobservable	4600	690	542	0.70	0.15
[redacted]	Unobservable	4812	719	602	0.52	-0.08
[redacted]	Unobservable	4669	657	545	0.82	0.15
[redacted]	Unobservable	4246	700	620	0.40	0.05
[redacted]	Unobservable	5373	798	558	0.70	-0.08
[redacted]	Unobservable	4494	664	552	0.40	0.00
[redacted]	Unobservable	4181	794	685	0.40	0.15
[redacted]	Unobservable	4288	752	493	1.52	0.00
[redacted]	Unobservable	2273	1212	728	2.00	0.15
[redacted]	Unobservable	1726	854	668	1.00	0.70
[redacted]	Unobservable	4843	691	574	0.82	0.00

Adverse events occurred in 11 of 12 patients (91.7%). Adverse events reported by ≥2 patients were eye pain and nasopharyngitis in 4 patients (33.3%) each, constipation in 3 patients (25.0%), and intraocular pressure increased and diarrhoea in 2 patients (16.7%) each. Neither serious adverse events nor deaths were reported.

7.3 Japanese clinical research (CTD 5.3.5.4.1, Study CHCEC R-01 [Study period, ongoing since [redacted] 20[redacted]])

An open-label, uncontrolled study (clinical research) was conducted at a single study center to evaluate the safety of CHCECs[6)] transplanted at a dose of 0.5 to 1 × 10^6 CHCECs into the anterior chamber of patients with bullous keratopathy (target sample size, 45 patients). The "Treatment period" was 2 years after CHCEC transplant (Week 104).

All 38 enrolled patients received CHCEC transplant. Bullous keratopathy in the patients were classified into the following etiological subtypes: Fuchs endothelial corneal dystrophy in 11 patients, laser iridotomy-induced bullous keratopathy in 9 patients, post-transplant bullous keratopathy in 6 patients.

Within 2 years after the transplant, adverse events occurred in 16 of 38 patients (42.1%). Serious adverse events occurred in 3 of 38 patients (7.9%) and were intraocular pressure increased in 3 patients and cytomegalovirus (CMV) infection in 1 patient. For all the events, a causal relationship to the transplanted CHCECs was denied. No deaths were reported.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA reviewed the efficacy and safety of Vyznova with focus on results from Studies CHCEC-201 and CHCEC-301, which were submitted as the evaluation data in this application. Given that Study CHCEC-301, which is considered as a confirmatory study, was an open-label, uncontrolled study, and there were no agreed indicators for the efficacy evaluation in clinical studies in patients with bullous

6) Products manufactured through Process B to Process E were used (quality comparability of Process B to Process D to the proposed process has not been confirmed) [see Section "2.3 Manufacturing process development (comparability)"].

keratopathy, PMDA reviewed the efficacy evaluation of Vyznova, taking discussion results on design and efficacy endpoints of Study CHCEC-301 into account.

7.R.2 Efficacy

As a result of the review below, PMDA has concluded that Vyznova has efficacy in the treatment of bullous keratopathy to a certain extent.

7.R.2.1 Design and efficacy endpoints of Study CHCEC-301

The applicant's explanation about reasons for conducting Study CHCEC-301 as an open-label, uncontrolled study:

- Corneal transplant is an available treatment option for bullous keratopathy but it is not feasible to use this option as the control because of difficulty in securing the donors.
- Corneal endothelial cells are known to be non-proliferative in the human body (*Exp Eye Res.* 2012;95:16-23).
- It is difficult to mask information about the surgery-based Vyznova transplant to physicians and patients.

The applicant's explanation about the efficacy endpoints:

The primary endpoint in Study CHCEC-301 was "proportion of patients who achieved the corneal endothelial cell density ≥1,000 cells/mm^2 at Week 24 of transplant." The concerned endpoint is considered appropriate because of the following definitions in the Grading for Corneal Endothelial Damage (*Journal of Japanese Ophthalmological Society.* 2014;118:81-3): A condition of the corneal endothelial cell density ≥1,000 cells/mm^2 is classified as Grade 1 corneal endothelium damage or the normal (≥2,000 cells/mm^2) and deemed "unlikely to lead to bullous keratopathy," while a condition of the corneal endothelial cell density <1,000 cells/mm^2 is classified as Grade ≥2 corneal endothelium damage and described as "a critical state in maintaining the corneal transparency where a minimal endogenous or exogenous invasion may trigger progression to bullous keratopathy."

The secondary endpoints were specified for the following reasons:

- The corneal thickness was specified as an indicator to assess corneal oedema associated with bullous keratopathy. Of note, based on epidemiological research in Japan (*Am J Ophthalmol.* 2007;144:152-4, *Am J Ophthalmol.* 2010;150:279-286), etc., the corneal thickness of >630 μm was considered out of the normal range, and thus the corneal thickness of <630 μm was defined as "improved."
- To evaluate the efficacy of Vyznova on corneal endothelium functions comprehensively, a post-transplant change from baseline in best-corrected visual acuity (logarithmic minimum angle of resolution [logMAR]) was specified. Of note, a study in adults without eye disease or patients with eye disease shows that a change of ≥0.2 logMAR is required for reliable distinction from no change in terms of sensitivity and specificity (*Invest Ophthalmol Vis Sci.* 2003;44:3278-81), and thus a ≥0.2 decrease in logMAR was defined as "improvement" of visual acuity.

PMDA's view:

Bullous keratopathy is a pathological condition not expected to resolve spontaneously, and the definitive treatment is reconstruction of corneal endothelium tissue. In view of these clinical aspects, PMDA

considered it possible to evaluate the efficacy of Vyznova mainly based on data from Study CHCEC-301, which was conducted as an open-label, uncontrolled study. The improved corneal endothelial cell density by Vyznova transplant is expected to alleviate clinical symptoms such as reduced visual acuity attributable to bullous keratopathy, and such alleviation is considered clinically meaningful. PMDA therefore decided to evaluate the efficacy based on not only results on the primary endpoint but also those on the secondary endpoints such as visual acuity.

7.R.2.2 Efficacy results

The applicant's explanation about efficacy results from Study CHCEC-301:
The proportion of patients who achieved the corneal endothelial cell density ≥1,000 cells/mm^2 at Week 24 of transplant, the primary endpoint, was 100.0% (12 of 12 patients, 95% confidence interval [CI] [73.5, 100]), which was significantly different from the predetermined threshold of 10% (one-sided *P* value <0.001, one-sided significance level of 2.5%, exact test for binomial proportion). In addition, the proportions of patients who achieved corneal thickness of <630 μm and improved visual acuity with a ≥0.2 decrease in logMAR from baseline at Week 24 of Vyznova transplant were 75.0% (9 of 12 patients) and 100.0% (12 of 12 patients), respectively.

The applicant's explanation about the long-term efficacy of Vyznova:
At Week 52 of Vyznova transplant in the high dose group in Study CHCEC-201, the proportion of patients who achieved the corneal endothelial cell density ≥1,000 cells/mm^2 was 80.0% (4 of 5 patients), and the proportions of patients who achieved corneal thickness of <630 μm and improved visual acuity with a ≥0.2 decrease in logMAR from baseline were both 100% (5 of 5 patients). Of 4 patients who achieved the corneal endothelial cell density ≥1,000 cells/mm^2 at Week 52 of transplant, all patients had already achieved the corneal endothelial cell density ≥1,000 cells/mm^2 at Week 8, demonstrating the long-term maintenance of the efficacy up to Week 52. In the patient who had the corneal endothelial cell density <1,000 cells/mm^2 at Week 52, the corneal endothelial cell density reached ≥1,000 cells/mm^2 at Week 8 but was found below this level at Week 24. Transient inflammation in the anterior chamber on Day 2 of transplant might have led to the decrease of corneal endothelial cells.

In Study CHCEC R-01, 34 of 38 patients were included in the efficacy evaluation at 2 years of transplant, except patients with missing data. At 2 years of transplant, the proportion of patients who achieved the corneal endothelial cell density ≥1,000 cells/mm^2 was 91.2% (31 of 34 patients), and the proportions of patients who achieved corneal thickness of <630 μm and improved visual acuity with a ≥0.2 decrease in logMAR from baseline were 85.3% (29 of 34 patients) and 94.1% (32 of 34 patients), respectively.

PMDA's view:
Studies CHCEC-201 and CHCEC-301 show that the corneal endothelial cell density, which defines severity of corneal endothelial damage, had been decreased to an unobservable state in most of the patients before Vyznova transplant, but increased to ≥1,000 cells/mm^2 after that, and Vyznova transplant led to the decreased corneal thickness and improvement of the best-corrected visual acuity [see Table 15 in Section "7.1 Japanese Phase II study (CTD 5.3.5.2.1, Study CHCEC-201, [Study period, [redacted] to [redacted]])" and Table 18 (Section "7.2 Japanese phase III study (CTD 5.3.5.2.2, Study CHCEC-301, [Study period, [redacted] to [redacted]])"]. On the basis of the above results, the efficacy of Vyznova in the

treatment of bullous keratopathy has been demonstrated to a certain extent. For the long-term efficacy, on the other hand, currently available information is limited, and a decrease in corneal endothelial cell density was observed in some patients at Week 52 of Vyznova transplant. Therefore, the applicant should collect information about the safety and efficacy adequately in the post-marketing setting and, if a new finding is obtained, provide the information to healthcare professionals appropriately.

7.R.3 Safety

As a result of the review below, PMDA considered that adverse events requiring special attention for Vyznova transplant were intraocular pressure increased, macular oedema including cystoid macular oedema, and eye infection. Risks associated with Vyznova transplant is considered acceptable, provided that the applicant appropriately informs healthcare professionals of adverse events in Studies CHCEC-201 and CHCEC-301; and in view of the concerned information, physicians with adequate knowledge and experience in the treatment of bullous keratopathy take appropriate measures such as monitoring and controlling of adverse events.

7.R.3.1 Incidences of adverse events in Studies CHCEC-201 and CHCEC-301

The applicant's explanation about safety of Vyznova:

Table 20 shows the incidences of adverse events in Studies CHCEC-201 and CHCEC-301. No deaths were reported, and in Study CHCEC-201, serious adverse events occurred in 2 patients (gastric cancer, papillary thyroid cancer, and gastrointestinal submucosal tumour; and femoral neck fracture in 1 patient each), but a causal relationship has been denied for all the events. In Study CHCEC-301, no serious adverse events occurred. No events potentially raising a safety concern for Vyznova transplant in patients with bullous keratopathy were found.

Table 20. Adverse events reported by ≥2 patients in Study CHCEC-201 or CHCEC-301

	Study CHCEC-201 (n = 15)		Study CHCEC-301 (n = 12)
	Before Week 24	Weeks 24 to 52	Before Week 24
All adverse events	13 (86.7)	6 (40.0)	11 (91.7)
Adverse drug reactions	7 (46.7)	0 (0.0)	5 (41.7)
Serious adverse events	1 (6.7)	2 (13.3)	0 (0.0)
Major adverse events			
Eye pain	5 (33.3)	1 (6.7)	4 (33.3)
Nasopharyngitis	2 (13.3)	1 (6.7)	4 (33.3)
Constipation	2 (13.3)	0 (0.0)	3 (25.0)
Intraocular pressure increased	2 (13.3)	0 (0.0)	2 (16.7)
Diarrhoea	0 (0.0)	0 (0.0)	2 (16.7)
Eyelid oedema	2 (13.3)	0 (0.0)	0 (0.0)
Lacrimation increased	2 (13.3)	0 (0.0)	0 (0.0)
Musculoskeletal pain	2 (13.3)	0 (0.0)	0 (0.0)
Insomnia	2 (13.3)	0 (0.0)	0 (0.0)

Number of patients with event (incidence [%])

PMDA considers that no particular safety concerns associated with Vyznova transplant are found except the eye. In the sections below, PMDA reviews mainly ocular adverse events that are considered to pose an important risk in the treatment with Vyznova.

7.R.3.2 Safety by event

7.R.3.2.1 Intraocular pressure increased

The applicant's explanation about intraocular pressure increased after Vyznova transplant:

Intraocular pressure increased occurred in 2 of 15 patients (13.3%) (1 patient each in the low dose group and high dose group) in Study CHCEC-201 and 2 of 12 patients (16.7%) in Study CHCEC-301. A causal relationship to Vyznova could not be ruled out for the events in both 2 patients in Study CHCEC-201, but they were mild in severity and resolved with antiglaucoma eye drop. On the other hand, a causal relationship to Vyznova was denied for the events in both 2 patients in Study CHCEC-301, and they were mild in severity and resolved with antiglaucoma eye drop. In Study CHCEC R-01, however, intraocular pressure increased requiring glaucoma surgery also occurred. These adverse events of intraocular pressure increased occurred ≥1 week after transplant. For intraocular pressure increased, a causal relationship to steroids[7)] used for controlling of postoperative inflammation and suppression of rejection cannot be ruled out, but the applicant will include cautionary statement about a risk of intraocular pressure increased and glaucoma in the package insert.

PMDA's view:

There were events for which a causal relationship to Vyznova could not be ruled out, and steroid eye drop is expected to be used for a long time to suppress rejections after Vyznova transplant. In view of these points, the cautionary statement about intraocular pressure increased after Vyznova transplant should be included in the package insert. Changes in intraocular pressure after Vyznova transplant warrant careful attention, and if an increase is observed, an appropriate measure must be taken.

7.R.3.2.2 Macular oedema including cystoid macular oedema

The applicant's explanation about macular oedema including cystoid macular oedema after Vyznova transplant:

Cystoid macular oedema occurred in 1 of 15 patients in Study CHCEC-201, and macular oedema occurred in 1 of 12 patients in Study CHCEC-301. A causal relationship to Vyznova could not be ruled out for both events, and they were mild in severity and resolved with eye drop of non-steroidal anti-inflammatory drugs (NSAIDs). Vyznova transplant-emergent cystoid macular oedema and macular oedema are unlikely to occur frequently and become severe diseases and considered to resolve with appropriate treatment in response to the onset. In addition, because cystoid macular oedema occurs after conventional penetrating keratoplasty (PKP) or corneal endothelium transplant, the applicant will not include the relevant cautionary statement in the package insert.

PMDA's view:

There were events for which a causal relationship to Vyznova could not be ruled out, and thus the cautionary statement about macular oedema including cystoid macular oedema after Vyznova transplant should be included in the package insert, and treatment must be provided in a timely manner.

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7) In Studies CHCEC-201, CHCEC-301, and CHCEC R-01, it was recommended that steroids should be administered systemically from the day before CHCEC transplant to 3 to 7 days after that and locally from 1 to 2 days after CHCEC transplant to the end of the study. In Study CHCEC-301, local steroids were used with the dose adjusted as appropriate after Week 24 or end of the study.

7.R.3.2.3 Eye infection

The applicant's explanation about eye infection after Vyznova transplant:

Adverse events related to eye infections (conjunctivitis, keratitis, endophthalmitis, etc.) did not occur in either Study CHCEC-201 or CHCEC-301. In Study CHCEC R-01, a serious adverse event of CMV infection (CMV corneal endotheliitis in the recipient eye) occurred in 1 patient between Weeks 24 and 104 of transplant, but a causal relationship to the transplanted CHCECs was denied for the event. For Vyznova transplant, an incision is smaller than that for the conventional corneal endothelium transplant. Considering the low infection risk, the applicant will not include the relevant cautionary statement in the package insert.

PMDA's view:

In Studies CHCEC-201 and CHCEC-301 where antimicrobial eye drops and systemic administration of antimicrobial agents during the perioperative period were recommended long-term from the pre-transplant to the post-transplant stages, no eye infections occurred. The infection risk, however, is associated with Vyznova transplant, and steroids are expected to be used for controlling of postoperative inflammation and suppression of rejection. Vyznova transplant therefore requires adequate measures and cautions against infections.

7.R.3.2.4 Eye pain

The applicant's explanation about eye pain after Vyznova transplant:

In Study CHCEC-201, eye pain occurred in 5 of 15 patients. All of the 5 events that occurred in 5 patients just after the procedure were assessed as causally related to Vyznova and resolved. One patient who experienced eye pain 11 months after Vyznova transplant was a patient in the middle dose group who never achieved the corneal endothelial cell density ≥1,000 cells/mm^2 at any of the examination time points after transplant. The event was caused by bullous keratopathy and resolving with ointment, etc. In Study CHCEC-301, eye pain occurred in 4 of 12 patients. All of the events were assessed as causally related to Vyznova. Of them, 3 patients experienced the event just after transplant and all recovered. The eye pain just after the procedure was considered attributable to corneal epithelial abrasion, a part of the surgical manipulations. Although a possibility of a series of surgical procedures causing eye pain cannot be ruled out, the events resolved during follow-up or with oral analgesic drugs and/or application of eye ointment, and thus the concerned event raises no safety problem.

PMDA's view:

Eye pain after Vyznova transplant is mainly considered as postoperative pain and can be treated because the events promptly resolved during follow-up or with analgesic drugs. Information should be appropriately delivered, and preparedness for the event must be in place so that treatment can be provided where necessary.

7.R.3.2.5 Rejection

The applicant's explanation about rejection after Vyznova transplant:

Adverse events related to rejection did not occur in either Study CHCEC-201 or CHCEC-301. The incidence of immunological rejection after the corneal endothelium transplant is reported to be 10% in patients undergoing Descemet's stripping automated endothelial keratoplasty (DSEK/DSAEK)

(*Ophthalmology.* 2009;116:1818-30) and 1.9% in patients undergoing Descemet membrane endothelial keratoplasty (DMEK) (*Ophthalmology.* 2018;125:295-310), and the incidence after PKP is reported to be 20% to 35% (*Japanese Journal of Ophthalmic Surgery.* 2003;16:315-19). In Study CHCEC-301, local and systemic administration of steroids was performed as a care equivalent to the standard care for conventional corneal transplant, and no adverse events related to rejection occurred. The applicant will not include the relevant cautionary statement in the package insert.

PMDA's view:
According to the explanation, steroids administered from the pre-Vyznova-transplant stage for suppression of rejection resulted in no occurrence of adverse events related to rejection in Study CHCEC-201 or CHCEC-301. The applicant therefore should provide information about the use of steroids for suppression of rejection equivalent to that for corneal transplant, which was recommended for Vyznova transplant in the clinical study, appropriately. In addition, the applicant should continue collecting information in the post-marketing setting and, if a new finding is obtained, provide the information to healthcare professionals appropriately.

7.R.3.2.6 Tumorigenesis

The applicant's explanation about the risk of tumorigenesis associated with Vyznova transplant:
In Study CHCEC-201, a 7[redacted]-year old man experienced gastric cancer and papillary thyroid cancer on Day 129 of transplant and gastrointestinal submucosal tumour on Day 225, which were assessed as serious adverse events, but a causal relationship to Vyznova was denied for these events. In Study CHCEC-301, no adverse events related to tumorigenesis occurred. Additionally taking the non-clinical study results [see Section "6.R Outline of the review conducted by PMDA"] into account, the applicant considers the tumorigenicity risk of Vyznova extremely low but, because of the limited number of Vyznova recipients, will specify it as a survey item in the post-marketing surveillance and thereby implement risk management.

PMDA considers that the applicant should carefully collect information about the tumorigenicity risk after Vyznova transplant via the post-marketing surveillance.

7.R.3.2.7 Long-term safety

The applicant's explanation about the long-term safety after Vyznova transplant:
Of 38 patients enrolled in Study CHCEC R-01, 16 patients experienced 42 adverse events until Week 104 of CHCEC transplant. The events included 29 events of intraocular pressure increased in 11 patients, 8 events of cystoid macular oedema in 7 patients, and 1 event each of glaucoma, keratic precipitates, CMV infection, diarrhoea, and hypoaesthesia in 1 patient each. The results from Study CHCEC R-01 indicated that intraocular pressure increased requires special attention for a long time after Vyznova transplant. The first 11 patients in Study CHCEC R-01 were placed on a 5-year follow-up, and no adverse events such as immunological rejection and infections occurred (*Ophthalmol.* 2021;128:504-14). On the basis of the above, the applicant considers that Vyznova has the acceptable long-term safety.

PMDA's view:

For the long-term safety after Vyznova transplant, attention should be paid especially to intraocular pressure increased in view of the long-term use of steroid eye drop, which would be needed after Vyznova transplant. Because information about the long-term safety of Vyznova is extremely limited, the applicant should collect information about the long-term safety including not only intraocular pressure increased but also other events in the post-marketing setting appropriately, and healthcare professionals should be immediately cautioned if any problematic events are identified.

7.R.4 Clinical positioning, indication, or performance

The proposed "Indication or Performance" of Vyznova was "bullous keratopathy." The "Precautions Concerning Indication or Performance" section was not proposed.

On the basis of Sections "7.R.2 Efficacy," "7.R.3 Safety," and the review in the sections below, PMDA concluded that the "Indication or Performance" should be "bullous keratopathy" as proposed by the applicant, with the following cautionary advice included in the "Precautions Concerning Indication or Performance" section.

- Appropriate patients should be selected by physicians with a full understanding of the information about characteristics of patients enrolled in the clinical studies (ocular conditions, etc.) provided in the "Clinical Studies" section and of the efficacy and safety of Vyznova.

7.R.4.1 Clinical positioning and target patients

The applicant's explanation about clinical positioning and target patients of Vyznova:

Of corneal transplant procedures for bullous keratopathy, corneal endothelium transplant procedures (DSEK/DSAEK and DMEK, etc.) are the recent first-line treatment, and for patients not suitable for these procedures, PKP is generally chosen. Corneal transplant, however, has had issues such as a decrease in corneal endothelial cell density over a long time of period, long waiting period owing to global shortage of donors' corneas (*IRYO.* 2008;62:451-7, *Diagnosis and Treatment.* 2014;102:1521-7), rejection, and operative invasion.

Studies CHCEC-201 and CHCEC-301 in patients with bullous keratopathy demonstrated that Vyznova transplant restored the corneal endothelial cell density to ≥1,000 cells/mm^2 and improved visual acuity. In view of the issues of the conventional procedures, Vyznova is considered to be a new therapeutic option to patients with bullous keratopathy. Vyznova is a therapeutic procedure by which CHCECs with functions equivalent to those of healthy corneal endothelial cells are transplanted at a cellular level to restore the inherent functions of the corneal endothelium tissue in the eye as done by corneal endothelium transplant, the conventional procedure. In bullous keratopathy, replacement of the damaged corneal endothelium tissue, irrespective of the etiology, with the intact tissue has been demonstrated to alleviate opacity and oedema of the cornea by outcome of the corneal endothelium transplant (DSEK/DSAEK, DMEK, etc.) and PKP, the conventional procedures performed previously. As with the corneal transplant, the conventional procedures, Vyznova can be expected to be effective in and available for the treatment of bullous keratopathy overall irrespective of the etiology.

PMDA's view:

Although there are no study results that allow a comparison of the efficacy and safety between Vyznova and the conventional corneal endothelium transplant in the treatment of bullous keratopathy, in view of the issues of the conventional procedures, Vyznova may be positioned as a new therapeutic option to patients with bullous keratopathy based on results in Studies CHCEC-201 and CHCEC-301.

In view of the concept and presumed mechanism of action of Vyznova, the applicant's discussion that Vyznova can be expected to show efficacy in the treatment of bullous keratopathy irrespective of the etiology is understandable. However, it is essential that the use of Vyznova should be determined by physicians with an understanding of the efficacy and safety of Vyznova demonstrated in the clinical studies while taking into account the patient's coexisting ocular diseases, pathological conditions, and potential causes for the reduced visual acuity. To inform healthcare professionals appropriately of the target patients in the clinical studies in which the efficacy and safety of Vyznova were demonstrated, accordingly, the "Clinical Studies" section in the package insert should include information about ocular diseases and pathological conditions of the patients in the clinical studies. In addition, the "Precautions Concerning Indication or Performance" section should include the following statement: Appropriate patients should be selected by physicians with a full understanding of the information provided in the "Clinical Studies" section and of the efficacy and safety of Vyznova.

7.R.5 Dosage and administration or method of use

The proposed "Dosage and administration or method of use" of Vyznova was as follows:

Dosage and Administration or Method of Use

After an incision is made at the corneal limbus, while the anterior chamber is perfused with intraocular perfusate for maintenance, degenerated corneal endothelial cells and extracellular matrix are stripped from the posterior surface of the cornea with a corneal endothelium stripper. Then, the perfusate is applied (100 μL/dose, approximately 2 doses). The incision is sutured. Next, the perfusate is suctioned for removal. Then, 300 μL of the corneal endothelial cell preparation (1.0×10^6 cells) is transplanted into the anterior chamber. The patient is immediately placed in a prone position and held for 3 hours to enhance adhesion of the transplanted cells.

The applicant's explanation about rationales for specifying the "Dosage and administration or method of use":

The "Dosage and administration or method of use" of Vyznova was proposed based on Studies CHCEC-201 and CHCEC-301 in view of the following doses.

- In Study CHCEC-201, 3 doses of low (2×10^5 cells), middle (5×10^5 cells), and high (1×10^6 cells) doses per target eye were examined. The efficacy primary endpoint was "proportion of patients who achieved the corneal endothelial cell density ≥1,000 cells/mm^2 at Week 12 of transplant," and the proportion of 100.0% was found in the middle (4 of 4 patients) and high dose groups. None of the dose groups had particular safety problems. In view of the concept that the higher number of cells transplanted would secure a more stable and favorable outcome especially in the treatment of a severely damaged corneal endothelium surface, a dose of 1×10^6 cells was selected in Study CHCEC-301. Study CHCEC-301 demonstrated the efficacy and safety, and thus the dose of 1×10^6 cells was proposed for Vyznova.

PMDA's view:
The above applicant's explanation is acceptable, and the "Dosage and administration or method of use" may be specified based on settings, etc. in Study CHCEC-301.

The applicant, however, should prepare informative materials and modify procedures for the Vyznova transplant method and provide the information to healthcare professionals appropriately. In addition, information about concomitant drugs such as steroids, of which use was recommended from the pre-Vyznova-transplant stage for suppression of rejection in the clinical studies, should be provided via informative materials, etc. appropriately.

7.R.5.1 Re-transplant

PMDA asked the applicant to explain re-transplant of Vyznova.

The applicant's explanation about the possibility of Vyznova re-transplant into the same eye:
Vyznova re-transplant may be needed because corneal transplant, the conventional procedures for the treatment of bullous keratopathy, had the long-term outcome of decreased corneal endothelial cell density (*Japanese Journal of Ophthalmic Surgery.* 2021;34:489-95, *BMJ Open Ophth.* 2020;5:e000354, etc.); and intraocular surgery performed after Vyznova transplant, if any, might cause a decrease in corneal endothelial cell density. The period to Vyznova re-transplant is presumed to be approximately ≥5 years in view of the following findings: The 5-year graft survival after the corneal endothelium transplant (DSAEK) for the treatment of bullous keratopathy was approximately 85% (*BMJ Open Ophth.* 2016;57:4452-63); and that after the corneal endothelium transplant for the treatment of bullous keratopathy with filtering bleb following trabeculectomy or tube-shunt surgery for the treatment of glaucoma was 47% (*BMJ Open Ophth.* 2020;5:e000354). If the transplant results in survival failure because of rejection, Vyznova re-transplant may be performed as soon as possible. Of note, the 3-year graft survival after the corneal endothelium transplant (DSAEK) performed in response to graft failure after PKP was 68.6% *(Int Ophthalmol.* 2012;32:15-23) and 86.4% (*Am J Ophthalmol.* 2014;158:1221-1227).

The applicant's explanation about transplant into the contralateral eye:
One patient in Study CHCEC-201 and 2 patients in Study CHCEC-301 received prior CHCEC transplant in the contralateral eye, and the first transplant was performed in 2 patients in Study CHCEC R-01 and 1 patient in Study CHCEC-201. Even in patients with prior CHCEC transplant in the contralateral eye, the target eye has responded to the investigational transplant favorably without post-transplant rejection or specific adverse events. In standard clinical practices, corneal transplant procedures performed on both eyes, if any, are separated by ≥6 months. Vyznova transplant may be performed on both eyes at a similar interval.

PMDA's view on re-transplant of Vyznova:
Because Vyznova has not been re-transplanted into the same eye, the applicant should appropriately present information that the efficacy and safety of re-transplanted Vyznova are unknown. In the clinical studies conducted for this application, the long-term results that would support the necessity of re-transplant have not been evaluated. If patients who have undergone re-transplant are found in post-

marketing setting, the applicant should collect and evaluate the information. For survival failure caused by rejection at an early stage of post-Vyznova-transplant, a possibility cannot be ruled out that the use of Vyznova in the concerned patient itself was problematic. At present, re-transplant performed at the earliest possible opportunity is considered inappropriate. The applicable cases should be subjected to adequate cause investigation and discussion. If they are accrued, patient characteristics and perioperative management should be investigated and searched for common points, and additional points to note should be considered. There are no rationales for prohibiting re-transplant of Vyznova into the same eye performed a long time after the previous procedure. However, if such a re-transplant is performed in a post-marketing setting, the information should be collected and immediately evaluated to determine if additional cautionary advice should be issued.

Regarding transplant of Vyznova into the contralateral eye, the information is limited at present. Therefore, the applicant should firstly provide information such as rules about intervals of transplant in the clinical studies and collect the relevant information in a post-marketing setting.

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

The applicant's explanation about the post-marketing surveillance plan for Vyznova:
The applicant plans to conduct a post-marketing surveillance to evaluate the safety and efficacy of Vyznova in all patients treated with Vyznova in post-marketing clinical setting.

The safety specification of this surveillance includes "intraocular pressure increased," "rejection to Vyznova," "infection," "hypersensitivity," and "tumor lesion at the transplant site," which are risks potentially occurring in Vyznova recipients in a post-marketing setting.

The planned sample size for the surveillance is 220 patients in light of the expected number of patients using Vyznova in post-marketing setting (6 years from marketing launch of Vyznova) and incidences of the risks included in the safety specification in Studies CHCEC-201 and CHCEC-301.

The observation period was specified as a period up to Week 52 of Vyznova transplant to evaluate each item of the specification.

PMDA's view:
Because of extremely limited experience in the use of Vyznova, the post-marketing surveillance needs to cover all patients treated with Vyznova in the post-marketing setting to collect information about the safety and efficacy of Vyznova in a prompt and unbiased manner. The above applicant's explanation about the surveillance plan (safety specification, planned sample size for the surveillance, and observation period) has been acceptable.

On the basis of the review in Section "7.R.3 Safety," in addition to the proposed safety specification in the post-marketing surveillance, "macular oedema including cystoid macular oedema" should be investigated, and using the information gathered, the incidence, seriousness, time-to-onset, causal relationship, etc. should be discussed. Furthermore, information about patient characteristics including coexisting diseases and prior treatment, medication and surgeries additionally provided after Vyznova

transplant, and other relevant care should be collected to investigate factors potentially impacting the efficacy and safety. If re-transplant of Vyznova is performed, information about the case including background leading to re-transplant should be appropriately collected and evaluated. If these investigations indicate information suggesting the populations or events for which caution should be raised, the concerned information should be provided to healthcare professionals appropriately.

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

At present, the inspection is in progress. The results and PMDA's conclusion will be presented in the Review Report (2).

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

At present, the inspection is in progress. The results and PMDA's conclusion will be presented in the Review Report (2).

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

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

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

Review Report (2)

February 1, 2023

Product Submitted for Approval

Brand Name	Vyznova
Non-proprietary Name	Neltependocel
Applicant	Aurion Biotech Japan, LLC
Date of Application	June 21, 2022

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 Vyznova has efficacy in the treatment of bullous keratopathy.

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 Vyznova does not raise particular concerns. A risk associated with Vyznova transplant is considered acceptable, provided that the applicant informs healthcare professionals of adverse events in Studies CHCEC-201 and CHCEC-301; and in view of the concerned information, physicians with adequate knowledge and experience in the treatment of bullous keratopathy take appropriate measures such as monitoring and controlling of adverse events.

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

1.3 Clinical positioning, indication, or performance

As a result of the review in Section "7.R.4 Clinical positioning, indication, or performance" of the Review Report (1), PMDA has concluded that the "Indication or Performance" of Vyznova should be defined as "bullous keratopathy"; the "Clinical Studies" section in the package insert should include details of the patients enrolled in Studies CHCEC-201 and CHCEC-301; and then the "Precautions

Concerning Indication or Performance" section should include the following statement: Appropriate patients should be selected by physicians with a full understanding of the information provided in the "Clinical Studies" section and of the efficacy and safety of Vyznova.

In addition to comments supporting PMDA's conclusion, the following comment was raised from the expert advisors at the Expert Discussion:

- In a patient with bullous keratopathy worsened to corneal stromal opacity, the corneal endothelium transplant cannot be expected to restore corneal transparency and thus is of low therapeutic significance, and thus Vyznova should not be applied to such a patient.

In view of the above comment raised from the expert advisors, PMDA requested the applicant to modify the "Precautions Concerning Indication or Performance" section by including the statement to the effect that necessity for Vyznova transplant should be assessed in view of the outcome such as visual acuity as shown below. The applicant responded that they would take appropriate measure, and PMDA accepted the response.

Precautions Concerning Indication or Performance

- Appropriate patients should be selected by physicians with a full understanding of the information about characteristics of patients enrolled in the clinical studies (ocular conditions, etc.) provided in the "Clinical Studies" section and of the efficacy and safety of Vyznova.
- Before use of Vyznova, the need for Vyznova transplant should be determined in view of the outcome such as visual acuity.

1.4 Dosage and administration or method of use

As a result of the review in Section "7.R.5 Dosage and administration or method of use" of the Review Report (1), PMDA has concluded that the "Dosage and Administration or Method of Use" of Vyznova should be described based on the setting, etc. in Study CHCEC-301 as proposed in the mentioned section of the Review Report (1).

At the Expert Discussion, the expert advisors commented that manipulations for suture of the incision and suction of Vyznova perfusate for removal were not specific. The modified version of the "Dosage and Administration or Method of Use" was presented as shown below. The expert advisors agreed.

Dosage and Administration or Method of Use

After an incision is made at the corneal limbus, while the anterior chamber is perfused with intraocular perfusate for maintenance, degenerated corneal endothelial cells and extracellular matrix are stripped from the posterior surface of the cornea with a corneal endothelium stripper. Then, the perfusate is applied (100 μL/dose, approximately 2 doses). The incision is sutured. Next, an injection needle is inserted through the corneal limbus into the anterior chamber, and the perfusate is suctioned for removal. Then, 300 μL of the corneal endothelial cell preparation (1.0×10^6 cells) is transplanted into the anterior chamber. The patient is immediately placed in a prone position and held for 3 hours to enhance adhesion of the transplanted cells.

PMDA asked the applicant to modify the "Dosage and Administration or Method of Use" as described above. The applicant responded appropriately, and PMDA accepted the response.

1.5 Post-marketing surveillance plan (draft)

At the time of application, the applicant had proposed a plan of post-marketing surveillance covering all patients treated with Vyznova to evaluate the safety and efficacy of Vyznova in post-marketing clinical use. The planned sample size was 220 patients. The planned observation period was up to a period to Week 52 of Vyznova transplant.

As a result of the review in Section "8. Risk Analysis and Outline of the Review Conducted by PMDA" of the Review Report (1), PMDA has concluded that "macular oedema including cystoid macular oedema" should be added to the proposed safety specification ("intraocular pressure increased," "rejection to Vyznova," "infection," "hypersensitivity," and "tumor lesion at the transplant site") in the proposed post-marketing surveillance plan.

At the Expert Discussion, PMDA's conclusion was largely supported, but the following comments were raised from the expert advisors:

- Manipulation for Vyznova administration may trigger intraocular inflammation, which could secondarily cause macular oedema including cystoid macular oedema and intraocular pressure increased. In view of this possibility, intraocular inflammation after Vyznova administration should be captured in the post-marketing surveillance.
- Vyznova may be used in more patients than expected after launch. In view of this possibility, the planned sample size should be reconsidered after clearly identifying the specification in the post-marketing surveillance.

In consideration of the above comments from the expert advisors and the applicant's explanation shown below, PMDA concluded that the post-marketing surveillance presented in Table 21 should be implemented.

- To the safety specification, "macular oedema including cystoid macular oedema" and "intraocular inflammation" will be added.
- The planned sample size will be changed to 600 patients, which is expected to allow detection of adverse events at the incidence of 0.5% with the probability of ≥95%, because experience in the use of Vyznova in the clinical studies was too limited to detect potential adverse events at a low incidence, and the change of the size is decided to detect these events.

Table 21. Outline of post-marketing surveillance plan (draft)

Objective	To evaluate the safety etc. of Vyznova in clinical use
Survey method	All-case surveillance
Observation period	52 weeks
Study population	Patients with bullous keratopathy
Planned sample size	600 patients
Main survey items	Safety specification Intraocular pressure increased, rejection to Vyznova, infection, hypersensitivity, tumor lesion at the transplant site, macular oedema including cystoid macular oedema, and intraocular inflammation

1.6 Others

1.6.1 Designation of specified regenerative medical product

On the basis of "Principles for designation of biological products, specified biological products, and specified regenerative medical products" (PFSB/ELD Notifications No. 1105-1 and 1105-2 dated November 5, 2014, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW), PMDA has concluded that Vyznova should be designated as a specified regenerative medical product because it is a regenerative medical product manufactured using allogeneic cells as the starting material.

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

2.1 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 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.

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

The new regenerative medical product application data (CTD 5.3.5.2.2) 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.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the proposed indication or performance and dosage and administration or method of use modified 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

Bullous keratopathy

Dosage and Administration or Method of Use

After an incision is made at the corneal limbus, while the anterior chamber is perfused with intraocular perfusate for maintenance, degenerated corneal endothelial cells and extracellular matrix are stripped from the posterior surface of the cornea with a corneal endothelium stripper. Then, the perfusate is applied (100 μL/dose, 2 doses). The incision is sutured. Next, an injection needle is inserted through the corneal limbus into the anterior chamber, and the perfusate is suctioned for removal. Then, 300 μL of the corneal endothelial cell preparation (1.0×10^6 cells) is transplanted into the anterior chamber. The

patient is immediately placed in a prone position and held for 3 hours to enhance adhesion of the transplanted cells.

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 the physicians with adequate knowledge and experience in bullous keratopathy acquire full skills of the product usage and knowledge in complications associated with the procedures and that physicians use the product in compliance with the “Indication or Performance” and “Dosage and Administration or Method of Use” at medical institutions with an established system for treatment of bullous keratopathy.
2. Since only a limited number of Japanese 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 after the market launch until data from a certain number of patients are collected in order to identify 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.

Appendix

List of Abbreviations

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Approval application	Application for marketing approval
CHCEC	Cultured human corneal endothelial cell
CI	Confidence interval
[redacted]	[redacted]
DMEK	Descemet membrane endothelial keratoplasty
DMEM	Dulbecco's Modified Eagle's Medium
DSEK/DSAEK	Descemet's stripping automated endothelial keratoplasty
DTH	Delayed type hypersensitivity
EBAA	Eye Bank Association of America
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
FAS	Full analysis set
FBS	Fetal bovine serum
GCP	Good clinical practice
gDNA	genome deoxyribonucleic acid
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
[redacted]	[redacted]
HTLV	Human T-cell leukemia virus
ISCN	An International System for Human Cytogenomic Nomenclature
KLHL17	Kelch-like protein 17
logMAR	Logarithmic minimum angle of resolution
MAP	Mitogen activated protein
MCEC	Monkey corneal endothelial cell
mpCEC	Mouse primary corneal endothelial cell
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
[redacted]	[redacted]
NPHP4	Nephrocystin4
NSAIDs	Non-steroidal anti-inflammatory drugs
[redacted]	[redacted]
PCR	Polymerase chain reaction
[redacted]	[redacted]
[redacted]	[redacted]
PKP	Penetrating keratoplasty
PMDA	Pharmaceuticals and Medical Devices Agency
QDs655	Quantum dots 655
QOL	Quality of life
RCEC	Rabbit corneal endothelial cell
ROCK	Rho-associated coiled-coil forming kinase

RT-PCR	Reverse transcription polymerase chain reaction
[redacted]	[redacted]
[redacted]	[redacted]
SLE	Systemic lupus erythematosus
α-SMA	α-Smooth muscle actin
TGF-β	Transforming growth factor-β
[redacted]	[redacted]
Y-27632	ROCK inhibitor
[redacted]	[redacted]
Vyznova	Vyznova